16TH WORLD CONGRESS OF BIOLOGICAL PSYCHIATRY

2024

WORLD CONGRESS

PROGRAM & ABSTRACT BOOK

İSTANBUL, TÜRKIYE

5 JUNE - 8 JUNE 2024

ISTANBUL LUTFI KIRDAR INTERNATIONAL CONVENTION & EXHIBITION CENTER

WELCOME TO THE 16TH WORLD CONGRESS OF BIOLOGICAL PSYCHIATRY

On behalf of the executive committee of the World Federation of the Societies of Biological Psychiatry (WFSBP), we are delighted to invite you to attend the 16th World Congress of Biological Psychiatry, to be held 5 June through 8 June 2024 at the Istanbul Lutfi Kirdar International Convention & Exhibition Center in İstanbul, Türkiye.

The theme of this year's Congress, "Translational Psychiatry: From Innovation to Practice," emphasizes the importance of bridging the gap between cutting-edge research and clinical application to improve mental health care. By focusing on translating scientific discoveries into practical treatments, it aims to advance patient outcomes and foster innovation in psychiatric practices.

The congress brings together experts, researchers, and clinicians from all continents in the field of biological psychiatry to share the latest scientific advancements, clinical practices, and innovative research.

This year's program features plenary sessions, debates, symposia, workshops, and poster presentations, focusing on the integration of biological research with psychiatric etiology, diagnosis, and treatment; all of them on very interesting topics to be presented by prominent researchers/ scientists in their respective fields.

We are looking forward to meeting you in İstanbul, Türkiye and interacting with you both socially and professionally.

With our best wishes,

Prof. Lakshmi N. Yatham
WFSBP President

Prof. Soraya Seedat
Chair, Scientific Program Committee

Prof. Bilgen Taneli
Chair, Regional Organizing Committee

ABOUT **WFSBP**

HISTORY

Founded in 1974, the World Federation of Societies of Biological Psychiatry is a non-profit worldwide organization comprising 64 National Societies of Biological Psychiatry and individual members representing professionals from over 70 countries. With this multitude of countries represented in its worldwide community, the World Federation has built an international network of opinion leaders, the majority of whom are key opinion leaders in the practice of biological psychiatry.

PURPOSE

- To foster and encourage scientific research and advancement in the field of biological psychiatry
- To improve the quality of training spanning all the biological psychiatry sciences
- To promote education and achieve the highest level of knowledge and understanding within the field
- To provide information and guidance to all institutions, societies, or individuals with an interest in biological psychiatry
- To establish, build, and maintain solid collaboration with international and national organizations related to biological psychiatry

2024 WFSBP WORLD CONGRESS
SCHEDULE AT A **GLANCE**

Wednesday 5 June 2024

Pre-Conference Workshop 12:00 PM - 4:00 PM		
Antipsychotic Treatment of Schizophrenia - A Practical Course for Early Career Psychiatrists	*Concurrent Room 1*	Istvan Bitter (Hungary)
Using AI in Systematic Review Screening with Asreview	*Concurrent Room 2*	Jelle Teijema (Netherlands)
Writing for a High-Quality Psychiatry Journal	*Concurrent Room 3*	Rajiv Tandon (USA), Joan Marsh (United Kingdom), Yasin Hasan Balcioglu (Türkiye)
Concurrent Symposia I 4:15 PM - 5:45 PM		
Revising Construct of Schizophrenia: Relevance to Biological Research	*Concurrent Room 1*	**Rajiv Tandon (United States)**, *Wolfgang Gaebel (Germany)*, Florence Thibaut (France), Peter Falkai (Germany)
Biomarkers in Insomnia: Evidence Derived from a WFSBP Task Force Consensus Statement	*Concurrent Room 2*	**Constantin Soldatos (Greece)**, *Martin Hatzinger (Switzerland)*, Adam Wichniak (Poland), Thorsten Mikoteit (Switzerland), Dimitris Dikeos (Greece)
Predictive Biomarkers and New Methodological Approaches for Mental Disorders	*Concurrent Room 3*	**Oliver Pogarell (Germany)**, *Tomiki Sumiyoshi (Japan)*, Jonas Björklund (Germany), Sebastian Olbrich (Switzerland), Maximilian Maywald (Germany)
The Different Faces of Depression across the Life span: From Social Isolation to Suicide	*Concurrent Room 4*	**Paolo Brambilla (Italy)**, Maria Gloria Rossetti (Italy), Aiste Lengvenyte (France), Jean-Charles Roy (France), Eleonora Maggioni (Italy)
Welcome, Ceremonial Opening & Honorific Awards Session 6:00PM - 6:30PM		
Opening Plenary 6:30PM - 7:30PM		
Reflections on The Future of Psychiatry Drug Discovery	*Auditorium*	**Lakshmi Yatham (Canada)**, *Benicio Frey (Canada)*, John Krystal (United States)
Opening Reception 7:30 - 9:00 PM	*Foyer*	

2024 WFSBP WORLD CONGRESS
SCHEDULE AT A **GLANCE**

Thursday 6 June 2024

Plenary Session II 8:00AM - 9:00AM		
Substance Use and Abuse: Advances in Neurobiology and Treatment of Substance Use Disorders	*Auditorium*	**Nora Volkow (United States),** Allan Young (United Kingdom), Florence Thibaut (France),
Educational Breakouts II 9:30AM - 11:00AM		
Free Communication/Orals Session I- Group 1	*Concurrent Room 1*	Kar Kin Albert Chung (Hong Kong), Samer El Hayek (United Arab Emirates), Mirjam Wolfschlag (Sweden), Nicolaja Girone (Italy), Jaanus Harro (Estonia), Severine Crettol (Switzerland), Arvin Haghighatfard (Iran), Florian Raabe (Germany)
Understanding Body Dysmorphic Disorder (BDD): Latest International Research	*Auditorium*	**Susan Rossell (Australia)**, Jamie Feusner (Canada), Sabine Wilhelm (United States), *David Castle (Australia)*, Georgina Krebs (United Kingdom)
From Damaged DNA to morbidity: Mitochondrial Dysfunction in Bipolar Disorder as a Novel Therapeutic Target	*Concurrent Room 4*	**Aysegul Ozerdem (United States)**, Mete Ercis (United States), Michael Berk (Australia), Deniz Ceylan (Türkiye)
Social Isolation in Youths: Prevention and Treatment Strategies	*Concurrent Room 5*	**Paolo Brambilla (Italy)**, *Andrea Raballo (Switzerland)*, Stefan Borgwardt (Germany), Takahiro Kato (Japan), Dulce Alarcón Yaquetto (United Kingdom), Maria Gloria Rossetti (Italy)
Free Communication/Orals Session I- Group 2	*Concurrent Room 2*	Yuyanan Zhang (China), Cécile Gras (Switzerland), Iris Popovic (Switzerland), Aurélie Reymond-Delacrétaz (Switzerland), Joanna Moussiopoulou (Germany), Zhe Lu (China), Guy Hindley (Norway), Tuana Kant (Canada), Marianna Piras (Switzerland)
Free Communication/Orals Session I- Group 3	*Concurrent Room 3*	Laura Cremaschi (Italy), Shaojia Lu (China), Brenda Cabrera-Mendoza (United States), Rubai Zhou (China), Reiji Yoshimura (Japan), Manish Jha (United States), Jussi Jokinen (Sweden), Madalina-Octavia Buciuman (Germany), Yi Lu (Sweden)
Poster Session I and Lunch 11:15 AM - 1:15 PM	*Poster Area*	
Pharmaceutical Pipeline Pipeline Symposium: Innovations of Tomorrow 11:30 AM - 1:00 PM	*Auditorium*	**Michael Berk (Australia)**, Zuzana Blahova (Austria), Ravi Anand (Switzerland), Maximilian Schuier (United States)
Concurrent Symposia III 1:30PM - 3:00PM		
Digital Technologies and New Advancements in Psychiatry	*Auditorium*	**Oguz Karamustafalıoglu (Türkiye)**, *Kato Tadafumi* (Japan), John Torous (United States)
New Insight and Development of Integrative Treatment in Schizophrenia	*Concurrent Room 1*	**Peter Falkai (Germany)**, *Jingxia Lin (Hong Kong)*, Lukas Roell (Germany), Frank Padberg (Germany), Christoph Correll (United States)
The Art of Prescribing Clozapine: Novel Developments	*Concurrent Room 2*	**Dragana Ignjatovbic Ristic (Serbia)**, Hans de Haas (Netherlands), Wai Hong Man (Netherlands), Dan Cohen (Netherlands)
Exploring Current and Future Directions in the Microbiome – a Focus on Neuropsychiatric Disorders	*Concurrent Room 3*	**Sian Hemmings (South Africa)**, *Stefanie Malan-Muller (Spain)*, Sahar El Aidy (Netherlands), Walter Pirovano (Netherlands)
Grant Writing Workshop	*Concurrent Room 4*	**Sophia Frangou (Canada)**, Paolo Brambilla (Italy)
Neuroprogression in Psychiatric Disorders: Early Detection, Intervention and Prevention	*Concurrent Room 5*	**Angelos Halaris (United States)**, Stephen Murata (United States), Andy Zamar (United Kingdom), Michael Berk (Australia)
Debate Session I 3:30PM - 5:00PM		
What Has Neuroimaging Done for Biological Psychiatry?	*Auditorium*	**Bilgen Taneli (Türkiye)**, *Florence Thibaut (France)*, Stephen Lawrie (United States), Deanna Barch (United States)
Concurrent Symposia IV 3:30PM - 5:00PM		
Dysregulations of Endogenous Amino Acids and Related Neurocircuits in Psychiatric Disorders	*Concurrent Room 1*	**Hsien-Yuan Lane (Taiwan)**, Andrea de Bartolomeis (Italy), Alessandro Usiello (Italy), Chieh-Hsin Lin (Taiwan)
Immune-Metabolic Dysfunction in Mental Disorders: An Update on Current Evidence	*Concurrent Room 2*	**Ishrat Husain (Canada)**, Preethi Veerappa Reddy (India), Fabiana Corsi-Zuelli (Brazil), Bruna Panizzutti (Australia), Omair Husain (Canada)
Innovation in Opioid Agonist Therapy and Withdrawal Management	*Concurrent Room 3*	**Marc Vogel (Switzerland)**, *Pouya Azar (Canada)*, Maximilian Meyer (Switzerland)
Applying Personalized Medicine to Bipolar Disorder	*Concurrent Room 4*	**David Bond (United States)**, Benicio Frey (Canada), Magdalini Ioannou (Netherlands), Jan Steinheimer (Germany)
Personalized Treatment of Bipolar Disorder	*Concurrent Room 5*	**Martin Alda (Canada)**, Abigail Ortiz, David Cousins, Claudia Pisanu
Concurrent Symposia V 5:00PM - 6:30PM		
Update on Treatment Resistant Depression	*Auditorium*	**Siegfried Kasper (Austria)**, Roger McIntyre (Canada), Dan Rujescu-Balcu (Austria), Christoph Kraus (Austria)
International Studies on Brain Maturation and Developmental psychopathology: From Birth to Adulthood	*Concurrent Room 1*	**Paolo Brambilla (Italy)**, *Brenda Penninx (Netherlands)*, Chiara Nosarti (United Kingdom), Maria Nobile (Italy), Tilo Kircher (Germany), Brenda Penninx (Netherlands)
Neuro Science Based Nomenclature	*Concurrent Room 2*	**Oguz Karamustafalıoglu (Türkiye)**, *Joseph Zohar (Isreal)*, Asilay Seker (United Kingdom), Sasson Zemach (Isreal)
Translating Psychiatric Genetics to Clinical Applications with Novel Statistical and Machine Learning Approaches	*Concurrent Room 3*	**Ole Andreassen (Norway)**, *Yi Lu (Sweden)*, Elise Koch (Norway), Oleksandr Frei (Norway), Bayram Akdeniz (Norway), Pravesh Parekh (Norway)
Psychiatric Electrophysiology as Add-On Tool in the Management of Addiction Disorders	*Concurrent Room 4*	**Oliver Pogarell (Germany)**, Mehmet Kemal Arıkan (Türkiye), Salvatore Campanella (Belgium), Bruna Sanader Vukadinovic (United Kingdom)
The Role of Reward System in Psychiatric Disorders: A Transdiagnostic Approach	*Concurrent Room 5*	**Esin Erdogan (Türkiye)**, *Merve Babalioglu (Türkiye)*, Aslihan Bilge Bektas (Türkiye), Vefa Erbasan (Türkiye),
General Assembly 6:30 PM - 7:15 PM	*Auditorium*	

2024 WFSBP WORLD CONGRESS
SCHEDULE AT A **GLANCE**

Friday 7 June 2024

Plenary Session III 8:00AM - 9:00AM		
A New Era in AD Drug Trials: Translating Hope into Impact	*Auditorium*	**Catherine Mummery (United States),** Soraya Seedat (South Africa), Adriana Rivetti (Argentina), Catherine Mummery (United States)
Educational Sessions II 9:30AM - 11:00 AM		
Free Communication Session/Orals II -Group 4	*Concurrent Room 1*	Frederike Stein (Germany), Neelabja Roy (India), Bhagyalakshmi Shankarappa (India), Tilo Kircher (Germany), Chiara Colli (Italy), Kazutaka Ohi (Japan), Fiona Coutts (United Kingdom), Yuji Yamada (Japan), Marianna Piras (Switzerland)
The Role of Dopamine in Bipolar Disorder Mood Cycling and Dysregulated Circadian Cycles: A Dopaminergic Rhythmopathy ?	*Auditorium*	**Sameer Jauhar (United Kingdom),** *Melvin McInnis (United States),* Outi Linnaranta (Finland), Kai-Florian Storch (Canada)
Decoding Mental Disorders - Deciphering the Genetic Basis and Exploring Animal and iPSC Models	*Concurrent Room 4*	**Florian Raabe (Germany),** *Peter Falkai (German),* JO Andressoo (Finland), Dorit Ben-Shachar (Isreal), Ole Andreassen (Norway)
Potential Clinical Tools Across Psychiatric Disorders: From Biomarkers to Clinical Markers	*Concurrent Room 5*	**Bo Cao (Canada),** *Tao Li (China),* Xiaoping Wang (China), Hongbo He (China), Fei Wang (China)
Free Communication Session/Orals II- Group 5	*Concurrent Room 2*	Gaia Scaccabarozzi (Italy), Lindokuhle Thela (South Africa), Severine Crettol (Switzerland), Céline Dubath (Switzerland), Laura Camillo (Italy), Clara Weyer (Germany), Chiara Galbiati (Italy), Ulrich Rabl (Austria), Bruna Panizzutti (Australia)
Free Communication Session/Orals II -Group 6	*Concurrent Room 3*	Safak Caglayan (Norway), Samer El Hayek (Samer El Hayek), Thorsten Mikoteit (Switzerland), Cathy Barr (Canada), Aleksei Afonin (Finland), Arvin Haghighatfard (Iran), Adyasha Khuntia (Germany), Elif Sarisik (Germany), Rubai Zhou (China)
How to be PRO: Protecting Schizophrenia Patients from Hyperprolactinaemia, Satellite Symposia Presented by Gedeon Richter 11:15 AM - 12:45 PM	*Auditorium*	
Poster Session II and Lunch 12:00 PM - 1:45 PM	*Poster Area*	
Concurrent Symposia VII 2:00 PM - 3:30PM		
Big Data Approaches to Discover Disease Mechanisms of Mental Illness	*Concurrent Room 1*	**Ole Andreassen (Norway),** Guy Hindley (Norway), Shahram Bahrami (Norway), Nadine Parker (Norway), Bayram Akdeniz (Norway)
Manuscript Writing Workshop	*Auditorium*	**Florence Thibaut (France),** *Dan Rujescu-Balcu (Austria)***,** Michael Berk (Australia)
Lifestyle and CAM Therapies for Wellness and Treatment of Depressive Disorders	*Concurrent Room 2*	**Arun Ravindran (Canada),** *Michael Berk (Australia),* Felice Jacka (Australia), Brendon Stubbs (United Kingdom), Kaviraja Udupa (India)
Early Intervention for Bipolar Disorder: From Cutting Edge Science to Transformative Clinical Practice	*Concurrent Room 3*	**David Bond (United States)**, Muralidharan Kesavan (India), Rajakumari Reddy (India), Kamyar Karamatian (Canada)
Translational Addiction Studies of Novel Psychoactive Substances	*Concurrent Room 4*	**Maria De Luca (Italy)** , Giorgia Corli (Italy), Aviv Weinstein (Isreal)
Presentation Skills Workshop	*Concurrent Room 5*	**Peter Falkai (Germany)**, David Castle (Australia), Susan Rossell (Australia)
Debate Session II 3:30 PM - 5:00PM	*Auditorium*	**Peter Falkai (Germany)**, *Dan Rujescu-Balcu (Austria)*, Dan Evangelos Vassos (United Kingdom) , Ole Andreassen (Norway)
Concurrent Workshop I 3:30PM - 5:00PM		
Sexual Violence and Women	*Concurrent Room 1*	**Florence Thibaut (France),** Victoria Valdez (Ecuador), Marc Potenza (USA)
WFSBP Task Force Treatment Guidelines Unipolar Depressive Disorders	*Concurrent Room 2*	**Michael Bauer (Germany),** Allan Young (United Kingdom), Anthony Cleare (United Kingdom), Andrea Pfennig (Germany)
Neuropsychiatric Applications of Non-Invasive Brain Stimulation	*Concurrent Room 3*	**Peter Fried (United States)**, Mouhsin Shafi (United States), Shirley Fecteau (Canada), Paula Davila Pérez (Spain), Asli Demirtas-Tatlidede (Turkey)
Autism-Spectrum-Disorder in the Setting of Practical Adult Psychiatry: Clinical Presentation and Therapeutic Approaches	*Concurrent Room 4*	**Frederico Garcia (Brazil),** *Taiwo Sheikh (Nigeria),*Ludger Tebartz van Elst (Germany)
World Guidelines for Mental Disorders: WFSBP, CINP and WPA Special Collaboration	*Concurrent Room 5*	**Lakshmi Yatham (Canada)**, *Afzal Javed (Turkey)*, Joseph Zohar (Isreal), Kostas Fountoulakis (Greece)
Presidential Dinner 6:30	**Visit registration desk for tickets*	ALL ATTENDEES MUST UTILIZE BUSES, The last bus will leave the ICEC at 6:00 PM

2024 WFSBP WORLD CONGRESS
SCHEDULE AT A **GLANCE**

Saturday 8 June 2024

Plenary Session IV 8:00AM - 9:00AM		
Can We Re-Medicalise the Psychedelic Experience?	*Auditorium*	**Guy Goodwin (United Kingdom),** Michael Berk (Australia), Lakshmi Yatham (Canada)
Concurrent Symposia VIII 9:30AM - 11:00AM		
Preventing and Ameliorating Treatment-Resistant Depression: Best Practice and Beyond	*Auditorium*	**Allan Young (United Kingdom),** Anthony Cleare (United Kingdom),Viktoriya Nikolova (United Kingdom), Roos van Westrhenen (Netherlands), Rebecca Strawbridge (United Kingdom)
Neuroprogression in Psychiatric Disorders: Biomarkers for Staging and Interventions for Prevention	*Concurrent Room 1*	**Angelos Halaris (United States),** Xenia Gonda (Hungary), Ebrahim Haroon(United States), Dimitris Dikeos (Greece), Dominique Endres (Germany)
Updates in ECT Practice and Research: New Applications	*Concurrent Room 2*	**Georgios Petrides (United States**), Stella Rosson (United Kingdom) ,Soren Dinesen Ostergaard (Denmark), Brent Forester (United States), Sohag Sanghani (United States),
GALENOS: A new living evidence resource for research prioritisation in mental health	*Concurrent Room 3*	**Niall Boyce (United Kingdom),** *Andrea Cipriani (United Kingdom)*, Georgia Salanti (Switzerland), Soraya Seedat (South Africa), Tatenda Kambeu (United Kingdom)
Heterogeneity in Psychotic Disorders across Levels of Research	*Concurrent Room 4*	**Sinan Guloksuz (Netherlands)**, Tao Li (China), Evangelos Vassos (United Kingdom), Michael Benros (Denmark)
Lunch on Your Own 11:15 AM - 1:15 PM		
GALENOS Meeting 11:15 AM - 1:15 PM	*Concurrent Room 1*	*All attendees are invited
Concurrent Symposia IX 1:30PM - 3:00PM		
The Pharmacological Treatment of Eating Disorders: New Guidelines, Insights, and Perspectives	*Auditorium*	**Siegfried Kasper (India)**, Ece Sengun Filiz (United Kingdom), Hubertus Himmerich (Germany), Jochen Seitz (Germany), Walter Kaye (United States)
Genetic Risk Predictions and Biological Mechanisms in ADHD - Towards Precision Medicine	*Concurrent Room 1*	**James Kennedy (Canada),** *Meryem Ozlem Kutuk (Turkey)*, Tuana Kant (Canada), Cathy Barr (Canada), Erika Nurmi (United States)
Innovations in Pharmacogenomic Research: Translation and Clinical Utility	*Concurrent Room 2*	**Bernhard Baune (Germany),** Júlia Perera Bel (United States), Alessandra Minelli (United States), Jurjen Luykx (Netherlands)
PARAM: A Neurodevelopmental Cohort from India	*Concurrent Room 3*	**Vivek Benegal (India)**, Bharath Holla (India), Eesha Sharma (India), Nilakshi Vaidya (Germany), Jayant Mahadevan (India)
Tools for Optimizing Pharmacotherapy in Psychiatry: Focus on Antipsychotics	*Concurrent Room 4*	**Xenia Hart (German),** *Chin Bin Eap (Switzerland),* Frederik Vandenberghe (Switerland), Céline Verstuyft (France), Gerhard Gründer(German)
White Matter in Mental Illness, as a Biomarker and Therapeutic Target	*Concurrent Room 5*	**Xinmin Li (Canada),** *Xin Yu (China),* Weihua Yue (China), Haiyun Xu(China), Jue He (China), Mengzhou Xue Xue (China)
Plenary Debate III 3:30 PM - 5:00 PM		
Does Nature Favour Dimensional or Categorical Diagnoses?	*Auditorium*	**Benicio Frey (Canada),** Anthony Pelosi (Scotland), Steven Hyman (United States)
Concurrent Symposia X 3:30PM - 5:00PM		
When Randomized Trials Aren't an Option: Target Trial Emulation in Psychiatric Research	*Concurrent Room 1*	**Helene Speyer (Denmark)**, Alejandro Szmulewicz (United States), Gonzalo Martínez-Alés (United States), Kaisla Komulainen (Helinski)
Precision Psychiatry Approach for Mood Disorders: Role of Brain Biomarkers and Dysfunctional Immune Response	*Concurrent Room 2*	**Manish Jha (United States)**, *Oguz Karamustafalıoglu (Turkey)*, Sameer Jauhar (United Kingdom), Arjun Athreya (United States), Michael Berk (Australia)
Oligodendrocyte Pathology and Cognition in Severe Mental Disorders	*Concurrent Room 3*	**Peter Falkai (Germany),** Florian Raabe (Germany), Siegfried Kasper (Austria), Bernhard Baune (Germany)
Cognitive Impairment in Bipolar Disorders	*Concurrent Room 4*	**Allan Young (London),** *Nese Direk (Turkey)*, Nefize Yalin (United States), Lakshmi Yatham (Canada)

PLENARY SESSION

Reflections on The Future of Psychiatry Drug Discovery

Wednesday, 5 June 2024, 6:30 PM

John Krystal, MD | Yale Department of Psychiatry

Presenter Bio

Dr. Krystal is McNeil Professor and Chair of Psychiatry at Yale and Yale-New Haven Hospital. He studies the neurobiology and treatment of psychiatric disorders. His laboratory discovered the rapid antidepressant effects of ketamine. He directs the Yale Center for Clinical Investigation, Center for the Translational Neuroscience of Alcohol, and Neuroscience Division of the National Center for PTSD. He is a member of the National Academy of Medicine; Fellow of the American Association for the Advancement of Science; co-director of the Neuroscience Forum of the National Academies of Sciences, Engineering, and Medicine; editor of Biological Psychiatry; and co-founder of Freedom Biosciences.

Objective

To review challenges that have traditionally plagued the development of medications for psychiatry indications and to highlight two areas of exciting recent developments: 1) ketamine and psychedelics and 2) antipsychotics that may work via targets other than the dopamine D2 receptor.

PLENARY SESSION

Substance Use and Abuse: Advances in Neurobiology and Treatment of Substance Use Disorders

Thursday, 6 June 2024, 8:00 AM

Nora Volkow, MD | NIDA

Presenter Bio

Nora D. Volkow, M.D., is the Director of the National Institute on Drug Abuse (NIDA), which supports most of the world's research on the health aspects of drug abuse and addiction. Dr. Volkow's scientific research was instrumental in demonstrating that drug addiction is a disease of the human brain and, as NIDA Director, her work has promoted research that improves the prevention and treatment of substance use disorders. As a research psychiatrist, Dr. Volkow pioneered the use of brain imaging to investigate the toxic and addictive effects of abusable drugs. Her studies documented disruption of the dopamine system in addiction with its consequential functional impairment of frontal brain regions involved with motivation, executive function and self-regulation. She has also made important contributions to the neurobiology of obesity, and ADHD and has published more than 920 peer-reviewed articles, written more than 120 book chapters and non-peer-reviewed manuscripts, co-edited a Neuroscience Encyclopedia and edited four books on neuroimaging for mental and addictive disorders.

Objective

Addiction, a complex disorder linking genes, development and the social environment has, for decades, been illuminating our understanding of the human brain and is leading the way toward promising strategies for its effective treatment.

PLENARY SESSION

A New Era in AD Drug Trials: Translating Hope into Impact

Friday, 7 June 2024, 8:00 AM

Catherine Mummery, PhD | University College London

Presenter Bio

Cath Mummery is a consultant neurologist at the National Hospital for Neurology and Neurosurgery. She is chair of the NIHR Dementia Translational Research Collaboration, building a national unified trials network for early phase clinical trials, accelerating dementia translational research in the UK. She is Head of Clinical Trials at the Dementia Research Centre, University College London, and Deputy Director for the Leonard Wolfson Experimental Neurology Centre, a cutting-edge research facility dedicated to the conduct of early phase trials in neurodegeneration. Over the past 17 years, she has been chief investigator on over 20 early phase drug trials of potential disease modifying agents in sporadic Alzheimer's disease (AD) and genetic forms of AD and frontotemporal dementia, with a particular focus on novel mechanisms in first-in-human trials including checkpoint inhibitors, gene silencing and AAV genetic therapies. As clinical lead for the UCL Neurogenetic Therapies Programme, she leads a programme of innovative collaboration between industry and academia to accelerate progress in genetic therapies in dementia. Her driving ambition is to ensure we not only have treatments that can alter the course of neurodegenerative diseases like Alzheimer's, but that we can deliver them promptly, safely and equitably.

Objective

The search for treatments for Alzheimer's disease has been a long and arduous one with many negative trials and heated debate on what we should be targetting, and how. However, recent results on anti amyloid immunotherapies have shown for the first time that we can alter the course of the disease and, while modest, have given us a foundation on which to build.

PLENARY SESSION

Can We Re-Medicalise the Psychedelic Experience?

Saturday, 8 June 2024, 8:00 AM

Guy Goodwin, FRCPsych | University of Oxford

Presenter Bio

Guy Goodwin is CMO, Compass pathways and Emeritus Professor of Psychiatry at the University of Oxford, UK. His research interests are the treatment of mood disorder and the potential to improve treatment using new technology and new drugs, notably the psychedelics. He is a Fellow of the American College of Neuropsychopharmacology, has previously held the position of President of the British Association for Psychopharmacology and the European College of Neuropsychopharmacology (ECNP).

Objective

Despite the widespread availability of multiple antidepressant treatments, depression remains a common and oftentimes debilitating disorder. A proportion of patients with major depressive disorder fail two or more antidepressant treatments and are considered to have treatment-resistant depression (TRD). Recent attention has turned to psilocybin and other psychedelic compounds as potential rapidly acting and durable episodic treatments for psychiatric disorders including depression.

DEBATE SESSIONS


What Has Neuroimaging Done for Biological Psychiatry?

Thursday, 6 June 2024, 3:30 PM

Stephen Lawrie, FRCPsych, MD | University of Edinburgh

Deanna Barch, PhD | Washington University in St. Louis

Polygenic Risk Scores in Psychiatry - Utility or Futility?


Friday, 7 June 2024, 3:30 PM

Evangelos Vassos, MD | King's College London

Ole Andreassen, MD, PhD | University of Oslo


Does Nature Favour Dimensional or Categorical Diagnoses

Saturday, 8 June 2024, 3:30 PM

Anthony Pelosi, MRCPsych | University of Glasgow

Steven Hyman, MA, MD | Harvard University

WFSBP AWARDS

LIFETIME ACHIEVEMENT

Siegfried Kasper

Austria

LIFETIME ACHIEVEMENT

Marie Asberg

Sweden

RESEARCH

Dominique Endres

Germany

EXCELLENCE IN EDUCATION

Rajiv Tandon

United States

RESEARCH

Tadafumi Kato

Japan

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Continuing Education (CE) Language Statement

World Federation of Societies of Biological Psychiatry
2024 WFSBP Annual Congress
June 5 - 8, 2024
Istanbul, Turkey

Joint Accreditation Statement
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and World Federation of Societies of Biological Psychiatry (WFSBP). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Professions in scope for this activity are listed below.

Physicians
Amedco LLC designates this enduring material for a maximum of 22.50 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

VIEW LEARNER NOTIFICATION

LEARNING OBJECTIVES

- Summarize the latest findings in translational neurobiological research related to psychiatric disorders, including developments in genetics, neuroimaging, and biomarker identification.
- Learn about new and emerging therapeutic approaches for the treatment of psychiatric disorders e.g., novel pharmacological treatments, neuromodulation techniques, and personalized medicine strategies.
- Understand strategies for fostering interdisciplinary collaboration among researchers, clinicians, patients, industry and other stakeholders to enhance the integration of biological psychiatry insights into clinical practice and public health policies.

Disclosures

- Click here to view the Disclosures of the 2024 speakers, plenary, symposia, workshop, oral presentations and poster presenters.

Conference Evaluation

- All conference attendees are urged to complete an evaluation of the meeting. Attendees who are requesting CME (ACCME) credit for the meeting are required to complete the evaluation. The evaluation link will be emailed to all attendees on 8 June 2024. All evaluations must be completed by 31 July 2024.

Videotaping Sessions

- Attendees may not videotape, audiotape, or photograph (camera or camera phone) presentations at the conference without permission from the session chair.

Abstracts

- Abstracts for all presentations are available online and at the end of this program book. Click here to access the Online Congress Schedule.

VIEW LEARNER NOTIFICATION

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YOUNG INVESTIGATOR TRAVEL AWARDEES

Brenda Cabrera-Mendoza (United States)
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Kashypi Garg (India)
Arvin Haghighatfard (Iran)
Ishrat Husain (Canada)
Manish Jha (United States)
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Jee Kim (Australia)
Daisuke Koshiyama (Japan)
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5034A Thoroughbred Lane, Brentwood, TN 37027

Wednesday, June 5, 2024

12:00 p.m. - 4:00 p.m.

Pre-Conference Workshops

ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA - A PRACTICAL COURSE FOR EARLY CAREER PSYCHIATRISTS *Istvan Bitter, Semmelweis University*

Overall Abstract: Antipsychotic treatment of schizophrenia - a practical course for early career psychiatrists. Course director: Prof. Istvan Bitter, Semmelweis University, Budapest, Hungary. This interactive course will summarize evidence-based knowledge based on randomized clinical trials and real-world data about the efficacy and safety of antipsychotic drugs in the acute and maintenance treatment of schizophrenia. The course will address how to individually use different antipsychotic drugs with the help of such information as their pharmacological effects on the neurotransmitter systems (e.g. dopamine D2 occupancy; D2 partial agonists), pharmacokinetic parameters (e.g. the potential roll of metabolites; elimination half-life; long acting injectable antipsychotics) and their clinical effects (use of rating scales or real world data such as time to discontinuation of taking a drug, risk of re/hospitalization and mortality). The importance of regular evaluation of extrapyramidal and metabolic side effects will be highlighted. Such specific topics as the differential diagnosis and treatment of negative symptoms and the management of treatment resistance in schizophrenia will also be discussed. The participants - who request - will receive a short list of selected literature linked to the topic of the course, that could provide help in their daily practice.

USING AI IN SYSTEMATIC REVIEW SCREENING WITH ASREVIEW

Jelle Teijema, Utrecht University

Pre-Conference Workshop Synopsis: This workshop will delve into ASReview, an innovative AI based software designed to transform the process of systematic literature review, making it faster, more accurate, and less labor-intensive. Systematic reviews are foundational to evidence-based practices across disciplines, yet they are time-consuming and prone to bias. ASReview leverages machine learning algorithms to significantly reduce the amount of time researchers spend screening titles and abstracts by prioritizing relevant studies for inclusion. The session will commence with an introduction to the challenges of traditional literature review processes, setting the stage for a detailed exploration of ASReview. Participants will gain insights into the underlying technology, including the machine learning models that power ASReview, and how these models adapt and improve through user interaction. We will address critical questions around the efficacy of ASReview, its impact on reducing researcher workload, and the quality and reliability of the results it produces. A portion of the workshop will be dedicated to hands-on activities, where attendees will have the opportunity to interact with ASReview directly, requiring a laptop. This practical experience aims to equip participants with the knowledge to set up and begin using the software for their own systematic reviews. Additionally, there will be ample time for discussion, allowing participants to raise questions, share experiences, and discuss the implications of integrating such technologies into their research practices. The workshop promises to be an engaging and informative session, offering a blend of theoretical knowledge and practical skills. By the end, participants will be well-prepared to adopt ASReview, enhancing their research efficiency and contributing to the advancement of evidence-based findings.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL *Joan Marsh, The Lancet Psychiatry* **Pre-Conference Workshop Synopsis:** The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry. The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines. The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions. The workshop will include questions and answers throughout and group discussions.

SUCCESSFUL PUBLISHING IN A QUALITY PSYCHIATRY JOURNAL

*RajivTandon*1*
1

University of Michigan Medical Center

Objective: This interactive workshop is designed to learn essential steps and augment skills that will enable attendees to successfully publish their scholarship in writing for peer-reviewed journals. Information about what happens to a manuscript after submission will be summarized, with the focus on the editorial and review process.
Methods: This workshop is organized in three parts:
a)40-minute didactic introduction;
b)30-minute interactive process with participants, reviewing vignettes (or personal publishing experiences) that illustrate successful negotiation of challenges across the many steps in the publishing process; and
c)20-minute summation with 7 KEYS to SUCCESSFUL PUBLISHING IN PSYCHIATRY
Results: Participants will discover rich information and techniques for:
(i)Successfully navigating the manuscript publication process after submission;
(ii)Recognize the expectations and priorities of the multiple audiences (editor, reviewer, reader) of the manuscript;
(iii)Producing effective scientific writing that meets expectations of these audiences (specifically editor and reviewers);
(iv) Learn how to respond to reviewers
(v)Being attentive to ethical issues during publication
Conclusion: Attendees will learn specific techniques and receive a checklist that will facilitate acceptance of their manuscripts for publication in high quality scientific journals.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL

*Joan Marsh1, Yasin Hasan Balcioglu*2*
[1]The Lancet Psychiatry, 2Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery

Objective: The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry.
Methods: The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines.
Results: The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions.
Conclusion: The workshop will include questions and answers throughout and group discussions.

4:15 p.m. - 5:45 p.m.
Concurrent Symposia I

REVISING CONSTRUCT OF SCHIZOPHRENIA: RELEVANCE TO BIOLOGICAL RESEARCH

Rajiv Tandon, University of Michigan Medical Center

Symposium Synopsis: An increasing number of researchers are debating about how schizophrenia has devolved into an "inherently flawed construct". Even as we accumulate increasing amounts of new knowledge about schizophrenia, its definition gets fuzzier. It is clearly time to take stock of what is known and what remains to be known about this syndrome, seriously examine the increasingly mosaic construct/s of schizophrenia, more clearly define the contours of the multiple disease entities encompassed by this term, and identify potential future directions for better understanding and treatment of this complex and heterogeneous syndrome.
In this symposium, we will review the nature of and problems with the current construct/s of schizophrenia, discuss challenges in developing reliable and valid biological markers, and consider the implications for future biological research of ongoing efforts to redefine this entity. Wolfgang Gaebel will briefly summarize the history of schizophrenia leading up to the current ICD-11 definition and description. Rajiv Tandon will review the DSM-5 characterization and outline an ongoing international initiative at reconceptualizing this entity (Schizophrenia Research; 2022, Volume 242; and 2023, 252, 345-347). Florence Thibaut will summarize the current status of biological markers for schizophrenia, updating the WFSBP workgroup report on biological markers. Peter Falkai will discuss implications of the evolving concepts of psychosis and schizophrenia for ongoing and future biological research.

SCHIZOPHRENIA OR OTHER PRIMARY PSYCHOTIC DISORDERS: ICD-11 AND THE ROAD AHEAD

Wolfgang Gaebel*[1]
[1]*German Society for Biological Psychiatry*

Objective: ICD-11 was released by WHO in 2018 and approved by the World Health Assembly (WHA) in 2019 as a global medical classification system. Development, Concept and Structure of ICD-11 will be briefly outlined with the focus on Schizophrenia or other primary psychotic disorders, their potential for adaptation and the debated need for reconstruction in the context of neuroscientific and related developments.
Methods: The development of the new chapter 06 Mental, Behavioural or Neurodevelopmental Disorders including psychotic disorders was guided by the principles of global applicability, scientific validity, reliability, and clinical utility. At that time, neither for DSM-5 nor for ICD-11 schizophrenia spectrum or primary psychotic disorders a conceptual 'paradigm shift' by including biomarkers or other valid diagnostic criteria seemed to be justified.
Results: ICD-11 innovations of primary psychotic disorders diagnostic criteria, dimensional symptom specifiers and course indicators according to the new CDDR (Clinical Descriptions and Diagnostic Criteria) and options for complex digital coding with potential impact on diagnostics, treatment and care will be outlined. Challenges for reconceptualizing the current construct and for national implementation will be briefly summarized.
Conclusion: The presentation will inform about innovations in classifying schizophrenia and other psychosis according to ICD-11 and give an outlook on future options for modifying the construct based on innovative scientific approaches in biological psychiatry.
References: Gaebel W, Stricker J, Kerst A. Changes from ICD-10 to ICD-11 and future directions in psychiatric classification. doi:10.31887/DCNS.2020.22.1/wgaebel
Gaebel W, Salveridou-Hof E. Reinventing schizophrenia: Updating the construct – Primary schizophrenia 2021 – The road ahead. doi.org/10.1016/j.schres.2021.12.021

DSM-5 SCHIZOPHRENIA: DEFINITION AND CLINICAL AND RESEARCH IMPLICATIONS

Rajiv Tandon*[1]
[1]
University of Michigan Medical Center

Objective: Schizophrenia, as currently defined in DSM-5-TR and ICD-11, is conceptualized as a multi-dimensional singular disorder. As questions arise about the very construct of schizophrenia, it is useful to review all that we know about this disease entity and examine what these data reveal about its essential nature. Although the DSM-5 description of schizophrenia was published a decade ago, its essence is still incompletely understood.
Methods: The DSM-5 definition of schizophrenia will be summarized. The outlines of a 2-year ongoing international effort to reconceptualize schizophrenia will be presented.
Results: The DSM-5 definition of schizophrenia is categorical with dimensional elaboration- this will be discussed and its clinical and research implications will be summarized. The initial output from a 50-person international collaboration on redefining schizophrenia will be presented (Schizophrenia Research 2022; Volume 242, 1-3).
Conclusion: Collectively, "facts of schizophrenia" argue against a singular disease entity but do not explicitly elucidate the nature and number of composite disease entities. Research implications of the initial international collaboration formulation of schizophrenia and related psychotic disorders will be outlined.

BIOLOGICAL MARKERS IN PSYCHIATRY

Florence Thibaut**1*

[1]*University Paris Cité*

Objective: A biological marker is an indicator of the pathogenic process of a disease, or of the pharmacological response to a therapeutic intervention. Biological markers may be trait markers (persistent abnormalities) or state-dependent markers (episodic markers).

Methods: Some examples of biomarkers which might be used in psychiatry will be described.

Results: Markers may be used as diagnostic tools, markers of the disease progression, to study the pathophysiology of the disease (risk factors), or to monitor treatment efficacy or side effects (pharmacogenetics).

Conclusion: The sensitivity, specificity and ease-of-use of a biomarker (especially for diagnosis) are the most important factors.

References: Thibaut F, Boutros NN, Jarema M, Oranje B, Hasan A, Daskalakis ZJ, Wichniak A, Schmitt A, Riederer P, Falkai P; WFSBP Task Force on Biological Markers. Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. World J Biol Psychiatry. 2015;16(5):280-90

Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, Collier DA, Corrales A, DeLisi LE, Gallo C, Gill M, Kennedy JL, Leboyer M, Maier W, Marquez M, Massat I, Mors O, Muglia P, Nöthen MM, Ospina-Duque J, Owen MJ, Propping P, Shi Y, St Clair D, Thibaut F, Cichon S, Mendlewicz J, O'Donovan MC, Rujescu D. Genetics of schizophrenia: A consensus paper of the WFSBP Task Force on Genetics. World J Biol Psychiatry. 2017 Oct;18(7):492-505

BEYOND SCHIZOPHRENIA IN DSM-5 AND ICD-11: NEW OPTIONS FOR RESEARCH

Peter Falkai**1*

[1] _____

German Society for Biological Psychiatry

Objective: The classification of schizophrenia has a long history starting with the description of Dementia praecox and Manic-depressive insanity by E Kraepelin paving the way for a dichotomy which still influences our thinking and clinical activities today. ICD-11 and DSM-5 have modified a lot of these assumptions but research has shown that the neurobiological underpinnings of these disorders rather form clusters than sticking to the current classification systems. RDoC and HiTOP will be introduced as examples to use a dimensional approach focussing on the neurobiology and on the other hand using psychopathological dimensions organized into increasingly broad, transdiagnostic spectra.

Methods: Advances and shortcomings of DSM-5 and ICD-11 will be based on published studies.

Results: For future studies a mixture of RDoC and HiTOP might be an optimal way to characterize patients and controls from childhood to old age. New scales need to be developed optimally based on self-rating, being short and having a better validity than currently used classification systems.

Conclusion: The presentation will analyse the shortcomings of currently available classification systems for clinical research and will give an outlook what advantages new systems like RDoC and HiTOP might give to characterize healthy and diseased subjects for research.

BIOMARKERS IN INSOMNIA: EVIDENCE DERIVED FROM A WFSBP TASK FORCE CONSENSUS STATEMENT

Constantin Soldatos, National and Kapodistrian University of Athens

Symposium Synopsis: Thus far, the diagnosis of insomnia is based on purely clinical criteria. Although a broad range of altered physiological parameters has been identified in insomniacs, the evidence to establish their diagnostic usefulness is very limited. Purpose of this symposium is to present a

summary of a WFSBP Task Force consensus statement, based on a systematic evaluation of a series of biomarkers as potential diagnostic tools for insomnia. **Methods:** A newly created grading system was used for assessing the validity of various measurements in establishing the diagnosis of insomnia; these measurements originated from relevant studies selected and reviewed by experts. **Results:** The measurements with the highest diagnostic performance were those derived frompsychometric instruments. Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy, and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm, and certain neuroimaging patterns. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPAaxis, and inflammation indices were not shown to be of satisfactory diagnostic value. Most of the above findings regarding biological measurements, however, need replication as well as establishment of commonly accepted methodology and diagnostic cut-off points. **Conclusions:** Apart from psychometric instruments which are confirmed to be the gold standard in diagnosing insomnia, six biomarkers emerge as being potentially useful for this purpose. **Reference:** D.Dikeos et al. "The potential of biomarkers for diagnosing insomnia: Consensus statement of the WFSBP Task Force on Sleep Disorders" World J Biol Psychiatr (In Press) 2023.

SLEEP EEG AND ACTIGRAPHY IN THE DIAGNOSIS OF INSOMNIA

Adam Wichniak**1*

1

Institute of Psychiatry and Neurology, Warsaw

Objective: Although objective assessment of sleep parameters is not necessary for the diagnosis of insomnia, polysomnography and actigraphy frequently provide information that is important for the diagnostic process. The aim of the study was to summarize the evidence on the use of polysomnography and actigraphy in the assessment of insomnia.

Methods: The presentation is based on data from a consensus paper on the diagnostic usefulness of polysomnography and actigraphy in insomnia and results of an original study in 126 insomnia patients that was aimed to assess factors contributing to differences in the assessment of sleep parameters between actigraphy and sleep diary in patients with insomnia.

Results: Polysomnography and more advanced sleep EEG evaluation methods like EEG spectral analysis favor the hypothesis of an increased CNS hyperarousal in patients with insomnia. However, polysomnographic data do not correlate very strongly with the subjective assessment of sleep in sleep diaries. The same observation is true for actigraphy. There are large and variable differences in the assessment of sleep parameters between sleep diaries and actigraphy, which are not strongly related to insomnia severity.

Conclusion: While some studies have confirmed satisfactory accuracy, especially of actigraphy for the evaluation of normal sleep quality, the use of PSG and actigraphy in the assessment of insomnia is limited and indicated only in certain cases, for example in patients with chronic therapy refractory insomnia, when sleep-disordered breathing is suspected (polysomnography) or in case of clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders (actigraphy).

LABORATORY BIOMARKERS FOR INSOMNIA OTHER THAN THOSE DERIVED FROM SLEEP EEG AND ACTIGRAPHY

Thorsten Mikoteit*[1], *Anne Eckert[2], Martin Hatzinger[3]*

[1]Swiss Society for Biological Psychiatry, 2University Clinics of Psychiatry Basel, 3Psychiatric Services Solothurn and University of Basel

Objective: Laboratory measurements are easy and mostly non-invasive to assess, and they might allow to link insomnia to more basic pathways of neuropathology like models of neuroendocrinology, neuroinflammation or neuroplasticity. Further, the advances of neuroimaging have provided findings of alterations in brain activity and connectivity in insomnia. The aim of this review was to evaluate the diagnostic possibility to identify laboratory and neuroimaging biomarkers for insomnia.

Methods: Five different laboratory biomarkers were considered: Markers of the hypothalamic-pituitary-adrenal (HPA) axis, melatonin, inflammatory markers such as C-reactive protein (CRP), and serum brain-derived neurotrophic factor (BDNF) as a proxy of neuroplasticity. Moreover, we considered five neuroimaging studies of insomnia.

Results: Findings of HPA activity patterns were inconsistent. Elevated cortisol levels in the first half of the night and in the morning were found rather in insomnia with shortened total sleep time than in insomnia with normal total sleep time. Melatonin levels revealed a more flattened circadian rhythm in individuals with insomnia, but night-time blood sampling was a limitation for itsclinical application. As reported by two independent studies, the best diagnostic accuracy was provided by measurements of low serum BDNF in insomnia. Neuroimaging studies showed that a key feature of insomnia is a corticolimbic overactivity in brain areas involved in activation, emotion regulation, cognition and conscious awareness.

Conclusion: For laboratory measurements, low serum BDNF levels had the highest diagnostic value for insomnia, linking clinical insomnia to a decreased neuroplasticity. The pattern of neuroimaging findings supported the hyperarousal hypothesis of insomnia. More research is needed to replicate findings and enlarge the body of evidence, to establish appropriate methods and diagnostic cut-offs.

PSYCHOMETRICS IN THE DIAGNOSIS OF INSOMNIA

Dimitris Dikeos*[1]

[1] National and Kapodistrian University of Athens

Objective: To evaluate the diagnostic potential for insomnia of psychometric instruments.

Methods: (a) Search for well cited original papers of scales, questionnaires and personality inventories, which reported on suitable measures of diagnostic validity for insomnia, based on a well-defined population of insomniacs versus a sample of non-insomniac controls. (b) Creation of a novel grading system for establishing diagnostic usefulness for insomnia, based on the one hand on the degree of pertinence of each study's methodology to diagnose insomnia and on the other on the level of diagnostic accuracy for insomnia of the instrument utilized in each study.

Results: Three main categories of psychometric instruments were found to be of diagnostic value for insomnia. Scales and questionnaires for diagnosing insomnia or for evaluating beliefs about sleep were proven to be the gold standard for the diagnosis of insomnia, based on established cut-off scores. Among personality inventories the potential of MMPI as a tool for diagnosing insomnia was found to be quite satisfactory.

Conclusion: Psychometric instruments are a well-proven means for the diagnosis of insomnia, reflecting its subjective nature.

OVERVIEW OF THE DIAGNOSTICS FOR INSOMNIA

Constantin Soldatos*[1]
[1]*National and Kapodistrian University of Athens*

Objective: To synthesise the systematic evaluation of biomarkers as potential diagnostic tools for insomnia based on measures of diagnostic accuracy, as well as an identical assessment of the diagnostic accuracy of psychometric instruments in diagnosing insomnia.
Methods: The findings of a large array of various instruments and methods for diagnosing insomnia, which were presented by the previous three symposium panelists will be comprehensively discussed
Results: Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm and certain neuroimaging patterns. These findings need replication, establishment of commonly accepted methodology and diagnostic cut-off points. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPA axis and inflammation indices were not shown to be of satisfactory diagnostic value. Psychometric instruments are confirmed to be the gold standard in diagnosing insomnia.
Conclusion: Various biomarkers emerge as potentially useful for the diagnosis of insomnia, although psychometric instruments remain the strongest means.

PREDICTIVE BIOMARKERS AND NEW METHODOLOGICAL APPROACHES FOR MENTAL DISORDERS

Oliver Pogarell, University Hospital, LMU Munich

Symposium Synopsis: In psychiatry, a wide spectrum of therapeutic interventions are applied to effectively improve signs and symptoms. However, individual response and remission rates are limited and to date, there are no unequivocal personalized clinical or auxiliary measures to identify responders or predict the course of symptoms under treatment.
Regarding predictive biomarkers new developments in neurophysiological research could play an important role. QEEG or fMRI at rest or under activation are tools for the investigation of different brain states under various conditions including monitoring. Novel analyses address temporal dynamics and functional connectivities that may show differences between disorders or disease states.
We will discuss the potential of neurophysiological biomarkers for the prediction of response or outcomes in psychiatric disorders. This includes novel analyses of QEEG, machine learning techniques or the extraction of treatment related neurophysiological repsonses, e.g. under non-invasive brain stimulation or neurofeedback.
Jonas Björklund will present data on brain oscillations in patients with schizophrenia. He demonstrates the viability of a biomarker predicting transition to full psychosis based on EEG connectivity disturbances. Machine learning techniques applied on physiological EEG/EOG data as demonstrated by Sebastian Olbrich, allow the generation of predictive markers from samples of large cohorts. It will be shown how automated analyses can be used for individual assessments in a clinical setting. Tomiki Sumiyoshi will report data indicating the ability of near-infrared spectroscopy to predict resonse to tDCS in schizophrenia. Finally, Max Maywald applied novel treatment interventions such as rt-fMRI neurofeedback showing that neurophysiological modulations under treatment correlate with response characteristics.

PREDICTIVE PROPERTIES OF QEEG AND OSCILLATIONS

Jonas Björklund*[1], *Moritz Haaf2, Sebastian Vauth2, Saskia Steinmann2, Jonas Rauh2, Christoph Mulert2, Gregor Leicht2*

[1]LMU, 2University Medical Center Hamburg-Eppendorf

Objective: Early detection and prediction of transition to full psychosis in high-risk individuals is crucial for early intervention and improved treatment outcomes. EEG and fMRI-based analyses provide opportunities to assess connectivity disturbances before the onset of clinical symptoms. In a previous study, we demonstrated reduced gamma response in an auditory processing network in individuals at high risk of psychosis (HRP) using EEG-informed fMRI analysis. This study aims to investigate the predictive nature of EEG connectivity disturbances in HRP individuals and explore the potential of using specific EEG-based connectivity disturbances to predict progression to psychosis based on disturbed gamma band oscillations.

Methods: We analyzed datasets of 27 HRP individuals and 26 healthy controls, including combined EEG-fMRI data recorded during an auditory reaction task. We employed Granger causality analysis, correlation analysis, and gPPI to calculate a matrix of individual connectivity values between previously identified ROIs in the dACC, DLPFC and the auditory cortices. Connectivity analysis methods were used to calculate individual connectivity values per subject. By comparing connectivity values between healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis, we aimed to predict the likelihood of developing psychosis within 12 months. Follow-up clinical data and combined EEG-fMRI recordings after 12 months were used to assess the degree of connectivity changes over time.

Results: We observed alterations in connectivity across domains when comparing healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis during the 12-month follow-up. We used data generated during the 12-month follow-up visit to verify if early changes in single-subject gamma connectivity persist and correlate with clinical disease progression.

Conclusion: By measuring gamma network disturbance using simultaneous EEG and EEG-informed fMRI, we aim to predict individual likelihoods of developing full psychosis within the next 12 months. EEG-based biomarkers are a relatively low-cost and widely available tool to aid in clinical decision making. The identification of specific EEG gamma band disturbances associated with disease progression and treatment response may enable more personalized treatment strategies for individuals with psychosis.

AUTOMATED AND MACHINE LEARNING ANALYSES OF EEG AND ECG DATA FOR TREATMENT PREDICTION IN MENTAL DISORDERS

Sebastian Olbrich*[1]

[1]Psychiatric University Hospital Zurich

Objective: Addressing the profound impact of psychiatric disorders on global health and socioeconomic systems necessitates a paradigm shift in treatment modalities. The reliance on subjective assessments in psychiatric care underlines a critical need for more objective treatment indicators to enhance patient outcomes across various mental health conditions.

Methods: This presentation will delineate the utilization of automated processing pipelines applied to electrophysiological time series data obtained from electroencephalograms (EEG) and electrocardiograms (ECG). The integration of these methodologies into routine clinical practice through comprehensive biomarker reports will be showcased. Additionally, the session will provide an update on the latest advancements in machine learning and deep learning techniques applied to EEG and ECG data, drawing from extensive datasets from the UK-Biobank and the CANBIND study.

Results: Contemporary advancements in automated electrophysiological processing and biomarker computation have reached a level of sophistication that permits their application in clinical settings. Over recent years, a plethora of biomarkers pertinent to treatment prediction—particularly within the context of major depressive disorders—have been identified, rigorously validated, and consistently replicated. **Conclusion:** The implementation of electrophysiological biomarkers in psychiatric care emerges as a compelling strategy to foster a more stratified approach to patient treatment. The clinical applicability of these biomarkers has been substantiated, with accumulating evidence indicating their potential to significantly influence the management of mental health disorders and enhance patient outcomes.

TRANSCRANIAL

AND DIRECT CURRENT STIMULATION FOR ENHANCING SYMPTOMS FUNCTIONALITY IN PATIENTS WITH SCHIZOPHRENIA; PREDICTION WITH NEUROPHYSIOLOGICAL TOOLS

Tomiki Sumiyoshi*[1], *Yuji Yamada2*
[1]National Institute of Mental Health, National Center of Neurology and Psychiatry, 2National Center Hospital, National Center of Neurology and Psychiatry

Objective: Schizophrenia is one of the most prominent causes of disease burdens worldwide. In addition to positive and negative symptoms, patients with the illness show disturbances of several types of cognitive function (e.g., neurocognition and social cognition). Importantly, cognitive impairment leads to a decline in real-world functional outcome for patients.
Methods: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that modulates neural activity by applying electric currents. tDCS (anodal stimulation) delivered to the dorsolateral prefrontal cortex (DLPFC) alleviates hallucinations and negative symptoms, and improves neurocognitive function, particularly working memory in patients with schizophrenia. Specifically, our group in National Center of Neurology and Psychiatry has reported the first data indicating the ability of neural responses, as measured by the near infra-red spectroscopy, to predict efficacy of tDCS for ameliorating psychotic symptoms in these patients.
Results: This talk will also provide the current state of endeavor to alleviate cognitive impairment and higher-level functional outcomes, by means of tDCS, in patients with schizophrenia. These findings may add to efforts to increase the chance of recovery for patients by using feasible and non-invasive brain stimulation methods.
Conclusion: References; Narita et al. J Psychiatr Res 2018; 103:5-9

PREDICTIVE BIOMARKERS IN REAL-TIME FMRI NEUROFEEDBACK

Maximilian Maywald*[1], *Marco Paolini2, Boris Rauchmann2, Christian Gerz2, Jan Heppe2, Annika Wolf2, Linda Lerchenberger2, Igor Tominschek3, Sophia Stöcklein2, Paul Reidler2, Nadja Tschentscher2, Birgit Ertl-Wagner2, Oliver Pogarell2, Daniel Keeser2, Susanne Karch2*
[1]Psychiatric Hospital of the LMU University Munich, 2University Hospital, LMU Munich, [3]Psychosomatic Day Care Unit Westend, Munich

Objective: The aim of this pilot study was to investigate whether individualized rtfMRI NF training as an adjunct to a psychotherapeutic program can increase connectivity between the insula and the dlPFC and thereby improve symptoms in patients with major depressive disorder (MDD, ICD-10). The second aim was to investigate if there are biomarkers of successful real-time fMRI neurofeedback?
Methods: Sixteen patients with MDD and 19 matched healthy controls (HC) participated in a rtfMRI NF training consisting of two sessions with three runs each, within an interval of one week. RtfMRI NF was applied during a sequence of negative emotional pictures to modulate the connectivity

between the dlPFC and the insula. The MDD REAL group was divided into a 'Responder' (N=6) and a 'Non-Responder' group (N=7). **Results:** The comparison of hemodynamic responses during the first compared to during the last NF session demonstrated significantly increased BOLD-activation in the medial orbitofrontal cortex (mOFC) in patients and HC, and additionally in the lateral OFC in patients with MDD. These findings were particularly due to the MDD Responder group, as the MDD Non-Responder group showed no increase in this region during the last NF run. There was a decrease of neural activation in emotional processing brain regions in both groups in the last NF run compared to the first (HC: insula, parahippocampal gyrus, basal ganglia, and cingulate gyrus; MDD: parahippocampal gyrus). There was no significant reduction of BDI scores after NF training in patients. **Conclusion:** The activation of the mOFC seems to be a predictive biomarker of improved control- strategies and association-learning processes. The increased lOFC activation could indicate a stronger sensitivity to failed NF attempts in MDD. Overall, the rtfMRI NF had an impact on neurobiological mechanisms, but not on psychometric measures in patients with MDD.

THE DIFFERENT FACES OF DEPRESSION ACROSS THE LIFE SPAN: FROM SOCIAL ISOLATION TO SUICIDE

Paolo Brambilla, University of Milan

Symposium Synopsis: Suicidal ideation, also known as suicidal thoughts, is a broad term used to describe a range of thoughts about death and self-harming behaviours. Rates of suicide deaths and suicidal thoughts and behaviours have risen by more than 50% among young people in the past decade, making suicide the second leading cause of death among those aged under 20. Most importantly, suicidal ideation represents a trans-diagnostic feature characterizing several psychiatric conditions (e.g., depression, psychosis) that seems to increase the risk of completed suicide. For instance, it has been shown that treatment-resistant depression (TRD) may increase an individual's likelihood of engaging in suicidal behaviours and up to 30% of people with TRD will attempt suicide at some point in their life. Although individual, environmental, and clinical risk factors (such as social isolation, social stress, apathy and elderly depression) for suicidal thoughts and behaviours have been
well established, these factors have demonstrated low predictive validity. In response, the number of studies examining neurobiological underpinnings of suicidal thoughts and behaviours, in and out of psychiatric populations, has grown exponentially. Nevertheless, understanding the neural mechanisms underlying social isolation, suicidal thoughts and behaviours and their clinical utility remains elusive. Therefore, the present symposium aims at summarizing and discussing recent evidence on the morphofunctional brain correlates of social isolation, social stress, apathy, elderly depression, and suicidal ideation, with a particular focus on their clinical implications for the development of trans-diagnostic tailored treatments.

NEUROIMAGING OF SOCIAL BRAIN

*Marcella Bellani1, Maria Gloria Rossetti*1, Paolo Brambilla2*
[1]University of Verona, 2University of Milan

Objective: According to the social brain hypothesis, the human brain includes a network designed for the processing of social information. This network includes several brain regions that elaborate social cues, interactions and contexts, i.e. prefrontal paracingulate and parietal cortices, amygdala, temporal lobes and the posterior superior temporal sulcus. While current literature suggests the importance of this network from both a psychological and evolutionary perspective, little is known about its neurobiological bases. Specifically, only a paucity of studies explored the neural

underpinnings of constructs that are ascribed to the social brain network functioning, i.e. objective social isolation and perceived loneliness. **Methods:** Overview of neuroimaging studies that investigated social isolation in healthy subjects. **Results:** Social isolation correlated with both structural and functional alterations within the social brain network and in other regions that seem to support mentalising and social processes (i.e. hippocampus, insula, ventral striatum and cerebellum). **Conclusion:** However, results are mixed possibly due to the heterogeneity of methods and study design. Future neuroimaging studies with longitudinal designs are needed to measure the effect of social isolation in experimental v. control groups and to explore its relationship with perceived loneliness, ultimately helping to clarify the neural correlates of the social brain.

SOCIAL STRESS AND SUICIDE: MECANISTIC HYPOTHESES

Aiste Lengvenyte**1*, *Emilie Olié2, Emma Sebti2, Adrian Alacreu3, Philippe Courtet2*

[1]CHU Montpellier, 2University of Montpellier, 3University of Zaragosa

Objective: To assess the biological underpinnings of social adversity that lead to suicidal behaviour.
Methods: Depressed patients are submitted to the Trier Social Stress Test (TSST) in order to examine the changes in emotional and biological markers according to their past history of suicidal behaviour.
Results: We will discuss the association of suicidal behaviour with measures of cortisol, of the autonomous nervous system and inflammatory markers during and after the TSST.
Conclusion: Objective markers of response to a social exclusion task using different kinds of parameters may help to define specific groups of patients at risk of suicide in order to foster a personalized suicide prevention.

CEREBRAL NETWORK OF APATHY AND GOAL-ORIENTED BEHAVIOURS

Jean-Charles Roy**1*, *Julie Cologner1, Gabriel Robert1*

[1] EMPENN Unit, Rennes 1 University, ERL U1228 Inserm, INRIA, CNRS

Objective: We aimed to identify the structural and functional brain subnetworks associated with apathy in LLD in the core resting-state networks (RSN) putatively underlying goal-directed behaviors.
Methods: Diffusion-weighted and Resting-state functional MRI data were collected from 39 non-demented depressed elderly and 26 healthy elderly from October 2019 to April 2022. Apathy was evaluated using the diagnostic criteria for apathy, the apathy evaluation scale and the apathy motivation index. Participants' daily activity was recorded via an accelerometer worn at the wrist for three days. Principal components were derived from accelerometer data to provide a qualitative and quantitative interpretation of daily activity. The clinical significance of these principal components in terms of apathy were assessed by regression with the apathy scales. Brain sub-networks associated with the principal components of activity were identified via the threshold-free network-based statistics. This method combines the network-based statistics approach with the threshold-free cluster enhancement algorithm, producing a powerful identification of the significant sub-networks while controlling for multiple comparisons. Structural tracts were identified via deterministic tractography. Association between the apathy and accelerometry on the diffusion metrics - derived from a multicompartment model - were evaluated by mixed-effect modelling.
Results: LLD patients had an altered intranetwork resting-state connectivity in the default-mode, the cingulo-opercular and the frontoparietal networks compared to healthy controls. The first and second principal components of daily activity were associated with apathy measures, corresponding respectively with a reduced mean diurnal activity and with a late-rise/late-bedtime. Apathy and daily activity were associated with modified intranetwork resting state connectivity in the same networks distinguishing LLD from controls. These networks involved reduced activity of the pregenual cingulate

regions, the dorsal anterior cingulate cortex, the middle insula, but increased connectivity in the dorsolateral prefrontal regions. Internetwork resting-state connectivity of cortical regions related to goal-oriented behavior showed a decoupling between pregenual and dorsal anterior cingulate cortices associated with apathy. Principal components associated with apathy were also associated with increased orientation dispersion index, a measure of inflammation, in the anterior commissure. **Conclusion:** This study suggests that accelerometry provides a proxy for an ecological evaluation of apathy in LLD. Apathy and accelerometry are consistently associated with changes in intra and inter- network connectivity of regions implied in goal-oriented behaviors.

THE FUNCTIONAL NETWORKS OF DEPRESSION IN THE ELDERLY

*Eleonora Maggioni*1, Federica Goffi1, Paolo Brambilla2*
1Politecnico di Milano, 2University of Milan

Objective: To disentangle the complex relationships among environmental risk factors, functional brain connectivity, autonomic nervous system regulation, and frailty and adult-onset depression.
Methods: Control subjects and individuals with adult-onset major depressive disorder (MDD) took part in the study. The dataset included sociodemographic, environmental, and psychopathological information, and simultaneous electrocardiographic (ECG) and functional Magnetic Resonance Imaging (fMRI) data. The ECG and fMRI data were processed to extract information on heart rate variability (HRV) and functional brain connectivity. The associations among stressful life events, frailty level, MDD diagnosis, and HRV and functional brain connectivity were extracted using integrated HRV-fMRI analyses and multivariate models.
Results: The MDD diagnosis was associated with alterations in the activity and connectivity of brain regions that are key nodes of the central autonomic network. Traumatic events and perceived stress were correlated with HRV metrics and showed interactions with depressive symptomatology and sex.
Conclusion: Evidence from our study suggests an impact of environmental risk factors on heart-brain interactions and in turn on depressive symptomatology onsetting in adulthood, and further supports the potential of HRV-fMRI analyses in providing novel information on the neurobiological bases of depression.

MANUSCRIPT WRITING WORKSHOP

Florence Thibaut, University Paris Cité

HOW TO WRITE A SCIENTIFIC PAPER

Dan Rujescu-Balcu1
1Medical University of Vienna

Objective: The World Journal of Biological Psychiatry is a major clinically oriented journal on biological psychiatry. The opportunity to educate (through critical review papers, treatment guidelines and consensus reports), publish original work and observations (original papers and brief reports) and to express personal opinions (Letters to the Editor) makes The World Journal of Biological Psychiatry an extremely important medium in the field of biological psychiatry all over the world.
The aim is to meet the Chief Editor and to discuss all steps from formulating hypotheses, study design, data generation, analysis and finally publication.
Methods: A short presentation of the Journal will be followed by a lively discussion.
Results: N/A

Conclusion: It is important to oversee the whole process from asking the scientific question to study design and generation of original data to manuscript writing, submission and finally publication in a scientific journal.

HOW TO WRITE A SCIENTIFIC PAPER

Michael Berk1
[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: Scientific Journals are a key platform for disseminating critical reviews, treatment guidelines, consensus reports, original research, and personal opinions in the field of biological psychiatry. This session aims to guide participants through the publication process, from formulating hypotheses and designing studies to generating data, analyzing results, and ultimately publishing in scientific journals. Attendees will have the opportunity to engage with the Chief Editor and gain insights into each step of the publication journey.
Methods: The session will begin with a brief presentation on the scope and significance of The World Journal of Biological Psychiatry. This will be followed by an interactive discussion, where participants can ask questions and receive practical tips on navigating the publication process.
Results: While this session does not generate experimental results, it will equip participants with valuable knowledge and strategies to enhance their chances of successfully publishing their research in peer-reviewed journals.
Conclusion: Understanding the comprehensive process of scientific publication—from formulating a research question and designing a study to writing and submitting a manuscript—can significantly increase the likelihood of acceptance in a scientific journal. By attending this session, researchers will be better prepared to contribute meaningful findings to the field of biological psychiatry, thereby advancing evidence-based practice and scientific knowledge.

HOW TO WRITE A SCIENTIFIC PAPER

Florence Thibaut1
[1]*University Paris Cité*

Objective: Publication of scientific papers is important to improve evidence-based practice or scientific knowledge. Most importantly, failure to publish important findings significantly diminishes the potential impact that your findings may have.
Methods: This educational session is intended to give you tips to help you publish in scientific journals.
Results: Most clinical studies are published in peer-reviewed journals, where author's peers, or experts in the area, evaluate the manuscript.
Conclusion: Following this review, the manuscript is recommended for publication, revision or rejection. Having an understanding of the process and structure used to produce a peer-reviewed publication will increase the likelihood that a submitted manuscript will result in a successful publication.

6:30 p.m. - 7:30 p.m.
Opening Plenary I - John Krystal

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

Lakshmi Yatham, The University of British Columbia

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

John Krystal1

[1]Yale

Objective: To review challenges that have traditionally plagued the development of medications for psychiatry indications and to highlight two areas of exciting recent developments: 1) ketamine and psychedelics and 2) antipsychotics that may work via targets other than the dopamine D2 receptor.

Methods: This presentation will focus on the advances in neuroscience that have laid the groundwork for the development of Esketamine and the recent “non-D2” antipsychotics. It will begin by tracing steps to understand the mechanisms through which ketamine produces its therapeutic effects. It will then highlight ways that this search has led to ways to optimize ketamine efficacy. It will also highlight ways that insights related to ketamine’s effects that point to other potential novel treatment mechanisms, such as psychedelics, that have convergent effects on neuroplasticity.

Results: This presentation will present a model for cortical microcircuit dysfunction that emerged from studies of ketamine effects in healthy humans and schizophrenia patients. This model highlights the potential for cortical network disinhibition, including disinhibition of projections to the striatum, to be a contributor to pathophysiology in some patients. This model sets the stage for developing a mechanistic context for recent clinical trial data suggesting that drugs enhancing muscarinic M4 receptors (KarXT, Emraclidine) and TAAR1 (Ulotorant) might be effective antipsychotic medications without blocking dopamine D2 receptors.

Conclusion: This presentation will conclude by raising remaining challenges as we grapple with the complexity of the neurobiology of psychiatric disorders, particularly the opportunities and challenges that emerge as we try to translate the genetics of psychiatric disorders to novel therapeutics.

Thursday, June 6, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session II - Nora Volkow

SUBSTANCE USE AND ABUSE: ADVANCES IN NEUROBIOLOGY AND TREATMENT OF SUBSTANCE USE DISORDERS

Allan Young, King's College

HOW HAS THE SCIENCE OF ADDICTION ILLUMINATED OUR UNDERSTANDING OF THE HUMAN BRAIN

Nora Volkow1

[1]*NIDA*

Objective: Addiction, a complex disorder linking genes, development and the social environment has, for decades, been illuminating our understanding of the human brain and is leading the way toward promising strategies for its effective treatment.

Methods: Studies employing neuroimaging technology paired with behavioral measurements, and more recently genetics, have led to remarkable progress in elucidating neurochemical and functional changes that occur in the brains of addicted subjects and the neurocircuits that modulate risk for substance use disorders.

Results: Although large and rapid increases in dopamine have been linked with the rewarding properties of drugs, the addicted state, in striking contrast, is marked by significant decreases in brain dopamine D2 receptor mediated signaling and the downstream dysfunction of circuits that it modulates through striato cortical and limbic projections. Among the most prominently affected is the prefrontal cortex (PFC), including ventral PFC implicated in salience attribution and motivation (orbitofrontal cortex, and anteroventral cingulate gyrus), and dorsal PFC including dorsolateral and medial PFC implicated in executive function and internal awareness.

Conclusion: These PFC disruptions underlie the enhanced value given to drugs and drug-related stimuli at the expense of other reinforcers and the impulsive and inflexible behaviors that lead to compulsive drug consumption. In parallel, dysfunction of limbic projections are believed to underlie the enhanced stress reactivity and negative emotional states that emerge during drug withdrawal.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia II

UNDERSTANDING BODY DYSMORPHIC DISORDER (BDD): LATEST INTERNATIONAL RESEARCH

Susan Rossell, Swinburne University

Symposium Synopsis: Body dysmorphic disorder (BDD) affects 1.7-2.4% of the population worldwide. However, until the last 20 years relatively little was known about BDD, and there was a paucity of research. The aim of this symposium is to bring together and present comprehensive data from four internationally respected research sites specialising in BDD.

Methods: The authors will provide the latest updates on epidemiology, clinical characteristics, brain mechanisms as well as novel treatment insights in relation to BDD.

Results: The four presentations will include recent data on: 1) the epidemiology of BDD using a representative, population-based sample of young people in England. 2) An update on clinical and cognitive characteristics of BDD, including some novel findings on hallucinatory experiences in BDD. 3) A discussion of recent brain imaging data in BDD involving white matter microstructure and dynamic effective brain connectivity in visual systems, and their relationships to appearance

appraisals. 4) Finally, we will review the efficacy, predictors and long-term outcomes of an app-based cognitive behavioral therapy for BDD with coach support. **Conclusion:** Given the prevalence of BDD improving clinicians understanding of this disorder is critical. The authors of this symposium hope by presenting advanced and novel data the audience will improve their awareness of BDD and how to treat it.

EPIDEMIOLOGY OF BODY DYSMORPHIC DISORDER IN YOUTH: PREVALENCE, COMORBIDITY AND PSYCHOSOCIAL IMPAIRMENT

Georgina Krebs**1*, *Bruce Clark2, Tamsin Ford3, Argyris Stringaris1*

[1]University College London, 2South London and Maudsley NHS Foundation Trust, 3University of Cambridge

Objective: Little is known about the epidemiology of body dysmorphic disorder in youth. We evaluated the prevalence, comorbidity, and psychosocial impairment associated with BDD and more broadly defined appearance preoccupation among children and adolescents.

Methods: Data were drawn from the 2017 Mental Health of Children and Young People in England survey. BDD and psychiatric comorbidity were assessed in 5-19 year olds (N = 7,654) according to DSM-5 criteria, using a clinician-rated standardised diagnostic assessment. Psychosocial impairment was measured with a quantitative scale, and also indexed by reported self-harm and suicide attempts, and service utilisation, which were assessed using structured interviews.

Results: The point prevalence of BDD was 1.0% (95% CI 0.8 – 1.3%). BDD was significantly more common among adolescents than children (1.9 vs 0.1%; OR = 22.5, $p < 0.001$), and females than males (1.8% vs 0.3%; OR = 7.3, $p < .001$). Similar age and sex effects were observed for appearance preoccupation. Approximately 70% of young people with BDD had psychiatric comorbidity, most commonly internalising disorders. BDD was associated with self- and parent-reported psychosocial impairment, self-harm and suicide attempts, and service utilisation. Appearance preoccupation was more common than full syndrome BDD, but showed similar age and sex effects, patterns of comorbidity, and associated impairment.

Conclusion: BDD and appearance preoccupation are relatively common, especially among adolescent girls, and associated with substantial co-occurring psychopathology, risk, and impairment. Improved screening is needed to increase detection and diagnosis of BDD, and to facilitate access to evidence-based treatment. Future research should seek to examine appearance preoccupation as a possible target for early intervention.

UNDERSTANDING PSYCHOTIC EXPERIENCES IN PEOPLE WITH BODY DYSMORPHIC DISORDER (BDD)

Susan Rossell**1*, *Grace Fountas1, Wei Lin Toh1*

[1] Swinburne University

Objective: Body dysmorphic disorder (BDD) is a severe mental illness characterised by a preoccupation with a perceived flaw in appearance, along with repetitive behaviours and/or mental acts that occur in response to the preoccupation. Referential delusions (people take special notice of me owing to how I look) are frequently noted in BDD. In DSM-5, there is an optional specifier “with absent insight/delusional beliefs” for patients who hold high conviction that their BDD beliefs are accurate and aligned with reality. This marks a key departure from past editions of the DSM (that is, from DSM-III-R onwards), where non-delusional and delusional variants of BDD were alleged to exist, with the latter double-coded as a delusional disorder, somatic subtype. However, there are only a handful of empirical studies which have examined the presence of delusions and insight in BDD; and no work to date to have explored the existence of hallucinations. Thus, further work is needed in BDD

to characterise the psychotic symptoms of the disorder, especially to understand the possible differences or similarities that may exist with schizophrenia. **Methods:** Data from three clinical will be presented, examining: a) delusions and insight in BDD using Peters Delusion Inventory (PDI) and the Brown Assessment of Beliefs (BABS), respectively; and b) differences in the presentation of psychotic symptoms between BDD and schizophrenia using the Questionnaire for Psychotic Experiences (QPE). **Results:** The data from the PDI and BABS established that the majority of individuals with BDD hold substantial delusional beliefs, which are a) not restricted to referential delusions in terms of delusional themes, and typically include appearance-based (somatic) delusions, and b) the vast majority (>89%) of BDD patients are classified as having absent insight. Further, an extensive examination of hallucinatory experiences using the QPE in BDD has demonstrated that only somatic hallucinations are endorsed more frequently and qualitatively different from healthy controls (there were no differences for auditory, visual, olfactory, gustatory or multimodal hallucinations). With these somatic experiences akin to those present in schizophrenia. **Conclusion:** This is the first study to have reported on hallucinatory experiences in BDD. In conclusion, this work suggests considerable similarities between BDD and schizophrenia in the somatosensory domain when examining psychotic symptoms.

MICROSTRUCTURE AND FUNCTIONAL CONNECTIVITY OF THE VERTICAL OCCIPITAL FASCICULUS IN BODY DYSMORPHIC DISORDER

Jamie Feusner**1*, *Wan Wa Wong2, Joel Diaz1, Ryan Cabeen3*

[1]Centre for Addiction and Mental Health, University of Toronto, 2Centre for Addiction and Mental Health, 3University of Southern California

Objective: Body dysmorphic disorder (BDD) is marked by preoccupations with misperceived appearance flaws, which may be due to disturbances in visual information processing. Previous studies suggest abnormally reduced global visual processing in BDD. While previous fMRI data are informative about the functional global/local visual processing imbalances, the underlying structural connections have been less explored. The vertical occipital fasciculus (VOF) is the major fibre bundle connecting the dorsal and ventral visual systems. Here, we investigated the white matter (WM) microstructure of the VOF, estimated with neurite orientation dispersion and density imaging (NODDI) and diffusion tensor imaging (DTI) metrics, and tested their associations with psychometric measures and dynamic effective connectivity (DEC) during task fMRI.
Methods: 21 unmedicated adults with BDD with face concerns and 23 healthy controls were included. Tractography was performed to obtain microstructure maps of the right and left VOF. Geometric models of WM connectivity were reconstructed from fibre orientation data estimated from diffusion MRI. Bundle-specific analysis was performed, enabling quantitative estimation of NODDI and DTI metrics of the whole bundle. For fMRI, they viewed photos of their own face naturally. Four regions of interest (ROIs) in the dorsal visual stream (DVS), and 4 ROIs in the ventral visual stream (VVS) were selected. DEC, a measure of directional connectivity, was computed using time-varying Granger causality. Linear regressions were used to test associations between NODDI/DTI metrics, psychometric measures, and DEC from DVS to VVS.
Results: In BDD, neurite density index (NDI) (R=.7, FDR-adjusted P=.0076) and fractional anisotropy (FA) (R=.63, FDR-adjusted P=.036) were positively associated with Body Image State Scale (BISS) scores. Mean diffusivity (MD) was positively associated with DEC during face viewing (R=.61, FDR-adjusted P=.046), and there was a trend for NDI negatively associated with DEC (R=-.61, FDR-adjusted P=.053). In healthy controls, no significant associations were found between the NODDI or DTI metrics and BISS scores. In controls, associations between DEC and WM microstructure were

nonsignificant, with only trends for orientation dispersion index (ODI) negatively associated with DEC (R=-.41, unadjusted P=.068), and FA positively associated with DEC (R=.45, unadjusted P=.043).
Conclusion: Those with BDD with worse evaluative body experiences have a lower proportion of axons or dendrites and a lower degree of anisotropy along the vertical occipital fasciculus, which could reflect lower tract integrity. Further, there were different function/structure relationships among those with BDD than among healthy controls. These results provide early insights into how the structural integrity of WM connections involved in the integration between global and local visual processing systems in BDD relate to subjective appraisals of their appearance.

LATEST ADVANCES IN THE TREATMENT OF BODY DYSMORPHIC DISORDER: APP BASED COGNITIVE BEHAVIORAL THERAPY WITH COACH SUPPORT

Sabine Wilhelm*[1], *Jennifer L. Greenberg[2], Hilary Weingarden[2], Susanne S. Hoeppner[2], Ivar Snorrason[2], Emily E. Bernstein[2], Thomas H. McCoy[2], Oliver Harrison[3]*

[1]Harvard Medical School, [2]Massachusetts General Hospital and Harvard Medical School, [3]Koa Health

Objective: This presentation summarizes the current state of the field of cognitive behavioral therapy (CBT) for Body Dysmorphic Disorder (BDD) and offers a vision for the future.
empirically supported psychotherapy for BDD. While this treatment has a lot of promise, we still have a long way to go. Currently, most individuals in need of treatment for BDD receive no mental health services at all, and even those who do often do not receive optimal care. New technology-enhanced therapies have the potential to expand the reach of our interventions to those for whom traditional treatments are currently unavailable. Dr. Wilhelm will present the result of a smartphone-based treatment with coach support, including predictors of treatment outcome.
Methods: A randomized waitlist-controlled trial was conducted. Adults (N = 80) with primary BDD were randomized to 12 weeks of app based CBT or waitlist. Coaches supported engagement and answered questions via in-app messaging and phone calls. BDD severity was measured at baseline, mid-treatment, and end of treatment by blinded independent evaluators. Secondary outcomes, predictors of treatment outcome and long-term outcomes were also examined.
Results: App-based CBT was associated with significantly lower BDD-YBOCS severity at end of treatment (M [SD]: 16.8 [7.5]) compared to the waitlist (26.7 [6.2]; $p < 0.001$, $d = 1.44$). App-based CBT was associated with greater improvements across all secondary measures, including BDD-related insight, depression, quality of life, and functioning. We also examined several predictors of treatment outcome as well as maintenance of treatment gains.
Conclusion: App-based CBT, supported by a bachelor's-level coach, is an efficacious, scalable treatment for adults with BDD. Our results also highlight the importance of efforts to develop stratified care models to optimize treatment allocation.

FROM DAMAGED DNA TO MORBIDITY: MITOCHONDRIAL DYSFUNCTION IN BIPOLAR DISORDER AS A NOVEL THERAPEUTIC TARGET

Aysegul Ozerdem, Mayo Clinic

Symposium Synopsis: Bipolar disorder (BD) is commonly associated with substantial medical comorbidities, premature aging, and mortality. Mitochondria, inflammation, and oxidative stress are important links in the pathogenesis of mood disorders. A crosstalk between nuclear DNA and mitochondrial DNA is needed for proper cellular functioning and homeostasis. Evidence shows alterations in the base excision repair (BER) mechanism of the oxidatively induced DNA damage in BD. Accumulation of DNA damage or mutations and mitochondrial dysfunction are theorized to contribute to the early ageing and age-related diseases which are frequently seen in BD. Reduced

mitochondrial DNA-copy number has been associated with inducing cancer progression via hypermethylation of nuclear DNA promoters. Dysregulated mitochondrial biogenesis often occurs together with other comorbidities in BD such as non-alcoholic fatty liver disease (NAFLD), diabetes and osteoporosis. Mechanism of action of lithium, the gold standard medication for treatment of BD involves regulation of mitochondrial bioenergetics and PARP, an enzyme involved in DNA repair. This symposium aims to explore the interaction between various comorbidities including breast cancer, NAFLD, osteoporosis and bipolar disorder in the context of illness progression and increased morbidity and identify novel treatment targets via regulation of mitochondrial dysfunction for better illness outcome. Another objective of the symposium is to explore if changes in mitochondrial copy numbers, and mitochondrial DNA methylation levels in response to treatment in BD can be a marker for treatment outcome. Data from large cohorts with and without comorbid BD and data from clinical trials will be presented.

MITOCHONDRIAL DNA MODIFICATIONS IN MOOD DISORDERS

Deniz Ceylan*[1], *Bilge Karaçiçek[2], Kemal Uğur Tüfekci[3], Şevin Hun Şenol[1], Şermin Genç[2]*

[1]*Koç University, 2Izmir Biomedicine and Genome Center, 3Izmir Demokrasi University*

Objective: Mood disorders are significant psychiatric conditions that result from a complex interplay of genetic and environmental factors. One intriguing avenue of research in the realm of mood disorders involves investigating alterations in mitochondrial DNA (mtDNA). In the scope of this study, our primary objective was to explore changes in mtDNA in individuals with depressive disorder (MDD) and bipolar disorder (BD).

Methods: Displacement loop methylation (D-loop-met), mitochondrial DNA copy number (mtDNA-cn), and mitochondrial DNA oxidation (mtDNA-oxi) were scrutinized in DNA samples from individuals with major depressive disorder (MDD; n = 34), bipolar disorder (BD; n = 23), and a control group of healthy individuals (HC; n = 40) using real-time polymerase chain reaction. Blood samples were collected from a subgroup of individuals with MDD (n = 15) both during a depressive episode (baseline) and after achieving remission (at the 8th week).

Results: The study groups displayed notable distinctions in D-loop-methylation (D-loop-met) ($p = 0.020$), while mitochondrial DNA copy number (mtDNA-cn) and mitochondrial DNA oxidation (mtDNA-oxi) yielded similar results. During the remission phase (8th week), there were decreased levels of mtDNA-cn ($Z = -2.783$, $p = 0.005$) and D-loop-methylation ($Z = -3.180$, $p = 0.001$) in comparison to the acute MDD baseline, with no significant alteration observed in mtDNA-oxidation levels.

Conclusion: Our findings suggest that there are distinct modifications in mtDNA associated with these conditions. Furthermore, the observed changes in mitochondrial mtDNA-cn and D-loop methylation during the remission phase suggest a potential involvement of mtDNA alterations in the underlying mechanisms of MDD.

This work was supported by TUSEB (TUSEB 20131-Deniz Ceylan) and a BAGEP award by the Science Academy of Turkey

BIPOLAR DISORDER AND BREAST CANCER: CLINICAL INSIGHTS INTO DNA DAMAGE-RELATED MECHANISMS

Mete Ercis*[1], *Melissa Solares-Bravo1, Kathryn J. Ruddy1, Fergus J. Couch1, Vanessa M. Pazdernik1, Nicole L. Larson1, Jorge A. Sanchez-Ruiz1, Mark A. Frye1, Janet Olson1, Stacey J. Winham1, Aysegul Ozerdem1*

[1]*Mayo Clinic*

Objective: Bipolar disorder (BD) is associated with an increased risk of breast cancer in women. The causality between BD and breast cancer is unclear. BD is associated with increased DNA damage and concomitant alteration in gene expression levels of the enzymes operating on base-excision repair (BER) of both nuclear and mitochondrial DNA. FEN1 and PARP1, the two genes of the BER mechanism that are involved in cancer treatment showed genome-wide significant association with BD and significant association with lithium response respectively. Given the involvement of DNA damage and repair mechanisms in both conditions, we aimed to explore the effect of having BD on clinical features of breast cancer including age at breast cancer diagnosis, presenting cancer stage, and survival.
Methods: Our sample included female patients from the Mayo Clinic Breast Disease Registry (MCBDR) with breast cancer only (BC-Only; n=9390) diagnosis and patients with breast cancer and BD comorbidity (BC+BD; n=59). All available information from electronic health records was used to ascertain the diagnosis of BD. Clinical features of breast cancer and lifestyle characteristics of individuals were obtained from the MCBDR data repository. Fisher exact tests, Wilcoxon rank sum tests, Kaplan-Meier survival curves, and Cox proportional hazards models were used to compare BC+BD and BC-Only groups. A multivariable regression on age at breast cancer diagnosis was conducted to estimate the effect of comorbid BD while adjusting for confounding variables.
Results: Age at breast cancer diagnosis was significantly earlier in the BC+BD group (52.8±10.5 years) compared to BC-Only (57.1±12.5 years, p=0.005). BD diagnosis was consistently associated with earlier age at breast cancer diagnosis after adjusting for potential confounders that differed significantly among groups, such as smoking, exercise, and BMI (β=-5.88, p=0.016). Presenting stage of breast cancer or survival did not differ between groups (both $p > 0.05$). Among BC+BD patients, lifetime lithium users had an older age at breast cancer diagnosis (n=32, 54.3±11.5 years) than non-users (n=27, 51.0±9.0 years) although the difference was not statistically significant (p=0.315). Lithium use was not associated with presenting cancer stage, or survival (both $p > 0.05$).
Conclusion: Our initial findings highlight that BD diagnosis is associated with breast cancer development approximately five years earlier than non-BD individuals even after adjusting for confounders, suggesting a possible shared mechanism between the two diseases beyond lifestyle characteristics. Examining the shared genetic mechanisms between breast cancer and BD including their
those involving mitochondrial DNA repair will provide a deeper understanding of pathophysiology toward identifying novel therapeutic targets.

MITOCHONDRIAL TARGETS FOR NOVEL THERAPY DEVELOPMENT

Michael Berk**1*, *Jee Hyun Kim2, Bruna Panizzutti2, Zoe Liu2, Olivia Dean2, Johnny Park2, Ken Walder2*
[1]Australasian Society for Bipolar and Depressive Disorders Ltd, 2Deakin University

Objective: This presentation will highlight the evidence regarding abnormal mitochondrial energy generation in bipolar disorder as a treatment target. Mitochondria are cellular organelles involved in energy production. Symptomatically, bipolar disorder is a biphasic disorder of energy generation. Mania is characterised by increased energy in mania and in depression, by decreased energy. Bipolar disorder can be seen as a biphasic dysregulation of mitochondrial energy generation, typified in depression by inability to upregulate biogenesis in response to metabolic demands, and in mania to downregulate generation when demand abates. There is preclinical, electron microscopic, and post-mortem evidence of mitochondrial changes, and evidence of altered energy generation in the disorder. Many widely used psychotropic agents have effects on mitochondrial energy generation, implying that this is a viable therapeutic target. Several agents that enhance antioxidant defences or mitochondrial functioning have been studied for the treatment of mood disorders as adjuvant

therapy to pharmacological treatments. This could be especially beneficial for treatment-resistant patients.

Methods: This presentation will summarise the evidence supporting the involvement of mitochondrial dysfunction in mood disorders, the effects of current therapies on mitochondrial functions, and highlight novel targeted therapies acting on mitochondrial pathways that might be useful for the treatment of mood disorders. In addition, this presentation will highlight a novel stem cell derived platform for drug repurposing that highlights a mitochondrial therapeutic as having potential for the treatment of bipolar disorder, trimetazidine.

Results: Trimetazidine was identified with no a-priori hypothesis. We used a gene expression signature to determine the effects of a combination of known drugs used to treat bipolar disorder. We then screened a library of off-patent drugs in cultured human neuronal-like cells, identifying trimetazidine. Trimetazidine has cytoprotective and metabolic effects, leading to improved glucose utilization for energy production. It is used to treat angina pectoris and has an excellent safety profile. The preclinical and clinical literature strongly support trimetazidine's potential to treat bipolar depression, as the agent has anti-inflammatory and antioxidant properties while normalizing compromised mitochondrial function. Preclinical models suggest antidepressant effects.

Conclusion: Trimetazidine's established safety and tolerability provide a robust rationale for clinical trials to trial its efficacy to treat bipolar depression that could progress its repurposing to address arguably the major unmet need in the disorder.

SOCIAL ISOLATION IN YOUTHS: PREVENTION AND TREATMENT STRATEGIES

Paolo Brambilla, University of Milan

Symposium Synopsis: Human nature is thought to be rooted in its social interactions and relationships, which support the development and preservation of physical and mental health. In humans, extreme cases of social isolation can lead to the complete avoidance of social contexts including work, school and those involving significant others. This condition is known as Hikikomori syndrome, a phenomenon that affects roughly 2% of the Japanese general population. The evidence to date shows that this phenomenon is growing in both Eastern and Western countries, possibly influenced by cultural and environmental factors and the recent COVID-19 pandemic, with particular regard to the most fragile subgroups such as juvenile and elderly populations. Notably, social isolation and related loneliness have been associated with increased mortality and depressive symptoms, poorer cognitive functioning, faster cognitive decline and alterations in the neuroendocrine systems in healthy individuals. Furthermore, social isolation often constitutes a prodromal symptom of severe psychiatric conditions such as social anxiety disorder, psychosis and depression. Therefore, early interventions aimed at treating social isolation could lead to a more favourable outcome for young patients and reduce the burden on the national health systems. In this symposium, we will discuss the current challenges of preventing and treating social isolation-related disorders in fragile populations in and out of psychiatric trajectories.

SOLITAIRE - DIGITAL INTERVENTIONS FOR SOCIAL ISOLATION IN YOUTHS AND THEIR FAMILIES

Maria Gloria Rossetti*[1]

[1] *University of Verona*

Objective: Social Isolation (SI) is a condition that can lead to complete withdrawal from society, with particular regard to the most fragile subgroups such as juvenile and elderly populations. It often constitutes a core symptom (often prodromal) of severe psychiatric disorders such as the Hikikomori syndrome, social anxiety disorder, psychosis, depression, mood-dysregulation and others. If not treated, SI can degenerate into a complete withdrawal from society. Therefore, early interventions

aimed at treating SI could result in a more favourable outcome for young patients. However, due to the social interaction barrier intrinsic to the condition, current treatments alone are problematic and only partially effective in treating SI. SOLITAIRE aims at implementing a multi-component digital psychiatric intervention to remotely help youths suffering from Social Isolation (SI), based on cognitive behavioural therapy (CBT), Cognitive Remediation (CR) and Psychoeducation (PE) for family members. SOLITAIRE will overcome most barriers and limitations of standard clinical interventions.
Methods: SOLITAIRE aims to test the feasibility and preliminary efficacy of two digital interventions for treating young adults and adolescents suffering from severe social isolation. Recruited participants will be randomly assigned to two arms i.e., experimental versus control. In the experimental arm, patients will undergo a brief cycle of CBT combined with computerized CR. In the control arm, patients will receive only CBT. Additionally, for all recruited patients, a psychoeducational intervention (PE) is planned for family members to alleviate the psychological burden associated with caring for socially withdrawn relatives. SOLITAIRE started in June 2023, and recruitment is ongoing.
Results: In this talk, I will present the preliminary findings of the SOLITAIRE study, with particular emphasis on the challenges encountered during the study design, the implementation of the digital interventions and the data collection.
Conclusion: Due to its multimodal digital approach, SOLITAIRE is expected to significantly impact patients' quality of life and well-being addressing previously unmet clinical needs, possibly exacerbated by the recent pandemic. Moreover, the synergistic CBT+CR intervention is thought to stimulate cognitive processes implied in social cognition and we expect that clinical improvements will be generalized to more ecological scenarios and daily life contexts.

PREDICTORS OF EARLY PSYCHOSIS AND SOCIAL ISOLATION

Stefan Borgwardt*[1]
[1] *University of Lübeck*

Objective: Social isolation has been associated with increased psychopathological symptomatology, poorer cognitive functioning and constitutes a prodromal symptom of psychosis. In this presentation, we will review predictors for early psychosis in the context of social isolation. Furthermore, current challenges of preventing and treating social isolation in people at high-clinical risk for developing severe mental disorders will be reviewed.
Methods: Review of findings from international longitudinal consortia (Psy-Scan, PRONIA, NAPLS 2) and available evidence from early psychosis studies
Results: Social isolation plays a crucial role in longitudinal clinical trajectories of people presenting with attenuated symptoms of psychosis and at clinical high risk for psychosis (CHR).
Conclusion: Further search for improved treatments for social isolation and a comprehensive prediction and prevention model for early psychosis is needed.

HIKIKOMORI: PSYCHOPATHOLOGICAL AND BIOLOGICAL UNDERSTANDING OF SOCIALLY ISOLATED PERSONS

Takahiro Kato*[1]
[1]*Graduate School of Medical Sciences, Kyushu University*

Objective: Hikikomori, a severe form of social withdrawal for more than six months, is originally observed in Japan and now becoming a global mental health issue. I have established the world-first hikikomori research clinic/system to understand/treat multidimensional aspects of hikikomori based on bio-psycho-social analyses. I introduce our hikikomori research system and also show our updated biological data.

Methods: Drug-free patients with hikikomori (n=42) and healthy controls (n=41) were recruited. The severity of hikikomori was assessed using the HQ-25. Blood biochemical tests and plasma metabolome analysis were performed. Based on the integrated information, machine-learning models were created to discriminate cases of hikikomori from healthy controls, predict hikikomori severity, stratify the cases, and identify metabolic signatures that contribute to each model. **Results:** Long-chain acylcarnitine levels were remarkably higher in patients with hikikomori; bilirubin, arginine, ornithine, and serum arginase were significantly different in male patients with hikikomori. The discriminative random forest model was highly performant, exhibiting an area under the ROC curve of 0.854. To predict hikikomori severity, a partial least squares PLS-regression model was successfully created with high linearity and practical accuracy. Additionally, blood serum uric acid and plasma cholesterol esters contributed to the stratification of cases. **Conclusion:** Our findings reveal the blood metabolic signatures of hikikomori, which are key to elucidating the pathophysiology of hikikomori. Our data have suggested the importance of biological understandings of hikikomori in addition to sociocultural aspects.

LONELINESS IN PEOPLE WITH SEVERE MENTAL ILLNESS: A DATA SCIENCE INVESTIGATION

Dulce Alarcón Yaquetto**1*, *Robert Stewart1, Mariana Pinto da Costa1*

1 Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Loneliness is prevalent and has been linked with different health outcomes.

Objective: To investigate if loneliness is associated with clinical phenotypes of psychosis in people with severe mental illness (SMI).

Methods: We used the Clinical Record Interactive Search (CRIS) platform which provides anonymised copies of the South London and Maudsley NHS Foundation Trust (SLaM) electronic health records. A previously validated natural language processing (NLP) algorithm that identifies instances of loneliness was used to assess exposure.

Results: We identified people based on their first diagnosis of SMI and assessed if loneliness was a predictor of negative, depressive, and manic symptoms during a 12 month follow-up. We will present the findings obtained, with a focus on age and other individual characteristics. The advantages and challenges of using data science and large real world health electronic records to study loneliness will be discussed.

Conclusion: Loneliness can be studied as a predictor of clinical phenotypes in SMI using electronic health records coupled with NLP. As a potentially modifiable factor, this opens up opportunities for future research and interventions aimed at improving treatment outcomes and recovery in SMI patients.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia III

DIGITAL TECHNOLOGIES AND NEW ADVANCEMENTS IN PSYCHIATRY

Oğuz Karamustafalıoğlu, İstanbul-University Cerrahpaşa

ADVANCES IN DIGITAL PHENOTYPING FOR BRIDGING BIOLOGICAL RESEARCH AND CLINICAL CARE

John Torous

State-of-the-Art Synopsis: Digital phenotyping is an increasingly popular method that takes advantage of the multiple sensors and interactions that people have with their smartphones. It enables clinicians and researchers to capture various data streams, including mobility patterns (from GPS and accelerometer sensors), social patterns (from anonymized call and text message logs), self-

reported symptoms (from on-phone surveys), cognition (assessed through response time to on-screen tasks or more formal cognitive tests), and other real-time data on individual functioning. However, like all data streams, there are limitations including patient engagement, data quality, and replicable derived features. This talk will review the state of the art for digital phenotyping with a focus on validation and verification efforts to highlight the current and future use cases for this data. Biological research targets including current ready-to-analyze digital phenotyping datasets as well as clinical use cases of the data will be reviewed to frame the translational potential. Finally, ethical and equity issues concerning digital phenotyping will be presented with action-oriented steps toward ensuring the method is used appropriately. **Objective:** To define digital phenotyping and review relevant data streams. To highlight digital phenotyping data processing pipelines (machine learning) with the goal of highlighting potential sources of bias. To review recent evidence for the use of the method in both biological research and clinical care. To also explore reasons for currently contradictory results. To discuss the ethics of digital phenotyping and present a solutions oriented approach. **Methods:** This talk will draw evidence from published research, the ongoing AMP-Schizophrenia study, and Dr. Torous personal experiences applying it in research/care. **Conclusion:** Digital phenotyping remains a promising method to advance both biological psychiatry and clinical care. However, it is not a panacea and requires thoughtful applications and careful research to yield breakthroughs. The low barriers to entry and use of digital phenotyping mean that a global consortium to advance digital phenotyping is not only possible but necessary to realize its full potential.

NEW INSIGHT AND DEVELOPMENT OF INTEGRATIVE TREATMENT IN SCHIZOPHRENIA

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: The development of integrative treatment of pharmacological and non-pharmacological treatment for people affected by schizophrenia spectrum disorders has been identified as an important and urgent priority. Due to the adverse events and limited effects of medication treatment for schizophrenia, there is a need to identify effective combined interventions that can improve functioning recovery and can be provided within routine care services. This symposium will bring together the evidence evaluating these novel interventions.

Current antipsychotic treatments do not lead to beneficial effects on primary negative symptoms and
cognitive deficits in schizophrenia. Given that these domains of the disorder contribute substantially to low recovery rates and unfavorable disease course, new treatment approaches are warranted. In recent years, different types of exercise interventions have been proposed as promising add-on treatments. L Roell summarizes all current meta-analyses targeting effects of exercise on negative symptoms and cognitive impairments in schizophrenia. He further compares the observed effects sizes to other additional treatment approaches such as cognitive remediation and provides recent evidence on the underlying neural mechanisms that may drive these improvements on the clinical level.

POTENTIAL NEURAL MECHANISMS EXPLAINING BENEFICIAL EFFECTS OF PHYSICAL EXERCISE IN SCHIZOPHRENIA

Lukas Roell**1*, *Daniel Keeser2, Andrea Schmitt3, Alkomiet Hasan3, Isabel Maurus1, Peter Falkai3*

[1]LMU, 2University Hospital, LMU Munich, 3German Society for Biological Psychiatry

Objective: As demonstrated by multiple large-scale meta-analyses, physical exercise interventions in people with schizophrenia improve negative symptoms, cognition, social and occupational functioning, and general disorder severity. However, the underlying neural mechanisms that drive

these improvements remain to be determined. Therefore, we conducted a global exploratory analysis of structural and functional neural adaptations after exercise and explored their clinical implications. **Methods:** Combining meta-analytic techniques with original data of 91 patients with schizophrenia from a large-scale multicentre randomized-controlled trial, we investigated stuctural and functional neural adaptations induced by different types of exercise based on multimodal neuroimaging acquisitions. We further linked obtained changes in the brain to several relevant clinical outcomes. **Results:** Our results indicated that physical exercise in people with schizophrenia can induce structural and functional adaptations within the hippocampal formation, the default-mode network, the cortico-striato-pallido-thalamo-cortical loop, and the cerebello-thalamo-cortical pathway. We further observed that volume increases in the right posterior cingulate gyrus as a central node of the default-mode network were linked to improvements in general disorder severity. **Conclusion:** These findings suggest a positive impact of physical exercise on several neural networks involved in the pathophysiology of schizophrenia and thus provide further insights into neural mechanisms underlying clinical improvements after exercise. A more comprehensive understanding of these mechanisms is essential to gain a deeper insight into the pathophysiology of schizophrenia which in turn may facilitate the development of treatments that specifically target respective mechanisms.

WHAT DOES NON-INVASIVE BRAIN STIMULATION CONTRIBUTE TO THE TREATMENT OF PEOPLE LIVING WITH SCHIZOPHRENIA?

Frank Padberg**1*

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University Hospital, LMU Munich

Objective: Non-invasive brain stimulation (NIBS) approaches comprise an array neurophysiologically distinct methods, e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES). NIBS methods have been applied for treating clinical conditions within the spectrum schizophrenia syndromes, mainly predominant negative symptoms and persistent auditory hallucinations. The further implementation of NIBS interventions in clinical routines is a matter of debate.

Methods: The array of NIBS methods and their underlying mechanistic principles will be introduced. The current evidence for efficacy and safety of NIBS in schizophrenia will be critically reviewed and discussed based on the available evidence from randomized controlled trials (RCTs) and meta-analyses.

Results: Two main research lines focusing on predominant negative symptoms (target area: prefrontal cortex subregions) and persistent auditory verbal hallucinations (target area: temporoparietal cortex) have been established over the last two decades, and data from RCTs support their efficacy and safety. Across NIBS approaches and target regions, findings are nevertheless heterogeneous probably also due to different mechanisms of neuroplasticity induction. To date, there is very limited evidence how NIBS interventions could be implemented in clinical care and treatment algorithms.

Conclusion: Growing evidence supports the notion that NIBS methods (mainly rTMS and tES) are efficacious for treatment psychopathological syndroms in people with schizophrenia and could be easily implemented in combined treatment protocols due to their good safety profile and application modalities which are easily scalable for various clinical settings. Future studies should focus on gaining a deeper mechanistic understanding of the respective NIBS methods and systematically include NIBS in RCTs as active comparators to other treatment modalities.

A PILOT RANDOMIZED CONTROLLED TRIAL OF AN INTEGRATIVE INTERVENTION OF TDCS AND YOGA FOR COGNITIVE FUNCTION IN CHRONIC SCHIZOPHRENIA

Jingxia Lin*[1]
[1]*The Hong Kong Polytechnic University*

Objective: The pilot randomized controlled trial aimed to examine the feasibility and effectiveness of a 2-week combined intervention of active tDCS and yoga on cognitive function and clinical symptoms in individuals with chronic schizophrenia.

Methods: A total of 18 participants with chronic schizophrenia were recruited and randomized into two arms: (1) 2-week active tDCS + yoga (a-tDCS-Y) (n=9), and (2) 2-week sham tDCS + yoga (s-tDCS-Y) (n=9). Both interventions were conducted five sessions weekly for two weeks, with each session lasting 1 hour. Active tDCS was applied using a wearable stimulator (LifTid) with a constant stimulation intensity of 1.2mA for 20 minutes, and sham tDCS was performed using the same device but without stimulation. During the yoga training, all participants wore the device and a facilitator turned on the stimulation for participants receiving a-tDCS-Y intervention, and pretended to turn on the stimulation for participants receiving s-tDCS-Y intervention after the first 10-minute warm-up. Outcome measures were conducted at baseline and post-intervention including cognitive tests, quality of life, and clinical symptoms.

Results: There were 16 participants completed the pilot trial with an attrition rate of 11%. Mean age was 44.5 years old, and mean duration of illness was 7.5 years. There were no significant differences in the demographic characteristics between two groups at the baseline. We found a-tDCS-Y had a small-to-medium effect size in executive function measured by the Verbal Fluency Test (Cohen's d=0.39) compared with s-tDCS-Y group. We also found a significant time × group interaction effect on physical function assessed by SF-36 (Cohen's d=0.61) with superior improvements in a-tDCS-Y group. Both groups showed a trend of improving working memory and clinical symptoms (Cohen's d ranged from 0.21 to 0.55).

Conclusion: Overall, the pilot study provides preliminary evidence for the feasibility of our approach and showed encouraging findings on executive function after a 10-session active tDCS + yoga intervention in chronic schizophrenia. Further full-scale RCT to evaluate the additive and synergistic effects of tDCS and yoga on neurocognitive function and to examine the underlying neuro-mechanisms using imaging approach is highly recommended.

OPTIMIZING CARE FOR PEOPLE LIVING WITH SCHIZOPHRENIA THROUGH NON-PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS

Christoph Correll*[1]
[1]*Zucker School of Medicine at Hofstra/Northwell, Hempstead*

Objective: This presentation will focus on the effects of nonpharmacologic psychological and psychosocial treatments when added to antipsychotics across a broad range of outcomes. Additionally, data on the combination of antipsychotic treatment with healthy lifestyle education, instruction or management interventions with be presented, either alone or in conjunction with pharmacologic treatments aimed at reducing appetite, food intake and cardiometabolic risk factors or poor outcomes in people with mental illness. Finally, adaptive monitoring and management strategies will be proposed.

Methods: Review of systematic reviews and meta-analyses as well as umbrella reviews on the topics of nonpharmacologic psychological and psychosocial treatments added to antipsychotics across a broad range of outcomes for people with schizophrenia.

Results: Several meta-analyses, network meta-analyses and umbrella reviews exist regarding the effects of adjunctive nonpharmacologic psychological, psychosocial and lifestyle interventions for

mental and physical health outcomes. In patients with early-phase schizophrenia, integrated or "coordinated specialty" care seems to be the most promising approach. Otherwise, among psychological interventions, cognitive behavioral therapy and family interventions had the most data in support of their adjunctive use. For cognitive health, cognitive remediation and exercise were more effective than control groups. Regarding lifestyle interventions, coached and group interventions had the biggest effect, including on physical health and global as well as social cognition. **Conclusion:** Adjunctive nonpharmacologic psychological and psychosocial treatments as well as healthy lifestyle counseling and interventions are viable options for people with schizophrenia to improve a range of relevant mental and physical health outcomes. Ways to increase initiation of, engagement in and retention related to such interventions as well as their effects on longer-term biopsychosocial outcomes requires further study.

THE ART OF PRESCRIBING CLOZAPINE: NOVEL DEVELOPMENTS

Dragana Ignjatovbic Ristic, University of Kragujevac

Symposium Synopsis: Clozapine is a cornerstone of the management of treatment-resistant schizophrenia, presents unique challenges in clinical management and is underprescribed. Our symposium delves into three key facets of clozapine treatment: therapy adherence, blood levels, and neutrophil counts.

The first presentation explores a novel approach to monitor long-term adherence to clozapine. Utilizing data from the Utrecht Patient Oriented Database, it reveals a significant association between clozapine use and enhanced FL3 neutrophil granulocyte fluorescence. This finding opens avenues for using FL3-fluorescence as a potential biomarker for clozapine adherence, a crucial aspect in schizophrenia management.

Our second presentation shifts focus to therapeutic drug monitoring (TDM) of clozapine. The study analyzed clozapine levels in patients with treatment-resistant schizophrenia in a middle income country who were titrated without TDM. This revealed a substantial interindividual variation in clozapine levels, absence of a relationship between levels and side effects, and only a weak relationship between levels and functional outcome. These results challenge strict adherence to the conventional therapeutic range and support a more personalized approach.

The final presentation revisits the history and current practices surrounding clozapine-induced agranulocytosis. Reviewing literature from 1975-2022, it suggests a reevaluation of the mandatory intensive blood monitoring protocols, advocating for a more nuanced approach that balances the risks and benefits of clozapine treatment, especially in the initial weeks of therapy.

Together, these presentations underscore the importance of personalized, evidence-based approaches in optimizing clozapine treatment for schizophrenia. In this way this symposium hopes to contribute to the removal of hurdles to clozapine treatment.

CLOZAPINE LEVELS AND OUTCOMES IN SERBIAN PATIENTS WITH THERAPY RESISTANT SCHIZOPHRENIA PREVIOUSLY TREATED WITHOUT MEASURING CLOZAPINE LEVELS

Hans de Haas*[1], *Dan Cohen[2], Mariken de Koning[3], Geke van Weringh[4], Veroljub Petrovic[5], Lieuwe de Haan[6], Daan Touw[7], Dragana Ignatovic-Ristic[8]*

[1]Arkin Mental Health, [2]MHO North-Holland North, Amsterdam, [3]Arking Mental Health, Amsterdam, [4]Onze Lieve Vrouwe Gasthuis, Amsterdam, [5]Special Hospital for Psychiatric Disorders Kovin, [6]Amsterdam University Medical Center, [7]University Medical Center Groningen, [8]University of Kragujevac, Faculty of Medical Sciences

Objective: Clozapine remains the only pharmacological treatment option for therapy resistant schizophrenia. Therapeutic drug monitoring (TDM) of clozapine is recommended, although the evidence for the therapeutic range of 350-600 ng/ml is limited. In various countries including Serbia, TDM of clozapine is not routinely performed. This study evaluated the distribution of clozapine levels in Serbian patients who had not undergone prior TDM and investigated the relationship of clozapine levels with clinical outcomes. **Methods:** Clozapine levels were measured by dried blood spot (DBS) analysis

in patients with therapy resistant schizophrenia. DBS samples were taken in Serbia, and shipped to The Netherlands for analysis. Side effects were evaluated by GASS-c, severity of symptoms and functional impairment with WHODAS, CGI-S and GAF.

Results: Clozapine was determined for 129 of 140 enrolled patients. 51.2% had subtherapeutic levels, 24.8% were in the therapeutic window and 24% had supratherapeutic levels. Clozapine levels were not associated with side effects, and showed a weak positive association with symptom severity and functional impairment. No severe side effects were observed in patients with clozapine levels surpassing 1000 ng/ml (n=8).

Conclusion: Current findings revealed substantial interindividual variation. Especially when patients are titrated without TDM, some patients achieve high clozapine levels with apparently good tolerance and others experience side effects with relatively low clozapine levels. We propose that the upper limit of the therapeutic range should not be regarded as an absolute barrier, and guidelines should allow for a personalized approach when prescribing clozapine.

NEUTROPHIL FLUORESCENCE IN CLOZAPINE TREATMENT: THE FIRST BIOLOGICAL MARKER OF LONG-TERM DRUG ADHERENCE

Wai Hong Man**1*, *Maarten ten Berg1, Ingeborg Wilting1, Albert Huisman1, Wiepke Cahn1, Jan Willem Douma2, Hanneke den Breeijen1, Eibert Heerdink1, Toine Egberts1, Wouter van Solinge1*

[1]University Medical Center Utrecht, 2Tjongerschans Hospital, Heerenveen

Objective: Non-adherence to medication is a major issue in the treatment of schizophrenia in general and in particular for those treated with clozapine. A reliable tool to quantify patients long-term adherence to clozapine is currently unavailable. Enhanced FL3 neutrophil granulocyte fluorescence was serendipitously observed in a small population of schizophrenic patients treated with clozapine. The present study was aimed at assessing the association between clozapine use and FL3-fluorescence.

Methods: A cross-sectional study was performed using data from the Utrecht Patient Oriented Database (UPOD). A total of 38 390 inpatients were included, of which 124 (0.33%) used clozapine.

Results: FL3-fluorescence was significantly higher (U=240 179, P LESS THAN 0.001) in clozapine users (mean (SD)= 90.5 (11.8)) than in non-users (mean (SD)= 69.8 (3.3)). Observed FL3-fluorescence was found to increase with increasing clozapine dose. The area under the receiver operating characteristic curve was 0.95.

Conclusion: Our results confirm the association between use of clozapine and elevated FL3-fluorescence. Further research is needed to unravel the underlying mechanism and to investigate the true potential of FL3-fluorescence as a clozapine-adherence in clinical practice.

MODIFIED LEUKOCYTE MONITORING IN CLOZAPINE: PROPOSAL BY THE DUTCH CLOZAPINE COLLABORATION GROUP

Dan Cohen**1*, *Peter FJ Schulte1, Selene Veerman1, Jan PAM Bogers2*

[1]MHO North-Holland North, 2MHO Rivierduinen

Objective: After the introduction of clozapine in 1975 in Finland, eight Finnish patients died after developing agranulocytosis, whereupon clozapine was withdrawn from the market. Its reintroduction – from 1990 onwards – was accompanied by mandatory white blood cell monitoring if treatment lasts and strict thresholds at which clozapine must be discontinued definitively. The fear of agranulocytosis and the need for intensive blood monitoring is and remains the single most important barrier for prescribers and patients alike and leads to under prescription of the only effective and approved medication for treatment-resistant schizophrenia.
Methods: We review the literature from 1975-2022 on the incidence of clozapine-associated agranulocytosis and the relation between the occurrence of the agranulocytosis with treatment duration
Results: The risk of agranulocytosis is smaller than perceived at the time of reintroduction, b. the risk of agranulocytosis is concentrated in the first 18 weeks of treatment, c. such risk is not greater than with other antipsychotics and d. that frequent blood monitoring has not demonstrably decreased the rate of agranulocytosis.
Conclusion: 1) Restrict mandatory monitoring of the absolute neutrophil count (ANC) to the first 18 weeks of clozapine treatment, 2) the prescriber and the well-informed patient decide together about further monitoring frequency, 3) Clozapine treatment must be stopped if the ANC falls below 1.0×10^9/L. Continuation of clozapine or a rechallenge are possible if prescriber and patient together determine that the benefits outweigh the risks. 4) National registries which control hematologic monitoring are unnecessary and should be abolished.

EXPLORING CURRENT AND FUTURE DIRECTIONS IN THE MICROBIOME – A FOCUS ON NEUROPSYCHIATRIC DISORDERS

Sian Hemmings, Stellenbosch University

Symposium Synopsis: Humans have co-evolved with the trillions of microbiota that occupy every inch of our bodies, creating habitat-specific ecosystems that play a crucial role in bodily functions. Over the past decade, the interest in the role of that microbiota play in neuropsychiatric disorders, including autism spectrum disorder, posttraumatic stress disorder (PTSD), major depressive disorder and Parkinson's Disease has exploded. Recent evidence has indicated that the microbiome plays a key role in the brain and behaviour at critical windows across the lifespan, with numerous studies supporting the role of the gut microbiome in neurodevelopment. This symposium will bring together four leaders in the field of microbiome research, to discuss the current and future directions in microbiome research in neuropsychiatric disorders across the lifespan. Dr Hemmings will provide an overview of the role of the microbiome in neurodevelopmental disorders, with a focus on fetal alcohol spectrum disorders; Dr Malan-Muller will discuss the emerging role of the gut and oral microbiome in common mental disorders, such as PTSD, anxiety and depression, and Dr El-Aidy will discuss gut microbiome adaptations and implications for Parkinson's Disease treatment. Finally, Dr Walter Pirovano will provide insight into standardised and robust approaches for the identification of microbial markers in neuropsychiatric disorders.
This symposium will feature preclinical and clinical microbiome findings, and discuss the gut microbiome as a potential therapeutic target. Future considerations for holistically investigating the gut microbiome and untangling the molecular mechanisms whereby it influences the brain and behaviour, will also be discussed.

FETAL ALCOHOL SPECTRUM DISORDER: INSIGHTS FROM THE MICROBIOME

Sian Hemmings*[1], *Sian Hemmings2, Natasha Kitchin2, Lauren Martin2, Philip May3, Lindsay Hall4, Raymond Kiu5, Matthew Dalby5, Jacqueline Womersley2, Anna-Susan Marais1, Marlene de Vries1, Soraya Seedat2*

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Objective: Fetal alcohol spectrum disorder (FASD) is an overarching term describing four diagnoses along a severity spectrum, that occur consequential to prenatal alcohol exposure (PAE). Arguably the most profound consequences of FASD are the enduring neurodevelopmental abnormalities and cognitive deficits. In South Africa, the prevalence of FASD is reported to be higher than anywhere else in the world, with prevalences of up to 170-233 per 1,000 children reported, compared to the global prevalence of 7.7 per 1,000. Although FASD is a serious public health problem, both locally and internationally, treatment options are limited and further research is required in order to uncover novel therapeutic targets. Microbiome studies are a rapidly growing area of neuropsychiatric and neurodevelopmental research. Vertical and horizontal transfer of microbes from mother to child during and shortly after birth results in the acquisition of intestinal bacteria which, via the microbiome-gut-brain axis, have been found to play a significant role in neurodevelopment. Microbial alterations in the maternal gut and vaginal bacteriome, as well as the infant gut microbiome, may therefore increase the risk of FASD.

Methods: Participants (n=207) provided both stool and vaginal swab samples. Additionally, stool samples were collected from their infants at birth, six weeks, and nine months of age. Maternal alcohol use was assessed using AUDIT questionnaire and physiological markers of alcohol use. FASD diagnoses were made by triangulating data from dysmorphology examinations, neurodevelopmental assessments, and maternal interviews. Microbial DNA was extracted from maternal stool and vaginal samples, and infant samples at birth, 6 weeks and 9 months of age, and the V1-V2 hypervariable region of the 16S rRNA gene was sequenced. Microbial composition and diversity analyses were performed using R packages dada2, vegan, phyloseq, and MaAsLin2.

Results: Relative abundances of maternal gut Subdoligranulum and Bifidobacterium were lower in participants who birthed infants with FASD, compared to participants who birthed infants not diagnosed with FASD ($q = 0.026$; $q = 0.034$, respectively). Between the ages of 6 weeks and 9 months, Streptococcus relative abundance increased in the gut of infants without FASD, but decreased in infants diagnosed with FASD ($p = 0.023$), while the relative abundance of Bacteroides decreased in infants without FASD, but increased in those with FASD ($p = 0.073$).

Conclusion: Our research findings shed light on the nature and persistence of PAE-induced changes in the gut microbiome, and how alcohol-induced alterations in the microbiome may correlate with the development of FASD symptomology. These studies provide the first step in facilitating the identification of robust maternal and infant biomarkers of FASD, which may enable early identification of individuals most at risk for FASD, offer an early window for intervention, and contribute towards mitigating FASD-related disabilities in later life.

EXPLORING THE ORAL-GUT-MICROBIOME-BRAIN AXIS: ADVANCING FROM ASSOCIATION STUDIES TO MECHANISTIC INSIGHTS AND BEYOND

Stefanie Malan-Muller*[1], *Thomaz Bastiaanssen2, Rebeca Vidal1, Juan Carlos Leza3*
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Objective: Investigate the intricate interplay between the microbiomes of the oral cavity and the gut and explore the underlying molecular mechanisms that link these microbial ecosystems and their influence on anxiety, depression, and trauma-related symptoms.

Methods: In a Spanish cohort, we studied the connection between mental health and fecal and oral microbial characteristics, covering self-reported symptoms and clinical diagnoses of anxiety, depression, and PTSD.

We collected stool, saliva, and blood samples from 290 participants who completed questionnaires. Microbial communities in the gut and mouth were analyzed via 16S rRNA sequencing, examining diversity, structure, and taxonomic abundance. Linear models were used to assess associations between taxonomic abundance and variables while adjusting for covariates.

We used PICRUSt2 to identify Gut-Brain Modules (GBMs) and Gut Metabolic Modules (GMMs) and employed linear models to uncover modules significantly linked to mental health. Analysis of the oral microbiome is ongoing.

We measured plasma LPS levels with ELISA and are currently assessing levels of kynurenine, tryptophan, serotonin, and various inflammatory markers.

Results: A substantial proportion of individuals exhibited anxiety (72.41%), depression (41.38%), and PTSD symptoms (20%), often overlapping. Lower Simpson's diversity was found in those with anxiety disorders and psychiatric medication use. Microbial composition was affected by general health, depression/bipolar disorder diagnoses, childhood abuse, and neglect.

Certain microbial abundances correlated with symptoms: Duodenibacillus, Desulfovibrio, and Senegalimassilia positively correlated, while Parasutterella negatively correlated with CTQ scores. Severe/moderate childhood emotional abuse was linked to higher Prevotella and lower Parasutterella abundances. Severe/moderate childhood physical abuse correlated with higher Desulfovibrio and Senegalimassilia levels.

Individuals with depression symptoms had lower Monoglobus abundances. Those with depression symptoms, diagnosed depression, or PTSD symptoms had reduced Monoglobus and Hungatella compared to mentally healthy controls. Comorbid depression+anxiety and PTSD+depression+anxiety individuals exhibited lower Hungatella and Monoglobus levels. Desulfovibrio positively correlated, while Hungatella negatively correlated with PCL scores.

Comorbid PTSD+depression and PTSD+depression+anxiety cases showed increased glycine degradation. Individuals with depressive symptoms and childhood physical neglect had elevated plasma LPS levels.

Conclusion: In a population-based study, we've uncovered vital connections between gut microbes and mental health. Notably, lower Simpson's diversity was found in anxiety disorders, echoing generalized anxiety disorder trends. Parasutterella negatively correlates with childhood trauma and autism spectrum. Prevotella is higher in childhood emotional abuse cases. We identified lower Hungatella levels in those with multiple mental health symptoms, corrected for psychoactive drug effects. Reduced Monoglobus, linked to poorer life quality, is seen in significant depressive symptoms. Higher glycine degradation is tied to PTSD, depression, and anxiety. Elevated LPS levels

indicate increased gut permeability in individuals with childhood neglect and depressive symptoms. These findings suggest potential early-life interventions for improved mental health.

GUT MICROBIOME ADAPTATION AND TREATMENT IMPLICATIONS IN PARKINSON'S DISEASE

Sahar El Aidy*[1]

[1]*University of Groningen*

Objective: The intricate interplay of the microbiome within the human body is integral to determining overall health. Of particular significance is the dynamic nature of the gut microbiome, influenced by multifaceted factors such as nutrient availability, and interactions with the host. Disruptions in these factors have been observed in conditions like Parkinson's disease, often accompanied by discernible alterations in the microbiome profile. However, the field faces challenges in reconciling conflicting findings that assign specific roles to individual microbes in the development and progression of the disease.
Methods: In this context, research from my lab has shown how specific gut bacteria diminish the bioavailability of the primary treatment for Parkinson's disease (1, 2), and how their metabolic activities affect bowel movement and the overall microbiome profile (3, 4).
Results: Our recent investigations have brought to light the presence of distinct bacterial strains in Parkinson's patients, displaying unique genotypic and phenotypic traits (unpublished data).
Conclusion: Ultimately, these discoveries promise to provide a deeper understanding of how certain microbial community members adapt and flourish within the gut environment, thereby facilitating the development of tailored microbiome-targeted interventions.

NEUROPSYCHIATRIC DISORDERS AND THE MICROBIOME: TOWARDS STANDARDIZED AND ROBUST APPROACHES FOR THE IDENTIFICATION OF MICROBIAL MARKERS

Walter Pirovano*[1]

[1]*Vrije Universiteit Amsterdam*

Objective: In recent years, an increasing number of studies has allocated an important role to the microbiome in the proliferation of neuropsychiatric disorders. Many of these studies focus on the characterization of microbiota imbalances (dysbiosis) and the impact this may have on functioning of the central nervous system by means of the direct and indirect gut-brain axis communication pathways. The differences in sample processing and data analysis methods however result in findings which are often inconsistent and difficult to replicate. To overcome this more standardized and robust approaches are warranted, but we argue also larger and/or combined cohorts are essential to increase the statistical power.
Methods: We reviewed microbiome association studies that link microbial shifts to neuropsychiatric disorders, and summarized the findings together with the study design, lab- and data analysis procedures. The statistical power and suitability of the normalization technique used within each study was assessed as well. Next, studies that shared an overlapping setup were combined and analyzed using different analysis approaches to identify dysbiosis, to link taxa with metadata covariates and to quantify taxa-taxa interactions. The results were compared against findings obtained on the individual datasets as well as the findings of the original studies.
Results: We show that the use of different study designs, lab- and analyses methods have a profound impact on the outcomes of microbiome association studies in neuropsychiatric disorders. We show that the choice of the (biostatistical) analysis method is of particular importance to this regard. That said, the impact of the method is considerably lower when using larger and/or combined cohorts.
Conclusion: We conclude the use of different study setups and protocols for sample processing and data analysis lead to a divergent microbial landscape associated with neuropsychiatric illness. In

order to improve the coherence of studies, the use of standardized and statistically robust approaches is essential. Yet significantly larger and/or combined cohorts are needed to increase the statistical power and to gain a more comprehensive insight into the mechanisms that microbes use to trigger the development of psychiatric illnesses.

GRANT WRITING WORKSHOP

Sophia Frangou, The University of British Columbia

STRATEGIES FOR SUCCESS IN OBTAINING RESEARCH FUNDING

Sophia Frangou1
1 The University of British Columbia

Objective: Present strategies for successful grant writing in psychiatry.
Methods: The presentation will cover the following:
(a) Types of research funding available
(b) Writing a research proposal
(c) What the reviewer are looking for
(d) What the funding agencies are looking for
Results: Participants should be better equipped to apply for competitive funding.
Conclusion: Research funding is very competitive, and applicants benefit for using proven strategies.

EUROPEAN JOURNALS AND IMPACT FACTOR

Paolo Brambilla1
1 University of Milan
Paolo Brambilla, University of Milan

Objective: Young researchers often wonder whether the impact factor or the number of citations is more relevant. My very personal view is that citations become increasingly important with increasing maturity of the career of a scientists.
The older scientists get the more they will be judged for the consistency of their output (how many papers per year during the last 5 or 10 years – but also how many 'excellent' papers per year based on the impact factor and/or citations).
Young researchers often have only one or two publications which are pretty new, thus, the number of citations is limited.
Therefore, for pragmatic reasons, funding institutions and universities will use the impact factor of the journal as a proxy of their scientific excellence. To evaluate the output of more mature scientists the h-index or the m-index may be used which are both based exclusively on citations and not on impact factors.
Thus, young researchers are confronted with the problem that their scientific quality will be judged based on the impact factors of their publications – especially in contexts which are highly relevant for their early careers such as in selection committees (to get hired) and grant committees (to get funding).
Methods: How to build a CV and become an independent researcher.
Find facilities and mentor (also you got to be lucky and causality may help sometimes)
Learn a method, balance quantity and quality of publications in a 2-3 years span, start Networking with colleagues, present posters at conferences, try oral presentations, apply for congresses' awards, and start preparing proposal grants.
intramural / local / national / european-international

The following strategies are well known among senior scientists and will primarily help young researchers to look for feasible ways to improve their studies within the limits of their contract and budget.

1. Look for a mechanism not for a phenomenon
2. Address the same question with additional methods
3. Re-analyze your samples with a different or more complex method
4. Add fancy techniques
5. Develop a fancy technology
6. Collaborate with a statistician
7. Fuse smaller studies
8. Collaborate with experts in the field
9. Look for a journal with the perfect scope and check where your competitors publish
10. Submit to a journal with a much higher impact factor to get reviewers comments

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: EARLY DETECTION, INTERVENTION AND PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Symptoms related to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, loss of synaptic plasticity and nucleotide polymorphisms. Activation of the immune response can alter neurotransmission leading to transmitter deficiency, and increased production of neurotoxic substances. Aberrant levels of proinflammatory cytokines can be detected in serum, plasma, and cerebrospinal fluid. A persistent proinflammatory state, gone undetected and untreated, contributes to neuroprogression. Predicting risk and intervening to prevent and reverse a neuroprogressive course remain a challenge. This symposium will focus on assessment of the homeostatic balance of the autonomic nervous system focusing on vagal nerve activity by measuring heart rate variability. The cholinergic anti-inflammatory pathway of the vagus regulates peripheral immune response. Restoring vagal nerve activity by non-pharmacologic interventions restores normal immune response. Baseline systemic immune-inflammation index (SII) is an indicator of immune response and systemic inflammation based on peripheral blood platelet, lymphocyte, and neutrophil counts, and is a simple way to objectively assess the balance between inflammatory and immune responses. The association between elevated neutrophils (along with SII) and treatment resistance may allude to the role of oxidative stress in the pathophysiology of Bipolar Disorder. Selective genomic testing pertaining to the thyroid pathway can provide guidance in determining vulnerability to treatment resistance, and a neuroprogressive course. Mutations in deiodinase enzymes peripherally and in CNS may explain the pathophysiology and progression of the disease up to cerebral atrophy. These mutations, when addressed with high dose thyroid hormones and rTMS, yield long term stable remission.

HEART RATE VARIABILITY IS AN INDEX OF AUTONOMIC DYSFUNCTION AND A TOOL TO ASSESS NEUROPROGRESSION

Angelos Halaris**1*

[1]*Loyola University Chicago Stritch School of Medicine*

Objective: Autonomic nervous system (ANS) dysregulation is associated with various symptoms of depressive disorder. The beat-to-beat pattern of heart rate (Heart Rate Variability) (HRV) provides a noninvasive portal to ANS function through the quantification of periodic heart rate patterns. In this study we quantified two components of HRV: Respiratory Sinus Arrhythmia (RSA), and Low

Frequency HRV (LFHRV). Both of these components have been extensively reported in studies of depression and have been at least partially associated with reduction in vagal nerve tone. We quantified RSA and LF-HRV in patients with Major Depressive Disorder (MDD) and Bipolar Depression as measures of ANS regulation seeking to establish the utility of components of HRV as potential diagnostic and prognostic biomarkers for treatment outcome. Given the regulatory effect of the vagal pathway on cells of the immune system, HRV provides a non-invasive index of the peripheral inflammatory status of the individual. **Methods:** Respiratory sinus arrhythmia (RSA), low-frequency (LF) of HRV, and systolic blood pressure (SBP) were assessed in patients with bipolar depression (31) and major depressive disorder (MDD=32), and in healthy controls (HCs=32). Since bipolar depressed subjects were maintained on specific medications to manage manic/hypomanic symptoms, we explored whether mood stabilizers (atypical antipsychotics and anticonvulsants or their combinations) could independently affect the physiological parameters. **Results:** When the autonomic measures were analyzed by a multivariate analysis of variance (MANCOVA), after controlling for BMI, the combination of variables (RSA, LF, SBP) discriminated patients with bipolar depression and MDD from HC ($F(6, 178)=3.036$, $p=0.007$, $\Lambda=0.823$, partial $\eta 2=0.093$). In any case, we cannot exclude that mood stabilizers might have affected SBP values in the bipolar group. To deconstruct this multivariate effect, pairwise ANOVAs and discriminant analyses contrasted groups and documented that RSA was the primary variable distinguishing the groups. Discriminant function analyses showed that RSA had a significant discriminating weight between bipolar depressed patients and HC subjects (p LESS THAN 0.0005). By contrast, RSA showed a trend towards statistical significance in discriminating between bipolar depression and MDD patients ($p=0.06$). **Conclusion:** In conclusion, physiological parameters (e.g., RSA and SBP) can be easily assessed in outpatient settings, thus facilitating the differential diagnosis of affective disorders. In addition to other clinical tools, such as pharmacogenomic testing, history, and questionnaires, HRV analyses and BP measurement can add relevant physiological parameters to reach the final diagnosis. Components of HRV may be predictive of antidepressant response in MDD patients. Lastly, we highlight the regulatory influence the ANS exerts on the immune system. It has been shown that inflammation can increase symptomatology in affective disorders, and its modulation can reverse resistance to drug treatment.

THE ROLE OF CBC-BASED INDICES OF PERIPHERAL INFLAMMATION IN PREDICTING CLINICAL OUTCOMES AND NEUROPROGRESSION FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION

Stephen Murata*[1], *Nausheen Baig[2], Kyle Decker[2], Sakibur Hasan[3], Angelos Halaris[4]*

[1]Michigan State University, 2Loyola Stritch School of Medicine, 3Western Michigan University Stryker School of Medicine, 4Loyola University Medical Center

Objective: Dysregulation of the immune system has emerged as an important contributor to the pathophysiology neuropsychiatric illness, including bipolar disorder (BD) and its treatment-refractory depressed form (TRBDD). As we develop a wider armamentarium for treating TRBDD, there is a need for objective biomarkers for stratifying patients by their propensity to respond to treatment, including with augmentation by inflammatory modulators (Halaris et. al 2020), The objective of this study is to characterize the relationship of systemic inflammatory burden with categorical and continuous clinical outcomes in TRBDD. To that end, our specific aims are to describe the relationship of baseline systemic inflammatory indices (constructed from markers in the complete blood count, or CBC) to (1) diagnosis of TRBDD compared to healthy controls (2) pre- and post-treatment

depressive severity after adjunctive celecoxib (COX-2 inhibitor) and (3) relationship to immune-metabolic biomarkers. **Methods:** This is a secondary analysis of biomarkers from our primary study (Halaris et. al 2020), which was a randomized, double-blind, placebo-controlled clinical trial of adjunctive celecoxib for TRBDD (total N=79, HC=32, TRBDD=37). Peripheral inflammatory indices were constructed from the CBC including the systemic inflammatory index (SII = neutrophils x platelets / lymphocytes) and the systemic inflammatory response index (SIRI = neutrophils x monocytes / lymphocytes). SIRI and SII were subjected to (1) group comparisons according to diagnosis and treatment arm and (2) univariate associations with pre- and post-treatment depressive severity (HAMD-17) and biomarkers. We modelled post-treatment depression (main outcome) according to baseline SII or SIRI, adjusted by pre-treatment depression and relevant covariates. **Results:** Inflammatory indices (SII or SIRI) were not distinguished by diagnosis or treatment arm. However, SIRI ($p=0.008$) and monocytes ($p=0.04$) were independently associated with pre-treatment HAMD-17. On multivariate modelling, post-treatment HAMD-17 was associated with pre-treatment SII in older patients ($p=0.001$), and SIRI in more depressed patients at baseline ($p < 0.001$), but no interaction with treatment arm. There were several significant associations with inflammatory indices and cytokines, chemokines, neurotrophic factors, and kynurenine pathway (KP) metabolites. **Conclusion:** There is a need for objective and economical biomarkers to assist in clinical assessment/treatment of neuropsychiatric illness, including TRBDD. These preliminary findings support the potential relevance of blood-based indices of peripheral inflammatory burden (monocytes, SII, and SIRI) as candidate pre-treatment indicators of treatment response, specifically for select subsets of TRBDD patients. Further, larger studies are needed to qualify these results. Once the utility of these blood-based biomarkers has been confirmed, it can also be used to stage and treat neuroprogression.

BIPOLAR SPECTRUM DISORDERS: THYROID PATHWAY GENETIC PROGNOSTIC MARKERS: IMPLICATIONS FOR ASSESSMENT, STAGING OF NEUROPROGRESSION AND TREATMENT

Andy Zamar**[1]*

[1] *The London Psychiatry Centre*

Objective: We aim to incorporate the assessment of SNPs and blood tests specific to those SNPs as well as the management using rTMS / HDT as a standard in the management of bipolar disorders particularly subthreshold presentations. Currently there are no confirmed results for the treatment of subthreshold bipolar disorder, which constitutes 60% of bipolar disorder with a prevalence of 2.5% in the United States. Furthermore, many patients with bipolar disorder 1 and 2 also present with subthreshold symptoms in between episodes and may indeed present only with disabling subthreshold symptoms while on treatment, such as mood stabilizers and antipsychotics which as a rule fail to induce full remission. The mortality of bipolar disorders is as high as circa 60% with 4 out of 10 dying of cardiovascular disease 10 years before the general population and 2 out of 10 dying of suicide and accidents. There is a very high disability rate which a WHO global study found to be higher than cancer, depression, heart disease, and epilepsy.

Methods: We present genetic findings in a cohort of 199 patients with SNPs in Deiodinase enzymes 1 and 2 and SLCO1C1 intracerebral thyroid protein transporter, as well as treatment outcomes in 2 cohorts (20 and 55 subjects). We explore the role of thyroid hormones on mitochondrial function, and the impact of the combined induction of neuroplasticity using rTMS and supraphysiological doses of Levothyroxine (HDT) and discuss their proposed mechanism of action. We also discuss the use of genetics and blood tests to predict tolerability and response to treatment.

Results: Patients achieved a long stable remission of depressive, hypomanic and mixed symptoms in Bipolar 1, 2 and BD-NOS with very few effects or disease burden. They were assessed using the Sheehan Disability Scale, a commonly used WHO scale to measure disease burden.

Conclusion: Precision medicine targeting treatments of mitochondrial dysfunction neuroplasticity provide a valid treatment option for bipolar disorders. The combination of HDT and rTMS is promising and well tolerated. Further studies of mitochondrial function before and after treatment and a randomized Controlled trial of the protocol are warranted. This is the first-time subthreshold symptoms / bipolar disorders are treated to full stable remission of an average of 2 years. The combination of inducing neuroplasticity and use of HDT is novel and may be a valuable tool in assessing the course of neuroprogression and possibly arresting if not reversing it. We are not aware of any guidelines to treat subthreshold symptoms and not even case reports, cohort studies or RCTs.

FROM NEUROPROGRESSION TO DISEASE MODIFICATION IN BIPOLAR DISORDER

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to identify the operative elements of the process of neuroprogression in order to identify clinical targets. The other objective is to define disease modification as a potential treatment effect and therapeutic goal.

Methods: Bipolar disorder progresses from an at-risk period, to the prodrome, a first episode, recurrence then chronicity. Along this path, the illness course and response patterns change, with poorer response in later stages where a greater risk of recurrence and more easily triggered recurrence are evident. There is both evidence of both progressive neurostructural change and cognitive decline aligned with a biological process of neuroprogression that appears to mediate this process.

Results: Many psychotropic agents, especially lithium, but also antidepressants and atypical antipsychotics impact the biological elements of the neuroprogressive cascade. Several repurposed and novel agents including N-acetyl cysteine, statins and anti-inflammatory agents such as statins and metformin may have neuroprotective potential. However the agent was the greatest evidence of ability to modify the clinical course the disorder is lithium. It's also likely that a state of remission regardless of how it is achieved is neuroprotective.

Conclusion: In conclusion it is important to identify disease modification as a realistic and important clinical task and to prioritise agents and clinical strategies that facilitate that goal.

3:30 p.m. - 5:00 p.m. Debate Session I -Stephen Lawrie and Deanna Barch

WHAT HAS NEUROIMAGING DONE FOR BIOLOGICAL PSYCHIATRY?

Stephen Lawrie[1]*

[1]*University of Edinburgh*

Objective: To seek out established facts from neuroimaging studies in people with major mental illness.

Methods: A systematic review of systematic reviews, augmented by adequately powered recent studies

Results: There are highly replicated demonstrations of reduced grey and white matter, hypofrontality and increased dopamine turnover in schizophrenia. These are related to key risk factors, pathophysiologies, symptoms and outcome measures - and show potential for early detection and prognostication. Comparatively little progress has been made in other conditions or in applying these findings to benefit patients. **Conclusion:** Neuroimaging studies tend to be small, noisy and underpowered, but have advanced our understanding of schizophrenia. Co-ordinated large international studies are required in other disorders and to make progress in usefully applying neuroimaging in clinical practice.

HOW HAS NEUROIMAGING HELPED US UNDERSTAND CLINICAL PREDICTION AND TREATMENT

Deanna Barch[*1]*

[1]*Washington University in St. Louis*

Objective: The goal of this debate is to discuss the ways in which neuroimaging has or has not helped us understand effective clinical prediction or treatment outcomes or treatment selection. This will include discussion of the relatively utility of neuroimaging in predicting the development of various forms of mental illness, the magnitude of effect sizes, and what type of data are needed to enhance such predictive utility. It will also include evidence that neuroimaging metrics can help us predict who will respond to treatment and who should be offered one treatment versus another.

3:30 p.m. - 5:00 p.m.
Symposia Concurrent IV

DYSREGULATIONS OF ENDOGENOUS AMINO ACIDS AND RELATED NEUROCIRCUITS IN PSYCHIATRIC DISORDERS

Hsien-Yuan Lane, Graduate Institute of Biomedical Sciences, China Medical University

Symposium Synopsis: Antipsychotic/D2 receptor occupancy triggers multiple trans-synaptic effects. Brain connectivity analysis based on key postsynaptic density proteins' expression (i.e., Homer1) is addressed in animal modeling to disentangle antipsychotics response. Patients' brain connectivity is tackled by novel 18FDG- PET approach to explore antipsychotics' response/resistance. The role of D-amino-acids in antipsychotics-resistance is also envisioned. Animal brain connectivity, patients' in vivo connectivity and metabolic marker altogether represent a multimodal strategy to understand antipsychotics resistance and highlight putative targets for novel treatments.

D-aspartate, an atypical amino acid, acts as an NMDAR agonist. Machine learning findings suggest a link between D-aspartate dysmetabolism and schizophrenia. We investigated serum levels of L-glutamate, D-serine, glycine, L- aspartate, and D-aspartate and found that, compared to healthy controls, schizophrenia patients had decreased D-serine and altered D-aspartate levels, thus confirming abnormal NMDA signaling in schizophrenia.

In addition to lower D-serine, higher D-amino acid oxidase (DAAO) expression/activity was observed in schizophrenia patients. Inhibiting DAAO (to slow D-serine degradation and enhance NMDAR) and multi-target drugs are promising for refractory schizophrenia. Sodium benzoate, targeting DAAO activator (G72)-DAAO-NMDA pathway, antioxidants-anti-inflammatory pathway, and sex hormones, improved clozapine-resistant schizophrenia in a placebo-controlled trial.

NMDAR activation plays critical roles in preventing neurodegenerative disorders. Serum DAAO increased with cognitive decline in elderly in cross-section and prospective studies, supporting hypo-NMDAR hypothesis of Alzheimer's disease. NMDAR enhancement via inhibiting DAAO improved cognition of early-phase Alzheimer's patients. Oxidative stress also leads to neurodegeneration. Glutathione, catalase, superoxide dismutase, etc. may also be implicated in neurodegeneration. Sodium benzoate's effects on antioxidants deserves further investigation.

TRANS-SYNAPTIC AND CONNECTIVITY EFFECTS OF ANTIPSYCHOTICS: IMPLICATION FOR TREATMENT RESISTANT SCHIZOPHRENIA AND ROLE OF D-AMINO ACIDS

Andrea de Bartolomeis*[1], *Felice Iasevoli[1]*

[1]*University of Naples Federico II*

Objective: Treatment-resistant schizophrenia is a severe clinical condition affecting cognition and overall patient functioning. Therefore, there is a need to better understand the molecular basis of antipsychotics' action and to unveil new strategies for TRS. Dopamine D2 receptor occupancy, the main mechanism of action shared by all the available antipsychotics, may trigger multiple trans-synaptic effects strongly associated with dopamine-glutamate interaction. Here we address antipsychotics-dependent modulation of brain connectivity in a preclinical and clinical setting by multimodal imaging and its relevance in treatment-resistant schizophrenia.

Methods: 1) Brain connectivity analysis based on change of key glutamatergic postsynaptic density proteins' expression (i.e. Homer1, PSD.95) was analyzed in animal modeling to disentangle antipsychotics response, 2) Patients' brain metabolic pattern and connectivity were addressed by a18FDG- PET approach to explore brain metabolic related response or resistance to antipsychotics. 3)Structural MRI, TDI, and brain amino-acid in vivo quantitation by MRI spectroscopy were applied for multimodal analysis in a sample of adolescents responsive or resistant to antipsychotic treatment.

Results: 1) Brain networks showed differences in global efficiency and clustering coefficient. The" haloperidol network" showed enhanced interactivity between cortical and striatal regions, and within the caudate-putamen subdivision.

2) Restricted areas of significant bilateral relative hypometabolism in the superior frontal gyrus characterized TRS compared to non-TRS patients. Reduced parietal and frontal metabolism was associated with high PANSS disorganization factor scores in TRS ($P < .001$ voxel level uncorrected, $P < .05$ cluster level FWE-corrected).

3) significant increase of glutamate (absolute integral and ratio values) was detected in the cingulate cortex in TRS patients, compared to HCs (glutamate mean value: patients = 0.95, HCs = 0.66; $p < 0,001$; glutamate/creatine ratio: patients = 0.92, HCs = 0.6; $p < 0.001$)

Conclusion: Altogether, animal modeling of brain connectivity, in vivo brain metabolic detection, and connectivity in patients may suggest that 1) antipsychotics impact trans-synaptically the expression of glutamatergic postsynaptic density proteins and brain connectivity based on postsynaptic density immediate-early gene-based network analysis. 2) the response or resistance to antipsychotics is associated with different metabolism and connectivity in discrete brain regions.
3) Brain concentration of amino acids in patients as measured in vivo by MRI spectroscopy separate normal controls from schizophrenia patients and antipsychotic non-responsive to responsive patients. These changes may support a possible role for glutamatergic-based augmentation therapy such as D-amino acids, whose concentration was demonstrated to be altered in schizophrenia patients' post-mortem brains, enhancing the response to antipsychotics in treatment-resistant schizophrenia patients.

INVOLVEMENT OF THE PRENATAL D-ASPARTATE METABOLISM IN NEURODEVELOPMENTAL DISORDERS

Alessandro Usiello*[1], *Francesco Errico2, Tommaso Nuzzo1*

[1]*University of Naples SUN, 2University of Naples Federico II*

Objective: The atypical amino acid D-aspartate (D-Asp) acts as an N-methyl D-aspartate receptor (NMDAR) agonist. D-Asp has a peculiar spatiotemporal pattern of occurrence in the central nervous system (CNS) of mammals. Indeed, it is abundant throughout prenatal stages and decreases dramatically after birth in concomitance with the expression onset of the catabolic enzyme, D-

aspartate oxidase (DDO) Hence, D-Asp metabolism dysfunction might represent a putative candidate involved in glutamatergic-related neurodevelopmental disorders including schizophrenia (SCZ) and autism spectrum disorders (ASD). **Methods:** This symposium reviews the involvement of D-Asp metabolism dysregulation in neurodevelopmental disorders, including SCZ and autism spectrum disorders (ASD). **Results:** In line with a possible modulatory role of this endogenous NMDA agonist in modulating SCZ related phenotypes, we found that greater D-Asp brain levels in mice are able to attenuate PCP- induced PPI deficits and cerebral activity dysfunction, measured by functional magnetic resonance imaging (fMRI). In addition, consistent with its involvement in NMDA related processes, we have also shown that D-Asp modulates CNS metabolome, as assessed by nuclear magnetic resonance (NMR)- based analysis in mice brain during development. Beyond preclinical results, recently we documented the first clinical case of a young patient with severe intellectual disability (ID) and autism spectrum disorders (ASD)-related symptoms harboring a DNA duplication of 127.8 kb on chromosome 6, including the entire DDO gene. Interestingly, we found that constitutive DDO overexpression and the resulting cerebral D-Asp depletion induce cognitive and social recognition abnormalities and smaller cortical grey-matter volume in adult Ddoov mice, associated with reduced number of dorsal pallium neurons during corticogenesis. In agreement with the involvement of D-Asp in modulating cortical phenotypes, we documented that a human DDO gene variant (rs3757351) leading to lower mRNA expression in the cortex of healthy subjects is associated with increased prefrontal grey matter and prefrontal activity during working memory tasks, as measured by fMRI. Further supporting a possible involvement of D-Asp metabolism in the modulation of cortical processes related to NMDAR signaling, we recently evidenced that a machine learning hypothesis-free algorithm included D-Asp/total Asp ratio within a stable molecular cluster discriminating SCZ patients from non-psychiatric controls in the post-mortem dorsolateral PFC. Remarkably, this observation mirrors a significant 30-40% reduction in D-Asp levels found in the PFC of two post-mortem cohorts of SCZ patients, compared with non-psychiatric subjects. **Conclusion:** Altogether, our findings unveil an intriguing influence of early D-Asp metabolism in the regulation of neurodevelopmental processes and, consequently, provide a translational significance to metabolic D-Asp deregulations as a possible signature of neurodevelopmental psychiatric disorders, including SCZ and ASD.

NOVEL TREATMENT WITH MULTI-TARGETS FOR CLOZAPINE-RESISTANT SCHIZOPHRENIA: MODULATION OF NMDA RECEPTOR, D-AMINO ACIDS, AND RELATED PATHWAYS

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Objective: NMDA receptor (NMDAR) hypofunction is implicated in schizophrenia. Compared with healthy controls, schizophrenia patients had lower D-serine levels in CSF and blood, and higher blood levels of D-amino acid oxidase (DAAO) (Lin et al., Front Bioeng Biotechnol 2020) and DAAO activator (DAOA, or named G72) (Lin et al., Mol Psychiatry 2014). For discovering novel NMDAR enhancers to improve schizophrenia treatment, D-serine and other NMDAR co-agonists were examined in randomized, double-bind, placebo-controlled clinical trials (RDCs), albeit with mixed results. The second route, inhibition of glycine transporter-I, showed promising potential in improving clinical symptoms and cognitive function of schizophrenia (Lane et al., Arch Gen Psychiatry 2005; Chang et al., J Psychopharmacol et al., 2020; Fleischhacker et al., Lancet Psychiatry 2021). However, these strategies have failed in the treatment for the most resistant (clozapine [the last-line antipsychotic agent] resistant) schizophrenia patients (Goff et al., CNS Spectr 2001; Lane et al., Biol Psychiatry 2006). For potentially better treatment, the third avenue is inhibition of DAAO for slowing D-serine

degradation and thereby enhancing NMDAR function (Kuo et al., CNS Drug 2022; Cheng et al., Neuropsychopharmacology 2023). Moreover, multi-target drugs are a promising approach against refractory schizophrenia (Lin et al., Curr Drug Targets 2020). **Methods:** This symposium reviews current status of clinical trials and related mechanisms for treatment-resistant, including, clozapine-resistant schizophrenia. We also address future directions in developing better treatments for the hardest-to-treat schizophrenia. **Results:** We are the first group to discover that sodium benzoate, a pivotal DAAO inhibitor, is more efficacious than other NMDAR enhancers (Chang et al., J Psychopharmacol et al., 2019; Lin et al., Int J Neuropsychopharmacol 2022). In initial RDCs, sodium benzoate improved cognitive function of patients with chronic schizophrenia, no matter it improved clinical symptoms or not (Lane et al., JAMA Psychiatry 2013, Lin et al., World J Biol Psychiatry 2017). Later, benzoate also improved both positive and negative symptoms of clozapine (the last-line antipsychotics)-resistant schizophrenia patients in a RDC (Lin et al., Biol Psychiatry 2018). While the underlying mechanisms require more studies (Huang et al., Neurochem Res 2023), sodium benzoate has been found to possess multi- targets on the NMDA pathway, the antioxidants-anti-inflammatory pathway, and sex hormones (Lin et al., Biol Psychiatry 2018; Lin et al., JAMA Netw Open 2021; Lane et al., Psychiatry Clin Neurosci 2023). In addition to sodium benzoate, other DAAO inhibitors are promising; for example, luvadaxistat was found to be able to improve cognitive function of schizophrenia patients (Kuo et al., CNS Drugs 2022). Furthermore, combination of benzoate and brain stimulation deserves more studies too (Lane et al., Psychiatry Res 2023). **Conclusion:** If these findings can be reconfirmed, modulation of NMDAR, D-amino acids, and related pathways may instill hope for the treatment of the most resistant schizophrenia. However, 6-week benzoate treatment (at doses of 1 and 2 gm/day) still didn't improve cognitive function of clozapine- resistant patients (Lin et al., Biol Psychiatry 2018). More novel approaches are needed to develop effective therapies for the cognitive dysfunction in clozapine-resistant patients (Lin and Lane, Schizophr Res 2023 [Invited Commentary]).

THE CHANGES OF D-AMINO ACIDS AND NMDA RECEPTOR MODULATORS IN NEURODEGENERATION

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Objective: Glutamate NMDA receptor (NMDAR) activation plays a critical role in cognitive function. Dysregulation of NMDAR is the core of neurodegenerative mental disorders (Lin et al., Curr Pharm Des 2014). As the agonist or co-agonists of NMDAR, D-glutamate, D-serine, and D-alanine differ in their roles in cognitive decline in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) (Lin et al., Pharmacol Biochem Behav 2019). The clinical implications of the changes of D-amino acids and modulators of NMDAR in neurodegeneration deserve studies.

Methods: This symposium reviews the roles of D-amino acids in neurodegeneration as well as the effects of NMDAR modulators in neurodegenerative disorders.

Results: Previously, D-serine levels have been found to be altered in the AD patients. We recently found that peripheral blood levels of D-glutamate were associated with cognitive impairment, therefore a potentially suitable peripheral biomarker for MCI and AD (Chang et al., Psychopharmacol 2021). Of note, serum D-amino acid oxidase (DAAO) levels were significantly associated with D-glutamate and D-serine levels (Lin et al., Sci Rep 2017). Further, DAAO levels increased with the severity of the cognitive deficits in elderly individuals in a cross-section study (Lin

et al., Sci Rep 2017) and a prospective study (Lin and Lane, Int J Neuropsychopharmacol 2022), thereby supporting the hypo-NMDAR hypothesis of Alzheimer's disease (AD). DAAO activator (DAOA, or G72) levels also increase in patients with early phase of AD (Lin et al., Sci Rep 2019). Combination of G72 and cystine/glutamate antiporter SLC7A11 in blood can sensitively and specifically diagnose AD (Lane and Lin, Int J Neuropsychopharmacol 2022). Glutathione, catalase, superoxide dismutase and other endogenous antioxidants may also play important roles in the process of neurodegeneration (Chiang et al., Clin Psychopharmacol Neurosci 2021; Lin and Lane, Antioxidants 2021). NMDAR enhancement via inhibiting DAAO activity by sodium benzoate can improve cognitive function of patients with early-phase AD or late-life depression (Lin et al., Biol Psychiatry 2014; Lane et al., Psychiatry Clin Neurosci 2022; Lin et al., Int J Neuropsychopharmacol 2022) and alter brain activity in MCI patients (Lane et al., Int J Neuropsychopharmacol 2021), while raising blood levels of two endogenous antioxidants, glutathione and catalase (Lane et al., Psychiatry Clin Neurosci 2022). Sodium benzoate also improved cognitive function of women with behavioral and psychological symptoms of dementia (BPSD) with increased estradiol to follicle-stimulating hormone ratios in blood (Lin et al., JAMA Netw Open 2021).

Conclusion: If these findings can be reconfirmed, several potential biomarkers can aid in the diagnoses of neurodegenerative disorders and modulation of NMDAR through inhibition of DAAO may be a novel approach for the treatment of these disorders. In addition, the effects of sodium benzoate on endogenous antioxidants and sex hormones and their roles in precision medicine deserve more studies.

IMMUNE-METABOLIC DYSFUNCTION IN MENTAL DISORDERS: AN UPDATE ON CURRENT EVIDENCE

Ishrat Husain, Centre for Addiction and Mental Health, University of Toronto

Symposium Synopsis: There has been increasing interest in the role of immune-metabolic dysfunction in the pathophysiology of mood and psychotic disorders. Replicating evidence suggests that individuals with mental disorders are more prone to chronic inflammatory illnesses, and metabolic syndrome. Even in the absence of physical illness, individuals with mental disorders display altered levels of peripheral inflammatory markers. Given these associations, several clinical trials have evaluated repurposed agents targeting immune-metabolic pathways in depression, bipolar disorders and psychosis, with mixed results. In order to advance the field of immunopsychiatry, it is important to identify specific subtypes of mental disorders that would benefit from these repurposed agents. Further research is needed to determine specific behavioural symptom subsets that are prevalent among patients with mental disorders and concurrent immune-metabolic dysfunction. The aim of the proposed symposium is to provide an update on evidence for immune-metabolic subtypes of mood and psychotic disorders. We will present synthesized data from observational studies that provide insights into potential pragmatic molecular and genetic biomarkers of "inflamed" subtypes of depression and psychosis. In addition we will present results from recent clinical trials of lipid lowering agents and anti-inflammatory drugs as add-on treatments for treatment-resistant depression and schizophrenia-spectrum disorders. Finally, we will make recommendations for innovative trial designs that may enhance clinical translation of transdiagnostic treatments that target immune-metabolic dysfunction across mental disorders.

UNDERSTANDING THE POTENTIAL ROLE OF INFLAMMATORY MARKERS IN NEUROPROGRESSION ACROSS THE CLINICAL STAGES OF BIPOLAR I DISORDER

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Objective: In Bipolar Disorder (BD), illness progression has been linked to worse treatment outcomes and cognitive/functional impairment. Multiple instances of the disease may have the ability to cause neuronal systems to change permanently, according to the kindling model. In contrast to the West, the clinical course of BD-I in India is mania-dominant and is linked to increased intellectual loss and poor functionality. Our study was planned to examine and compare the serum levels of immuno- inflammatory, across different clinical stages of BD-I High risk, early BD, and multiple episode BD (stage 1-3) and healthy controls (HC) **Methods:** Our research was cross-sectional and involved the following groups: high-risk participants (BD-I-Stage 1), early BD-I (First episode), established BD-I (Stage 3), and age- and gender-matched healthy controls (HC). The inflammatory markers that we compared across groups were Interleukin (IL)-1β, IL-6, and Tumor necrosis factor (TNF)-α measured on a Bioplex 200 platform utilizing a multiplex suspension array and soluble TNF receptors 1 and 2 (sTNFR-1 and 2) measured using sandwich enzyme-linked immune-sorbent assay technique. SPSS-16/R software was used to do the statistical analysis. Kruskal Wallis was used to compare the inflammatory markers. **Results:** We recruited a total of 172 subjects, with 43 in each group. In the total sample, we had 100 males and 72 females. There was no group difference in gender noted. The age at assessment there was a group difference (p LESS THAN 0.001), the ME group had a higher age than the other three, who did not differ from each other. The two BD groups did not show any difference in the age of illness onset or the onset of the first episode of mania (p=0.56), family history of psychiatric illness (p=0.11), and duration of remission (p=0.10). There was a significant difference in the duration of illness the ME group by definition had a longer duration of illness compared to FEM ($p < 0.001$). In terms of the inflammatory markers, IL-1β (p=0.66) and TNF-α (p=0.44) levels did not show any group difference. IL-6 levels were significantly higher among the ME and FE-BD groups compared to the controls (h=11.26, p=0.01). ME group also had higher levels than the HR group. sTNF- R1 levels were significantly higher among the ME group compared to the FE, HR, and control groups (h=14.35, p=0.002). These three groups did not show any difference. sTNF-R2 levels were significantly higher (h=29.87, $p < 0.001$) in the patient group (ME and FEM) compared to the non-patient group (HR and HC). **Conclusion:** The important findings of the increased levels of sTNFR-1 in ME compared to FE suggest that the higher the no of manic episodes, the higher the levels of inflammatory markers like sTNFR- 1. The high-risk group did not show any difference from the control group which suggested that probably the inflammatory pathway gets involved after the disease onset. We also noted increased levels of sTNFR-2 in the BD patients compared to high-risk and controls, but no difference between the ME and FE groups. These two are important proteins that are activated in the process of apoptosis (cell death). This is one of the mechanisms of how neuroprogressive changes occur in the brain. This study emphasizes the need for longitudinal studies to evaluate these markers across the stages of BD and establish them as biomarkers of neuroprogression and staging.

NEUTROPHIL EXTRACELLULAR TRAPS (NETS): A NOVEL CELLULAR-BASED MECHANISM IN SCHIZOPHRENIA AND THE IMPLICATIONS OF EARLY-LIFE ADVERSITIES

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Objective: Previous studies using blood cytokines to stratify patients with schizophrenia suggest that only a subset presents a low-grade inflammatory state. However, these studies have not addressed whether environmental factors such as childhood maltreatment contributed to identifying

inflammatory clusters. Moreover, a neutrophil-related mechanism (NETs) has never been investigated in the field. We investigated NETs as a novel biological mechanism in early schizophrenia and their role together with interleukin-(IL-6) and childhood maltreatment in identifying cluster subgroups. **Methods:** Clinical study: We used data available from the STREAM study, a case-sibling-control investigation conducted in the Ribeirão Preto catchment area (São Paulo, Brazil). The sample included individuals with early-stage schizophrenia spectrum (n=78), sex and age-matched controls (n=78), and unaffected siblings of patients (n=25). Childhood maltreatment was evaluated using the Childhood Trauma Questionnaire. NETs and IL-6 in plasma were evaluated using the Quant-iT PicoGreen kit and multiplex, respectively. Fresh neutrophils were isolated from healthy donors to test the effect of antipsychotic drugs (haloperidol or risperidone) on NETs release in vitro. Group differences on NETs and IL-6 were evaluated using general linear models with Bonferroni post-hoc, adjusted for sex, body mass index (BMI), tobacco smoking, and psychoactive substance use. Two-way ANOVA with Bonferroni post-hoc was used to test the effect of antipsychotics on NETs in vitro.To identify clusters, we applied unsupervised two-step clustering analyses with Bayesian Criterion to estimate the maximum number of clusters after integrating values of NETs, IL-6, and childhood maltreatment scores. Rodent model: Juvenile male Sprague-Dawley rats (postnatal day, PND 24) were exposed to an adolescent early stress protocol (a combination of daily inescapable footshock from PD31-40, and three restraint stress sessions, PD31, 32, and 40) or left undisturbed (controls). At PN51, NETs and IL-6 were evaluated in serum. We also measured levels of NETs released from fresh neutrophils isolated from rats' bone marrow. **Results:** We found increased NETs levels in patients with early schizophrenia compared to their unaffected siblings and community controls ($F=50.79, df=2, p < 0.001$). Using an in vitro assay, we showed that haloperidol and risperidone do not induce but inhibited NETs release from stimulated neutrophils. Using unsupervised two-step clustering analysis, we identified two main clusters; childhood maltreatment scores and NETs were the most important variables contributing to cluster separation (high-CL1 and low-CL2). Patients with high-CL1 (61.5%) had significantly higher childhood maltreatment scores ($F=26.23, df=5, p < 0.001$), NETs ($F=25.17,5, p < 0.001$), and IL-6 ($F=3.87, df=5, p < 0.002$) levels than the remaining groups. Using a rat model based on stress exposure, we found that adolescent stressed rats had higher NETs ($t16=5.18, p < 0.001$) and IL-6 ($t10=6.33, p < 0.001$) levels in serum compared to non-stressed rats, with a tendency to produce more NETs from the bone marrow. **Conclusion:** We demonstrate for the first time a novel cellular mechanism in schizophrenia that suggests neutrophils are in an active and functional state. We further suggest that NETs and early stress should be considered in future studies aiming to identify immune biological subgroups for more personalised treatments.

EXPLORING IMMUNE-INFLAMMATORY MARKERS IN RESPONSE TO ADJUNCTIVE MINOCYCLINE TREATMENT FOR DEPRESSION.

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Deakin University

Objective: These series of studies aimed to explore the underlying biological response reflecting the clinical improvement seen in participants who took part in a clinical trial of adjunctive minocycline. Markers in the kynurenine pathway and associated inflammatory markers were explored.

Methods: A randomised placebo-controlled trial of adjunctive minocycline (200 mg/day) for people with major depressive disorder (n=71) was conducted and blood samples were collected at baseline

and the end of the treatment phase (week 12). Serum samples were analysed by the Karolinska Institutet and Deakin University to determine levels of biological makers. **Results:** Following correction for false discovery rates, changes in complement C3, IL-1Ra, IL-8/CXCL8, and ICAM-1 were found to be associated with changes in depression scores following adjunctive minocycline treatment. We have new data available on RAGE pathways that we expect to also present at the meeting. **Conclusion:** There has been considerable exploration of individual markers of treatment response in depression. This has led to heterogenous outcomes and difficulties in understanding the specificity of markers in predicting response to treatment. This study used a multi-marker approach to explore the kynurenine pathway to provide a more comprehensive understanding of the treatment response to adjunctive minocycline treatment. These studies provide valuable information alone, but moreover are contributing to a larger study encompassing multipole markers, disorders and therapeutic agents.

EFFICACY OF METHOTREXATE POINTS TO IMMUNE DYSFUNCTION IN PSYCHOSIS

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Objective: There is growing evidence implicating inflammatory processes in the pathogenesis of schizophrenia. NMDA receptor encephalitis presenting as schizophrenia suggests the possible role of cell-mediated immune processes. Several inflammatory cytokines including IL-2, IFN-gamma, TNF-alpha and soluble IL-2 receptor may be elevated in schizophrenia relapse and reduced in remission. In this presentation we will summarise evidence for the use of novel anti-inflammatory agents in the treatment of schizophrenia with a focus on methotrexate.
Methods: We tested if low-dose methotrexate as used in the treatment of systemic autoimmune disorders would be tolerable and effective in people with schizophrenia in a feasibility double-blind randomized control trial. Ninety-two participants within 5 years of schizophrenia diagnosis were randomised to receive once weekly 10mg oral methotrexate (n = 45) or matching placebo (n = 47) both with daily 5mg folic acid, in addition to treatment as usual for 12-weeks.
Results: There were eight dropouts per group. Side effects were non-significantly more common in those on methotrexate and were not severe. One person developed leukopenia. Positive symptom scores improved more in those receiving methotrexate than placebo (β = −2.5; [95% CI −4.7 to −0.4]), whereas negative symptoms were unaffected by treatment (β = −0.39; [95% CI −2.01 to 1.23]).
Conclusion: We conclude that further studies are feasible but should be focussed on subgroups identified by advances in neuroimmune profiling. Methotrexate is thought to work in autoimmune disorders by resetting systemic regulatory T- cell control of immune signalling; we show that a similar action in the CNS would account for otherwise puzzling features of the immuno-pathogenesis of schizophrenia.

INNOVATION IN OPIOID AGONIST THERAPY AND WITHDRAWAL MANAGEMENT

Marc Vogel, Psychiatric University Clinics Basel

Symposium Synopsis: The ongoing epidemic of opioid use disorder (OUD) remains one of the biggest public health problems in the world. Recent years have brought rising numbers of opioid overdose deaths particularly in North America but also in European countries and Australia. The increasing role of ultrapotent opioids such as fentanyl challenges conventional treatment practice. Opioid agonist therapy (OAT) constitutes the treatment of choice but has often not been able to reach vulnerable

populations. Furthermore, retention rates in many parts of the world remain insufficient. The implementation of innovative and patient-centered measures is needed. **Methods:** In this symposium, we present promising new and innovative methods aiming to improve withdrawal management, induction and delivery of OAT. **Results:** Opioid agoinists have different side effect profiles which may allow a patient-centered choice of medication. Buprenorphine microdosing is an innovative approach suitable for inpatient and outpatient initiation of buprenorphine OAT without the need for preceding withdrawal symptoms as in conventional induction. Symptoms inhibited fentanyl induction is an intervention to determine opioid tolerance and rotate patients on a dose of full mu-opioid-agonists suitable for OAT in the course of one day. Nasal diacetylmorphine is a new treatment option for patients not responding to oral OAT, or patients in injectable OAT transferring to a less harmful alternative. **Conclusion:** The OUD epidemic requires an expansion and further development of treatment options. There are several promising innovations in OAT suitable to improve withdrawal symptoms, treatment induction and delivery, expanding treatment access for populations not reached with current treatment methods.

NASAL OPIOID AGONIST TREATMENT

Marc Vogel**1*

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Psychiatric University Clinics Basel

Objective: Not all patients with opioid use disorder respond to oral opioid agonist treatment (OAT). Therefore, other routes of administration have been successfully introduced, e.g. injectable or smokable diacetylmorphine. However, these routes are associated with a higher risk of adverse events. Nasal OAT is a new treatment option likely associated with fewer risks and suitable to reach patients primarily sniffing opioids but not stabilizing in oral OAT.

Methods: We present the method of nasal application and data from an ongoing multicenter prospective observational cohort study accompanying the introduction of nasal OAT in Switzerland's heroin assisted treatment (HAT) centers.

Results: As of 2023, 139 patients of 16 centers initiated nasal HAT, the majority of which were male. Main reason for switching to the nasal route were sniffing being the preferred route of administration, and patients on diacetylmorphine (heroin) tablets desiring a more rapid onset of effect. At 4 and 52 weeks, 88% and 53% respectively were still prescribed the nasal route of administration. Additional substance use remained largely unaltered. Adverse events were rare, and treatment satisfaction was high among those remaining in the nasal route.

Conclusion: Nasal OAT seems to be a viable treatment option for a subpopulation of patients in HAT. It is associated with few adverse events. With switching routes of administration being common in Swiss HAT, patients with higher satisfaction remained with the nasal route. Further research is required on optimizing the application method and to determine which subpopulaton is likely to benefit from nasal OAT.

RAPID LOW-DOSE BUPRENORPHINE INDUCTIONS & SYMPTOM-INHIBITED HYDROMORPHONE & FENTANYL INDUCTIONS

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1Vancouver General Hospital

Objective: The high prevalence of fentanyl and its analogues in the unregulated drug supply has led to tragic levels of mortality and morbidity in North America and Europe, posing challenges in the clinical management of opioid use disorder due to escalating opioid tolerances. We will share our experiences with the development, implementation, and evaluation of innovative opioid withdrawal

management and opioid agonist treatment (OAT) approaches in Vancouver, the epicentre of the overdose crisis in Canada. **Methods:** We will present our low-dose buprenorphine induction protocols, which involve the administration of small, frequent does of buprenorphine, eliminating the need for a prior period of withdrawal and opioid abstinence. We will also present our pharmacokinetically-guided protocols utilizing hydromorphone and fentanyl to manage withdrawal, facilitate rapid methadone and slow- release oral morphine initiation, and promote adherence to medical treatment. **Results:** We will teach our protocols utilizing practical real-life cases and patient testimonial videos. We will share our results from clinical trials and retrospective chart reviews, and our experiences in the implementation of our protocols. **Conclusion:** Participants will gain a comprehensive understanding of the current landscape of opioid use disorder, overdose fatalities, and withdrawal management and OAT approaches to treat patients who use unregulated fentanyl and its analogues.

SIDE EFFECTS OF DIFFERENT AGONISTS IN OPIOID AGONIST TREATMENT - SYSTEMATIC REVIEW AND META-ANALYSIS

Maximilian Meyer**1*

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Psychiatric University Clinics Basel

Objective: Opioid agonist treatment (OAT) is the treatment of choice for opioid use disorder. Most often, methadone or buprenorphine are used. However, coverage rates are fairly low and conventional OAT does not reach large parts of the target population. In order to expand treatment access and allow a more patient-centered approach, other opioid agonists such as diacetylmorphine or slow-release morphine, and other routes of administration (injectable, depot) have been introduced. With similar retention rates, the choice of opioid agonist in the future will be guided by the side effects profile.

Methods: We present data of a meta-analysis of side effects in randomized controlled trials of different opioid agonists for treatment of opioid use disorder.

Results: We identified 181 studies, 25 of which were included for potential meta-analysis. Reported opioid agonists were methadone, LAAM, methadyl acetate, buprenorphine, buprenorphine/naloxone, slow-release morphine (SROM), diacetylmorphine, hydromorphone, opium tincture. Where groupe meta-analysis was possible, buprenorphine (all formulations combined) was associated with less risk of sedation than methadone (RR 0.68; 95% CI 0.56-0.82), SROM with higher risk (0.63; 0.58-0.69). Methadone had a lower risk of nausea (0.56; 0.37-0.85) and sweating than methadyl acetate (0.73; 0.59-0.90). Some known side effects were not systematically reported although highly relevant for clinical practice, e.g. sexual dysfunction or QTc-prolongation.

Conclusion: Overall, the quality of side effect reporting in many studies was low and insufficient. Our results challenge some traditional clinical teaching about side effects (e.g. in direct comparison, the risk for sweating was not lower for buprenorphine than for methadone). Future research should actively investigate side effects given their importance for a patient-centered treatment decision. This is particularly true for side effects such as sexual dysfunction and QTc-prolongation, which have high clinical relevance but were not systematically reported at all.

APPLYING PERSONALIZED MEDICINE TO BIPOLAR DISORDER

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: Patients with bipolar disorder (BD) urgently need personalized, data-driven treatments guided by empirically validated predictive biomarkers. In this symposium, we will provide an inspiring overview of cutting-edge, biomarker-driven approaches to precision medicine in BD.

These will include biomarkers as predictors of treatment response, and the application of cutting-edge network analysis methods. First, markers of the gut-brain axis (intestinal permeability, intestinal inflammation and microbiome) will be reviewed as potential biomarkers of treatment response to probiotics. Second, gene expression studies to evaluate CHOP, a pro-apoptotic endoplasmic reticulum stress marker, and ELISA assays to assess mesencephalic astrocyte-derived neurotrophic factor (MANF) levels in BD patients and controls will be reviewed as biomarkers of response to intranasally administered MANF. MANF is an ER resident protein that promotes cellular resilience. Third, an overview of Th17 cells as a potential target for precision medicine approaches will be reviewed. Finally, causal discovery modeling (CDM) will be introduced as a method for interrogating mania and depression symptom networks to identify high-value treatment targets and BD subtypes. CDM uses a combination of graph theory and machine learning to identify central symptoms – those with the densest causal relationships to other symptoms in symptom networks. It offers the promise of a data-driven approach to determining the richest treatment targets and identifying subgroups of patients with different network structures. The symposium will conclude with a discussion of the promise and challenges of data driven discovery of treatment biomarkers and potential future directions.

USING CAUSAL DISCOVERY MODELING TO INTERROGATE MANIC AND DEPRESSIVE SYMPTOM NETWORKS IN BIPOLAR DISORDER

David Bond**1*, *Rahul Mehta2, Kathleen Miley3, Erich Kummerfeld4*

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Objective: Network theory proposes that psychiatric syndromes like depression and mania are networks of causally interacting symptoms. Depression and mania are triggered when the activation of one symptom leads to activation of the network via the web of causal relationships between symptoms. Feedback loops between symptoms lead to persistent network activation, making episodes self-sustaining. Persistent network activation is most likely in dense (highly interconnected) networks and when central symptoms (those with numerous connections to other symptoms) are activated.

Methods: Causal discovery modelling (CDM) combines causal modeling theory, graph theory, statistics, and machine learning to generate inferences about causal relationships between symptoms in symptom networks. We used CDM to identify causal relationships in manic and depressive symptom networks. We searched the National Database of Clinical Trials for studies that used the Young Mania Rating Scale and Montgomery-Asberg Depression Rating Scale to measure manic and depressive symptoms in bipolar disorder. We used the Greedy Fast Causal Inference (GFCI) algorithm, implemented in Tetrad 6.9, to learn a partial ancestral graph (PAG) of causal relationships.

Results: We obtained data from 19 studies (N=7269). The manic and depressive symptom networks were both densely connected, especially the depressive network. Feedback loops were identified in both networks. Irritability was an important bridge symptom with dense causal relationships to both the manic and depressive networks.

Conclusion: These findings suggest hypotheses about how causal relationships in manic and depressive symptom networks lead to the perpetuation of mania and depression; and why mania and depression can co-occur.

INTRANASAL MESENCEPHALIC ASTROCYTE-DERIVED NEUROTROPHIC FACTOR (MANF) AS A NOVEL TREATMENT FOR BIPOLAR DISORDER

Benicio Frey**1*, *Mohammad Ali2, Bianca Wollenhaupt-de-Aguiar2, Todd Hoare2, Ram Mishra2*

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Objective: Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an endoplasmic reticulum (ER) resident protein that promotes cellular resilience through modulation of ER stress response. We have recently found that lithium promotes ER homeostasis by increasing MANF gene expression (Abu-Hijleh et al., 2021). Our objective is to develop a new treatment option for individuals with bipolar disorder (BD) using hydrogel intranasal spray to administer MANF, and to further investigate the ER stress response pathway in the blood and postmortem brain tissue of individuals with BD.

Methods: Intranasal delivery of MANF was developed using functionalized starch nanoparticle carriers integrated into a mucoadhesive nanoparticle network hydrogel spray. Intranasal MANF is being tested in an animal model of mania. Gene expression was used to evaluate CHOP, a pro-apoptotic ER stress marker, and ELISA assays to assess MANF levels in the serum of 40 individuals with BD and 55 healthy controls, as well as in postmortem hippocampus brain tissues from 20 BD and 19 controls.

Results: The intranasal delivery of MANF is currently being evaluated in animal models to determine the efficacy of nose-to-brain delivery. Serum MANF protein levels were reduced in individuals with BD in a current depressive episode when compared to individuals with BD in euthymia (p=0.013) and controls (p=0.031). CHOP expression was increased in postmortem hippocampus brain tissues of individuals with BD (P LESS THAN 0.05).

Conclusion: These findings provide further evidence of the association between ER stress and BD.

INTESTINAL MARKERS TO PREDICT THE TREATMENT OUTCOME OF PROBIOTICS IN BIPOLAR DISORDER AND PSYCHOTIC DISORDERS

Magdalini Ioannou**1*, *Jenny Borkent1, Sergio Andreu-Sánchez1, Jingyuan Fu1, Iris Sommer1, Bartholomeus C.M. Haarman1*

[1]*University Medical Center Groningen*

Objective: Abnormal immune responses have been reported in patients with bipolar disorder (BD) and psychotic disorders (PD). What lies at the root of the immune system aberrations, however, is still unclear. Intestinal permeability aberrations and inflammation, along with alterations in the intestinal microbiota, may be a significant factor driving the immune dysregulation in these disorders. Probiotics are thought to be promising candidates to improve patients' symptomatology and functioning using lifestyle interventions. What makes these interventions especially relevant is that there are rational methods to personalize their application with biomarkers that measure intestinal inflammation, microbiome, and permeability.

In a novel randomized controlled trial (RCT) (GUTS, SMRI 18T-004, ZonMw 636320010), we investigate whether intestinal permeability improving probiotics influence symptom severity and cognition in patients with BD or PD, and whether we can personalize treatment with measurements of intestinal inflammation, permeability, and microbiome.

In this presentation we will present for the first time the baseline measurements of this thought-provoking study.

Methods: For this analysis, the baseline measurements of 130 patients that participate in the GUTS RCT and 130 healthy controls matched for age, sex, BMI and income were investigated. Measurements of intestinal inflammation (fecal calprotectin, alpha-antitrypsin), intestinal permeability (LPS binding protein, soluble CD14, serum zonulin and fecal zonulin) were performed using standard ELISA procedures. Intestinal microbiome analysis was performed using metagenomic shotgun sequencing.

Results: Analysis results will be available in March 2023 and will be presented for the first time during the conference. **Conclusion:** The results will be discussed in reflection to the applicability for future treatment personalization for gut targeting treatments for BD, e.g. probiotics, prebiotics and diet interventions.

TH17 CELLS: A POTENTIAL TARGET FOR PRECISION MEDICINE APPROACHES FOR BIPOLAR DISORDER

Carmen Schiweck*[1], *Magdalini Ioannou[2], Benno Haarman[2], Hemmo Drexhage[3]*

[1]Goethe University Frankfurt, [2]University Medical Center Groningen, [3]Erasmus MC Rotterdam

Objective: Patients with Bipolar Disorder (BD) have increased numbers of the pro-inflammatory, and potentially pathogenic T helper (Th)-17 cells (1,2). Interestingly, interleukin (IL)-17A, the major cytokine produced by Th17 cells, has also been associated with suicidality and inflammation in major depressive disorder, but to our knowledge this association has not yet been explored in BD. In addition, it has been shown that short chain fatty acids such as butyrate can reduce IL-17A production by Th17 cells and thereby reduce their pathogenicity, but to date, the effect on Th17 cells of patients with BD is unknown. The aim of this research was two-fold: first, we aimed to explore the association of Th17 cells with specific symptoms of patients with BD for the first time. Second we aimed to investigate the effect of short chain fatty acids on IL-17 production in Th17 cells of patients with BD and healthy controls to their efficacy as new and innovative, potential immunomodulatory strategy.
Methods: Th17 cell numbers and suicidality were assessed in 201 patients with a diagnosis of BD and 140 controls of the MOODINFLAME and GEPRO cohorts. Th17 cells were measured using fluorescence-activated cell sorting and confirmation of BD diagnosis and suicidality was assessed with the MINI neuropsychiatric Interview. Analysis of covariance was performed on Th17 cells, with suicidality as grouping variable, age, sex and BMI as covariates. For the in-vitro experiment, peripheral blood mononuclear cells (5 patients with BD, 8 controls, data collection ongoing) were harvested using Ficoll density gradient centrifugation. Naïve CD4+ T cells were extracted, cultured and differentiated to Th17 cells. IL-17 production was measured in cells exposed to butyrate or only medium.
Results: Patients with BD had higher Th17 cells compared to controls. High risk of suicide was rare in this predominantly euthymic patient group. Results regarding stratification according to sample characteristics including suicidality are currently being analysed and will be presented at the conference for the first time. Preliminary results of cell culture experiments revealed a strong reductive effect of butyrate on IL-17 production in Th17 cells (p LESS THAN 0.05).
Conclusion: Th17 cells are higher in patients with BD, and possible associations with suicidality will be presented. Results on short chain fatty acid exposure indicate a potential beneficial role on Th17 cell pathogenicity.
References: 1. Becking K, Haarman BCM, Grosse L, Nolen WA, Claes S, Arolt V, et al. (2018): The circulating levels of CD4+ t helper cells are higher in bipolar disorder as compared to major depressive disorder. J Neuroimmunol 319: 28–36.
2. Vogels RJ, Koenders MA, van Rossum EFC, Spijker AT, Drexhage HA (2017): T Cell Deficits and Overexpression of Hepatocyte Growth Factor in Anti-inflammatory Circulating Monocytes of Middle-Aged Patients with Bipolar Disorder Characterized by a High Prevalence of the Metabolic Syndrome. from Frontiers in Psychiatry, vol. 8. Retrieved https://www.frontiersin.org/articles/10.3389/fpsyt.2017.00034

PERSONALIZED TREATMENT OF BIPOLAR DISORDER

Martin Alda, Dalhousie University

Symposium Synopsis: There is a growing recognition that management of psychiatric disorders needs to be tailored to individual patients and their clinical and biological profiles -- in contrast to the common practice of trial-and-error. To optimize treatment decisions, psychiatry needs to identify reliable markers of diagnosis, relapse risk, and treatment response. Bipolar disorder is among the conditions with perhaps the greatest need for improved management: it is relatively prevalent, affects young people and runs a lifelong course. Poorly stabilized illness leads to a high risk of suicide and functional decline. The most recent treatment guidelines by CANMAT and ISBD recommend nine first-line and seven second-line maintenance treatments. However, there are no reliable guidelines as to how to choose among these options. The treatment decisions are not easy due to the highly variable, capricious clinical course of the illness, its heterogeneity, as well as poorly understood iatrogenic effects of certain medications. In this symposium, we will present data from the most promising modalities to guide the selection of long-term treatment. These include clinical and genomic patient profiles (M. Alda), electronic digital clinical monitoring (A. Ortiz), lithium magnetic resonance spectroscopy (D. Cousins), and epigenetic and microbiome measures (C. Pisanu).

CLINICAL AND GENOMIC DATA CAN INFORM TREATMENT DECISIONS IN BIPOLAR DISORDER

Martin Alda**1*, *Abraham Nunes1, William Stone1, Paul Grof2, Mirko Manchia3, Janusz Rybakowski4, Leonardo Tondo5*
[1]Dalhousie University, 2University of Toronto, 3University of Cagliari, 4University of Poznan, 5Centro Lucio Bini

Objective: Historically, the search for predictors of response to long term treatment of bipolar disorder (BD) started with clinical variables. After more than five decades of research, the most promising data are those related to the outcome of lithium maintenance. A number of clinical and family history measures associated with the outcome of lithium treatment emerged, many supported by replication studies and meta-analyses (e.g. Hui et al. Acta Psychiatrica Scand 2020). Yet, none of these variables have been tested for their predictive power. Here, we report the results of studies assessing the predictive power of clinical and genomic features.
Methods: In a large multi-site study of lithium treated patients, we used random forest machine learning algorithm to test of out sample predictive power of more than 150 clinical, demographic and family history variables in 1266 patients with BD. A total of 321 patients had available whole-genome genotypes. Using 47,465 directly genotyped SNPs we were able to differentiate prototypical responders (R) and nonresponders (NR) to lithium. Finally, we tested the model trained on lithium response in patients with data on their response to the anticonvulsants lamotrigine and valproate.
Results: Our results showed satisfactory predictive power of the clinical data (AUC ~ 0.8) to differentiate R and NR to lithium. Completely episodic clinical course was the hallmark of lithium responsiveness; a number of additional clinical features predicted the (non)response to both lithium and anticonvulsants. Whole genome genotypes discriminated poorly the two groups of patients in general (AUC ~ 0.57) but had an excellent power to differentiate clinically prototypical R and NR (AUC ~ 0.88). Gene ontology analyses identified four gene groups contributing most of the differentiation; these include G-protein coupled receptor genes, and genes in the muscarinic, amyloid secretase, and histaminergic gene families.
Conclusion: Our results support the possibility of using a combination of clinical and genomic data for optimizing long term treatment of BD once accounting for the disease heterogeneity.

IDENTIFYING PATIENT-SPECIFIC BEHAVIORS TO UNDERSTAND ILLNESS TRAJECTORIES AND PREDICT INDIVIDUAL TRAJECTORIES IN BIPOLAR DISORDER USING PASSIVE SENSING

Abigail Ortiz*[1], *Clara Park[2], Christina Gonzalez-Torres[2], Martin Alda[3], Daniel Blumberger[1], Rachael Burnett[2], Ishrat Husain[1], Marcos Sanches[2], Benoit Mulsant[1]*

[1]University of Toronto, 2Centre for Addiction and Mental Health, 3Dalhousie University

Objective: Several studies have reported on the feasibility of electronic (e-)monitoring using computers or smartphones in patients with mental disorders, including bipolar disorder (BD). While studies on e-monitoring have examined the role of demographic factors, such as age, gender, or socioeconomic status and use of health apps, to our knowledge, no study has examined clinical characteristics that might impact adherence with e-monitoring in patients with BD. Here, we describe our results on adherence to e-monitoring in patients with BD who are participating in an e-monitoring study and evaluated whether demographic and clinical factors would predict adherence to (i) daily self-rating scales; (ii) weekly self-rating scales or (iii) wearable use.

Methods: Eighty-seven participants with BD in different phases of the illness were included. Patterns of adherence for wearable use, daily and weekly self-rating scales over 15 months were analyzed to identify adherence trajectories using growth mixture models (GMM). Multinomial logistic regression models were fitted to compute the effects of predictors on GMM classes.

Results: Overall adherence rates were 79.5% for the wearable; 78.5% for weekly self-ratings; and 74.6% for daily self-ratings. GMM identified three latent class subgroups: participants with (i) excellent; (ii) good; and (iii) poor adherence. Women, participants with a history of suicide attempt, and those with a history of inpatient admission were more likely to belong to the group with good adherence.

Conclusion: Participants with higher illness burden (e.g., history of admission to hospital, history of suicide attempts) have higher adherence rates to e-monitoring. They might see e-monitoring as a tool for better documenting symptom change and better managing their illness, thus motivating their engagement.

ESTABLISHING MULTICENTRE MULTINUCLEAR BRAIN LITHIUM IMAGING IN BIPOLAR DISORDER

David Cousins*[1], *Pete Thelwall[1], Fiona Smith[1], Karthik Chary[1], Letizia Squarcina[2], Paolo Brambilla[2], Marie Chupin[3], Emmanuelle Gourieux[3], Fawzi Boumezbeur[4], Edouard Duchesney[4], R-LiNK Group[5], Frank Bellivier[6]*

[1]Newcastle University, 2Università degli Studi di Milano, 3CATI (Centre pour l'Acquisition and le Traitement des Images), 4Neurospin, CEA, 5https://rlink.eu.com, 6Université de Paris

Objective: The R-LiNK initiate is conducting a multicentre, multinational longitudinal study seeking to identify biomarkers/biosignatures capable of predicting response to lithium treatment in bipolar disorder. Brain lithium distribution, determined using a novel multinuclear imaging techniques (7Li-MRI), was identified as a potential marker but prior to the study initiation, its use was restricted to a small number of expert centres. Here we describe the steps taken to establish, coordinate and harmonise data acquisition and analysis in multiple sites.

Methods: Centres in the R-LiNK network were identified based on imaging platform capabilities and commonalities. Dual tuned 1H/7Li volume RF coils were procured and installed in each centre, together with bespoke test-objects (lithium phantoms) representative of the human brain. Acquisition sequences were optimised based on those previously published by our group, with harmonisation work conducted using the standardised phantoms. Data collection from enrolled patients proceeded in accordance with study protocol, supported by centralised sanity and quality

control checks. Acquisition processes were collated into standard operating procedures for Siemens and Philips MRI platforms. **Results:** The application of standard operating procedures enabled the collection of 7Li-MRI data (n**>** 45) from six centres as part of a longitudinal treatment study. Implementation of this novel imaging technique presented challenges, but these were surmountable and did not delay the project objectives. Close coordination between the lithium imaging and standard proton MRI work-package teams within R-LiNK, together with clear and responsive communication from participating sites was central to this success. Centralisation of data collection has proved to be advantageous in the development of novel processing pipelines. **Conclusion:** The R-LiNK initiative has established a network of centres capable of implementing 7Li-MRI as a potential marker for response to lithium as well as for future studies investigating the actions of lithium in various neuropsychiatric conditions. The development of standardised procedures and test-objects for harmonisation paves the way for an expansion of this imaging network to better understand this most important of medications.

MULTIOMICS ANALYSIS OF BLOOD METABOLOME, GUT MICROBIOTA AND GENOME-WIDE METHYLATION TO IDENTIFY BIOLOGICAL SIGNATURES OF RESPONSE TO LITHIUM IN BIPOLAR DISORDER

Claudia Pisanu*****[1], *Raffaella Ardau[2], Luigi Atzori[1], Bernardo Carpiniello[1], Donatella Congiu[1], Caterina Chillotti[2], Maria Del Zompo[1], Mirko Manchia[1], Aldo Manzin[1], Anna Meloni[1], Vanessa Palmas[1], Pasquale Paribello[1], Marco Pinna[1], Cristina Piras[1], Giovanni Severino[1], Martina Spada[1], Alessio Squassina[1]*

[1]*University of Cagliari, 2University Hospital Agency of Cagliari*

Objective: Bipolar disorder (BD) is among the major determinants of disability worldwide, with a very high socio-economic burden. The complex underlying neurobiology and the high heterogeneity in clinical response to the first-line treatments for BD, including lithium, severely impact on the management of this disorder, strongly calling for innovative integrated precision approaches. We will present results from two studies aimed at applying integrative analyses of different types of omics profiles (plasma metabolome, gut microbiota and genome-wide methylation) that represent important players in the relationship between genetic and environmental factors predisposing to psychiatric disorders and clinical response to psychotropic drugs.
Methods: In the first study we explored the role of gut microbiota and its possible interactions with the host metabolome in response to lithium in BD. To this end, we selected 50 patients with BD under lithium treatment at the time of recruitment and characterized as responders or non-responders using the “Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder” (Alda scale) and 50 patients treated with other mood stabilizers. The characterization of the blood metabolome (with nuclear magnetic resonance spectroscopy) and the gut microbiota composition (sequencing of the V3 and V4 hypervariable regions of bacterial 16S rRNA) are undergoing. In the second study, whole blood genome-wide methylation is being assessed with Infinium MethylationEPIC arrays in an extended sample of 70 patients with BD under lithium treatment and 30 controls. Data are analyzed to identify differentially methylated regions between diagnostic and lithium response groups. In addition, we will present data on differences in epigenetic age among studied groups and integrate them with other aging hallmarks measured in the same patients (leukocyte telomere length and mitochondrial DNA copy number), to explore the hypothesis of accelerated cellular aging in BD and of a potential protective effect of lithium treatment.
Results: We expect to find distinctive profiles of the gut microbial community, the host metabolome and methylation in patients exposed to lithium compared to patients treated with other mood

stabilizers or controls, as well as to identify specific biosignatures correlated with the clinical response. In addition, by applying integrative approaches to this multi-omics dataset using the Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO) method, we expect to identify multi-omics biomarker panels predictive of lithium response. **Conclusion:** By taking advantage of a multiomic approach applied to a deeply phenotyped sample of longitudinally followed-up patients, our studies aim to identify biological signatures underlying the clinical response to lithium.

5:00 p.m. - 6:30 p.m.
Symposia Concurrent V

UPDATE ON TREATMENT RESISTANT DEPRESSION

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: Treatment-resistant depression (TRD) is common and associated with multiple serious public health implications. A consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist. Instead, a plethora of definitions have been proposed, which vary significantly in their conceptual framework. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted the most used definition of TRD (i.e., inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment). Evidence indicates that a subset of MDD patients presenting with TRD may exhibit a failed antidepressant response as a consequence of a suboptimal bioavailability of the administered antidepressant, due to rapid metabolizer status. Identifying biomarkers and biosignatures associated with TRD as well as treatment response is an important future research vista. Intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) are established as efficacious in the management of TRD. Several second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine XR) are proven effective as antidepressant augmentation treatments in partial responders, but only the olanzapine-fluoxetine combination has been studied in FDA-defined TRD. The next decade can reasonably expect the regulatory approval of innovative pharmacological treatments targeting systems implicated in the pathophysiology of depression. Non-üphasrmacological treatment options are also available including both psychotherapy as well as ECt or TMS. There is as yet no clear distinction in the algorithm when to place these treatment modalities.

TREATMENT RESISTANT DEPRESSION: TREATMENT CONSIDERATIONS

Roger McIntyre**1*

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University of Toronto

Objective: To discuss the definition of treatment-resistant depression, the limitations of current definitions of treatment resistant depression, and to discuss treatment options used in major depressive disorder.

Methods: Methods are through a Delphi method and review of the literature.

Results: The results are treatment resistant depression does not have a consensus definition. Multiple definitions exist. Moreover, not a large number of treatments are available for major depressive disorder that is treatment resistant. In this program we are going to review the treatments for treatment resistant depression. **Conclusion:** A consensus definition of treatment resistant depression is required. Additionally, multiple treatment strategies are being evaluated which will be presented at this conference.

GENETIC BASIS OF TREATMENT RESISTANT DEPRESSION

Alessandro Serretti1, Chiara Fabbri1, Dan Rujescu**2*

[1]University of Bologna, 2German Society for Biological Psychiatry

Objective: Treatment resistant depression is largely modulated by genetic factors.

Methods: Several antidepressants already have a pharmacogenetic precaution/warning in their labeling for risk of side effects or interactions in CYP2D6 poor metabolizers. Conversely, rapid metabolizers may need higher doses. Other pharmacodynamic gene variants have been suggested, and, based on those evidence, over 40 commercially available pharmacogenetic assays have been implemented and their clinical applicability. While CYP polymorphisms are likely to inform about response/tolerability rates and reduce costs, single pharmacodynamic variants have little or no clinically relevant effects.

Results: More recently, the combined effect of polygenic risk scores has shown much more promising results in terms of reliability and possible drug choice and repurposing, but still explaining a relatively low variance of treatment resistant depression.

The integration of genetic information with clinical data and other biomarkers is a possible strategy to develop future more effective predictive algorithms.

Conclusion: Genetic factors are therefore at present already explaining a part of treatment resistant depression, but integrated models including further genetic and clinical predictors are needed.

DEVELOPMENT OF FAST ACTING ANTIDEPRESSANTS FOR TRD

Siegfried Kasper**1*

[1]Center for Brain Research

Objective: The development of fast acting antidepressants, specifically for treatment of so-called "TREatment resistant depression" will be presented, starting from clinical observations via randomised trials and underlying biological mechanisms

Methods: A literature overview will be given including own findings as part of Multicenter trials as well as own neuroimaging findings on esketamine.

Results: Since this is an overview, the available results published in the literature will be given

Conclusion: By the conclusion of the lecture the audience will be able to understand the development of rapid acting antidepressants with a specific focus on TRD.

NON-PHARMACOLOGICAL AND LONG-TERM TREATMENTS FOR TRD

Johan Saelens1, Anna Gramser1, Victoria Watzal1, Rupert Lanzenberger1, Christoph Kraus**1*

[1]Medical University of Vienna

Objective: Treatment strategies for treatment resistant depressions converge in repetitive trials of pharmaceutical substances with unclear maintenance treatments. Despite the successful establishment of novel rapid acting substances, several disadvantages such as adherence, side-effect profiles or long-term efficacy in relapse prevention remain. In addition, efficacious neuromodulatory treatments such as electroconvulsive therapy have their place in acute and maintenance treatment. However, in the treatment pathway for TRD, the position for other brain stimulation treatments such as transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) and vagus nerve stimulation

(VNS) remain unclear. The central aim of this talk is to present existing evidence on efficacy of neuromodulatory treatments in TRD and to compare efficacy to pharmaceutical treatment strategies. **Methods:** To compare efficacy of existing antidepressant treatments for TRD, we conducted a systematic literature research and network meta-analysis on all existing treatment modalities in TRD (as defined by non-response to two antidepressant treatment trials). Analysis was conducted in R with the netmeta package. **Results:** For the comparative network meta-analysis, 6698 abstracts were screened and 64 randomized, sham- or placebo-controlled trials with a total of 9976 patients were included. Six out of 28 antidepressant therapies in TRD had a significant higher response rate compared to placebo (ECT (OR = 13.78), minocycline (OR = 6.5), theta-burst stimulation (OR = 5.02), rTMS (OR = 4.48), ketamine (OR = 3.31) and aripiprazole (OR = 1.9). Treatments are ranked based on their probability of being the treatment with the highest response rate, with ECT ((p = .85) and theta-burst (p = .84) leading the field. **Conclusion:** In this study, we demonstrate comparative and ranked efficacy of currently available and investigational antidepressant treatments in TRD. Neuromodulatory interventions such as ECT and TMS ranked highest as far as treatment response of acute episodes are concerned. The results of this trial together with a second comparative meta-analysis on efficacy of DBS will be presented in the talk. These novel results will be placed into the context of the current treatment pathway in TRD. The audience will learn about acute and maintenance treatment strategies with neuromodulatory techniques and treatment selection in the daily clinical practice.

INTERNATIONAL STUDIES ON BRAIN MATURATION AND DEVELOPMENTAL PSYCHOPATHOLOGY: FROM BIRTH TO ADULTHOOD

Paolo Brambilla, University of Milan

Symposium Synopsis: Adolescence represents a period of increased opportunity and vulnerability, during which a complex confluence of genetic and environmental factors influences brain growth trajectories, cognition, emotion regulation and mental health outcomes.
In this symposium, international studies focusing on the link between environment, genes, disease-related behaviour and the brain, using a multidisciplinary perspective bridging epidemiology, genetic, neuroimaging and psychopathology will be presented.
Specifically, we will discuss how genetic and environmental risks for developmental disorders translate to brain function, structure and connectivity and how this in turn – ultimately- translated to emotion regulation and behavioural development. In addition, we will explore examples of the long-term psychological and behavioural sequelae in individuals with typical and atypical development, particularly focusing on clinical phenotypes associated with emotional dysregulation and major psychiatric disorders such as schizophrenia, bipolar disorders, major depression and anxiety disorders. Ultimately, we will discuss potential origins transdiagnostically characterising these disorders, associating early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
In addition, while most treatment studies focus on recovery within weeks or months, the long-term course of the above-mentioned disorders remains less established. In this symposium it will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.
Finally, the key role of genetic and neurobiological markers to improve the early detection and personalised treatment of developmental disorders will be analysed, mentioning the role of machine learning techniques and AI.

LONGITUDINAL NEONATAL BRAIN DEVELOPMENT AND ENVIRONMENTAL CORRELATES OF INFANT OUTCOMES FOLLOWING PRETERM BIRTH

Lucy Vanes1, Sunniva Fenn-Moltu1, Laila Hadaya1, Sean Fitzgibbon1, Lucilio Cordero- Grande1, Anthony Price1, Andrew Chew1, Shona Falconer1, Tomoki Arichi1, Serena J. Counsell1, Joseph V. Hajnal1, Dafnis Batalle1, A. David Edwards1, Chiara Nosarti**1*

[1]King's College London

Objective: To characterise longitudinal development of neonatal regional brain volume and functional connectivity in the first weeks following preterm birth, sociodemographic factors, and their respective relationships to psychomotor outcomes and psychopathology in toddlerhood.

Methods: We studied 121 infants born preterm (i.e., before 37 completed weeks of gestation) who underwent magnetic resonance imaging shortly after birth, at term-equivalent age, or both. Longitudinal regional brain volume and functional connectivity were modelled as a function of psychopathology and psychomotor outcomes at 18 months.

Results: Better psychomotor functioning in toddlerhood was associated with greater relative right cerebellar volume and a more rapid decrease over time of sensorimotor degree centrality in the neonatal period. In contrast, increased 18-month psychopathology was associated with a more rapid decrease in relative regional subcortical volume. Furthermore, while socio-economic deprivation was related to both psychopathology and psychomotor outcomes, cognitively stimulating parenting predicted psychopathology only.

Conclusion: Our study highlights the importance of longitudinal imaging to better predict toddler outcomes following preterm birth, as well as disparate environmental influences on separable facets of behavioural development in this population.

INTERNALIZING AND EXTERNALIZING SYMPTOMS TRAJECTORIES FROM CHILDHOOD TO EARLY ADULTHOOD, THROUGH ADOLESCENCE, IN CLINICAL AND GENERAL POPULATION SAMPLES: RESULTS FROM THE REMIND PROJECT

Maria Nobile**1*, *Maddalena Mauri1, Silvia Grazioli1, Federica Tizzoni1, Laura Camillo1, Maurizio Bonati2, Antonio Clavenna2, Alessandra Frigerio1, Carolina Bonivento3, Paolo Brambilla4*

[1]Scientific Institute IRCCS 'E. Medea', Bosisio Parini (LC), 2IRCCS - Istituto di Ricerche Farmacologiche, [3]IRCCS E. Medea Scientific Institute, Polo Friuli Venezia Giulia, San Vito al Tagliamento (PN), [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan

Objective: The REMIND project aimed at identifying specific clusters of symptom trajectories in internalizing and externalizing areas and evaluating their different exposure to risk factors in a developmental perspective.

The involved subjects from a general and a help-seeking population were evaluated at pre-adolescence (T0), adolescence (T1) and young adulthood (T2).

Methods: Psychopathological symptoms were measured through ASEBA questionnaires at the 3 time points, also neurobiological markers were collected. A Multivariate Finite Mixture Model (MFMM) was used to estimate specific developmental clusters considering T1 and T2 symptoms. We evaluated whether belonging to a specific developmental cluster was associated with sociodemographic characteristics, environmental risks (i.e., perinatal complications and stressful life events) and psychopathological symptoms measured at T0.

Results: Anxious-Depressed and Somatic scales showed 3 developmental clusters (“stable high”, “stable low”, “low-to-high”), Withdrawn-Depressed scale showed 2 developmental clusters (“stable high”, “stable low”). Individuals belonging to the ‘stable high’ internalizing developmental clusters,

presented higher emotional/behavioral dysregulation during preadolescence, with the co-occurrence of higher internalizing and externalizing problems.
Conclusion: The longitudinal perspective suggested the presence of specific manifestations trajectories from adolescence to adulthood. The presence of clinical level of psychopathology during preadolescence is a strong predictor of its persistence through lifespan, highlighting both homotypic and heterotypic continuities. These data strongly suggest the importance of accounting for both homotypic and heterotypic continuity in psychopathological traits when planning interventions.

TRAJECTORIES OF BRAIN STRUCTURE IN THE MAJOR MENTAL DISORDERS: FINDINGS FROM LONGITUDINAL STUDIES IN MDD, BD AND SZ

Tilo Kircher**1*

[1]*Universitätsklinik für Psychiatrie und Psychotherapie Marburg*

Objective: Major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder (schizophrenia and schizoaffective disorder) overlap in symptomatology, risk factors, genetics, and other biological measures. It remains unclear whether there are shared regional grey matter volume alterations across these disorders, which past and current phenotypic factors and what course of illness moderate these alterations. We wanted to identify shared but also distinct grey matter volume alterations across patients compared to age- and sex-matched healthy controls.
Methods: Age- and sex matched healthy controls (n=110), DSM-IV-TR diagnosed major depressive disorder (n=110), bipolar disorder (n=110), and schizophrenia spectrum disorder patients (n=110), drawn from a sample of N=1927 were included. Grey matter volume (3T magnetic resonance imaging) was compared between HC and patients. We applied a conjunction analysis to identify shared grey matter volume alterations across the disorders. To identify potential origins of transdiagnostic GMV clusters, we associated them with early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
Results: Common to all diagnoses (vs. healthy controls), we identified grey matter volume reductions in the left hippocampus. This cluster was associated with stressful life events, the neuropsychology factor working memory/executive functioning, and with global assessment of functioning. Differential effects between groups were present in the bilateral frontal operculae and left insula, with volume variances across groups highly overlapping.
Conclusion: There are shared grey matter volume alterations in the left hippocampus across the major mental disorders. The hippocampus is a central network hub, orchestrating a wide range of mental functions. Our findings underscore the need for a novel stratification of mental disorders, besides categorical diagnoses.

COURSE PREDICTION OF DEPRESSION AND ANXIETY DISORDERS IN THE NESDA PROJECT

Brenda Penninx**1*

[1] *Amsterdam UMC*

Objective: While most treatment studies focus on recovery within weeks or months, the long-term course of depression and anxiety disorders remains less established. We examined the 2-6 year course trajectories of a large cohort of persons with depression and anxiety disorders, and evaluate whether we can predict chronicity by sociodemographic, clinical and biological data
Methods: Using 9-year longitudinal data from the Netherlands Study of Depression and Anxiety (NESDA, n=2981, 66% female, baseline mean age=42 yrs), we examined the naturalistic course of depression and anxiety disorders.

Results: 58% of the persons with a current depressive and/or anxiety disorder at baseline reported chronic episodes (24 months with symptoms without remission) over 6 years of follow-up (Verduijn et al. BMC Med 2018). Also switching between disorders was frequent. This is despite the fact that many persons in the study did receive pharmacotherapy, psychotherapy or a combination of these. For instance, after 6 year, also, when examining 9-year patterns in symptom severity reports, it appears that 63% of the sample belongs to the symptom cluster group that showed only a minimal improvement (Solis et al. J Affect Dis 2021). Machine learning analyses in which we considered basic clinical, psychological, lifestyle and biological predictors of course, yielded a significant prediction but with only moderate prediction value (accuracy 68%, Dinga et al. Transl Psychiatry 2018). Adding epigenetic or proteomic data did further improve predictive value (accuracy 75-75%, Clarck et al. Mol Psychiatry 2019; Habets et al. in progress). **Conclusion:** Unfortunately, chronicity appeared more the rule than the exception. Strongest predictors of chronicity of depressive and anxiety disorders are clinical baseline characteristics (including severity indicators). However, certain biological parameters did add additional predictive value. It will be presented what these findings tell us about the underlying biological mechanisms of chronicity. It will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.

NEUROSCIENCE BASED NOMENCLATURE

Oğuz Karamustafalıoğlu, İstanbul-University Cerrahpaşa

Symposium Synopsis: Symposium synopsis: neuroscience based nomenclature: a country experience:
Neuroscience based Nomenclature is a new classification system for psychotropic agents and now it (neuroscience based nomenclature), many years spent for introduction. It is now time for using NbN for clinical purposes. There is not clear information about how NbN is relevant in clinical use and will guide the clinicians, how different dosing and different pharmacology will change our clinical practice and use of NbN in psychosis and giving guidance for the clinicians. The implementation of NbN is an issue and the experience about implementation of NbN in specific country will be shared. The psychiatrists will be separated into two groups: child and adolescent and adult groups. Regarding the use of NbN the groups will differ in awareness, knowledge, use in practice and perspectives on NbN.

NBN IN THE TREATMENT OF PSYCHOSIS

Christoph Correll*[1]

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Objective: For the last seven decades, medications used to treat psychosis with regulatory approval based on randomized controlled efficacy studies have been dopamine receptor blockers. These medications have been called “antipsychotics”. However, this class of medications has also been used for and received regulatory approval for mania, bipolar depression, unipolar depression, tic disorders, indications that have nothing to do with psychosis. This indication-based nomenclature (is confusing for all stakeholders.

Methods: Review of the principles and procedures of neuroscience-based nomenclature (NbN) and how this approach pertains to treatments for psychosis. This presentation will outline the classification of dopamine blockers and partial agonists, as well as of other, emerging medications for psychosis in NbN.

Results: NbN proposes to categorize treatments for psychosis mechanistically based on the proximal effects as either blockers or enhancers with each of these proximal effects being able to lead to either

excitation or inhibition downstream. Examples of existing and emerging mechanisms of action for the treatment of psychosis are given.

Conclusion: Neuroscience-based nomenclature is a neuroscience and mechanism-based classification system of psychotropic drugs that will help with educating clinicians, patients and families about distinct actions of medications that map onto pharmacological mechanisms and thereby expected indications, benefits and adverse effect risks. Given that agents without dopamine receptor blocking effects are close to regulatory approval for schizophrenia, this NbN-based classification system is even more important for drugs for psychosis. This classification system will need to incorporate in a simple and straightforward way the complexities of proximal postsynaptic as well as presynaptic activity that can lead to either similar or opposite downstream effects.

IMPLEMENTATION NEUROSCIENCE BASED NOMENCLATURE IN TURKEY

Oğuz Karamustafalıoğlu*[1]

[1] *İstanbul-University Cerrahpaşa*

Objective: Neuroscience Based Nomenclature has been introduced more than a decade and even a second revision is published. The use of Neuroscience based Nomenclature is still limited both by adult psychiatrists and child and adolescent psychiatrists. The aim of the study is to understand the use of Neuroscience based Nomenclature among both adult psychiatrists and child and adolescent psychiatrists.

Methods: The questionnaire is prepared to give both adult psychiatrists and children and adolescents to understand the familiarity, purpose of use, their evaluations on various aspects are measured. Both groups are also compared.

Results: The knowledge of Neuroscience Based Nomenclature is limited among both groups. Both groups were not clear about the purpose of use of Neuroscience based Nomenclature .There are not enough information about how NbN is relevant in clinical use and will guide the clinicians how different dosing and different pharmacology will change our clinical practice and use of NbN in psychiatric disorders and giving guidance for the clinicians

Conclusion: The Knowledge of Neuroscience Based Nomenclature and Use of Neuroscience Based Nomenclature especially in clinical practice is very limited among both adult psychiatrists and child and adolescent psychiatrists. The barriers in the use of Neuroscience Based Nomenclature needs clear guidelines to overcome them.

NEUROSCIENCE-BASED NOMENCLATURE (NBN) - INTRODUCTION

Joseph Zohar*[1]

[1] *Post-Trauma Center, Sheba Medical Center; Tel Aviv University*

Objective: Psychopharmacology has advanced remarkably since the emergence of the first psychotropics in the 1950s. However, the pharmacological "language" still lags behind the new advances, leaving clinicians and patients with a disease-based terminology ("antipsychotics", "anxiolytics", "antidepressants'', etc) that is noninformative, stigmatizing and at times misleading. Neuroscience-based Nomenclature (NbN) is a pharmacologically-driven nomenclature, aiming to describe psychotropics through their neurobiological profile. Its main goal is to encourage more precise prescribing, help clinicians make rational and informed treatment choices and decrease patient stigma.

Methods: Chairing the symposium, Prof. Zohar will introduce the NbN concept, demonstrating the need for a new nomenclature amongst clinicians, trainees and patients. He will describe NbN's unprecedented development which was led by 5 major neuropsychiatric organizations (ECNP [European College of Neuropsychopharmacology], CINP [International], ACNP [American], AsCNP

[Asian], and IUPHAR [International Union of Basic and Clinical Pharmacology]), and will present its scope and coverage so far.

Results: NbN describes psychotropics through their mechanism, allowing for a broader understanding of treatment rationale, allowing a clearer view of the similarities and differences between medications and helping better planning of the "next pharmacological steps".

Conclusion: Neuroscience-based Nomenclature is an alternative classification system that strives to create a more scientific and precise pharmacological "language". This terminology might encourage a better understanding of psychopharmacology, help maximize the use of the current pharmacological tools available, and finally incorporate the vast knowledge available to day-to-day practice.

DIFFERENT DOSAGE DIFFERENT PHARMACOLOGY (DDDP)

Sasson Zemach*[1]

[1] *Hadassah-Hebrew University Medical Center*

Objective: Viewing medications through the "lens" of pharmacology, rather than indication, enables us to understand the underlying mechanism of each drug in a deeper level. The NbN way of thinking reveals that some medications act in differently in the pharmacodynamic level, depending on dosage, and therefore might serve different clinical uses at low dose and at full dose.

Methods: The talk will present some examples of using a medication at low dose for a certain purpose (e.g., low dose aripiprazole for the augmentation of depression), and full dose for an entirely different indication (e.g., aripiprazole for psychosis), while illuminating the pharmacological difference between low vs. full dose, and the clinical importance of distinguishing between these differences.

Results: Looking at the DDDP (Different Dose Different Pharmacology) concept illustrates how taking into consideration the dose of the medication has profound relevance, and how this difference might contribute to clinical practice and the research field alike.

Conclusion: Since continuous NbN contributes to a deeper understanding of psychopharmacology. the more precise our "language" is, the better is our ability to use the pharmacological tools available. DDDP is an example to where this understanding might extend.

TRANSLATING PSYCHIATRIC GENETICS TO CLINICAL APPLICATIONS WITH NOVEL STATISTICAL AND MACHINE LEARNING APPROACHES

Ole Andreassen, University of Oslo

Symposium Synopsis: With the advent of large-scale datasets, the field of psychiatric genetics is moving forward to an era of precision medicine to make individualized predictions. This is becoming possible with the development of novel statistical methods and machine learning techniques, leading to rapid new discoveries, and advancing the field towards clinical applications. In this symposium, we will present and discuss novel statistical methods and applications of machine learning principles in the context of precision medicine and psychiatric genetics that pave the way forward to clinical applications. Specifically, we will showcase a series of methods that we have developed for statistical genetics – boosting genetic discovery using an empirical Bayes approach, development of subject-specific trajectories using longitudinal genome-wide association studies, discovery of underlying biologically-relevant gene sets, and multimodal hazard analysis framework for predicting age of onset of different disorders. Using these novel statistical methods, we will not only present the conceptual foundations of these tools, but ground these in a clinically relevant framework and showcase how using these tools can lead to clinically relevant translational science. Speakers from Asia, Europe and North-America will cover new findings in relevant topics, including clozapine metabolism and clozapine-induced agranulocytosis, identification of gene-sets with greater biological specificity

associated with mental illness, providing new insights into the pathobiology of complex polygenic disorders, improvements in prediction performance of polygenic hazard score models, and longitudinal findings highlighting how the effect of SNPs change with time to reveal factors relevant for development of mental illness applying longitudinal cohorts.

SHARED GENETIC ARCHITECTURE BETWEEN CLOZAPINE METABOLISM, WHITE BLOOD CELL COUNTS, AND AGRANULOCYTOSIS

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Objective: Clozapine is the most effective antipsychotic drug, but its use is limited due to hematological side effects, characterized by a reduction of white blood cells (WBC) including potential life-threatening agranulocytosis. Clozapine´s adverse effect on WBC is likely related to its metabolism. Still, it is not possible to predict or prevent the risk of agranulocytosis with current therapeutic clozapine monitoring methods. Genome-wide association studies (GWAS) of clozapine metabolism and clozapine-induced agranulocytosis have identified only a few genetic loci. However, applying novel statistical genetics approaches could reveal more of the shared genetic etiology of clozapine metabolism and clozapine-induced agranulocytosis. We utilized the conditional false discovery rate (condFDR) method to increase power for genetic discovery of clozapine metabolism and clozapine-induced agranulocytosis, by conditioning on WBC counts.

Methods: We used the largest available GWAS summary statistics for clozapine metabolism (clozapine-to-norclozapine ratio), clozapine-induced agranulocytosis, and WBC counts. To boost discovery of genetic variants associated with clozapine metabolism as well as clozapine-induced agranulocytosis, we applied the condFDR method to identify overlapping single nucleotide polymorphism (SNP) associations across traits. The test statistics of separate GWAS is re-ranked in a primary trait (clozapine metabolism or clozapine-induced agranulocytosis) conditional on the associations in a secondary trait (WBC counts), thereby increasing discovery of trait-associated SNPs. For replication analyses in an independent sample, we used summary statistics from a GWAS on WBC counts in an East Asian sample. For SNPs identified to be significantly (condFDR < 0.01) associated with clozapine metabolism or clozapine-induced agranulocytosis, we tested for association with measures of clozapine metabolism and granulocyte levels in a Norwegian sample of 392 clozapine-treated individuals.

Results: After conditioning on WBC counts, we identified three novel loci associated with clozapine metabolism (condFDR), and six novel loci associated with clozapine-associated agranulocytosis. The majority of the identified loci replicated using the independent WBC count GWAS, and they were associated with clozapine-related measures in the sample of clozapine-treated individuals.

Conclusion: Our findings of shared genetic variants influencing clozapine metabolism, WBC counts, and clozapine-induced agranulocytosis may form the basis for developing prediction models for severe adverse effects of clozapine.

THE MIXER TOOLBOX FOR UNRAVELING GENETIC ARCHITECTURE OF COMPLEX TRAITS

Oleksandr Frei*[1], *Guy F. L. Hindley2, Nadine Parker2, Alexey A. Shadrin2, Dennis Van der Meer3, Bayram Akdeniz2, Espen Hagen2, Kevin S. O'Connell2, Shahram Bahrami2, Olav B. Smeland1, Ole Andreassen2, Anders M. Dale4*

[1]*University of Oslo; Oslo University Hospital, 2University of Oslo, 3University of Oslo; Maastricht University, 4University of California San Diego*

Objective: Genome-wide association studies (GWAS) are increasingly successful in discovering genomic loci associated with complex human traits and disorders, yet biological interpretation of these results and their translation into accurate and actionable polygenic prediction tools remains challenging. Based on GWAS results, the MiXeR framework has previously allowed us to quantify the polygenicity of complex traits, and the degree of polygenic overlap between traits. In this talk I will give an overview of these methods and introduce two new extensions: (1) GSA-MiXeR, allowing the quantification of partitioned heritability and fold enrichment for small gene-sets, and (2) MiXeR-Pred, a tool for calculating polygenic risk scores that leverage polygenic overlap between traits for improved prediction accuracy.

Methods: GSA-MiXeR applies stochastic gradient-based log-likelihood optimization to fit a model of gene-set heritability, evaluating its fold enrichment over a comprehensive baseline model to account for MAF- and LD-dependency of genetic effects, and for differential enrichment of functional categories, thus taking into account the unique genetic architecture of each trait, while also controlling for linkage disequilibrium (LD) between variants. MiXeR-Pred tool computes enhanced polygenic risk scores, building on the cross-trait MiXeR model to compute the posterior effect size for each trait. This approach differentiates between shared and trait-specific genetic variates using the bivariate distribution of GWAS z-scores, and the estimated pattern of genome-wide overlap between the traits.

Results: In both simulated and real data, we show GSA-MiXeR's capability to reorder gene-sets in a way that promotes smaller gene-sets (with 10 genes or less) while yielding an equivalent or higher replication rate compared to current standards in the field. For schizophrenia, we show that calcium channel function gene-sets had greater fold enrichment than larger gene-sets related to post-synaptic functioning; additionally, the top two most fold enriched gene-sets implicated in GSA-MiXeR analysis were related to dopaminergic neurotransmission, the leading theory of schizophrenia pathogenesis. Using MiXeR-Pred, we show how the latest GWAS of schizophrenia can improve the accuracy of predicting the onset of bipolar disorder in an independent sample, while at the same time reducing the number of SNPs used for prediction.

Conclusion: Our findings illustrate that GSA-MiXeR provides the granularity required to map GWAS tested findings to potentially more informative neurobiological processes which can be experimentally, thus facilitating better characterization of the pathobiology of schizophrenia with potential for identifying new druggable targets and clinical sub-groups. Improved prediction accuracy of the MiXeR-Pred tool is an important step in towards incorporating more accurate polygenic prediction into the MiXeR framework.

POLYGENIC HAZARD SCORE MODEL TO PREDICT AGE OF ONSET OF ALZHEIMER'S DISEASE IN EUROPEAN POPULATIONS

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Objective: Polygenic hazard score (PHS) models are being used to estimate age-dependent genetic risk of various diseases including Alzheimer's disease (AD). The original PHS model for predicting the age of AD onset included 31 common variants and APOE ε2/ ε4 alleles [1]. Here, our aim is to the predictive ability of the PHS model and validate the updated model using genotyping data from

the European Alzheimer and Dementia Biobank (EADB) which includes cohorts from several countries across different regions of Europe. **Methods:** EADB samples whose age of onset (for cases) or age of last follow-up (for controls) are lower than 60 years are excluded resulting in N= 14195 cases, 16956 controls. We split this data into 80% for training and 20% for test data. For developing EADB model we applied genome-wide filtering using existing genome-wide association study (GWAS) of EADB data for AD [2]. We have eliminated single-nucleotide polymorphisms (SNPs) with p-value >10-5. The remaining 12631 candidate SNPs were used for the development of the new PHS model. Training for developing the new model was done via stepwise regression framework as proposed in [1]. As a result, 94 candidate SNPs (including APOE 2/4 alleles) were identified and then incorporated into the Cox proportional hazards model. **Results:** We have evaluated the performance of the new model using the test data. We have plotted corresponding Kaplan Meier curves and Cox regression estimates of the risk groups classified using PHS calculated using both models (for both the original model and the new model). We then calculated the Hazard ratio (HR) between risk groups such as HR of the samples who are in the highest 20 percent with respect to PHS to the lowest 20 percent (HR80/20) and similarly, we calculated HR98/50. The new EADB model surpassed the original model in prediction performance: HR80/20 increased to 3.22 from 2.42 in the original model, and HR98/50 increased to 4.59 from 3.41 in the original model. Furthermore, in the new model, the concordance index of PHS scores increased to 0.65, compared to 0.62 for the original model. **Conclusion:** Preliminary results showed increased prediction performance with the new EADB PHS model compared to the original PHS model. The performance may be further improved by using Lasso Regression, and sex-dependent data. Together, the presented findings indicate that the PHS model for predicting AD has the potential for clinical utility. **References:** [1] Desikan, Rahul S., et al. "Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score." PLoS medicine 14.3 (2017): e1002258. [2] Bellenguez, Céline, et al. "New insights into the genetic etiology of Alzheimer's disease and related dementias." Nature genetics 54.4 (2022): 412-436.

FAST AND EFFICIENT MIXED-EFFECTS ALGORITHM (FEMA) FOR GENOME-WIDE ASSOCIATION STUDIES (GWAS) OF LONGITUDINAL PHENOTYPES

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Objective: Longitudinal data are critical for advancing our understanding of causal mechanisms of complex human diseases. Compared to cross-sectional data, longitudinal dataset provides a wealth of information on subject-specific temporal trajectories of different phenotypes and development of diseases, like psychiatric disorders. While large longitudinal population data have recently become available, there are numerous challenges in performing genome wide association studies (GWAS) for trajectories of phenotypes. We have developed the FEMA-GWAS, a novel analytical tool that allows nuanced analyses of longitudinal phenotypes as well as linear and non-linear interaction with age/time and show results from different phenotypes highlighting how we can leverage trajectories of phenotypes to make subject-specific predictions in mental disorders.
Methods: FEMA-GWAS builds upon FEMA, a recently developed computationally efficient solution to performing mixed effects analyses, enabling the analysis of non-independent observations. For

FEMA-GWAS, we extend FEMA to perform linear and non-linear interaction of each single nucleotide polymorphism (SNP) with time and sex, thereby revealing novel associations of different SNPs with longitudinal phenotypes. We have applied FEMA-GWAS to height, weight, and BMI from the Norwegian mother, father and child cohort study (MoBa), and cortical thickness from the Adolescent Brain Cognitive Development (ABCD) and the UK Biobank datasets.
Results: Our results reveal novel loci that are associated with longitudinal trajectories of height, weight, and BMI in children (from birth to adolescence), with change in cortical thickness during adolescence (ABCD), and with change in cortical thickness during mid-life (UK Biobank). Importantly, we discovered novel loci that show significant SNP×age interaction effect, highlighting how the effect of SNPs change in different periods of time. Further, using these discoveries, we present data on constructing subject-specific precision norms, which can help make predictions on susceptibilities to developing psychiatric illnesses.
Conclusion: We have developed a powerful new tool that can be used for the analysis of genetics of non-independent observations. Using FEMA-GWAS, we discovered promising genetic leads that can help identify individuals who deviate from the normative genetically determined developmental trajectories. This method of identifying individuals at risk for various psychiatric disorders can open up possibilities of early intervention targeting modifiable environmental factors. It also opens up the possibilities of clinical translation by leveraging longitudinal clinical information and genetics in making subject-specific genetically adjusted predictions, thereby bringing us closer to precision psychiatry.

PSYCHIATRIC ELECTROPHYSIOLOGY AS ADD-ON TOOL IN THE MANAGEMENT OF ADDICTION DISORDERS

Oliver Pogarell, University Hospital, LMU Munich

Symposium Synopsis: Addiction is a worldwide health problem, still presenting large relapse rates despite decades of research and treatment programs including withdrawal, medication and psychosocial support. Neurophysiological tools (such as qEEG, cognitive event-related potentials, the neuroimaging-guided neurofeedback) are tools to offer new perspectives regarding pathophysiological mechanisms triggering diverse forms of addictions, to monitor states of the disorder and to develop new add-on tools for treatment as well as for prevention. In this symposium, we will furnish up-to-date evidence about new and complementary neurophysiological ways to face with addictive disorders. QEEG studies point at altered brain electric states in subjects with addictions. The investigation of differences and similarities across disorders provide insight into differential pathophysiological aspects that may be relevant for the treatment of dual diagnoses. Cognitive potentials are used to monitor patients during addiction treatment programs and may be such as helpful for predicting treatment outcomes. Neurophysiology based treatments neurofeedback are novel options to augment and improve standard care of patients with addiction including related neurophysiological parameters that may serve as biomarkers to predict clinical short and long-term effects. In summary psychiatric electrophysiology is of increasing relevance not only for basic brain research but also as a contribution to diagnostic and treatment decisions, complementing treatment options in psychiatry.

QEEG CORRELATES OF ADDICTION IN BIPOLAR DISORDER

Mehmet Kemal Arıkan*[1]
[1]
Kemal Arıkan Psychiatry Clinic

Objective: High rates of alcohol and substance abuse have been found in patients diagnosed with bipolar disorder. This study aims to explore the electrophysiological differences in addicted bipolar

patients using quantitative electroencephalography as a technique to measure cerebral cortical activity. **Methods:** Retrospective screening was used to obtain data from patients admitted to a private psychiatry clinic. In the initial stage, the prevalence of alcohol and substance abuse was compared among the most common diagnoses. In the second phase, bipolar patients were compared to healthy individuals in terms of electrophysiology. Within this comparison, alcohol dependent and substance dependent bipolars were studied separately in contrast to the healthy group. Alongside the healthy control, bipolar patients deprived of substance or alcohol abuse were examined in both cases. Statistical analysis involved MANOVA and gender and age were taken into account. **Results:** 1) In the initial analysis of common psychiatric diagnoses (depression, anxiety, OCD, schizophrenia, and bipolar disorder), the percentage of alcohol or substance abuse was significantly higher than otherdiagnoses. 2) Electrophysiological comparison revealed distinct electrophysiological profiles between bipolar patients with addiction and those without, as well as the healthy control group. Specifically, individuals with bipolar disorder and without alcohol dependence exhibited higher general theta, beta, and temporal alpha power compared to those with dependence and healthy individuals. Additionally, the former group demonstrated higher occipital alpha power compared to the healthy control group only. 3) Patients with bipolar disorder, both with and without substance abuse, exhibited higher overall beta power than the healthy control group. **Conclusion:** It can be concluded that alcohol dependence led to significant alterations in brain activity in patients with bipolar disorder compared to non-addicted and healthy patients. In contrast, no such differences were observed in substance dependence, possibly due to the stimulant properties of the substance used. Future research could investigate the changes to the electrophysiological profile within this patient group, depending on the substance type with more detail.

COGNITIVE ERPS IN THE MANAGEMENT OF ADDICTIVE DISORDERS

Salvatore Campanella**1*

1 Université Libre de Bruxelles

Objective: Despite withdrawal, psychotherapy, social support and anti-craving medication, the relapse rate remains tremendous among addicted patients. Cognitive ERPs may be considered as an add-on tool in the management of these patients.
Methods: Different ERP studies dealing with the management of addictive disorders will be reviewed.
Results: Different ERP parameters, such as the oddball P300, the Nogo P3d and the ERN, were identified as interesting biomarkers of abstinence vs. relapse in addictive disorders.
Conclusion: It is time to include ERPs in the management of addictions in order to monitor the evolution of different neurocognitive functions that may subtend relapse.

RTFMR-NEUROFEEDBACK IN ADDICTION PSYCHIATRY - SHORT AND LONG TERM EFFECTS

Oliver Pogarell**1*, *Susanne Karch1, Daniel Keeser1, Maximilian Maywald1*

1 University Hospital, LMU Munich

Objective: Psychosocial therapies are first line treatments in addictions, but long-term abstinence rates are limited to 40 to 60 %, even if extensive inpatient treatment and rehab has been offered. One risk factor of relapse is craving, that can be induced by alcohol related cues. Neuroimaging studies have revealed evidence for the association of craving with ACC and medial frontal areas during cue exposure. The activity in these regions can be modified by neurofeedback techniques.

Aim of the studies is to investigate neurofeedback in patients with substance use disorders in terms of feasibility, short and long-term effects. **Methods:** We implemented a real-time fMRI design in patients with alcohol and tobacco use disorders. Subjects received fMRI with a paradigm presenting substance related cues to elicit individual brain activations and were asked to modulate the cue induced brain responses. **Results:** There were significant modulations of addiction related brain activities along with slight reductions in craving. Due to small samples long-term data did not show increased abstinence rates so far. Differences between abstainers and relapsers point at predictive properties. **Conclusion:** Neurofeedback is a promising tool to augment treatments in substance use disorders. Larger samples in prospective studies are required to further improve the technique and assess long- term clinical effects.

NEUROFEEDBACK FOR ALCOHOL ADDICTION: CHANGES IN RESTING STATE NETWORK ACTIVITY

Bruna Sanader Vukadinovic**[1]*, *Susanne Karch2, Marco Paolini3, Paul Reidler3, Boris Rauchmann3, Gabrielle Koller2, Oliver Pogarell2, Daniel Keeser2*

[1]University College London Hospitals, 2University Hospital, LMU Munich, 3Institute of Clinical Radiology, University Hospital LMU

Objective: The aim of this study was to investigate whether neurofeedback training can alter resting state fMRI activity in brain regions that play a crucial role in addiction disorders in patients with alcohol dependence.

Methods: For this purpose, a total of 52 patients were recruited for the present study, randomized, and divided into an active and a sham group. Patients in the active group received three sessions of neurofeedback training. A random sample (N=16) remained for the data analysis. We compared the resting state data in the active group as part of the NF training on six measurement days.

Results: When comparing the results of the active group from neurofeedback day 3 with baseline 1, a significant reduction in activated voxels in the ventral attention network area was seen. This suggests that reduced activity over the course of therapy in alcohol-dependent subjects may lead to greater independence from external stimuli. Overall, a global decrease in activated voxels within all three analysed networks compared to baseline was observed in the study.

Conclusion: The use of resting-state data as potential biomarkers in further studies may hold promise, as activity changes within these networks, may help restore cognitive processes and alcohol abuse-related craving and emotions.

THE ROLE OF REWARD SYSTEM IN PSYCHIATRIC DISORDERS: A TRANSDIAGNOSTIC APPROACH

Esin Erdogan, University of Health Sciences, Izmir Faculty of Medicine

Symposium Synopsis: The Diagnostic and Statistical Manual of Mental Disorders categorically classifies various neurodevelopmental and psychiatric disorders, despite their sharing common features in terms of symptoms, causes, and abnormal brain processes. In fact, there are numerous instances where different disorders exhibit similar underlying pathological mechanisms. This overlap suggests the potential benefits of investigating shared patterns of disrupted brain function and associated characteristics. The ultimate objective is to more accurately link these pathological processes to well-founded and targeted interventions. One area that has received growing research attention in both nonclinical and clinical settings is the development of reward-processing systems. This approach revolves around the identification of malfunctioning mechanistic processes that are common to disorders with seemingly distinct symptom profiles. This strategy represents a specific implementation of the endophenotypic approach to uncovering the underlying pathophysiological mechanisms of these diseases. In this symposium, we aim to discuss preclinical models and clinical

research addressing reward circuit dysfunction in various neurodevelopmental and psychiatric disorders such as schizophrenia, mood disorders, eating disorders, and ADHD.

REWARD PROCESSING DYSFUNCTION IN SCHIZOPHRENIA

Aslihan Bilge Bektas*[1]

[1]*İzmir Bozyaka Training and Research Hospital*

Objective: Schizophrenia is a heterogeneous clinical disease with symptoms classified as positive, negative, disorganized, neurocognitive. It is thought that dysfunctional cortico-striatal interactions that worsen the prognosis in schizophrenia, reduce the social functionality of patients, play a role in the formation of negative symptoms that are resistant to treatment prevent the decision-making processes to create goal-directed behavior and cause disruption in the reward processing system.
Methods: Various components of reward processing have been shown to be impaired in schizophrenia. These components include reinforcement learning, the calculation of reward value, effort estimation, action selection, and reward expectation. These impairments are associated with changes in the cortico-striatal pathway. Various models have been proposed in the literature to explain motivation deficits in schizophrenia.
Results: A common assumption in most of these models is that the hedonic response is preserved in schizophrenia. Strauss et al. have proposed an approach that suggests impairments in hedonic systems in schizophrenia.
While individuals diagnosed with schizophrenia have hedonic responses similar to those of healthy individuals, they are less engaged in activities aimed at obtaining rewards. According to Barch and Dowd, this is because these individuals have difficulty using internal representations of emotional experiences, previous rewards, and motivational goals. It is believed that these difficulties in individuals with schizophrenia result from impairments in the components of reward processing, such as reward expectation, representation of reward value, calculation of effort required for rewards, and the ability to plan goal-directed activities.
Similarly, Gold and colleagues have argued that the fundamental problem in reward processing in schizophrenia lies in the creation and maintenance of mental representations of reward value. The model proposed by Kring and Elis in 2013 takes a different approach to explaining reductions in reward seeking and goal-directed behavior.
Conclusion: These models are supported by neuroimaging studies. Previous studies have revealed that anhedonia in patients with schizophrenia is attributed to the dysregulation of the frontostriatal circuit and mesocortical and mesolimbic circuit systems. Reduced OFC and putamen/ventral striatum activity during reward anticipation is linked to greater anhedonia and depressive symptoms in patients with schizophrenia. The motivational deficits of schizophrenia are thought to result from a reduced ability to differentiate between signal gains and instances of loss-avoidance, which are associated with the dysfunction of the frontostriatal pathway, including the vmPFC, dorsal ACC, anterior insula, and ventral striatum. Furthermore, patients with schizophrenia exhibit an inverse correlation between anhedonia-associality and posterior cingulate and precuneus activity, a key part of the DMN, during an auditory oddball task. Dysfunction of the striatum, cortex, and limbic regions and impaired integration of the reward networks may also lead to anhedonia in patients with schizophrenia.
In this session, we planned to discuss the differences in the reward processing process in schizophrenia and its relationship with the clinic in the light of current developments.

REWARD DEFICIT AND ANHEDONIA IN MOOD DISORDERS

Merve Babalioglu*[1]

[1]*Health Sciences University İzmir Tepecik Training and Research Hospital*

Objective: To explain the clinical and behavioral presentation of anhedonia and reward deficit in mood disorders, as well as the differences and commonalities in the underlying neurocircuitry.
Methods: A selective literature search including both human and rat studies were conducted using PubMed and PsychINFO to identify anhedonia and reward deficit in mood disorders.
Results: Mood disorders are common and debilitating conditions characterized in part by profound deficits in reward-related behavioural domains. Evidence suggests that depression is characterized by hypofunction of the reward-related brain structures such as the nucleus accumbens, prefrontal cortex, amygdala and hippocampus, while bipolar disorder manifests dysregulation of the behavioral activation system that increases goal-directed reward behavior. Importantly, strong evidence does not exist to suggest significant differences in anhedonia severity between depressed unipolar and bipolar patients, suggesting that there are more nuanced fluctuations in reward processing deficits in bipolar patients depending on their state. Both euthymic unipolar and bipolar patients frequently report residual reward dysfunction, which highlights the potential of reward processing deficits that give rise to the clinical symptom of anhedonia to be trait factors of mood disorders.
Conclusion: Reward processing represents a potential diagnostic and treatment marker for mood disorders. Further research should systematically explore the facets of reward processing in at-risk, affected, and remitted patients.

WHICH COMES FIRST: ALTERED BRAIN REWARD CIRCUITS IN EATING DISORDERS?

Vefa Erbasan**1*

[1]*İzmir Tepecik Training and Research Hospital*

Objective: It was aimed to examine the role of changes in the brain reward system in eating disorders.
Methods: Eating disorders are multifaceted psychopathologies, and the transdiagnostic approach is currently considered a useful framework to understand their complexity. The transdiagnostic model of eating disorders represents a dimensional approach that cuts across traditional categorical diagnoses and goes beyond them by considering the processes that are relevant to both eating pathology and other psychological disorders. With this approach, reward processing systems were thought to be effective in the development of eating disorders.
Results: Recent evidence has proposed neurobiological and behavioral similarities between substance dependence and excessive consumption of highly processed foods. These findings led to the recognition of food addiction as a key trigger in eating disorders. There is now considerable evidence that food and drug addiction share similar pathways in dopaminergic, opioid, and cannabinoid systems. In fact, dopamine has been associated with the reward mechanism in both food and psychoactive substances. The more rewarding the food or drug evaluated, the greater the release of extracellular dopamine into the nucleus accumbens. Also, pharmacological blockage of dopamine receptors may reduce the reward of both high-sugar foods and drugs of abuse. Studies based on positron emission tomographic imaging have also shown that both obese and drug-dependent individuals have significantly lowered the levels of dopamine receptors.
Conclusion: All this information suggests that the changing brain reward system has an important role in the pathophysiology of eating disorders, and more research should be done in this field to better understand eating disorders.

NEURAL MECHANISMS UNDERLYING REWARD PROCESSING IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Esin Erdogan**1*

[1] *University of Health Sciences, Izmir Faculty of Medicine*

Objective: The prevailing view is that ADHD is characterized by deficits in different cognitive domains. In addition to executive functions, deficits are observed in reward processing, temporal processing and timing, speech and language, memory span, processing speed, response time variability, arousal/activation, and motor control tasks. The aim of this presentation is to enhance our understanding of the behavioral and neural factors associated with reward processing in adults with ADHD and to reconcile discrepancies found in the existing literature. **Methods:** Neuroimaging studies of reward processing (structural imaging studies, functional imaging studies, and imaging of the brain at rest) in ADHD have been examined. **Results:** Various imaging techniques have consistently shown that ADHD is linked to alterations in the neural system responsible for reward processing. Structural studies have identified volume reductions in the Ventral Striatum (VS) and Prefrontal Cortex (PFC). While the precise functional implications of these volumetric differences remain unclear, researchers have initiated functional investigations into reward processing. These efforts have consistently revealed functional changes in adults with ADHD, primarily characterized by reduced brain responses during the anticipation of rewards in the VS and anomalous signaling during the receipt of rewards in the Orbitofrontal Cortex (OFC). The signaling in the VS during reward anticipation has been proposed to reflect either the predicted value of an expected reward (Schultz 2010) or the incentive salience (Berridge and Robinson 2003). Responses in the OFC have been associated with signaling the value of stimuli in our environment, indicating that adults with ADHD may exhibit an exaggerated response to rewarded stimuli, potentially leading to imbalanced decision-making. The evidence regarding neural alterations linked to reward processing in young individuals with ADHD is less conclusive when compared to adults. There are several factors contributing to this uncertainty. Firstly, there have been fewer studies conducted in young participants, and the reported findings exhibit a high degree of inconsistency. These discrepancies pertain to the locations within neural structures where changes occur and the direction of these effects, whether they involve increases or decreases. Secondly, studies involving young participants with ADHD have generally worked with smaller sample sizes. In comparison, the largest study in adults included 136 participants (Hoogman et al. 2011), while studies in adolescents typically involved only 68 participants (Paloyelis et al. 2012). Thirdly, the majority of studies focusing on young participants with ADHD have concentrated solely on the aspect of reward anticipation. **Conclusion:** Hence, it is imperative to conduct further research involving young participants with ADHD, encompassing crucial elements of reward processing, including both anticipation and receipt of rewards. Additionally, the reported alterations in functional connectivity among young individuals with ADHD suggest that viewing brain reward processing from a network perspective could offer additional insights into the neural changes associated with this disorder. Given the absence of research on endophenotypic traits in neural measures associated with reward processing, familial studies are crucial for understanding the hereditary contributions to these neural characteristics.

Friday, June 7, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session III - Catherine Mummery

A NEW ERA IN AD DRUG TRIALS: TRANSLATING HOPE INTO IMPACT

Catherine Mummery1

[1]*University College London*

Objective: The search for treatments for Alzheimer's disease has been a long and arduous one with many negative trials and heated debate on what we should be targeting, and how. However, recent results on anti-amyloid immunotherapies have shown for the first time that we can alter the course of the disease and, while modest, have given us a foundation on which to build.

Methods: In this talk, I will summarise the results we have so far, and what they teach us in terms of next steps; I will then explore the novel targets and mechanisms that are developing and how we are using these in patients with earlier and genetic forms of disease to inform us about the future of treatments.

Results: I will outline some initial results from new genetic therapies as well as other novel therapies.

Conclusion: We are now in a position where we can be more than hopeful; we can be optimistic about the future. We are at the beginning of an era where we will build better disease modifying therapies and develop precision based medicines. We are at a real cornerstone - we are moving towards an ability to treat dementias as chronic diseases, not just offer palliative care for a terminal disease.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VI

THE ROLE OF DOPAMINE IN BIPOLAR DISORDER MOOD CYCLING AND DYSREGULATED CIRCADIAN CYCLES: A DOPAMINERGIC RHYTHMOPATHY? *Sameer Jauhar, King's College, London*

Symposium Synopsis: Mood cycling in bipolar disorders is a complex phenomenon driven by multiple
internal and external factors. We will present brain imaging data implicating Dopamine in this phenomenon, particularly, in mania and psychosis. We will also present data showing how a disrupted circadian cycle, especially by light and other factors, impacts sleep/activity and is associated with many mood symptoms from suicidal ideas to disrupted eating patterns. We will describe methods developed for quantitative ambulatory measurement of patterns in sleep and eating rhythms as well as associations between the two rhythms. Finally, we will integrate these phenomena into a coherent model integrating the role of a group of midbrain dopaminergic neurons
working as a non-circadian oscillator interacting with the circadian timer.

TESTING THE DOPAMINE HYPOTHESIS OF BIPOLAR DISORDER USING PET IN HUMANS

Sameer Jauhar*1, *Oliver Howes1*

[1]*King's College, London*

Objective: Delineate the role of the pre-synaptic dopamine system in bipolar disorder.

Methods: Case-control Positron Emission Tomography study in people with bipolar disorder and controls, using 18F-DOPA.

Results: Converging lines of evidence have implicated changes in the dopamine system in people with bipolar disorder, at trait and state levels. In this proposal I will present our data in first episode

mania psychosis, comparing it to schizophrenia psychosis, as well as newly acquired data in psychotic depression, addressing whether there is a transdiagnostic role for dopamine across these disorders. **Conclusion:** There does appear to be elevation in dopamine synthesis capacity in mania, with psychosis, and a probable reduction in dopamine synthesis capacity in the deprewssive pole of the illness, compared to this. Further longitudinal studies will shed further light on this.

DYSREGULATED RHYTHMS AND SYMPTOMATOLOGY IN BIPOLAR AND EATING DISORDERS

Outi Linnaranta**1*, *Serge Beaulieu2, Clement Bourguignon3, Elaine Tian4, Howard Steiger3, Kai-Florian Storch3*

[1]Finnish Institute for Health and Welfare, 2Canadian Network for Mood and Anxiety Treatments, [3]Douglas Mental Health University Institute, 4University of Hong Kong

Objective: To describe associations between sleep and eating rhythms in cohorts with patients with a diagnosis of a bipolar disorder (n=75) or an eating disorder (n=29).
Methods: Patients in both cohorts completed hourly charts of mood and eating occasions for two weeks. Locomotor activity was recorded continuously by wrist actigraphy for a minimum of 10 days, and sleep was calculated based on periods of inactivity. We computed the center of daily inactivity (CenDi) as a measure of sleep phasing and consolidation of the daily inactivity (ConDI) as a measure of daily sleep rhythm strength. We assessed interday irregularities in the temporal structure of food intake using the standard deviation (SD) of frequency (IFRQ), timing (ITIM), and interval (IINT) of food intake.
Results: In bipolar disorders, sleep timing and fragmentation were robustly associated with eating irregularity. In eating disorders, the phasing and rhythmic strength of sleep showed a moderate, positive correlation with the degree of eating irregularity. The similarity of findings despite several potential confounding factors and differences between the samples strengthen the notion of a potential shared rhythmopathy.
Conclusion: Two cohort studies showed shared rhythmopathy of sleep and circadian rhythms and eating rhythms. The presented methods are valid for descriptive studies on circadian rhythms in humans and deserve further development for use in clinical settings and in intervention studies.

A ROLE FOR MIDBRAIN DOPAMINE NEURONS IN BD CYCLICITY

Kai-Florian Storch**1*, *Pratap S. Markam1, Clement Bourguignon1, Lei Zhu2, Martin Darvas3, Bruno Giros1, Serge Beaulieu1, Outi Linnaranta1*
[1]McGill University2Douglas Mental Health University Institute, 3University of Washington

Objective: The mechanistic basis of cycling in bipolar disorder is poorly understood. Here we aimed to identify the neuronal substrate of cyclicity employing the mouse as a model.
Methods: Chronic treatment with methamphetamine in mice results in the emergence of a second rhythmic locomotor component that can reach periods of 48hrs, a frequency also found in bipolar disorder subjects exhibiting ultra-rapid cycling. We used genetic and pharmacological approaches to ablated or manipulate dopamine (DA) neurons in mice and then tested the resulting animals for deficits in second component emergence.
Results: We found that ablation of the DA neurons of the ventral tegmental area (VTA) abolished the ability of methamphetamine to induce the second component. Selective disruption of the tyrosine hydroxylase gene across the VTA equally led to a loss of second component emergence, while disruption of the gene for the vesicular monoamine transporter 2 in the VTA did not impede second component induction.

Conclusion: Our findings indicate that DA neurons of the VTA or their ability to produce DA are necessary for the emergence of a second rhythmic component regulating sleep-wake, likely harboring the oscillator that drives it. As the period of this component often reaches 48hrs, we suggest that DA neurons of the VTA also drive 48hr cycling in BD, where sleep length rhythmically alters alongside with mood.

DECODING MENTAL DISORDERS - DECIPHERING THE GENETIC BASIS AND EXPLORING ANIMAL AND IPSC MODELS

Florian Raabe, Max Planck Institute of Psychiatry

Symposium Synopsis: The goal of this symposium is to highlight the genetic basis of mental illness and advanced modeling with animal models and induced pluripotent stem cells (iPSCs).

Recent breakthroughs in genetic research have identified numerous risk genes associated with mental illness, and cutting-edge techniques have explored the functional implications of these identified risk genes.

By applying animal models that partially mimic the phenotypic characteristics of psychiatric conditions, researchers can investigate environmental factors that contribute to the development of mental illness and study gene-environment interactions.

The emerging field of induced pluripotent stem cells (iPSCs) enables the generation of various personalized neural subtypes, allowing for the dissection of cellular and molecular mechanisms in patient-derived neurobiological test systems.

The speakers of this symposium will discuss advancements in genetics, animal models, and iPSC technology, highlighting their strengths and limitations on the road towards personalized psychiatry.

PSYCHIATRIC GENETIC DISCOVERIES IN BIPOLAR DISORDERS - NEW INSIGHT IN UNDERLYING BIOLOGY

University of Oslo
Ole Andreassen[1]*, *Kevin O'Connell1, Bipolar Disorders PGC Working Group1*

Objective: We aimed to discover more of the the genetic architecture of bipolar disorders by applying a large transancestry sample.

Methods: Genome-wide association study of bipolar disorder with functional follow up of genetic loci. We analysed 158,036 bipolar disorders cases (including clinical, biobank and self-report cohorts) including diverse samples of European, East Asian, African American and Latino ancestries.

Results: We identified 337 independent genome-wide significant variants mapping to 298 loci. Exploratory enrichment analyses using the novel GSA-MiXeR tool highlighted enrichment of dopamine- and calcium-related biological processes and molecular functions, as well as GABAergic interneuron development, suggesting interesting molecular mechanisms and pathways to consider as targets for drug-repurposing. Genes fine-mapped to associated loci were also shown to be enriched for ultra rare damaging missense and protein-truncating variation in sequenced datasets, respectively, highlighting convergence of common and rare variant signals. We mapped genes to the 298 GWS loci using seven complementary approaches and identified a subset of 47 credible genes that were mapped to loci by at least three of these approaches.

Conclusion: Our findings highlight that increasing ancestral diversity in genetic studies of bipolar disorders improves discovery and ensures equitable benefit from genetic discoveries across ancestry groups.

EXCESS GDNF DEFINES SUBSET OF SCHIZOPHRENIA WITH ENHANCED STRIATAL DOPAMINE

JO Andressoo*[1]
[1]*University of Helsinki*

Objective: Recent evidence shows that only those schizophrenia (SCZ) patients who show striatal elevation in dopamine (DA) metabolism respond to DA blocking drugs. We investigated what mechanism can be responsible for the pathologically high DA metabolism in the striatum.
Methods: We analyzed post-mortem striatal gene expression in SCZ followed by analysis of targeted proteins in the CSF of first episode psychosis patients (FEP). We then analyzed the hit in mouse models.
Results: We found that glial cell line-derived neurotrophic factor (GDNF) mRNA levels are increased in post-mortem striata of SCZ patients. GDNF is among the strongest DA function enhancing proteins known. Similar increase in GDNF protein was found in first episode psychosis (FEP) patients CSF. In mice similar increase in brain endogenous GDNF expression starting from mid-pregnancy resulted in avolition, polydipsia, pre-pulse inhibition defect, enhanced striatal and reduced prefrontal DA metabolism thus resembling striatally DA elevated patients (Mätlik et al Andressoo Mol Psych 2022). Further post-mortem analysis of individual patients striata revealed “GDNF response” gene expression pattern in about 20% of patients which aligned with data from GDNF treated human DA neurons and with data from mice where endogenous brain GDNF expression was doubled at mid-pregnancy.
Conclusion: Our data suggest that excessive GDNF signaling may explain a subset of SCZ with elevated striatal DA. Ongoing work by ERANET NEURON Consortia GDNF UpReg focuses on patient stratification based on GDNF levels and explores options for pharmacological intervention.

MITOCHONDRIA PLAY A KEY ROLE IN THE GENESIS OF SCHIZOPHRENIA-LIKE CELLULAR, MOLECULAR AND BEHAVIORAL PATHOLOGIES IN HIPSCS AND RAT MODELS

Dorit Ben-Shachar*[1], *Hila Ene1, Rachel Karry1*
[1]*Technion, Israel Institute of Technology*

Objective: Ample evidence implicate mitochondria in psychiatric disorders in general and in schizophrenia in particular. Here we will show a causative role for mitochondria in neuronal development and in behavior. We will further suggest a molecular potential target to manipulate mitochondrial function.
Methods: Isolated active normal mitochondria (IAN-Mit) were transplanted into SZ and healthy subjects-derived lymphocyte cell lines (hLCLs) and iPSCs as well as into the medial prefrontal cortex (mPFC) of the Poly I:C SZ-model and healthy rats in adolescence. Cellular, structural, molecular, mitochondrial and behavioral alterations were assessed.
Results: IAN-Mit transplantation into SZ-iPSCs ameliorated mitochondrial function, neuronal sprouting and synaptic connectivity. In rats, IAN-MIT transplantation in adolescence significantly improvement mitochondrial function, neuronal sprouting and activity, enriched proteome metabolic in and neuronal development pathways, consequently restoring mPFC-regulated behaviors adulthood. Opposite effects in all parameters were induced by IAN-Mit in healthy rats. A similar disparate phenomenon was observed in schizophrenia and healthy subjects-derived LCLs. The possibility to mimic the effect of transplanted mitochondria in LCLs by molecular means will be discussed.
Conclusion: This study demonstrates the essential role of adolescent mitochondrial homeostasis in the development of a normal functioning adult brain. In addition, in order to ameliorate mitochondrial function in SZ, we suggest an alternative molecular tool to the transplantation of the double edge sword mitochondria.

IPSC TECHNOLOGY REVEALS COMMON MECHANISMS DESPITE DISTINCT INDIVIDUAL POLYGENIC RISK PROFILES

Florian Raabe*[1]

[1]*Max Planck Institute of Psychiatry*

Objective: Genetic studies have provided correlative evidence suggesting that distinct combinations of genetic risk factors in each patient converge onto common molecular mechanisms.

Methods: To validate this notion on a functional level, a cellular model system was employed, differentiating induced pluripotent stem cells (iPSCs) from 104 individuals with high polygenic risk load and controls into cortical glutamatergic neurons (iNs).

Results: Comprehensive multi-omics profiling revealed widespread differences of numerous synaptic transcripts between iNs derived from SCZ patients and healthy donors. Moreover, omics-based analysis highlights molecular mechanisms that regulate the neuronal transcriptomes that highly correlate with SCZ polygenic risk, and the affected genes were significantly enriched for common genetic variations associated with SCZ.

Conclusion: In summary, the results highlight that iPSC technology offers great potential for deciphering molecular mechanisms in SCZ and demonstrates that distinct individual polygenic risk profiles converge in common downstream signaling pathways.

POTENTIAL CLINICAL TOOLS ACROSS PSYCHIATRIC DISORDERS: FROM BIOMARKERS TO CLINICAL MARKERS

Bo Cao, University of Alberta

Symposium Synopsis: A major goal of translational psychiatry is to develop and identify effective clinical tools that can aid in the diagnosis, prognosis, and outcome prediction of mental illnesses. These tools can be developed from a variety of sources, including cross-species biomarker findings obtained through brain imaging, clinical markers obtained through clinical and behavioral assessments, or data obtained from clinical trials about the placebo effect in mental disorders. Additionally, innovative statistical and computational techniques, such as machine learning, can be leveraged to enhance the predictive power of these tools.

In this symposium, we have invited experts from a range of disciplines to present their latest research on the diagnosis and health outcomes of depression, bipolar disorder, schizophrenia, violence, and suicide. These investigations are all aimed at developing translational tools that can improve the delivery of mental health services.

We hope that this symposium will facilitate a lively discussion on the biological and clinical foundations of these tools, as well as the challenges and concerns associated with their translation into clinical practice. We believe that this symposium will provide a unique opportunity for attendees to explore new ideas and approaches in translational psychiatry for improving mental health services. Ultimately, we hope that this symposium will contribute to the ongoing efforts to provide better mental health care for all individuals, from innovation to practice.

CROSS-SPECIES NEUROIMAGING INTERMEDIATE PHENOTYPES DEEPEN OUR UNDERSTANDING OF DEPRESSION

Huiling Guo1, Shuai Dong1, Yao Xiao1, Jingyu Yang1, Pengfei Zhao1, Tongtong Zhao1, Aoling Cai1, Hui Wang2, Ruifang Hua2, Rongxun Liu2, Yange Wei2, Dandan Sun3, Zhongchun Liu4, Mingrui Xia5, Yong He5, Yankun Wu6, Tianmei Si6, Fay Womer7, Fuqiang Xu8, Jie Wang8, Weixiong Zhang9, Xizhe Zhang10, Fei Wang*[1]

[1]*Affiliated Nanjing Brain Hospital, Nanjing Medical University., 2School of Laboratory Medicine, Xinxiang Medical University., 3The People's Hospital of China Medical University and the People's*

Hospital of Liaoning Province, 4Renmin Hospital of Wuhan University, 5Beijing Normal University, 6Peking University Sixth Hospital, Peking University, 7Saint Louis University, 8Chinese Academy of Sciences-Wuhan National Laboratory for Optoelectronics, 9The Hong Kong Polytechnic University, 10School of Biomedical Engineering and Informatics, Nanjing Medical University.

Objective: Multiple genetic variants and their interplay with environmental factors have hindered the progress of mental disease research and the development of effective markers of neuropsychiatric disorders. Intermediate phenotypes like neuroimaging brain patterns offer unique opportunities to understand multifaceted etiologies of neuropsychiatric diseases such as depression. This study identified neuroimaging intermediate phenotypes bridging etiologic differences and disease behavioral features cross species.

Methods: We established rodent genetic (P11 knockout mice, N=11) and chronic unpredictable mild stress (CUMS, N=15) models of depression to illustrate the effects of different etiologies on neuroimaging patterns of the amplitude of low-frequency fluctuations (ALFF). To identify ALFF patterns in depressed individuals that correspond to the two rodent models, we used t-Distributed Stochastic Neighbor Embedding method and an agglomerative clustering algorithm to delineate two ALFF subtypes of depression in two independent datasets (N=438). Linear regression was performed to identify which ALFF alterations predicted core symptoms of depression across species.

Results: Compared to controls, opposite ALFF patterns in subcortical and sensorimotor regions were found between P11 knockout mice and CUMS. Similarly, two ALFF subtypes with opposite patterns in frontal-subcortical, and sensorimotor regions were clustered and validated in two independent depressed cohorts. Importantly, anhedonia was significantly increased across all rodent models and human subtypes when compared to controls, despite differences in ALFF patterns. Further, anhedonia correlated with subcortical-sensorimotor ALFF in rodent models and human cohorts.

Conclusion: Overall, subcortical-sensorimotor ALFF may serve as an intermediate phenotype that bridges etiologic differences and anhedonia in depression. These results deepened our knowledge of disease mechanisms underlying depression which may facilitate translational applications of animal models to humans with depression other psychiatric disorders.

DIFFERENTIAL POWER OF PLACEBO ACROSS MAJOR PSYCHIATRIC DISORDERS

Bo Cao*[1], *Yang Liu[2], Alessandro Selvitella[1], Diego Librenza-Garcia[2], Ives Passos[3], Jeffrey Sawalha[1], Pedro Ballester[4], Jianshan Chen[1], Shimiao Dong[1], Fei Wang[5], Flavio Kapczinski[2], Serdar Dursun[1], Xin-Min Li[1], Russell Greiner[1], Andrew Greenshaw[1]*

[1]University of Alberta 2McMaster University, 3Hospital de Clínicas de Porto Alegre; Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul, 4School of Technology, Pontifícia Universidade Católica do Rio Grande do Sul, 5China Medical University

Objective: The placebo effect across psychiatric disorders is still not well understood. In the present study, we conducted meta-analyses including meta-regression, and machine learning analyses to investigate whether the power of the placebo effect depends on the types of psychiatric disorders.

Methods: We included 108 clinical trials (32,035 participants) investigating pharmacological intervention effects on major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ). We developed measures based on clinical rating scales and Clinical Global Impression scores to compare placebo effects across these disorders. We performed meta-analysis including meta-regression using sample-size weighted bootstrapping techniques, and machine learning analysis to identify the disorder type included in a trial based on the placebo response.

Results: Consistently through multiple measures and analyses, we found differential placebo effects across the three disorders, and found lower placebo effect in SCZ compared to mood disorders. The

differential placebo effects could also distinguish the condition involved in each trial between SCZ and mood disorders with machine learning. **Conclusion:** Our study indicates differential placebo effect across MDD, BD, and SCZ, which is important for future neurobiological studies of placebo effects across psychiatric disorders and may lead to potential therapeutic applications of placebo on disorders more responsive to placebo compared to other conditions.

A CLINICAL RISK PREDICTION TOOL FOR IDENTIFYING THE RISK OF VIOLENT OFFENDING IN SEVERE MENTAL ILLNESS: A RETROSPECTIVE CASE-CONTROL STUDY

Xiaoping Wang**1*

1

Chinese Society of Neuroscience and Psychiatry

Objective: Individuals with severe mental illness are at higher risk of violence than the general population. However, there is a lack of available tools to assess the risk of violence in clinical settings. We aimed to develop an easy-to-use tool to identify risk of violent offences to assist decision-making in Chinese clinical settings.

Methods: We identified 1157 patients with severe mental illness who conducted violent offending and 1304 patients who were not suspected of violent offending in the matched living areas. We used stepwise regression and Lasso's method to screen for predictors, built a multivariate logistic regression model, and performed internal validation with the K-fold method to develop the final prediction model.

Results: The risk prediction model for violence in severe mental illness included age (beta coefficient, b=0.05), male sex (b=2.03), education (b=1.14), living in rural areas (b=1.21), history of homeless (b=0.62), history of previous aggression (b=1.56), parental history of mental illness (b=0.69), diagnosis of schizophrenia (b=1.36), episodes (b=-2.23), duration of illness (b=0.01). The area under curve (AUC) for the predictive model for risk of violence in severe mental disorder was 0.93 (95% CI: 0.92-0.94).

Conclusion: A predictive tool of violent offending containing 10 items that can be easily used for individuals with severe mental illness was constructed in this study. The model was internally validated to have good discrimination and high accuracy and have potential for assessing the risk of violence in patients with severe mental illness in routine care.

PROPHYLACTIC BLUE LIGHT THERAPY IMPROVES DEPRESSION: A STUDY OF LIGHT THERAPY WITH DIFFERENT PARAMETERS

Lingli Cheng1, Ying Yan1, Yang Yu1, Ni Fan1, Hongbo He**1*

1The Affiliated Brain Hospital of Guangzhou Medical University

Objective: Previous studies have demonstrated the therapeutic value of blue light therapy for treating depression. Yet the ideal light therapy parameters are not consistent. In the present study, blue light was prophylactically used to test the antidepressant effects of different light therapy parameters. This experiment explored the antidepressant effect of different duration（2 weeks or 3 weeks, or 4 weeks）, daily exposure time（2 hours or 3 hours or 4 hours）, and frequencies (0 Hz or 8 Hz or 40 Hz) of blue light therapy on improving depression-like behaviors.

Methods: Adult male C57/BL6 mice at the ages of 7–8 weeks were used in the present study. (Corticosterone was
Corticosterone-chronic restraint stress (Cort-Crs) depression model
administered subcutaneously at a dose of 20 mg/ kg , Restraint of 2 hours/day, over 4 weeks) was performed as a stress model to study depression along with blue light therapy. The light sources in this experiment are blue light sources with three different frequencies, Its details are as follows: LED, wavelength = 462.8 nm, Tc ≥ 25,000 K, flicking frequency = 0 Hz or 8 Hz or 40 Hz, irradiation power

density = 0.3 mW/cm2. Behavioral experiments including sucrose preference, open field, and tail suspension tests were assessed to evaluate the antidepressive effects of blue light therapy. **Results:** Cort-Crs procedure induced depression like behaviors. Prophylactic blue light therapy improves improved behavioral results. The optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters. **Conclusion:** The results showed that 40 Hz light therapies are the most effective. The antidepressant effect of blue light at various durations was examined for the first time in this study. We found that three weeks of blue light therapy had the greatest antidepressant effect. Moreover, we also found that three hours of blue light therapy per day had the best efficacies. Our results reconfirmed blue light is the effective component of light therapy for treatment of depression. And we determined the optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia VII

OLIGODENDROCYTE PATHOLOGY AND COGNITION IN SEVERE MENTAL DISORDERS

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: Cognitive deficits are a hallmark of severe mental disorders and remain after the acute treatment period. These symptoms respond only limited to treatment with psychotherapy or antipsychotics and cause disability in everyday life, including functional impairments that prevent social and professional reintegration. In this symposium we add to the new view that disturbed myelin plasticity, more precisely “dysmaturation of oligodendrocyte precursor cells (OPCs)”, is a critical pathophysiological substrate of cognitive disturbance in severe mental disorders and represents an unexplored target for treatment. OPCs generate oligodendrocytes that are capable of myelination. Their dysfunction leads to disturbances in myelination, connectivity, metabolic support of neurons and – on the functional level – cognitive deficits. Recent replicated findings of decreased oligodendrocyte number in the hippocampal subregion CA4 and new data from a postmortem study of OPCs in Schizophrenia will be provided. The relation to cognitive deficits and alterations in Major Depression and Bipolar Disorder will be discussed. Insight in molecular changes related to oligodendrocytes, synaptic plasticity and energy metabolism from proteomic studies in postmortem brains, hiPSCs and organoids in Schizophrenia will be given. An overview on cognitive deficits in Schizophrenia with emphasis on different cognitive domains will be provided. Finally, recent genome-wide association studies (GWAS) in in Major Depression, their relation to the neurobiological background of cognition and an introduction on the clinical relevance of cognition in Major Depression will be discussed.

LOSS OF OLIGODENDROCYTES IN SCHIZOPHRENIA AND ITS RELATION TO COGNITIVE DEFICITS

Peter Falkai*[1], *Andrea Schmitt2, Florian Raabe2, Isabel Maurus2, Sergi Papiol2, Anna Kessel3, Konstantin Schlaaff3, Johann Steiner3*

[1]German Society for Biological Psychiatry, 2LMU Munich, 3University of Magdeburg

Objective: In a diffusion tensor imaging (DTI) study, oligodendrocyte (OL)-related gene variants, such as myelin-associated glycoprotein (MAG), were related to white matter tract integrity and cognitive performance in schizophrenia patients. Interestingly, a single nucleotide polymorphism of the OL lineage transcription factor 2 (OLIG2), which is necessary for maturation of OPCs, was also associated

with reduced white matter fractional anisotropy, indicating impaired myelination in schizophrenia. Therefore in our studies we focused on oligodendrocyte numbers in brains of schizophrenia patients and their relation to cognitive deficits. **Methods:** Using unbiased design-based stereology in postmortem brains from schizophrenia patients, we estimated total number of oligodendrozytes, neurons and astrocytes in hippocampal subregions. In an independent postmortem sample in the hippocampus we tried to replicate these findings and extended the area of interest to the white matter of the cingulum. We applied immunohistochemical staining of breast carcinoma amplified sequence 1 (BCAS1) to identify and quantify density of early myelination oligodendrocyte precursor cells in the hippocampus. **Results:** Our stereological post-mortem findings demonstrated that a reduction in the number of OLs in the cornu ammonis 4 (CA4) subregion of the hippocampus was related to cognitive dysfunction in schizophrenia patients and has impact on the neuronal Papez Circuit. In an independent sample we replicated the finding of reduced OLs in CA4 and found a reduced number of OLs in white matter of the Cingulum. Results from immunohistochemical studies will be presented. **Conclusion:** Targeting the DLPFC in schizophrenia a previous stereological study revealed a loss of OLs, pointing to a network problem involving fronto-temporal regions. Taken together, these findings show that dysconnectivity in schizophrenia is likely related to oligodendrocyte deficits. New treatment strategies are needed that target deficits in OL-related pathological processes, for example by improving differentiation of OPCs to myelinating OLs, thereby promoting myelination and optimally abolishing cognitive symptoms.Physical exercise is so far the only existing means to enhance myelin plasticity and consequently improve cognition in schizophrenia. Accumulating evidence suggests that stimulating myelin plasticity (OPC differentiation and unidentified OL-based molecular mechanisms) represents a promising and thus far unexplored mechanism to enhance cognition.

OLIGODENDROCYTES AS TARGETS FOR SCHIZOPHRENIA TREATMENT

Valéria Almeida**1*, *Daniel Martins-de-Souza2*

[1]University of Muenster, 2University of Campinas (Unicamp)

Objective: Several studies have implicated oligodendrocyte dysfunction and myelin abnormalities, including altered expression of myelin-related genes, with schizophrenia. However, the molecular mechanisms subjacent of these alterations could still benefit of more studies.

Methods: Our group aimed at characterizing the biochemical profiles of different in vitro oligodendrocyte models when treated with the classical antipsychotics such as haloperidol and clozapine as well as with novel treatments such as D-serine and different cannabinoids. For that, we mostly employed shotgun proteomics, using 2DLC–HDMSe and label-free quantitation besides cellular validation assays.

Results: Biochemical pathways commonly affected by the classical antipsychotics were mainly associated to ubiquitination, proteasome degradation, lipid metabolism and DNA damage repair. In turn, metabolic processes, especially the metabolism of nitrogenous compounds, were a predominant target of modulation of clozapine + d-serine treatment. The modulation of cannabinoid signaling in cultured oligodencrocytes was found to affect pathways linked to cell proliferation, migration, and differentiation of oligodendrocyte progenitor cells. Additionally, we found that carbohydrate and lipid metabolism, as well as mitochondrial function, were modulated by different endo- and phytocannabinoids.

Conclusion: Our results open new roads of opportunities, suggesting that cannabinoid signaling in oligodendrocytes might be relevant in the context of demyelinating and neurodegenerative diseases.

COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

Siegfried Kasper**1*

[1]*Center for Brain Research*

Objective: Cognitive dysfunction in schizophrenia has been considered as a main component of the disease in numerous publications

Methods: A summary of the literature is given including recently available data

Results: Cognitive dysfunction in schizophrenia has been shown to be a main component of the disease and can be influenced by second generation antipsychotics but not for the older types of medication called typical neuroleptics. Newer psychopharmacological approaches have been taken which will be summarised.

Conclusion: There is considerable literature and data available to address cognition in schizophrenia and the influence of specific antipsychotic medication

CLINICAL IMPORTANCE AND GENETIC UNDERPINNINGS OF COGNITIVE DYSFUNCTION IN DEPRESSION

Bernhard Baune**1*

[1]*University of Münster*

Objective: Major Depressive Disorder (MDD) often is associated with significant cognitive dysfunction, both during a current episode of depression as well as a trait before onset or between episodes of depression. The biological underpinnings of cognitive function have been explored in healthy individuals, but remains elusive in severe mental illness, such as major depressive disorder (MDD) Here investigated the genetic foundations of cognitive function in MDD.

Methods: To this end, we conducted a meta-analysis of genome-wide interaction of MDD and cognitive function using data from four large European cohorts in a total of 3510 MDD cases and 6057 controls. In addition, we conducted analyses using polygenic risk scores (PRS) based on data from the Psychiatric Genomics Consortium (PGC) on the traits of MDD, Bipolar disorder (BD), Schizophrenia (SCZ), and mood instability (MIN). Functional exploration contained gene expression analyses and Ingenuity Pathway Analysis (IPA®).

Results: We identified a set of significantly interacting single nucleotide polymorphisms (SNPs) between MDD and the genome-wide association study (GWAS) of cognitive domains of executive function, processing speed, and global cognition. Several of these SNPs are located in genes expressed in brain, with important roles such as neuronal development (REST), oligodendrocyte maturation (TNFRSF21), and myelination (ARFGEF1). IPA® identified a set of core genes from our dataset that mapped to a wide range of canonical pathways and biological functions (MPO, FOXO1, PDE3A, TSLP, NLRP9, ADAMTS5, ROBO1, REST). Furthermore, IPA® identified upstream regulator molecules and causal networks impacting on the expression of dataset genes, providing a genetic basis for further clinical exploration (vitamin D receptor, beta-estradiol, tadalafil). PRS of MIN and meta-PRS of MDD, MIN and SCZ were significantly associated with all cognitive domains.

Conclusion: Our results suggest several genes involved in physiological processes for the development and maintenance of cognition in MDD, as well as potential novel therapeutic agents that could be explored in patients with MDD associated cognitive dysfunction.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Arun Ravindran, Canadian Network for Mood and Anxiety Treatments

Symposium Synopsis: Background: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing

subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.
Methods: Strength of evidence was rated based on published literature and clinical expertise. The systematic evaluation focused on the domains of CAM therapies: lifestyle interventions, physical therapies, nutraceuticals and herbal remedies.
Results: The first presentation will focus on lifestyle interventions, including diet and smoking cessation etc., and will outline evidence and recommendations. The second presentation will provide an update on the evidence for the benefit of physical therapies, nutraceuticals and herbal remedies for the treatment of MDD, followed by two presentations on the therapeutic benefit and the proposed neurobiological mechanisms of exercise and yoga. Recent publications confirm the benefit of exercise and yoga reported in previous guidelines, which recommended its use as adjunctive treatment in mild to moderate major depression.
Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

CLINICAL GUIDELINES FOR THE USE OF LIFESTYLE-BASED MENTAL HEALTH CARE IN MAJOR DEPRESSIVE DISORDER: WORLD FEDERATION OF SOCIETIES FOR BIOLOGICAL PSYCHIATRY (WFSBP) TASKFORCE

*Wolfgang Marx1, Sam Manger2, Mark Blencowe3, Greg Murray4, Fiona Yan-Yee Ho5, Sharon Lawn6, James Blumenthal7, Felipe Schuch8, Brendon Stubbs9, Anu Ruusunen10, Hanna Demelash Desyibelew11, Timothy G. Dinan12, Felice Jacka*1, Arun Ravindran13, Michael Berk1, Adrienne O'Neil1*
Deakin University, 2James Cook University, 3Australasian Society of Lifestyle Medicine, 4Swinburne University of Technology, 5The Chinese University of Hong Kong, 6Flinders University, 7Duke University Medical Center, 8Federal University of Santa Maria, 9King's College London, 10University of Eastern Finland, 11Bahir Dar University, 12University College Cork, 13University of Toronto

Objective: The primary objectives of these international guidelines were to provide a global audience of clinicians with (a) a series of evidence-based recommendations for the provision of lifestyle-based mental health care in clinical practice for adults with Major Depressive Disorder (MDD) and (b) a series of implementation considerations that may be applicable across a range of settings.
Methods: Recommendations and associated evidence-based gradings were based on a series of systematic literature searches of published research as well as the clinical expertise of taskforce members. The focus of the guidelines was eight lifestyle domains: physical activity and exercise, smoking cessation, work-directed interventions, mindfulness-based and stress management therapies, diet, sleep, loneliness and social support, and green space interaction.
Results: Nine recommendations were formed. The recommendations with the highest ratings to improve MDD were the use of physical activity and exercise, relaxation techniques, work-directed interventions, sleep, and mindfulness-based therapies (Grade 2). Interventions related to diet and green space were recommended, but with a lower strength of evidence (Grade 3). Recommendations regarding smoking cessation and loneliness and social support were based on expert opinion. Key implementation considerations included the need for input from allied health professionals and support networks to implement this type of approach, the importance of partnering such recommendations with behaviour change support, and the need to deliver interventions using a biopsychosocial-cultural framework.

Conclusion: Lifestyle-based interventions are recommended as a foundational component of mental health care in clinical practice for adults with Major Depressive Disorder, where other evidence-based therapies can be added or used in combination. Further work is also needed to develop innovative approaches for delivery and models of care, and to support the training of health professionals regarding lifestyle-based mental health care.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Brendon Stubbs*[1]
[1]*King's College London, Institute of Psychiatry*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Kaviraja Udupa*[1]
[1]*National Institute of Mental Health and Neurosciences (NIMHANS) Hosur Road, Bangalore*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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proposed neurobiological mechanisms of exercise and yoga. Recent publications confirm the benefit of exercise and yoga reported in previous guidelines, which recommended its use as adjunctive treatment in mild to moderate major depression. **Conclusion:** Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

EARLY INTERVENTION FOR BIPOLAR DISORDER: FROM CUTTING EDGE SCIENCE TO TRANSFORMATIVE CLINICAL PRACTICE

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: The success of early psychosis programs has shown that early intervention for serious mental illnesses is feasible, effective, and scalable. For example, building on the Recovery After an Initial Schizophrenia Episode (RAISE) study, a nationwide network of first episode psychosis programs called NAVIGATE was created in the United States to provide coordinated specialty care for people with schizophrenia. Early intervention is also important for bipolar disorder (BD) but early intervention efforts for BD are less advanced. This symposium will highlight scientific advances in identifying people with, and even at risk for, early-stage BD and the development of evidence based clinical interventions to treat them. We will show early results from cutting edge work using endophenotypes to identify people in the prodromal or early stages of BD. The endophenotypes of interest include cortical inhibition and mirror neuron system activity during transcranial magnetic stimulation (TMS), functional near infra-red spectroscopy (fNIRS), eye-movement tracking findings, abnormalities in retinal vasculature, and neurocognitive functioning. We will describe novel intervention programs for early-stage BD patients being developed in the United States and Canada. STRIDE, based at the University of Minnesota, adapts the NAVIGATE early psychosis model for early-stage BD. We will also show key aspects of a novel manualized psychological intervention for prodromal and early-stage BD based at the University of British Columbia. The presenters will highlight opportunities and challenges for early intervention in BD, including possibilities for harmonizing clinical research and treatment.

STRIDE: A BLUEPRINT FOR TAILORING COORDINATED SPECIALTY CARE FOR EARLY INTERVENTION IN BIPOLAR DISORDER

David Bond**1*, *Kathleen Miley2, Carissa Coudray3, Piper Meyer-Kalos3*

[1]Johns Hopkins University School of Medicine, 2Health Partners Institute, 3University of Minnesota

Objective: Early intervention for bipolar disorder (BD) has the potential to improve clinical and functional outcomes. Comprehensive clinical programs are needed. Coordinated specialty care (CSC) models such as NAVIGATE are evidence-based interventions for first episode psychosis that were widely implemented in the US and internationally following results from the Recovery After an Initial Schizophrenia Episode (RAISE) trial. We sought to adapt NAVIGATE to meet the unique needs of people with BD.

Methods: Adaptations to the NAVIGATE model for BD were determined through literature review, international expert consultation, and focus groups with stakeholders including patients, family members, and clinicians.

Results: A detailed model for CSC for BD, called STRIDE, was created based on this iterative process. Strengths of NAVIGATE, including shared decision making and a recovery focus, were maintained. Key adaptations for BD included 1) modification of psychotherapy modules to address prevention

and treatment of mood episodes, 2) new modules on circadian and social rhythms, affective regulation, and comorbidities common in BD, 3) creation of an early-stage BD prescribers manual, 4) broadened focus on health and wellbeing, 5) increased attention to co-occurring substance use disorders; 6) tailored family supports, and 7) incorporation of supported education and employment services. **Conclusion:** NAVIGATE has many strengths and can be adapted to meet the needs of people with BD. Next steps include evaluation of the feasibility of the STRIDE model.

CAN ENDOPHENOTYPES HELP IN EARLY IDENTIFICATION AND INTERVENTION PLANNING IN BIPOLAR DISORDER?

Muralidharan Kesavan**1*, *Sanjay Naik1, Ramkumar Segar1, Daniel Ritish Paul Kavati1, Abhishek Ramesh1, Nandhini Bojappen1, Shivani Sivaramkrishnan1, Preethi Reddy1, Rakshathi Basavaraju1, VijayaKumar KG1, Rajakumari P Reddy1, Urvakhsh Mehta1, Naren Rao1, Venkatasubramanian Ganesan1*

1

National Institute of Mental Health and Neurosciences

Objective: The role of first-episode mania (FEM) in the progression of bipolar disorder (BD) is well studied, with reported brain structural and neuropsychological deficits soon after FEM, very early in the course of the disorder. This has been linked to poor clinical and functional outcomes. Hence, there is a need to study biological risk markers for BD, which may be present in individuals at risk for BD, even before disease onset.

Methods: about a series of investigations - in individuals very early in the course of the disorder (BD I- FEM in remission) and in individuals who are yet to develop this disorder (matched healthy individuals with family history of BD I) as compared to healthy subjects (no personal or family history of psychiatric disorders). The three groups of subjects were investigated for (1) cortical inhibition, social cognition and mirror neuron system activity using transcranial magnetic stimulation (TMS), (2) functional near infra-red spectroscopy (fNIRS) during facial emotion recognition and cognitive task performance, (3) eye-movement tracking - saccades and smooth pursuit during facial emotion processing tasks (4) abnormalities in retinal vasculature using nonmydriatic fundus camera and (5) neuropsychological functioning. They were also examined using bedside tests of neurological soft-signs, minor physical anomalies.

Results: TMS markers of cortical inhibition, inteleukin-6, executive functions, emotion processing and eye movement tracking had endophenotypic potential while the other investigations were more of a disease marker rather than risk marker. Interestingly, on all investigations, the FEM subjects differed significantly from healthy subjects indicating that these investigations have tremendous potential in differentiating remitted early bipolar disorder from healthy subjects.

Conclusion: The endophenotypic and diagnostic potential of each of these investigations as well as its translational applications in clinical practice will be discussed.

COGNITIVE ENDOPHENOTYPES AND NEUROPSYCHOLOGICAL INTERVENTIONS IN EARLY BIPOLAR DISORDER

Rajakumari Reddy**1*, *Muralidharan Kesavan1, Ivan Torres2, Nandini Bhojappa1, Shyam Sundar1, Preethi Reddy1, Jayasree Basivireddy2, Lakshmi Yatham2*

[1]National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, 2University of British Columbia

Objective: Bipolar disorder (BD) is characterized by recurrent depressive and manic episodes. First episode of mania (FEM) determines bipolarity and is universally recognized as the onset of BD. The staging model of BD proposes early intervention to be more effective, which could mitigate clinical

and neurobiological consequences of the illness. Meta-analyses have shown that euthymic BD exhibit impairment on attention/working memory, verbal memory, speed and executive functions. Unaffected siblings of BD probands tend to show impairment in executive function and verbal learning and memory suggestive of potential endophenotype markers for BD. An understanding of the course of BD from the onset or even prior, may contribute to the development of early interventions. **Methods:** Site: 1 Cross sectional study using convenient sampling method (India) Remitted First episode mania patients (FEM; n=25), first-degree relatives of patients with BD (HR; n=25) and healthy subjects (HC) Site 2: Longitudinal Study, baseline, 1-year, and 3-year time points (Canada) (FEM, n= 91, 61 healthy subjects) Assessment tools: Cognitive domains assessed using neuropsychological battery, mood scales **Results:** Visual Memory and Verbal Fluency (Executive function) have endophenotypic potential thereby emphasising need for early cognitive screening and institution of early interventions. Patients showed deficits in all domains at baseline, and longitudinal trajectories compared to healthy participants with some gains with time. Cross sectional study indicates the impairment prior to onset, longitudinal study indicates impairment but suggests changes in trajectory. Both studies indicate cognitive deficits which could have cascading effects on course and functional outcome of the patients. **Conclusion:** Integrated approach might be beneficial which in turn could have an impact on the course and outcome of the illness. The intervention initiated early may have more benefits. Components of integrated neuropsychological intervention will be discussed in this context.

A NOVEL MANUALIZED PSYCHOEDUCATION AND RESILIENCE ENHANCEMENT PROGRAM FOR INDIVIDUALS AT HIGH RISK FOR BIPOLAR DISORDER: FINDINGS FROM A FEASIBILITY STUDY

Kamyar Karamatian*[1]

[1]

The University of British Columbia

Objective: Bipolar Disorder (BD) typically emerges during adolescence and early adulthood and is associated with significant cognitive impairment and functional disability. Despite the high prevalence and large disability burden, BD often goes unrecognized and untreated for several years leading to serious consequences including greater severity and frequency of mood episodes, higher number of hospitalizations, and elevated risk of suicide. However, no evidence-based intervention program aimed at early identification of BD has yet been developed. We have recently developed a prototype manualized telehealth-based group Psychoeducational and Resilience Enhancement Program for individuals at high risk for BD (PREP-BD). The overarching objective of our study is to determine whether PREP-BD can be feasibly and effectively implemented to increase knowledge of BD, reduce self-stigma, improve help-seeking and enhance resilience in individuals who are at high risk of developing BD.

Methods: Recruitment for this study started in May 2023 and is expected to be completed in March 2024. Participants, aged 15 to 24 years, who meet the Bipolar At-Risk (BAR) criteria (Bechdolf et al., 2010) are recruited into a single-arm before-and-after pilot study to examine the feasibility and acceptability of PREP-BD. The intervention consisted of 8 weekly group sessions, each 60 minutes in duration. Participants complete the following questionnaires before and after the intervention: Help-Seeking Questionnaire, Bipolar Disorders Knowledge Scale, Self-Stigma of Mental Illness Scale-Short Form, and Connor Davidson Resilience Scale. Following the completion of the intervention, a focus group is conducted after the final intervention session to elicit rich, detailed, and first-person accounts of participants' experiences and their suggestions for improving the intervention. In

addition, participants complete a Client Satisfaction Questionnaire (CSQ-8) and the sum of the individual CSQ-8 item scores are calculated as a measure of the intervention's acceptability.
Results: To date, all participants who were deemed eligible (N=14) signed up to participate in PREP-BD. Preliminary findings from this pilot study confirmed the feasibility and acceptability of PREP-BD.
Conclusion: Although preliminary, our results suggest that a telehealth-based psychoeducational intervention can be feasibly implemented to improve help-seeking and enhance resilience in individuals who are at high risk of developing BD. Directions for future research and clinical implications will be discussed.

TRANSLATIONAL ADDICTION STUDIES OF NOVEL PSYCHOACTIVE SUBSTANCES

Aviv Weinstein, Ariel University
Symposium Synopsis: During the last decade, there has been a worldwide increase in the use and consumption of Novel Psychoactive Substances (NPS) worldwide. NPS are becoming a major health issue because of rising consumption and increasing numbers every. The acute effects of NPS and their long-term side effects are not always known, and safety data regarding their toxicity are often unavailable. Given the rapid increase in the use of NPS, their potential for dependence and abuse, and harmful medical and psychiatric effects, there is a need for pre-clinical and clinical research. The aim of this symposium is to provide an overview on pre-clinical and clinical studies of two of the major classes of NPS, synthetic cannabinoids (SCs) and synthetic cathinones. Results from preclinical studies (behavioral and neurochemical) will be presented. Dr. Maria De Luca who will start by presenting novel findings on repeated exposure to JWH-018 (a major synthetic cannabinoid) in adult and adolescent rats and mice. Dr. Matteo Marti will present studies on the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of the SCs JWH-018 and 5F-PB22 in mice. Prof. Magi Farré will present human clinical studies on Pharmacological effects and toxicity of the synthetic cathinones methylone and clephedrone (4-CMC), and after intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP) evaluating acute pharmacological effects and pharmacokinetics in plasma and oral fluid. Finally, Prof. Weinstein will discuss cognitive and brain imaging studies in regular users of synthetic cannabinoids, with a special focus on mental health.

NEUROBIOLOGICAL SEQUELAE OF THE PASSIVE OR VOLUNTARY ADMINISTRATION OF THE SYNTHETIC CANNABINOID RECEPTOR AGONIST JWH-018

Maria De Luca*[1]
[1] *University of Cagliari*

Objective: The use of Synthetic Cannabinoid Receptor Agonist (SCRA) is growing among adults and adolescents, posing major medical and psychiatric risks. JWH-018 represents the reference compound of SCRA-containing products. Our preclinical studies were performed to evaluate the enduring effects of repeated JWH-018 passive or voluntarily exposure.
Methods: Studies were performed by both passive intraperitoneal (0.25 mg/kg ip for 14 days) or vaping administration (0.3 mg/ml vapor by LJARI vapor chambers for 21 consecutive days) in adult and adolescent rats, respectively. Additional studies were performed by intravenous self-administration (lever pressing, Fixed Ratio 1–3; 7.5 µg/kg/inf) in adolescent mice.
Results: Main results, obtained 24 hours and 7 days after drug discontinuation, showed that repeated JWH-018 exposure in adult rats: (i) induced anxious/aversive behaviors; (ii) decreased spontaneous activity and number of dopamine neurons in the VTA; and (iii) decreased dopamine sensitivity in the NAc shell and core, but not in the mPFC, to a first chocolate exposure; conversely, after a second exposure, dialysate dopamine fully increased in the NAc shell and core but not in the mPFC.

Moreover, passive JWH-018 induced: (iv) astrogliosis (mPFC, NAc shell/core, VTA), microgliosis (NAc shell/core), and downregulation of CB1 receptors (mPFC, NAc shell/core). In addition, we characterized the pharmacokinetic profile of JWH-018 in adolescent male and female rat plasma after passive JWH-018 inhalation. Other studies showed that adolescent JWH-018 IVSA induced at adulthood: (i) repetitive/compulsive-like behaviors; (ii) microgliosis (CPu, NAc) and astrocytopathy (CPu), as revealed by a decreased GFAP expression; (iii) increased of the chemokines MPC1 (striatum) and RANTES (cortex), and a decrease of the cytokines IL2 and IL13 (cortex). **Conclusion:** Taken together, these data suggest that the long-lasting behavioral and neurochemical effects of JWH-018 exposures may not differ substantially as a function of passive or voluntary administration except for some specific aspects of the brain immune response, that deserve further clarification. Nevertheless, this study provides results with high translational value in the field of psychiatric disorders by examining the interaction among environmental factors that are linked to increased psychiatric risk in humans, but also shedding light on the psychiatric risk associated with SCRA vaping, a habit that is becoming increasingly popular.

SEROTONINERGIC SYSTEM IS INVOLVED IN THE PHARMACO-TOXICOLOGICAL EFFECTS INDUCED BY SYNTHETIC CANNABINOIDS IN MICE: PRECLINICAL STUDIES ON JWH-018, 5F-PB22 AND AKB-48

Matteo Marti*[1], *Giorgia Corli[1], Sabrine Bilel[1], Marta Bassi[1], Fabrizio De Luca[2], Elisa Roda[3], Carlo Alessandro Locatelli[3]*

[1]University of Ferrara, [2]University of Milan, [3]Istituti Clinici Scientifici Maugeri, IRCCS Pavia

Objective: Since their first appearance on the illicit drugs market, Synthetic Cannabinoids (SCs) have been frequently detected in biological samples from patients involved in several intoxication and death cases. Consumption of these drugs has been related with the induction of psychotic symptoms, the underlying mechanisms of which are still to be clarified.

Methods: This study primarily investigated the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of indole-based SCs JWH-018 and 5F-PB22. Secondly, changes induced by the repeated administration of the indazole-based compound AKB48 in mice and neuroplasticity at CB1 and 5HT2A receptor and SERT adaptation have been evaluated.

Results: The present results pointed out that the tested substances deeply alter sensorimotor responses, nociceptive threshold, core temperature, and motor activity in mice. Pretreatment with the selective 5HT2A receptors antagonist MDL100907 at least partially prevented acute sensorimotor disruption, as well as antinociceptive and hypothermic effects induced by both JWH-018 and 5F-PB22. On the other hand, the effects of AKB48 have been significantly influenced by the repeated treatment, as the impairment induced by the third injection was strongly reduced in respect to that of previous administration. Alongside, repeated AKB48 injection caused a rapid downregulation of CB1 receptors and SERT expression, while 5HT2A were upregulated in cerebellar areas.

Conclusion: This evidence states for the first time the relevance of serotoninergic 5HT2A receptors in mechanisms underlying pharmaco-toxicological effects of SCs that may also significantly vary with recurrent use, thus suggesting the emergence of tolerance. Ultimately, the present findings suggest the high-risk profile of SCs as drugs of abuse with reference to the embedding of a possible increased vulnerability for psychotic-like symptoms, further related to mental disorders such as schizophrenia.

SYNTHETIC CATHINONES: ACUTE EFFECTS IN HUMANS

Magi Farre*[1], *Clara Pérez -Mañá[1], Esther Papaseit[1]*

[1]Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona

Objective: Cathinones are derivatives of phenylethylamine, the basic structure of amphetamines, which include a keto group, with cathinone being the most important active substance of the Catha edulis or khat shrub. In recent years, many cathinones of synthetic origin have appeared on the market, forming a relevant part of the so-called new psychoactive substances. The most important are mephedrone, methylone, methylenedioxypyrovalerone (MDPV) or eutylone, among others. These substances are consumed as alternatives to 3,4-methylenedioxymethamphetamine (ecstasy or MDMA). The information available on these substances in humans came from surveys, online description of effects and cases of intoxications. There are few published experimental studies on the pharmacokinetics and pharmacological effects associated with the administration of synthetic cathinones in humans (mephedrone, methylone).

The objective was to evaluate acute pharmacological effects and pharmacokinetics of three synthetic cathinones in humans.

Methods: This paper presents original results of the acute human pharmacology of three different synthetic cathinones. Studies were observational in a recreational setting. A group of 24 volunteers (men and women) were included. Substances include oral doses of clephedrone (4-CMC), and intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP). Vital signs and subjective effects were evaluated repeatedly along time. Samples of oral fluid, sweat and urine were collected.

Results: Results showed prototypical effects of psychostimulants in vitals and subjective effects (euphoria, well-being, empathy). The time course of effects/concentrations in saliva were faster after intranasal administration and delayed after oral administration.

Conclusion: The three new synthetic cathinones showed similar effects of other derivatives as methylone and mephedrone. Time course of effects and pharmacokinetics parameters showed some differences that can explain the preference for some substances.

THE EFFECTS OF SYNTHETIC CANNABINOIDS ON EXECUTIVE FUNCTION AND RELATED BRAIN ACTIVITY IN FMRI

Aviv Weinstein*[1], *Koby Cohen[1]*

[1]

Ariel University

Objective: The aims of our studies were to investigate the effects of chronic use of synthetic cannabinoids on the brain's structure and function, cognitive and emotional function and schizotypal personality disorder and big 5 personality traits.

Methods: Cognitive tasks measuring executive function (N-back, WCST, Go-No-GO, Stroop) Structural and functional brain imaging studies in fMRI measuring gray matter and brain activation. Questionnaires assessing depresion, anxiety, Big 5 Personality traits and schizotypal personality disorder.

Results: Synthetic cannabinoid users have exhibited overall smaller grey matter volume than control participants, and in specific regions: insula, the inferior frontal gyrus, the anterior cingulate cortex and the precuneus. These brain regions are rich with cannabinoid CB1-receptors and are associated with addictive behaviors, cannabis use and abstinence. Secondly, SC users were less accurate and showed longer reaction times on the 2-back and 1-back task than control participants. On the high the working memory load, control participants showed additional activation in both parahippocampal gyrus and the precuneus, areas associated with the default mode network. We have further found impairments in mental flexibility (WCST task), impulsivity (Go No Go task) and

response to emotional words (Stroop) in SC users. Furthermore, SC users were more depressed, had higher scores of schizotypal personality disorder and were more introverted, neurotic and less conscientious on the big five questionnaire compared with regular cannabis users and control participants. **Conclusion:** These findings may have major implications for our understanding of the long-term consequences of synthetic cannabis on cognitive and brain function. We currently run a study using F-DOPA in PET MR to assess dopamine function and neural networks in SC users which we hope to report.

PRESENTATION SKILLS WORKSHOP

Peter Falkai, German Society for Biological Psychiatry

PRESENTATION SKILLS WORKSHOP

David Castle1, Peter Falkai2, Susan Rossell3

[1]University of Tasmania, 2German Society for Biological Psychiatry, 3Swinburne University

Objective: To outline a set of strategies to enhance scientific presentations, with a view specifically to upskill more junior colleagues such that they refine and hone their presentation skills to ensure they are engaging, focussed and effective.

Methods: After a brief introduction to the topic, with basic 'do's and don'ts' of presenting skills, the three presenters will deliver examples of what they think are good and not-so-good elements and techniques, augmented by video footage of effective and not-so-effective communication styles from media, including movies and television. The presenters will then discuss amongst themselves and engage the audience in a discussion about what elements of each presentation were effective, and what was not. Tips and strategies will be provided, as well as role play opportunities provided to the audience (nobody will be forced to do anything they don't wish to do!). A particular component will be dedicated to the fine art of how to pose a 'question from the audience' in a succinct and circumscribed manner, as well as how to answer such questions politely and effectively.

Results: We will seek to deliver an interactive presentation skills workshop which will hopefully be both fun and instructive, and show numerous examples to illustrate strategies and techniques to enhance participants' skill set.

Conclusion: Presenting one's research is a key requirement for all researchers. Learning early in one's career can enhance effective skills and hopefully make the experience of future audiences better.

WHAT ARE THE SECRETS TO A GREAT CONFERENCE PRESENTATION?

Susan Rossell1
[1]Swinburne University

Objective: Presenting at conferences is a critical part of science communication for any researcher or academic. Developing a conference presentation is no different to developing any other presentation: you need to be well prepared, consistent throughout and ensure you're able to resonate with your audience. The aim of this workshop presentation will be to provide some important strategies to help deliver a great conference presentation.

Methods: One of the biggest challenges to giving a great presentation is managing your nerves. The current talk will provide some important dos and don'ts' to help you with your anxieties and deliver a professional talk.

Results: I will work through an important checklist, which will include: be prepared and map out what you are going to talk about; make sure that you work within your time constraints; use visuals appropriately; keep things simple and consistent; know your audience; rehearse, rehearse, rehearse; prepare, prepare, prepare; back up your backup; and breathe.

Conclusion: Once you have mastered these tips you will be all set to give a great presentation at any conference big or small.

HOW TO GIVE A TALK AND PRESENT MY SCIENCE AND MYSELF

Peter Falkai1, Florian Raabe2
[1]German Society for Biological Psychiatry, 2Max Planck Institute of Psychiatry
Objective: To show evidence to improve your presentation skills to give a presentation.
Methods: Narrative review of the literature and presenting own experience.
Results: Five tips are given to present yourself and your science successfully.
Conclusion: Taking some time to prepare a talk is a good investment into your career and future.

3:30 p.m. - 5:00 p.m.
Concurrent Workshop I

SEXUAL VIOLENCE AND WOMEN

Florence Thibaut, University Paris Cité

SEXUAL VIOLENCE IN ECUADOR, LATIN AMERICA

Victoria Valdez1
[1]Catholic University of Guayaquil Ecuador, Ecuadorian Society of Biological Psychiatry
Objective: Latin America has the highest rates of gender-based violence in the world, according to the Wilson Center.
Methods: This lecture will focus on gender-based violence, sexual violence concepts, societal factors, drug trafficking industry and present statistical research on this issue.
Results: Sexual violence reveals many areas that need to be explored such as migratory transit violence, migratory consequences, wars and gender-based violence.
INEC (Ecuadorian Statistics) established a total amount of gender-based violence 64.9%, sexual violence 32.7% CEPAM (ONG) complaints 8.682 (2006).
Conclusion: It is important to understand gender violence from a women's rights perspective and not merely as a criminal problem. This way, public policies on gender violence can be designed to include a more comprehensive and effective approach to prevention and treatment.

BEHAVIORAL AND NEURAL FACTORS IN GENDER-RELATED ASPECTS OF VIOLENCE AND ADDICTIONS

Marc Potenza
Objective: Males and females differ with respect to tendencies to engage in and experience violence and aggression as well as in substance and behavioral addictions that may often co-occur with violence and aggression. Understanding better such relationships and the etiological factors could help reduce the effects of aggression, violence and addictions.
Methods: Multiple methods including surveys and neuroimaging involving adolescents and adults have been used to assess and understand gender-related considerations relating to violence, aggression, and addictive behaviors. Factors related to these constructs (e.g., stress and trauma) have also been investigated using these methods, and findings from such studies will be presented.
Results: Gender-related differences exist in relationships between addictive behaviors and violence and aggression. Tendencies such as impulsivity/sensation-seeking appear particularly relevant in males, including at relatively early developmental stages. Women as compared to men tend to experience more stress and trauma in multiple domains (e.g., social, sexual) but not all (e.g., occupational), with stronger links between stress and addictive behaviors seen in women versus men. Sexual trauma is more frequently reported in females versus males, with associated adverse

effects. Gender-related differences in brain responses to stress in women versus implicate multiple cortical brain regions, resonating with gender-related responses to stress and drug cues in people with substance addictions. These findings also resonate with those from studies of youth with higher versus lower levels of childhood trauma, suggesting potential mechanisms for transgenerational cycles of risk for addictions and other poor outcomes. **Conclusion:** Understanding gender-related factors linked to violence, aggression, and addictive behaviors is important for improving the health and well-being of females and males across developmental stages. Neuroimaging approaches are being used to investigate relevant brain- behavior relationships in this regard. Translating an improved biological understanding into improved prevention, treatment and public health interventions is an important next step.

CHEMICAL SUBMISSION AND SEXUAL VIOLENCE

Florence Thibaut1

[1] *University Paris Cité*

Objective: The term chemical submission refers to a substance administration to a person without his/her knowledge to cause him/her a change in the state of consciousness and judgment. This state might be used to perpetrate sexual violence against the victim.

Methods: We will review the main characteristics of the chemical substances consumed and the profiles of victims and aggressors.

Results: It was estimated that up to 17% of sexual assaults could be classified as chemical submission due to the involuntary exposure of the victim to a psychoactive substance. Women under 20 are particularly vulnerable to this form of sexual offence.

Conclusion: Specific prevention programs and training of health personnel is crucial to make the diagnosis (Folgar et al. 2017).

In a changing world (social interactions, dating methods, new technologies) and with the increasing use of new synthetic drugs (designer benzodiazepines, GHB...), the modus operandi of the perpetrators themselves is changing and require increased vigilance at all levels (Chaouachi 2023).

WFSBP TASK FORCE TREATMENT GUIDELINES UNIPOLAR DEPRESSIVE DISORDERS

Michael Bauer, Technische Universität Dresden

RAPID-ACTING ANTIDEPRESSANT TREATMENTS: WHERE IS THEIR PLACE IN THE TREATMENT PATHWAY

Allan Young, King's College London

Background: Mood disorders impose the largest disease related burden related to mental ill-health in adults. Although effective treatments exist, many patients are treatment resistant. New rapidly acting antidepressant treatments (RAATS) are becoming available but their place in the treatment pathway remains to be fully determined.

Objectives: To review the evidence base and science related to RAATS (psychedelics, (s)ketamine).

Methods: Evidence and literature-based workshop.

Findings: Discussion about RAATS in the treatment pathway for mood disorders.

Conclusion: Conclusions: RAATS will play a part in our future treatment pathways.

TREATMENT-RESISTANT DEPRESSION (TRD)

Anthony Cleare1

[1] *Institute of Psychiatry, King's College London*

Objective: To discuss the definitions and epidemiology of TRD

To discuss latest evidence regarding pharmacological and other augmentation strategies in TRD

Methods: Synthesis of literature.
Results: Key findings in TRD include: (1) The need for continued refining of how we diagnose, stage and stratify patients with TRD; (2) Extensive treatment gaps, where few patients are getting optimal treatment (3) accumulating evidence that augmentation strategies are an effective option in TRD and (4) evidence that the poor naturalistic prognosis for many with TRD can be improved using optimised treatment. Data on comparative efficacy of augmentation strategies will be discussed.
Conclusion: TRD remains a key clinical problem. Synthesis of the latest evidence helps us understand the important, pharmacological, role that augmenting antidepressant therapy (with psychotherapeutic and/or neurostimulatory add-on treatments) can play in improving long term outcomes in TRD.

MODERN TREATMENT GUIDELINES: METHODOLOGICAL AND TECHNICAL ASPECTS

*Andrea Pfennig*1, Michael Bauer2, Bettina Soltmann1*

[1]University of Technology Dresden, 2German Society for Biological Psychiatry; University of Technology Dresden

Objective: Methodological and technical aspects of the development of modern treatment guidelines will be presented and discussed. Propositions for the future WFSBP guideline development will be deduced.
Methods: International standards for guideline development will be briefly summarized. The methods applied in the current version of the WFSBP treatment guidelines will be presented.
Results: Challenges in the developmental process of the current version of the WFSBP treatment guidelines will be discussed.
Conclusion: Strategies for the further development of WFSBP treatment guidelines will be presented and discussed including propositions to implement processes of living guideline concepts.

ESTABLISHED AND NOVEL ANTIDEPRESSANT APPROACHES IN THE TREATMENT OF MOOD DISORDERS

Philipp Ritter1

[1]Technische Universität Dresden

Objective: Pharmacological compounds targeting neural components of the monoaminergic signalling system remain the mainstay of treatment for mood disorders. Comparative efficacy, differing side effects profiles and special indications will be reviewed. These classical approaches have more recently been augmented by novel neurostimulatory techniques such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS). The heterogenous landscape of implementation protocols and current evidence base for antidepressant efficacy will be reviewed.
Methods: Evidence and literature-based workshop.
Results: Discussion on the pharmacological and neurostimulatory treatment of mood disorders.
Conclusion: Traditional pharmacological approaches in the treatment of depressive episodes may in future be augmented or in some cases superseded by neurostimulatory approaches to accelerate response and reduce side effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Peter Fried, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Mouhsin Shafi1

[1]Beth Israel Deaconess Medical Center

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.

Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.

Applications Across Neuroscience and Clinical Practice: The workshop will explore the diverse applications of NIBS techniques, including cognitive enhancement, neurophysiologic assessments, treatment of neuropsychiatric disorders, and neurorehabilitation. In-depth discussions will revolve around case studies and ongoing research projects.

Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).

Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions.

Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.

Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF CONCURRENT TRANSCRANIAL ELECTRICAL STIMULATION AND MAGNETIC RESONANCE IMAGING

Shirley Fecteau1

[1]Universite Laval Faculty of Medicine

Objective: We will discuss the use of Transcranial Electrical Stimulation (tES) in patients with neuropsychiatric disorders. We will first describe the main stimulation parameters to consider and the choice of study designs to optimize scientific rigor and clinical responses. We will also address concerns of negative results and the importance of including neuroimaging in tES studies in order to understand its clinical efficacy (or lack of).

When developing neuropsychiatric interventions, it is recommended to measure the hypothesized mechanisms of therapeutic change. Here, the hypothetical mechanism underlying the reduction of a given set of neuropsychiatric symptoms is that tES will modulate brain activity associated with these symptoms. In previous studies, we aimed to reduce symptoms or improve cognition, without identifying the effects of tES on brain activity. A limit of this approach is that when we get null results,

we do not know if they are because tES did not modulate brain activity associated with the targeted symptoms. Also, when the goal is to induce lasting clinical benefits, several tES sessions must be delivered, for example daily sessions for 4 weeks. The effects of a single tDCS session are short-lived. Therefore, before conducting long-term clinical trials, it is important to know whether the proposed tES parameters will likely modulate brain activity relevant to the targeted symptoms.
Methods: We conducted a series of concurrent tES-MRI studies. Specifically, we performed functional and spectroscopic MRI before, during and after tES in groups of healthy adults and adults with substance-related and addictive disorders. Our main questions were: 1) Does tES reach the cortex sufficiently to modulate brain activity? These patients often have cortical abnormalities that may prevent the current from sufficiently reaching the cortex. 2) If tES reaches the cortex, are these effects on brain activity relevant to the targeted symptoms? In this workshop, we will also discuss and demonstrate the technical aspects of how to concurrently use tES and MRI.
Results: Main findings indicate that tES can modulate functional connectivity and neurotransmitters levels. Some of these effects are significant during and/or after stimulation. Some are observed in healthy adults but not in patients, and vice versa. Further, some morphometric properties such as smaller frontal volume in patients correlate with changes induced by tES on functional connectivity and neurotransmitter levels. Functional connectivity of some networks prior to tES can predict tES changes on functional connectivity. Interestingly, none of the published studies from various teams (e.g., delivering tES on both frontal regions found functional connectivity changes inhibitory/excitatory effects) between these frontal regions, despite knowing that the current travels from the anode to the cathode electrodes. The effects are proximal or/and distal to the electrodes (e.g., fronto-parietal network).
Conclusion: Concurrent use of tES and neuroimaging can greatly contribute at understanding the mechanisms of tES and its clinical benefits. Findings from such study designs also contribute at building and developing more specific hypotheses of tES effects, such as potential effects during and after stimulation and how functional connectivity, and priming such connectivity, might influence tES effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Paula Davila Pérez1
1
Hospital Universitario Rey Juan Carlos

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.
Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.
Applications Across Neuroscience and Clinical Practice: The workshop will explore the diverse applications of NIBS techniques, including cognitive enhancement, neurophysiologic assessments, treatment of neuropsychiatric disorders, and neurorehabilitation. In-depth discussions will revolve around case studies and ongoing research projects.
Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).
Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision

targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions. Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development. **Conclusion:** Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Asli Demirtas-Tatlidede1
1

Bahcesehir University, Faculty of Medicine, Istanbul

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.
Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.
Applications Across Neuroscience and Clinical Practice: The workshop will explore the diverse applications of NIBS techniques, including cognitive enhancement, neurophysiologic assessments, treatment of neuropsychiatric disorders, and neurorehabilitation. In-depth discussions will revolve around case studies and ongoing research projects.
Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).
Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions.
Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.
Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

BIG DATA APPROACHES TO DISCOVER DISEASE MECHANISMS OF MENTAL ILLNESS *Ole Andreassen, University of Oslo*

Symposium Synopsis: The last decade has marked a period of growth in psychiatric genetics with new insights into the genetic etiology of psychiatric disorders. As the heritability and the extensive polygenicity of psychiatric disorders are now recognized, gaining a better understanding of the genetic architecture of each disorder is important. Driven by the discoveries of large consortia and big data efforts, large-scale genetic studies have uncovered many common and rare genetic variants associated with psychiatric disorders and related traits. However, there is still much unknown about the underlying disease mechanisms and potential for clinical utility.

As the field progresses and the datasets get larger, there is a need for advanced mathematical approaches. Such big data methodology for translating genetic findings into biological and clinical interpretations are critical to understand the disease mechanisms of psychiatric disorders. We will discuss new big data approaches in psychiatric genetics, to improve discovery, fine-mapping strategies, imaging genetics and clinical utility.

Dr. Nadine Parker (Canada) will present brain imaging genetics results. Dr. Bayram C. Akdeniz (Cypres) will introduce the MiXeR; a causal mixture model tool for estimating the number of causal variants. Naz Karadag (Turkey) will show how the (ConjFDR) tool identifying genetic overlap between neurological disorders and psychiatric disorders. Dr. Shahram Bahrami (Iran) will present the Multivariate Omnibus Statistical Test (MOSTest) and discuss the genetic architecture of hippocampal formation across brain disorders.

These four speakers will highlight the importance of big data approaches in psychiatry, enabling a better understanding of psychiatric disorders and their underlying brain mechanisms.

GENETIC OVERLAP BETWEEN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

*Naz Karadag1, Shahram Bahrami1, Guy F. L. Hindley2, Ole Kristian Drange3, Alexey A. Shadrin1, Srdjan Djurovic4, Anders M. Dale5, Oleksandr Frei1, Ole A. Andreassen6, Olav B. Smeland6, Guy Hindley*7*

1University of Oslo, 2University of Oslo; King's College London, 3Norwegian University of Science and Technology; St. Olavs Hospital, Trondheim University Hospital, 4Oslo University Hospital; University of Bergen, 5University of California, 6University of Oslo; Oslo University Hospital, 7NORMENT, Centre for Mental Disorders ResearchOslo University Hospital, Institute of Clinical Medicine, University of Oslo

Objective: Neurological disorders and psychiatric disorders are heritable brain disorders with overlapping clinical features and high comorbidity. However, the etiological mechanisms underlying the relationships between these disorders are poorly understood. In a series of projects we have aimed to identify overlapping genetic loci between specific neurological and psychiatric disorders to gain a better understanding of their comorbidity and shared clinical features.

Methods: We analyzed non-overlapping genome-wide association study (GWAS) data in over a million participants for neurological disorders epilepsy, migraine, Parkinson's disease and Alzheimer's disease; and for psychiatric disorders schizophrenia, bipolar disorder and depression. We analyzed GWAS summary data using the conjunctional false discovery rate (conjFDR) statistical tool to increase power for locus discovery. Identified genetic loci were then functionally annotated using FUMA.

Results: We find cross-trait genetic enrichment in neurological disorders conditional on associations with psychiatric disorders, and vice-versa, which indicates genetic overlap between these disorders. Several genomic loci have been identified between neurological disorders and psychiatric disorders.

Many of these loci show mixed effect directions, in line with the absent or weak genetic correlations previously reported between these disorders. **Conclusion:** The genetic overlap with mixed effect directions between neurological disorders and psychiatric disorders demonstrates a complex genetic relationship between these disorders and indicates that overlapping genetic risk may contribute to shared pathophysiological and clinical features between brain disorders.

DISTRIBUTED GENETIC ARCHITECTURE ACROSS THE HIPPOCAMPAL FORMATION IMPLIES COMMON NEUROPATHOLOGY ACROSS MAJOR BRAIN DISORDERS

Shahram Bahrami**1*, *Kaja Nordengen1, Alexey A. Shadrin1, Oleksandr Frei1, Dennis Van der Meer2, Anders M. Dale3, Lars T. Westlye1, Ole A. Andreassen1, Tobias Kaufmann4*

[1]University of Oslo, 2University of Oslo; Maastricht University, 3University of California, 4University of Oslo; University of Tübingen

Objective: The hippocampal formation on each side of the medial temporal lobes of the brain plays critical roles in spatial and episodic memory, navigation, emotions, and other complex human behaviours, yet is unexplored about the genetic architecture of the hippocampal formation and its involvement in psychiatric and neurological disorders.

Methods: First, we used multivariate genome-wide association analysis in volumetric data from 35,411 individuals from the UK Biobank (age range: 45–82 years, mean: 64.4 years, s.d.: 7.5 years, 51.7% females) for the main analysis, and of 5262 individuals with non-white ethnicity (age range: 45–81, mean: 62.9, s.d.: 7.6 years, 53.6% females) for the replication in independent data. Second, we used summary statistics from recent large-scale GWAS of total hippocampus volume to identify genetic overlap with eight major developmental and degenerative brain disorders (autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), schizophrenia (SCZ) and bipolar disorder (BIP), migraine (MIG), major depression (MD), Parkinson's disease (PD) and Alzheimer's disease (AD)) by conjunctional FDR statistics (FDR < 0.05).

Results: We revealed 173 unique genetic loci with distributed associations across the hippocampal formation including 153 loci that had not been previously identified. Also, Conjunctional FDR analysis allowed us to test for shared loci between the hippocampus and each of the disorders. We identified 8 loci significantly overlapping with ADHD, 4 loci with ASD, 77 with BIP, 161 with SCZ, 41 with MD, 80 with MIG, 19 with AD and 10 loci significantly overlapping with PD.

Conclusion: Our results suggest a polygenic architecture of the hippocampal formation, distributed across its subregions. The genetic overlap with various brain disorders with typical onset at different stages of life implicated genes, where common genes suggest partly age- and disorder-independent mechanisms underlying hippocampal pathology and it may be relevant targets for future studies.

GENETIC OVERLAP BETWEEN PSYCHIATRIC DISORDERS AND WHITE MATTER MICROSTRUCTURE IMPLICATE DEVELOPMENTAL AND NEURAL CELL BIOLOGY

Nadine Parker**1*, *Weiqiu Cheng1, Pravesh Parekh1, Guy F. L. Hindley2, Alexey A. Shadrin1, Anders M. Dale3, Oleksandr Frei1, Ole A. Andreassen1*

[1]University of Oslo, 2University of Oslo; King's College London, 3University of California San Diego

Objective: Many psychiatric disorders are associated with variations in brain white matter microstructure. A better understanding of the shared genetic basis of psychiatric disorders and white matter microstructure may provide insights into the biological underpinnings of these reported associations. This study aims to characterize the shared genetic architecture between three psychiatric disorders [bipolar disorder (BIP), major depressive disorder (MDD), and schizophrenia (SCZ)] and white matter fractional anisotropy (FA) as well as uncover potential underlying biology.

Methods: Summary statistics were acquired from genome-wide association studies (GWAS) of BIP, MDD, and SCZ from the Psychiatric Genomics Consortium as well as a GWAS of FA performed with UK Biobank participants. Genetic architecture (polygenicity and discoverability) and genetic overlap (genetic correlations and overlapping trait-influencing variants) were estimated along with identification of shared loci. Shared variants were mapped to genes and tested for enrichment among neurodevelopmental, cellular, and molecular gene-sets. The main analyses used average FA across brain white matter while secondary analyses assessed genetic overlap for 21 white matter tracts. **Results:** The polygenicity of BIP, MDD, and SCZ were at least seven-times greater than average FA, although, average FA was more genetically discoverable. Average FA shared an estimated 42.53%, 42.99%, and 90.68% of trait-influencing variants with BIP, MDD, and SCZ, respectively. Additionally, 12, 4, and 28 shared loci were identified for average FA with BIP, MDD, and SCZ, respectively. Enrichment analyses implicated neurodevelopmental gene expression, astrocytes, microglia, myelin, and cell adhesion molecules. The degree of these gene-level associations varied across each psychiatric disorder implicating differing underlying biology. For BIP and SCZ, case vs control tract- level differences in FA correlated with genetic correlations between those same tracts and the respective disorder. Tract-level analyses recapitulated a similar pattern of greater genetic overlap for SCZ followed by BIP and MDD. **Conclusion:** This study shows that BIP, MDD, and SCZ exhibit a polygenic overlap with white matter FA. This supports theories suggesting some psychiatric patients have impaired integration between brain regions while providing potential biological underpinnings.

FINEMAPPING CAUSAL VARIANTS IN HUMAN GENOME USING MIXER MODEL: CURRENT RESULTS AND FUTURE DIRECTIONS

Bayram Akdeniz*[1], *Oleksandr Frei[1], Alexey Shadrin[1], Dmitry Vetrov[2], Dmitry Kropotov[3], Eivind Hovig[4], Ole Andreassen[1], Anders Dale[5]*

[1] NORMENT Centre, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, [2]National Research University Higher School of Economics, Moscow, [3]Lomonosov Moscow State University, [4]Centre for Bioinformatics, University of Oslo, [5]Center for Multimodal Imaging and Genetics, University of California San Diego

Objective: Discoveries from genome-wide association studies can be hard to interpret especially due to the highly correlated genetic variants. Finemapping studies, which aim to identify causal SNPs associated with a trait at a given locus after controlling for correlation among genetic variants, become important in such cases. There are many proposed finemapping methods in the literature that focused on this problem using different approaches [1]. Among these methods, Bayesian methods demonstrated their effectiveness. FINEMAP [2] and SuSiE [3] methods can be considered some of those successful Bayesian methods in terms of accuracy and computational complexity. Our aim in this work is to develop a new finemapping method using a variational Bayesian approach and MiXeR model [4].

Methods: We propose a variational Bayesian approach for finemapping genomic data based on the optimization of Evidence Lower Bound (ELBO) of the likelihood function obtained from MiXeR model. Particularly, we derived the likelihood function of summary statistics using MiXeR model and then ELBO of this likelihood function is determined for optimization. The optimization is done by Adaptive Moment Estimation Algorithm by using the first derivatives of ELBO and corresponding posterior probabilities of being causal are obtained accordingly.

Results: We have tested our method on synthetic data (N=10.000) and UK Biobank (UKB) genome data (N=337.145) with standing height as the phenotype by comparing with FINEMAP and SuSiE. According to the results in both scenarios, our method has given promising results in terms of

accuracy to pinpoint actual causal variants and estimate the phenotype. In the extensive number of experiments both on synthetic data and UKB data, our method gives superior results compared to other methods in the majority of these experiments. **Conclusion:** We have developed a novel finemapping method using the MiXeR model to detect actual causal variants and estimate phenotype. The initial experiments gave promising results compared to the existing methods in the literature. Our next aim is to apply our method to mental disorders to identify underlying causal variants. Furthermore, we are focusing on expanding our mathematical model for cross-trait and trans-ethnic analysis. Another future work is integrating our approach with GSA-MiXeR gene set enrichment analysis to use enriched priors which leads to potential performance improvement [5].

References: [1] Schaid, Daniel J., Wenan Chen, and Nicholas B. Larson. "From genome-wide associations to candidate causal variants by statistical fine-mapping." Nature Reviews Genetics 19.8 (2018): 491-504. [2] Benner, C., Spencer, C. C., Havulinna, A. S., Salomaa, V., Ripatti, S., and Pirinen, M. (2016). FINEMAP: efficient variable selection using summary data from genome-wide association studies. Bioinformatics, 32(10), 1493-1501. [3] Zou, Y., Carbonetto, P., Wang, G., and Stephens, M. (2022). Fine-mapping from summary data with the “Sum of Single Effects” model. PLoS Genetics, 18(7), e1010299. [4] Holland, D., Frei, O., Desikan, R., Fan, C. C., Shadrin, A. A., Smeland, O. B., ... and Dale, A. M. (2020). Beyond SNP heritability: Polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. PLoS Genetics, 16(5), e1008612. [5] Frei, Oleksandr, et al. "Improved functional mapping with GSA-MiXeR implicates biologically specific gene-sets and estimates enrichment magnitude." medRxiv (2022): 2022-12.

Saturday, June 8, 2024
8:00 a.m. - 9:00 a.m.
Plenary Session IV- Guy Goodwin

CAN WE RE-MEDICALISE THE PSYCHEDELIC EXPERIENCE?

Guy Goodwin1
[1]University of Oxford

Objective: Despite the widespread availability of multiple antidepressant treatments, depression remains a common and oftentimes debilitating disorder. A proportion of patients with major depressive disorder fail two or more antidepressant treatments and are considered to have treatment-resistant depression (TRD). Recent attention has turned to psilocybin and other psychedelic compounds as potential rapidly acting and durable episodic treatments for psychiatric disorders including depression.

Methods: COMP 001 was the first large, multinational, randomized controlled trial to evaluate the investigational drug COMP360, a proprietary pharmaceutical-grade synthetic psilocybin formulation, optimized for stability and purity, developed by the sponsor COMPASS Pathfinder Ltd in patients with TRD. This was a dose-ranging study that randomized 233 participants equally to 25mg or 10mg, or the 1mg control treatment. Participants down-tapered and washed out any previous antidepressant medications, and received a single administration of COMP360 as monotherapy, after which they were followed for 12 weeks.

Results: On the primary efficacy measure, large dose-dependent reductions from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) scores were evident starting from Day 2. Clinically meaningful differences in MADRS score improvements between the 25mg and 1mg doses were statistically significant through week 6 and remained numerically evident at week 12. Results of secondary and additional efficacy measures were consistent with MADRS results.

Conclusion: COMP360 was generally well-tolerated; in both studies over 90% of adverse events were either mild or moderate in severity. Suicidality remains a concern in TRD studies. These results suggest that COMP360 has potential to become an important contribution to the treatment for TRD and warrant the further clinical development of COMP360 in rigorous, large, randomized controlled studies.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VIII

PREVENTING AND AMELIORATING TREATMENT-RESISTANT DEPRESSION: BEST PRACTICE AND BEYOND

Allan Young, King's College London

Symposium Synopsis: Depression is the leading cause of disability worldwide, despite the many effective pharmacological and non-pharmacological treatment options available. Treatment-resistant depression (TRD), which is often defined as an insufficient response to two or more adequate treatment trials, affects up to 50% of those with depression. TRD is associated with poorer prognosis, higher mortality, and higher healthcare utilisation costs. With every additional treatment step for depression comes a decreased likelihood of response, and therefore it is critical to optimise care at the earliest possible stage of illness. This symposium will focus on avenues to improving best practice care for depression, with a focus on reducing treatment resistance. Our speakers will cover their work focused around best practice augmentation options for TRD, probiotics as potential novel augmentation options, the potential use of inflammatory markers for treatment stratification and

optimising response through pharmacogenetic-informed treatment selection. All four avenues could provide hope for enhancing the future care of people with depressive illness.

PHARMACOLOGICAL AUGMENTATION STRATEGIES FOR TREATMENT RESISTANT DEPRESSION

Anthony Cleare**1*

[1]*Institute of Psychiatry, King's College London*

Objective: Pharmacological augmentation is one of the most effective interventions for treatment resistant depression (TRD), with accumulating evidence that it may be more effective than antidepressant-switching strategies. However, very few patients with TRD receive augmentation treatment (between 0.2% and 11% depending on setting). The most often recommended first line therapies are lithium, quetiapine and aripiprazole, with other well supported options including thyroid hormone, risperidone, olanzapine, (es)ketamine, mirtazapine, buspirone, lamotrigine and bupropion (British Association for Psychopharmacology/Maudsley Guidelines).

Methods: Despite a relative paucity of RCTs, network metanalyses have helped gain a broad feel for the relative efficacy of the available augmentation strategies, at least in the acute phase. However, relatively few studies directly comparing augmentation treatments head-to-head have been undertaken, and none have looked at longer term outcomes. The LQD Study is a pragmatic RCT that directly compared two of the first line augmentation treatments, lithium and quetiapine, in patients who had failed to respond to at least two adequate antidepressant treatment trials. Clinical and health economic outcomes were collected over 1 year of treatment to address the lack of knowledge regarding longer term effects. Additionally, as TRD response is highly variable with patients often moving between response/remission, partial response and relapse, longitudinal assessment was undertaken using weekly depression ratings.

Results: Detailed results from the LQD study will be presented, including comparative clinical outcomes with lithium versus quetiapine, cost-effectiveness analyses and differential predictors of treatment response.

Conclusion: Pharmacological augmentation strategies for TRD remain underused yet effective treatments. Results from the LQD study add further evidence for their long term efficacy, and will help clinicians in the choice of first line treatment options.

PROBIOTICS AS PUTATIVE AUGMENTATION STRATEGY IN DEPRESSION

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Objective: Research over recent years has outlined a clear role for the microbiota-gut-brain axis in the pathophysiology of depression and has given rise to the development of novel intervention strategies, such as probiotics. However, clinical trials of probiotics are still scarce and further safety and efficacy data are needed to support this treatment approach. Further, their underlying mechanisms of action in clinical populations remain largely unknown.

Methods: Data from meta-analyses identifying the most appropriate mode of administration of probiotics and the gut microbial alterations associated with depression will be presented. Then, this talk will focus on novel findings from a double-blind placebo-controlled pilot trial (RCT) that examined the effects of an 8-week adjunctive multi-strain probiotic intervention in adults with depression taking antidepressants. In addition to psychiatric and safety data, stool and blood samples were collected and a computer-based emotion recognition task was performed.

Results: 49 participants (18-55 years, n=38 female, residing in London, UK) were included in intent-to-treat analyses (n=24 probiotic, n=25 placebo) in the RCT. The intervention was acceptable and well-tolerated with 8% attrition rate (n=3 placebo, n=1 probiotic), 97% adherence rate and no serious

adverse reactions. Standardised effect sizes (SES) from linear mixed models demonstrated that the probiotic group attained greater improvements in depressive (IDS week 8: SES [95%CI]= 0.64 [0.03, 0.87]) and anxiety symptoms (HAMA week 8: SES [95%CI]= 0.79 [0.06, 1.05]), compared to the placebo group. 16SrRNA sequencing of stool samples indicated the probiotic was able to positively modulate the gut microbiota: (i) there was an increase in richness only in the probiotic group ($p < 0.05$); and (ii) post-treatment, only the placebo, but not the probiotic group, had significantly decreased alpha diversity compared to demographically matched healthy controls ($p < 0.05$). The probiotic increased levels of several bacteria, of which Bacilleceae and genus Bacillus remained significant post-FDR correction and correlated with anxiety improvement (rho=-0.43,$p < 0.05$). There was no impact on inflammatory cytokines (CRP, TNFα, IL-1β, IL-6, IL-17) or BDNF; however, probiotics showed a tendency to increase positive affective bias. **Conclusion:** Our research indicated that, compared to placebo, 8-week adjunctive probiotic intake resulted in greater and clinically meaningful improvement in depressive and anxiety scores. The beneficial effects of probiotics were partially mediated by modification of gut microbiota composition. The acceptability, tolerability and estimated effect sizes on key clinical outcomes encourage further investigation of probiotics as augmentation strategy in depression in large-scale clinical trials, with an expanded evaluation of mechanisms.

OPTIMISING RESPONSE THROUGH PHARMACOGENETIC-INFORMED TREATMENT SELECTION

Roos van Westrhenen*[1]

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Objective: Pharmacogenetics is a discipline that investigates genetic factors that affect the absorption, metabolism, and transport of drugs, thereby affecting therapy outcome. These genetic factors can, among other things, lead to differences in the activity of enzymes that metabolize drugs. Studies in depressed patients show that genotyping of drug-metabolizing enzymes can increase the effectiveness of treatment, which could benefit millions of patients worldwide. The audience will be updated on the potential of pharmacogenetics for psychiatry.

Methods: The current status quo of pharmacogenetics in psychiatry will be provided, by presenting an overview of relevant studies, available guidelines and also ongoing projects.

Results: The European guideline on clinical implementation of pharmacogenetics in psychiatry will be shortly discussed, as well as the other available guidelines on pharmacogenetics from the Dutch Pharmacogenetic Working group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). An overview of currently performed clinical studies in psychiatry will be provided, including the recently published Dutch PREPARE trial and the current ongoing Horizon2020-funded PSY-PGx project (www.psy-pgx.org).

Conclusion: Pharmacogenetics can be used to fine-tune medication prescription by assisting in selecting medication type and dosage, for indivdual patients. Guidelines are available for prescribing antidepressants and clinical application will be discussed. The actual implementation of pharmacogenetics in psychiatry is ongoing work and in this lecture potential ways forward will be suggested.

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CAN WE USE INFLAMMATORY MARKERS TO PERSONALISE TREATMENT FOR TREATMENT-RESISTANT DEPRESSION?

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Objective: It is now established that a subgroup of individuals with depressive illness have immune dysregulations. Treatment-resistant depression is frequently associated with elevated pro-inflammatory biomarkers, and it is likely that some recommended treatments for TRD have downregulatory effects on inflammation. This symposium will consider the effects of TRD treatments on inflammation and inflammatory biomarkers as putative predictors of (differential) treatment responses in TRD.

Methods: The symposium will present findings from naturalistic observational treatment studies in populations with (treatment resistant) depression and systematic review of the effects of recommended TRD treatments on peripheral inflammatory biomarkers across populations of patients.

Results: Ketamine and aripiprazole may reduce pro-inflammatory states. Despite mechanistic and preclinical support for ECT and lithium as anti-inflammatory, evidence of these effects in humans is mixed. Quetiapine may have less anti-inflammatory effects and be more suitable for patients without an apparent inflammatory component to TRD illness. More evidence is required for other therapies with potential anti-inflammatory effects, such as bupropion. Although overall, elevated inflammatory states precede a poor response to treatments in depression, there are some agents which appear to be more beneficial for patients with inflammatory dysregulations.

Conclusion: Inflammatory markers could be used to stratify individuals to optimised treatment. Particular treatments with anti-inflammatory mechanisms may be recommended for those with high inflammation, whereas others may be more suitable for patients without. This avenue of research has the potential to enhance TRD care by directing patients to the 'right' treatment earlier in the course of illness.

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: BIOMARKERS FOR STAGING AND INTERVENTIONS FOR PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Neuroprogression subsumes the progressive, recurrent and relapsing course of a specific disorder. In some instances, it is possible to ‘stage’ the course of the disorder based on clinical manifestations, and, to the extent that morphological, biochemical, neurochemical, immunological, physiological and genetic aspects have been established, such parameters as well. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, and loss of synaptic plasticity.

The presenters will discuss the potential utility of specific methods and biomarkers that may assist in identifying vulnerability, determining the stage of the neuroprogressive course, and arrest neuroprogression by utilizing appropriate interventions. Better endophenotypes for affective

disorders are needed to study their neurobiological correlates. Results from a GWAS study on affective temperaments will be presented to demonstrate how polygenic risk scores help understand their association with depressive phenotypes and in interaction with stressors. Development of biomarker profiles to predict mood disorders may also contribute to their staging. Depression with increased inflammation is associated with neurodegenerative changes in corticostriatal and corticolimbic structures and default mode circuitry, affective, and cognitive symptoms – predicting the risk of development of MCI and a neuroprogressive dementia course. Electrical brain activity and the its course in recurrent affective disorders assist in staging and possibly predicting neuroprogressive of course. Lastly, lithium has been associated with neuroprotective or neurotrophic effects. Using neuroimaging and preclinical studies, the model that lithium acts as a synaptic modulator and thus slows neuroprogression in affective disorder will be presented.

POLYGENIC RISK SCORES FOR AFFECTIVE TEMPERAMENTS MAY HELP PREDICT THE ROUTE TOWARDS DEVELOPMENT OF MOOD DISORDERS AND MAY AID STAGING

Xenia Gonda*[1], *Dorka Gyorik1, Zsofia Gal2, Gyorgy Bagdy2, Gabriella Juhasz2*

[1]*Semmelweis University, 2Semmelweis University; NAP-2-SE Neurochemistry Research Group*

Objective: Affective disorders show a moderate-to-high heritability depending on their severity. Furthermore, they are also characterised by remarkable heterogeneity which is paralleled by an equally divergent neurobiological and genetic background. Different subtypes of depression also differ in the relative weight of contributing genetic-internal and environmental-external factors, with the majority of genes playing a role in depression mediating the effects of stress. It is in part due to this large etiological heterogeneity that we still do not fully understand the biological background and genetic determinants of affective disorders. Identifying clinically relevant endophenotypes thus would aid research, and, consequentially, help us find better genetic and other biomarkers for screening, prediction and intervention. Affective temperaments, considered the subclinical manifestation of mood disorders and when present in a dominant form. In the present study we carried out a GWAS of affective temperaments, generated polygenic risk scores (PRS) and investigated their effect on depressive phenotypes in interaction with early traumas and recent life stressors.

Methods: Results of our previous GWAS on affective temperaments as measured by TEMPS-A in a general population was used as a discovery sample. The NewMood database containing 1820 European general population subjects' data on current depression measured by the BSI, as well as data on early childhood traumas and recent severe negative life events occurring in the past 12 months was used as the target sample. We calculated polygenic risk scores for the five affective temperaments (depressive, cyclothymic, irritable, anxious and hyperthymic) using PRSice and adjusting all models for age, gender and the first ten principal components. To calculate the empirical p-value, 10000 permutations were run. In the next step, we analysed the interaction of the five PRS-s with early traumas and recent stress using linear regression models.

Results: Polygenic risk scores calculated for anxious, cyclothymic, depressive and irritable temperaments had a significant effect on severity of current depressive symptoms explaining 0.26-0.71% of variance. In interaction with early childhood traumas, anxious, depressive and hyperthymic temperaments had a significant effect on current depression explaining approximately 10% of variance. Considering a combined effect of early childhood traumas and recent life stress, depressive temperament had a significant effect explaining 13.95% of the variance of current depression severity.

Conclusion: Our findings support the genetic and neurobiological role of affective temperaments in the development of affective disorders and may be useful for prediction and risk screening, as well

as for identifying both psychotherapeutic and pharmacological targets for intervention and possibly for prevention. The next step is to analyse the association of affective temperament PRS-s with different neuroprogressive stages in depression.

INFLAMMATION AND NEURODEGENERATION IN DEPRESSION

Ebrahim Haroon*[1], *Xiangchuan Chen1, Diana Beltran1, Deqiang Qiu1, Felicia Goldstein1, Blaine Roberts1, Jennifer Felger1, Andrew Miller1*

[1]*Emory University School of Medicine*

Objective: Depressed patients experience a 2-5 times higher risk of neurodegenerative disorders, including Alzheimer's dementia. However, predisposing risk factors that enable clinicians to stratify risk and initiate preventive measures are unclear. We propose that chronic inflammatory activation in depression promotes and sustains this risk. Our previous data have demonstrated that increased inflammation in depression increases the risk of glutamate toxicity and leads to toxic disorganization of neural systems linked to emotional and cognitive functions. Herein, we examined if increased inflammation in the brain as measured in cerebrospinal fluid (CSF) was associated with increases in both CSF and neuroimaging makers of neurodegeneration in depressed (with and without cognitive dysfunction) versus controls.

Methods: 54 subjects (35 depressed and 19 non-depressed control subjects) participated in the study and provided CSF samples and clinical and demographic information. Study participants were aged 35-65 and unmedicated with psychotropic medications. Depression was confirmed using SCID-5 for DSMV, and a standardized neurocognitive battery was used to measure psychomotor slowing and executive dysfunction. The immune marker panel included c-reactive protein (CRP), tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1beta, and their circulating receptors [type 2 TNF (TNFR2), IL-6 (IL6sr), and IL-1 receptor antagonist (IL1ra). The neurodegeneration panel included neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), hyperphosphorylated tau-181 (Tau), abeta-(ab)42, and ab40. Diffusion tensor imaging (DTI) and Neurite Orientation Dispersion Density Imaging (NODDI)-based diffusion measures were used to identify regions of interest (ROI) correlated with CSF immune biomarkers after multiple test corrections. The ROIs located in white matter space were identified using an automated probabilistic tractography atlas in the XTRACT toolbox in FSL. Extended instrumental variables regressions were used to compare groups. Linear models were used to examine biomarker/DTI associations.

Results: Of the inflammatory markers, CSF TNFR2 was differentially associated with neurodegeneration markers as a function of depressed group status. Indeed, there was a significant CSF TNFR2 by depressed group interaction that was positively associated with CSF NFL (p-corr=0.002) and CSF GFAP (p-corr < 0.001). CSF TNFR2/NFL association was significant in the DCD+ (pcorr=0.018) but not with DCD- (p=NS) and control (p=NS) groups. Similarly, CSF TNfR2/GFAP association was significant in the DCD+ (pcorr=0.006) and DCD- (p-corr=0.024) but not in the control (p=NS) groups. CSF NFL and GFAP were associated with decreased fractional anisotropy of the right frontal aslant tract (p-corr=0.02 and 0.03, respectively) and increased mean diffusivity of right anterior thalamic radiation (p-corr=0.047 and 0.008, respectively); and CSF NFL was associated with an increased orientation dispersion index (p-corr=0.04) in the left arcuate fasciculus only among depressed groups. No associations between DTI measure with CSF NFL and GFAP were noted in the control group.

Conclusion: Our data indicate that depressed subjects with increased inflammation may have a higher risk of cognitive decline and neurodegeneration. Treatment with immune-modulating or neuroprotective agents and well-known antidepressants may be useful in this group.

ELECTRICAL BRAIN ACTIVITY AND ITS COURSE IN RECCURENT AFFECTIVE DISORDERS

Dimitris Dikeos*[1], *Gerasimos Konstantinou2*
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Objective: Brain electrical activity is commonly used to assess certain neurofunctional aspects of psychiatric illness. This presentation will focus on relevant findings in mood disorders.
Methods: Search in pubmed and other databases for original papers, reviews and meta-analyses.
Results: In both major depressive disorder (MDD) and bipolar disorder (BD), electroencephalography (EEG) has revealed abnormalities in resting-state EEG and evoked-related potentials (ERPs); the latter are the result of averaging EEG activity time-locked to the onset of the presentation of a stimulus that leads to a stereotyped electrophysiological response consisting of a series of positive and negative voltage deflections.
Conclusion: The validity of the findings as potential biomarkers will be discussed, as well as their contribution to the theory of neuroprogression in affective illness, and the possibility of their use in treatment prediction.

ASSOCIATION OF IMMUNOPSYCHIATRY, TREATMENT RESISTANCE AND NEUROPROGRESSION

Dominique Endres*[1]
[1]*Medical Center - University of Freiburg,*

Objective: Immunopsychiatry is a transdiagnostic, multidisciplinary, and translational field. From a clinical perspective, the discovery of NMDA-R encephalitis has played a vital role in the development of immunopsychiatric research as it was found that neuronal autoantibodies can be associated with both neurological signs and psychotic symptoms. Several other central nervous system autoantibodies have also been described, and international consensus criteria for autoimmune psychosis have been derived from these findings. In addition, other autoimmune-mediated severe mental illnesses, such as autoimmune obsessive–compulsive disorder (OCD) and autoimmune affective syndromes, are also discussed.
Methods: The talk will provide an overview of the controversial field of clinical immunopsychiatry, focusing on autoantibody-associated syndromes.
Results: Case studies, first case series, and retrospectively analyzed groups of patients with psychoses, affective syndromes, and OCD will be presented. The underlying pathophysiological autoantibody mediated processes and relevant biomarkers using electroencephalography, brain imaging, and cerebrospinal fluid analyses will also be addressed.
Conclusion: Red-flag signs will be summarized, and the current immunopsychiatric experience will be discussed in the context of treatment resistance and neuroprogression.

UPDATES IN ECT PRACTICE AND RESEARCH: NEW APPLICATIONS

Georgios Petrides, Robert Wood Johnson Medical School

Symposium Synopsis: In this symposium we will review new data in clinical research of Electroconvulsive therapy (ECT) and discuss new clinical applications.
Dr. Stella Rosson will summarize the meta-analytical evidence and safety of ECT and discuss data from a comprehensive umbrella review of the literature for randomized control trials of non-pharmacologic somatic treatments such as Deep Brain Stimulation, Transcranial magnetic stimulation (TMS), transcranial Direct current stimulation (tDCS) and others.
Dr. Søren Dinesen Østergaard will present unpublished results from a study investigating clinical and sociodemographic characteristics associated with relapse following ECT for bipolar disorder, based on data from more than 1400 Danish patients. He will discuss identified markers indicating high risk for relapse.

Dr. Brent Forester will discuss evidence for the use of ECT for the treatment of agitation in patients with severe dementia, as well as the design and implementation of a multicenter study funded by the National Institute of Mental Health in United States. Dr. Sohag Sanghani will report on the novel use of ECT in patients with autoimmune encephalitis, including ant-NMDA receptor encephalitis, and medication resistant catatonia.

EFFICACY AND SAFETY OF ECT AND OTHER BIOLOGICAL TREATMENTS IN PSYCHIATRIC DISORDERS: RESULTS FROM AN UMBRELLA REVIEW

Stella Rosson*[1]

[1]*East London NHS Foundation Trust*

Objective: To provide a comprehensive overview of the extant evidence of efficacy and safety of electroconvulsive therapy and other biological non-pharmacological treatments in psychiatric disorders.

Methods: We conducted an umbrella review selecting the largest meta-analyses of randomised controlled trials reporting on efficacy and safety of biological non-pharmacological treatments. These were electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and light therapy.

Results: We collected evidence from 102 including meta-analyses. Biological non-pharmacological treatments were found effective in a variety of mental disorders. In depressive disorders, interventions superior to inactive treatment were, in order of magnitude of improvement, ECT (SMD=0.91), TMS (SMD=0.51), tDCS (SMD=0.46), DBS (SMD=0.42) and light therapy (SMD=0.41). In schizophrenia spectrum disorders, effective interventions compared to sham were ECT (SMD=0.88), tDCS (SMD=0.45), and TMS (SMD=0.42-0.58). Other disorders with evidence of efficacy were substance use disorder (TMS, SMD=0.77-1.16), obsessive-compulsive disorder (DBS, SMD=0.89, and TMS, SMD=0.64), post-traumatic stress disorder (TMS, SMD=0.46), generalised anxiety disorder (TMS, SMD=0.68), attention deficit-hyperactivity disorder (tDCS, SMD=0.23), and autism (tDCS, SMD=0.97).
In no case the acceptability of biological treatments was lower than inactive treatment.

Conclusion: There is a large body of evidence in the medical literature regarding efficacy and safety of biological non-pharmacological treatments in a broad array of mental disorders. Among treatments, ECT had the largest effect size in depressive disorders and schizophrenia spectrum disorders. These techniques can be considered as therapeutic tools in an increasing number of psychiatric conditions.

CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH RELAPSE FOLLOWING ELECTROCONVULSIVE THERAPY IN BIPOLAR DISORDER

Soren Dinesen Ostergaard*[1]

[1]*Aarhus University Hospital - Psychiatry*

Objective: Electroconvulsive therapy (ECT) is an effective treatment of severe episodes of bipolar disorder (BD), but relapse in the months following ECT is common. In the present study we aimed to identify clinical and sociodemographic characteristics associated with relapse following ECT in BD.

Methods: Using data from the Danish nationwide registers, we identified all patients receiving their first ECT series with an indication diagnosis of BD in the period from 2006 to 2019. These patients were followed for six months after ECT where relapse was defined as either psychiatric hospital admission or reinitiation of an ECT series. The association between clinical and sociodemographic characteristics and relapse was examined via multivariable Cox proportional hazards regression (survival analysis).

Results: A total of 1498 patients with bipolar disorder will be included in the data analyses, which are ongoing. The results will be shown at the 2024 WFSBP Congress.
Conclusion: The identified characteristics associated with relapse may guide targeted monitoring of patients with bipolar disorder following ECT.

THE SAFETY AND EFFICACY OF ECT FOR THE TREATMENT OF AGITATION IN DEMENTIA

Brent Forester*[1]
[1]*Tufts University School of Medicine*

Objective: We aim to determine the effect, tolerability, and safety of up to 9 Electroconvulsive Therapy (ECT) treatments plus usual care (ECT+UC) on severe agitation in participants with moderate to severe dementia including Alzheimer's Disease, Vascular dementia, Frontotemporal dementia, and Dementia with Lewy Bodies.
Methods: Subject enrollment is limited to individuals admitted to inpatient psychiatry or medical care units with a diagnosis of moderate to severe dementia. Cohen-Mansfield Agitation Inventory (CMAI) cut-off scores are used as the agitation and aggression standard for inclusion. ECT treatment consists of up to 9 ECT sessions administered up to 3 times per week.
Results: The primary outcome is agitation as measured by CMAI score. Secondary outcome measures include Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC), Neuropsychiatric Inventory – Clinician (NPI-C), and the Pittsburgh Agitation Scale (PAS). Participant safety is monitored by assessing cognitive function as measured by the 8-item Severe Impairment Battery (SIB-8), delirium as measured by the Confusion Assessment Method (CAM) and the Family-CAM (FAM-CAM), and routine medical monitoring.
Conclusion: Recruitment challenges, protocol modifications, recommendations for future research and clinical implications will be discussed.

ELECTROCONVULSIVE THERAPY FOR CATATONIC SYNDROME ASSOCIATED WITH AUTOIMMUNE ENCEPHALITIS AND NEW-ONSET PSYCHOSIS OF SUSPECTED IMMUNE ORIGIN: A RETROSPECTIVE CASE-SERIES

Sohag Sanghani*[1], *Georgios Petrides[2], Jason Andrus[1], Heela Azizi[1], Amy Mastrangelo[1], Marc Gordon[1], Cristina Fernandez-Carbonell[1], Simona Proteasa[1], Humaira Shoaib[1], Joanna Drucker[1], Samuel Greenstein[1], Xavier Jimenez[1], Robert Dicker[1], Sanjeev Kothare[1], Souhel Najjar[1]*

[1]*Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 2Robert Wood Johnson Medical School*

Objective: To determine efficacy and safety of ECT in management of catatonia associated with autoimmune encephalitis (AIE) and psychosis of suspected immune origin.
Methods: Medical records of all patients with catatonia and suspected autoimmune encephalitis, who were referred for ECT in the period of Jan 2017 to Dec 2022 at our health system were reviewed. Demographic, clinical characteristics, laboratory and outcome data were recorded. Catatonia symptoms were measured using Bush Francis Catatonia Rating Scale (BFCRS).
Results: Twelve cases that met the inclusion criteria were identified. Of them 4 were cases of anti-NMDA receptor encephalitis and 6 were seronegative cases of probable (n=4) and possible (n=2) origin as per the criteria described by Pollak et al. in 2020. Mean age of the patients was 26 years and about 58% were females. Their mean initial BFCRS score was 18.2 (range: 5-25). All patients showed some response within 3 ECT treatments. On average, patients required 11 (range: 3-21) ECT treatments to achieve maximum improvement. All patients (n=12) responded well to the combination of ECT and immunomodulatory treatments. Eleven of twelve patients (92%) had

complete resolution of catatonia. Introduction of ECT earlier in the course was associated with a relatively lower number of days spent with catatonia. **Conclusion:** To the best of our knowledge, this is the largest case series from a single institution, where ECT was used in the treatment of catatonia associated with autoimmune encephalitis and psychosis of suspected immune origin. Autoimmune Encephalitis is a severe condition that can have varying psychiatric presentations. The possibility of AIE should be considered in the event of new- onset catatonia or psychosis, especially in young individuals. ECT is a safe and effective treatment for catatonia and psychosis associated with AIE. It is not a substitute for immunomodulatory treatments. In the event of non-response to first line immunomodulatory treatments, early initiation of ECT may help to prevent a protracted medical course and may have a synergistic effect with concomitant immunomodulator administration.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Niall Boyce, Wellcome

Symposium Synopsis:
In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence helps to reduce waste and improve efficiency in research. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. This symposium provides a concise, comprehensive introduction to the project, presenting highlights of its work to date. The focus is on the innovative aspects of the project, including hypothesis-generating systematic reviews, meta-analyses aiming to measure effects of interventions and the role of risk factors, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

METHODOLOGY FOR LIVING SYSTEMATIC REVIEWS IN GALENOS

Georgia Salanti**1*

[1] *University of Bern*

Objective: The innovative nature of GALENOS requires methodological developments in the field of systematic reviews. The aim of this presentation is to give an overview of the novel methodological aspects underpinning the GALENOS living systematic reviews.

Methods: To answer the research questions asked in GALENOS, we have developed two types of reviews. Hypothesis testing reviews collect evidence from studies examining mechanisms of action of interventions on mental health outcomes. Then, the role of various biological or psychological mechanisms is evaluated in association evaluation reviews.

We have developed template protocols that describe the review and synthesis methodology from human and non-human studies, include instructions about how to evaluate the confidence in the evidence that these two study designs provide, and describe the planning of evidence triangulation. **Results:** The methodology will be exemplified via three systematic reviews: two association evaluation reviews (Trace amine-associated receptor 1 agonists for psychosis and pro-dopaminergic pharmacological interventions for anhedonia in depression) and one hypothesis-generating review (mechanisms through which exercise reduces symptom severity in posttraumatic stress disorder). **Conclusion:** Several sources of evidence from human and non-human studies and novel methods are required to make sense of the rapidly evolving literature.

LIVING EVIDENCE IN PURSUIT OF A STEP-CHANGE IN NOVEL INTERVENTIONS FOR ANXIETY AND TRAUMA-RELATED DISORDERS

Soraya Seedat**1*

[1]*South African Society of Biological Psychiatry*

Objective: This presentation will highlight the unique process adopted by GALENOS to identify and prioritise research questions for living systematic reviews (LSR) through a rigorous process entailing public private involvement, using an exemplar of a living systematic review on mechanisms of exercise as an intervention for posttraumatic stress disorder. The living systematic reviews produced by GALENOS focus on the most promising scientific findings (from basic laboratory and animal research to clinical studies in humans)

Methods: For the LSR on exercise for PTSD, independent searches were conducted in multiple electronic databases to identify non-human and human studies investigating the biopsychosocial mechanisms through which exercise facilitates extinction learning, memory regulation, and emotional regulation in PTSD. Ontologies were developed to facilitate study identification and data extraction. Two reviewers independently conducted the study selection, data extraction using piloted forms, and risk of bias assessment using relevant tools based on the study design. We extracted data on PTSD-related outcomes and variables that can act as mediators of the effect of exercise or as effect modifiers.

To explain the biopsychosocial mechanisms through which exercise affects the outcome of interest, we extracted effects that relate to the impact of exercise on potential mediating variables and the effect of the later outcomes. We will synthesise study results (total effects of exercise, indirect and direct effects) using meta-analyses, where appropriate.

Results: The results are currently being analysed and will be presented. Data from other living systematic reviews on PTSD/anxiety disorders undertaken by GALENOS until mid-2024 will also be presented.

Conclusion: Elucidating the potential mechanisms underlying the beneficial effects of exercise for PTSD is firstly important for fundamental knowledge; secondly, it can shed light on individual-level differences in the effectiveness of exercise for PTSD; and thirdly, it can inform the discovery of other interventions to target these mechanisms.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Tatenda Kambeu**1*, *Soraya Seedat2, Georgia Salanti3, Niall Boyce4, Andrea Cipriani5*

[1]*Global Experiential Advisory Board for The Global Alliance for Living Evidence on Anxiety, Depression and Psychosis, 2Stellenbosch University; Stellenbosch University/South African Medical Research Council Extramural Unit on the Genomics of Brain Disorders, 3Institute of Social and Preventive Medicine (ISPM), University of Bern, 4Wellcome, 5Oxford University*

Objective: In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence is one way to reduce waste and improve efficiency in research towards these ends. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) aims to provide openly accessible co-produced living systematic reviews to tackle the abovementioned challenges. **Methods:** The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. It is important for GALENOS that we coproduce everything we create with people with lived experience of mental illnesses. Hence, we have set up the GLEAB, a Global Experiential Advisory Board, to provide strategic oversight to the project. In practical terms, people with lived experience will be involved with: choosing the topics of the reviews, developing the review protocols and contributing to conducting them, helping with data analysis and the writing up of the findings. People with lived experience will also be involved in developing the mental health ontology as that develops and identifying research questions that should be prioritised in the future. **Results:** This symposium provides a concise but comprehensive introduction to the project and presents highlights of its work to date. **Conclusion:** The focus of the symposium will be on the innovative aspects of the project, including co-production with lived experience experts, hypothesis-testing meta-analyses, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

HETEROGENEITY IN PSYCHOTIC DISORDERS ACROSS LEVELS OF RESEARCH

Dost Ongur, McLean Hospital/Harvard Medical School

Symposium Synopsis: This symposium will focus on heterogeneity in psychotic disorders across multiple levels of research. The first presenter is Dr. Michael Benros who will present evidence from blood and CSF studies as well as epidemiology for an "inflammatory" subtype of psychosis linked to early life exposures that may trigger molecular mechanisms in the developing brain and lead to persistent neuroinflammation and ultimately emergence of psychosis. The second presenter is Dr. Tao Li who will present the results of her team's neuroimaging studies examining dynamic connectivity over time in psychotic and mood disorders. Next, Dr. Sinan Guloksuz will present data on lifetime exposures, clinical presentation, and treatment response which reveal significant heterogeneity within psychotic disorders. He will discuss concepts of subtyping vs. dimensional variation in the context of empirical data. Finally, Dr. John Hsu will present evidence from large population-based insurance claims databases which demonstrate highly variable pathways to care, treatment histories, and linkage to various outcomes such as hospitalization among patients diagnosed with psychotic disorders. Dr. Dost Ongur is the discussant, and he will summarize approaches to heterogeneity in psychotic disorders and propose next steps for the field.

IMMUNE-RELATED SUBTYPE OF PSYCHOTIC DISORDERS – EVIDENCE FROM LARGE-SCALE STUDIES TO DETAILED CLINICAL STUDIES

Michael Benros*[1]
[1]*Mental Health Centre Copenhagen*

Objective: The underlying causes of psychotic disorders are likely very heterogeneous with multiple biological underpinnings that are still not fully illuminated. Within the recent decades, the immune system has been shown to be implicated in an increasing number of medical diseases and immunemodulating treatments are one of the areas currently moving fastest within medicine. In this presentation the current evidence for an immune-related subtype of psychotic disorders will be summarized and perspectives for immunemodulating treatments in subgroups of patients with psychotic disorders will be discussed.

Methods: The presentation will include data from large-scale studies to detailed clinical studies within the immunopsychiatric field of psychotic disorders, including nationwide Danish registers and biobanks, large-scale genetic studies, preclinical studies, clinical studies with sampling of the cerebrospinal fluid, meta-analyses of clinical studies and RCTs of immunemodulating treatments for psychotic disorders.

Results: Utilizing Danish nationwide registers we have consistently displayed that infections and autoimmune diseases increases the risk of developing psychotic disorders in a dose-response relationship, where the risk of severe mental disorders particularly increases with the number of infections exposed to and in a temporal manner. Utilizing large national biobank data, we have shown a small immunogenetic contribution with moderate correlation between the genetic susceptibility for infections and mental disorders. Moreover, at diagnosis there are elevated levels of inflammatory markers in the blood, and studies on the cerebrospinal fluid surrounding the brain have shown some evidence for elevated immune markers in the CSF and signs of disrupted blood-brain barrier in some of the patients, making them more vulnerable to potential detrimental effects of immune components. Interestingly, our meta-analyses of randomized clinical trials have shown that anti-inflammatory treatment seems to some extent show promise for the treatment of psychotic disorders. However, studies identifying subgroups that would be most likely to respond to immune modulating add-on treatment are still warranted to pave the field forward.

Conclusion: Although there is compelling evidence for at least a smaller subgroup of psychotic disorders having immune-related underpinnings, it will be discussed what is lacking in the current evidence base, how do we best advance the current knowledge and what should be prioritized within future research to make immunopsychiatry even more clinically relevant for psychotic disorders.

DYNAMIC STRUCTURE–FUNCTION COUPLING ACROSS THREE MAJOR PSYCHIATRIC DISORDERS

Zhe Zhang1, Wei Wei2, Yu Sun1, Tao Li*[2]
[1]*, Zhejiang University, 2Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine*

Objective: Major psychiatric disorders have both similar and distinct patterns of manifestations and cognitive impairments, yet the underlying common and/or unique neural substrates are not well understood.

Methods: We perform a comprehensive brain structure–function coupling analysis to characterize the transdiagnostic and illness-specific neuroimaging patterns across major depressive disorder, bipolar disorder, and schizophrenia.

Results: We find similar abnormalities in the general dynamic structure–function coupling of the rich–club organization across the 3 disorders, and shared and specific regional coupling alterations in

the visual, cognitive control, and default mode regions. Additionally, disorder-dependent atypical associations between structure–function coupling and topological properties of functional networks are mainly dominated by two distinct functional configuration states. **Conclusion:** Our findings demonstrate brain abnormalities across 3 major psychiatric disorders from a perspective of dynamic structure–function relationships, thus opening new avenues for investigating the neurobiological mechanisms underlying these disorders.

INVESTIGATING THE UTILITY OF EXPOSOME SCORE FOR SCHIZOPHRENIA TO UNDERSTAND OUTCOME HETEROGENEITY IN PSYCHOSIS SPECTRUM DISORDER

Sinan Guloksuz**1*

[1]*University Hospital of Maastricht*

Objective: By using a predictive modeling approach, we have recently estimated the exposome score for schizophrenia (ES-SCZ), a cumulative environmental exposure score for schizophrenia, consisted of cannabis use, winter-birth, hearing impairment, bullying, and five domains of childhood adversities (emotional and physical neglect, along with emotional, sexual, and physical abuse)., The ES-SCZ successfully differentiated individuals with schizophrenia, explaining 28% of the variance in an independent case-control sample and showed a good discriminative function for schizophrenia (AUC = 0.84) in an epidemiologically representative general population cohort. Here we tested the performance of ES-SCZ for dissecting the functional and symptomatic outcome heterogeneity in psychosis.

Methods: Our analyses used data from three independent cohorts: the “vulnerability and severity” Work Package 6 of the EUGEI study including 1,261 patients with schizophrenia spectrum disorder, 1,282 unaffected siblings of these patients, and 1,525 healthy controls collected in Turkey, Spain, and the patient population of the GROUP study including 1,119 patients with schizophrenia spectrum disorder collected in the Netherlands; and the Athens First Episode Psychosis Research Study collected in Greece including 225 individuals with first episode psychosis. We investigated the cross-sectional and longitudinal associations of ES-SCZ with functioning and symptom severity assessed using the Global Assessment of Functioning (GAF), the Personal and Social Performance Scale (PSP), and the Positive and Negative Syndrome Scale (PANSS).

Results: Our analyses revealed that ES-SCZ was associated with both the GAF symptom and disability domains in the EUGEI across three groups (patients, their siblings and healthy controls), also after adjusting for polygenic risk score for schizophrenia. We were able to replicate these findings in the GROUP dataset. In the Athens FEP cohort, we replicated these findings. ES-SCZ was associated with the overall scores of GAF and PSP at the baseline and 1-month assessments. Even after adjusting for various other relevant explanatory variables such as environmental factors (ethnic minority status, obstetric complications, migration history), clinical features (symptom severity, antipsychotic use history, duration of untreated psychosis), and family history, these results remained significant. The evaluation of the explained variance (R2) of functioning further supported these findings. Specifically, ES-SCZ was found to be the greatest contributor to the explained variance for the total PSP score, as well as for PSP subscales that measure socially useful activities and personal/social relationships. ES-SCZ was also temporally associated with symptomatic improvement from baseline to 1-month assessment, particularly the negative symptom dimension.

Conclusion: Our findings indicate that ES-SCZ might be a marker for poor functioning and symptomatic improvement in patients diagnosed with schizophrenia spectrum disorder. In addition, the results obtained from the models that took into account polygenic risk score for schizophrenia and clinical features indicate that the links between ES-SCZ and functional outcomes cannot be explained solely by genetic and clinical risk indicators.

THE ROLE OF POLYGENIC SCORES IN STUDYING PHENOTYPIC AND ENVIRONMENTAL HETEROGENEITY OF PSYCHOSIS

Evangelos Vassos*[1]
[1]King's College London
Evangelos Vassos, King's College London

Objective: Psychotic disorders show high heritability and genome-wide association studies have been successful in identifying variants associated with the disease. These variants are combined to estimate polygenic scores, which provide a single measure of genetic predisposition to a disorder or trait. Polygenic scores have been used for risk prediction either in contrast to or in combination with environmental risk factors in studies aiming to explain the heterogeneity of psychotic disorders. In this session, I will present our studies using polygenic scores to predict the development of schizophrenia or affective psychosis among individuals with first episode psychosis and I will explore the limitations of the use of polygenic scores alongside environmental factors in risk prediction.
Methods: We studied two samples of First Episode Psychosis (FEP) patients and controls for association between polygenic scores and psychosis outcome (schizophrenia or affective psychosis). The first sample (Genetics and Psychosis; GAP) was collected in South London consisting of 445 cases and 265 controls and the second (Work Package 2 of the EUGEI study) in six different countries including the UK, Italy, France, Spain, Netherlands and Brazil, including 573 cases and 1005 controls of European ancestry. Environmental risk factors were tested alongside polygenic scores in prediction of affective and non-affective psychosis. Finally, to explore whether polygenic scores and environmental risk factors can be used as independent predictors, we performed a study in the UK Biobank, testing the association of polygenic scores for 8 psychiatric disorders with urbanicity, once of the most replicated risk factors for schizophrenia.
Results: In the GAP study we observed that in addition to the expected association between polygenic score for schizophrenia and case-control status in European ancestry individuals, the former also separated FEP patients who developed schizophrenia from those who developed other psychotic disorders (R2=9.2%, p=0.002). This finding was replicated in a second sample of patients with chronic psychosis.
In the EUGEI study, we found that not only schizophrenia but also depression polygenic scores have a role in separating affective from non-affective psychosis. Furthermore, we found that adding polygenic and poly-environmental risk scores further improves the predictive ability of our model.
In the UK Biobank study, we found evidence supporting the hypothesis of genetic selection of the environment we live in, which intersects the traditional gene-environment dichotomy.
Conclusion: When patients present with first episode psychosis, it is difficult to establish a definite diagnosis and predict the course of illness and optimal treatment. To that effect, better understanding and explaining the heterogeneity of psychosis has important clinical implications. In our studies we find that polygenic scores have a significant yet small effect in separating schizophrenia from affective psychoses and that adding non-genetic risk factors improves prediction. Finally, gene by environment correlation needs to be considered when adding both genetic and environmental factors in prediction models.

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDERS

Allan Young, King's College London

Symposium Synopsis: Cognitive impairment in bipolar disorders.

Impairment in processing speed, attention, verbal memory, and executive functions may be present in up to 50% of young and middle-aged euthymic patients with bipolar disorders. However, our

knowledge in elderly people with bipolar disorder is limited although cognitive impairment is likely more prevalent and severe in elderly patients with mood disorders. Furthermore, compared to healthy older adults, those with mood problems have a higher risk of dementia. In contrast to research on younger patients, clinical correlates of cognitive decline in geriatric patients with bipolar disorder have not been studied systematically. Cognitive impairment worsens psychosocial functioning and treatment response in mood disorders. Therefore, it is essential to prevent and treat cognitive impairment in these people. Few treatment options effectively treat persistent cognitive impairment in remitted phases of bipolar disorders. Cognitive remediation therapy (CRT) may improve cognitive and non-cognitive functioning and recent studies have shown CRT's efficacy. However, its long-term effects are still unknown, therefore additional studies are needed. Also, limited understanding of neurocircuitry characteristics in bipolar disorders hinders search for new treatments and improving current treatment methods, leaving it unclear if proposed treatments can effectively correct cognitive impairments. This symposium aims to address the common problem of bipolar disorder-related cognitive impairment, including the cognitive decline of older patients. Additionally, treatment guidelines and options—including CRT—will be discussed considering neuroimaging, which can be used to identify neural targets for the development of new treatments or the improvement of existing ones for bipolar disorders-related cognitive decline.

COGNITIVE IMPAIRMENT IN BD: IS IT TREATABLE?

Lakshmi Yatham*[1]

[1] *The University of British Columbia*

Objective: 1. To review evidence on magnitude of cognitive impairment in BD

2. To review new data on therapeutic strategies for managing cognitive impairment

Methods: This presentation will review new data on cognitive impairment in BD and present the results of new studies that assessed the efficacy of pharmacological and psychological interventions for treating cognitive impairment in BD.

Results: About two thirds of patients with BD have cognitive impairment even during euthymic periods, which impacts functioning. New clinical trial designs allow testing for efficacy of pharmacological and psychological treatments in improving cognition. The results of these new and novel studies will be presented in this session.

Conclusion: Cognitive impairment in BD can be treated with pharmacological and psychological strategies.

COGNITION IN GERIATRIC BIPOLAR DISORDER

Nese Direk*[1]

[1]*Istanbul University*

Objective: Mood disorders are common and complex, accounting for one of the leading causes of disability. Approximately half of adults with mood disorders have cognitive impairment, which has an impact on their occupational and social functioning as well as their life quality. Cognitive impairment is well-known in younger and middle-aged euthymic adults with mood disorders, with the most impairment reported in processing speed, attention, verbal memory, and executive functions. Cognitive impairment is more common and severe in geriatric patients with mood disorders. It is also known that the prevalence of dementia in patients with mood disorders is higher than in healthy geriatric people. The causes of cognitive impairment in elderly patients with mood disorders are still unknown. Some clinical features, such as the prevalence of previous psychotic episodes, the number of manic episodes, and cardiovascular risk factors, are linked to an increased

risk of cognitive impairment, but the results are mixed. This talk is aimed at elucidating the cognitive profiles and clinical correlates of cognition in geriatric bipolar patients. **Methods:** The Bipolar Disorder in Old Age (BipOld) Study is a longitudinal, open cohort study including bipolar patients aged 50 years and over, aiming to explore progress of bipolar disorder in elderly. Several cognitive domains such as attention, memory, executive functions, social cognition, neurological soft signs and retrospective clinical data was collected. In this talk, baseline results of the BipOld Study will be presented, and results will be discussed in the light of current studies in this field. **Results:** In total 70 bipolar patients aged 50 years and over and 70 healthy controls are compared in terms of cognition. Bipolar patients had worse cognition scores in all domains when compared to healthy controls. Number of psychotic episodes, baseline cognitive impairment, family history of bipolar disorder, number of hospitalizations were related with worse cognition. Even though numbers are limited, patients on lithium monotherapy had better cognitive profile. **Conclusion:** Cognition in elderly patients with bipolar disorder is worse than people with no psychiatric disorder. Associations of clinical characteristics with worse cognition may indicate toxic effects of episodes resulting in neurodegeneration in these patients.

THE PURSUIT OF TREATING COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: CAN MRI BE A USEFUL TOOL IN FINDING NEW TREATMENTS?

Nefize Yalin*[1], *Dimos Tsapekos[2], David Lythgoe[3], Peter Hawkins[3], Rebecca Strawbridge[2], Allan Young[2], Steve Williams[3], James Stone[4]*

[1]National Institute of Mental Health, [2]Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, [3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, [4]Brighton and Sussex Medical School

Objective: Cognitive remediation (CR) is one of the treatment modalities that may address cognitive impairment in bipolar disorder (BD). We recently showed that 12-week CR improves working memory and executive functioning in euthymic patients with BD when compared to the treatment as usual (TAU) group. In this study, we aimed to investigate the potential changes in structural magnetic resonance imaging (MRI), task-based functional MRI, and proton-magnetic resonance spectroscopy (1H-MRS) accompanying the cognitive improvement with CR in comparison to TAU.

Methods: We recruited 24 euthymic BD participants (CR: n = 12, TAU: n = 12). Neuroimaging data was collected using a 3T General Electric MRI at baseline and week 13. For T1 structural MRI images, cortical thickness (CT) and surface area (SA) measures were obtained with FreeSurfer version 7.1.1. Caudal and rostral middle frontal cortex and three subparts of inferior frontal cortex (pars opercularis, triangularis, and orbitalis) were chosen as regions of interest. Repeated measures and general linear models were used to compare CT and SA between groups. For 1H-MRS, glutamate and GABA levels were quantified from the dorsomedial prefrontal cortex (DMPFC) using the PRESS and MegaPRESS sequences, respectively. LC Model 6.3-1N was used for the analysis of spectral data, and the metabolite levels were corrected for cerebrospinal fluid, gray, and white matter fractions in the spectroscopy voxel obtained using Gannet 3.1. We assessed changes in glutamate and GABA levels using a general linear model with repeated measures.For functional MRI, the attentional-capture version of the Stop Signal Reaction-Time (SSRT) task was used to evaluate response inhibition. Regions-of-interest (ROIs) data were extracted with the MarsBaR toolbox for SPM-12. ROIs were cortical areas previously linked to response inhibition in BD, including the right inferior frontal gyrus (rIFG). Activation changes in selected ROIS were compared between groups using repeated measures general linear models.

Results: The mean age was 39.3 ± 12.6 for the CR group and 39.8 ± 14.1 for the TAU group (p = 0.93), and 66.7% of both CR and TAU groups were female (p = 1.0). In structural MRI, there was a significant change in left pars triangularis CT (p = 0.048) and a trend toward change in left rostral middle frontal CT (p = 0.069) and right caudal middle frontal SA (p = 0.054) from baseline to follow-up between groups. All changes showed an increase in CT in the CR group and a decrease in the TAU group from baseline to week 13. In 1H-MRS, we found DMPFC glutamate levels to be increased in the CR group following CR, whereas in the TAU group, glutamate levels were reduced (p = 0.037). We did not find any effect of CR on changes in GABA levels (p = 0.269). In functional MRI, CR relative to TAU was not significantly associated with SSRT-related changes in neural activity of pre-defined ROIs (all p > 0.05). For SSRT behavioral measures, there was only a trend for CR vs. TAU in the accuracy of the stop signal condition (p = 0.06). **Conclusion:** Cognitive improvement related to CRT may be mediated by structural changes and increases in DMPFC glutamate neurotransmission. MRI has a potential in identifying brain-based efficacy markers.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia IX

THE PHARMACOLOGICAL TREATMENT OF EATING DISORDERS: NEW GUIDELINES, INSIGHTS, AND PERSPECTIVES

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: This symposium on novel guidelines, insights, and perspectives for the pharmacological treatment of eating disorders is organized by the WFSBP Task Force Eating Disorders and consists of speakers with a broad range of scientific experience from Germany, Israel, the United Kingdom, and the United States of America and a Chair from Austria.
Over the last three years, the task force has worked on an update of the pharmacological treatment guidelines for eating disorders which will be presented first in this symposium. The new guidelines include several innovations such as a recommendation for lisdexamfetamine in the treatment of binge-eating disorder (BED) and an analysis of pharmacological research in avoidant restrictive food intake disorder (ARFID), rumination disorder and pica. The second presentation will display the results of meta-analytic research regarding the effect of second-generation antipsychotics (SGAs) on appetite and eating behavior which is clinically relevant for the use of SGAs in anorexia nervosa (AN), but also with respect to the resulting weight gain as a side effects of SGA treatment in schizophrenia or bipolar disorder. The second half of the symposium is dedicated to innovative and future treatments for AN. Thus, the third speaker will expound on the microbiome-gut-brain axis as a potential target for new treatment options by presenting new data on altered microbiota in patients with AN and the results from stool transplantation studies; and the fourth speaker will present and explain the study design and the results from studies testing psilocybin therapy in people with AN.

OLANZAPINE FOR YOUNG PEOPLE WITH ANOREXIA NERVOSA (OPEN): RESULTS OF A FEASIBILITY STUDY

Ece Sengun Filiz*[1], *Olena Said[2], Dominic Stringer[3], Ulrike Schmidt[4], Dasha Nicholls[1], Hubertus Himmerich[2]*

[1]Imperial College London, , 2Centre for Research in Eating and Weight Disorders (CREW), Institute of Psychiatry, Psychology and Neuroscience, King's College London, 3Institute of Psychiatry, Psychology and Neuroscience, King's College London, 4 King's College London

Objective: Despite evidence-based treatments for anorexia nervosa (AN), the remission rates are low, and the mortality is high. The atypical antipsychotic olanzapine is often used for the treatment of AN even though the evidence is limited to weight gain. The effect of olanzapine on eating disorders (ED) psychopathology, its efficacy and tolerability in children and young people, and its acceptability and adherence rate are unclear. **Methods:** We assessed the feasibility of a future definitive trial on olanzapine in young people with AN in an open-label, one-armed feasibility study, that aimed to include 55 patients with AN or atypical AN) aged 12-24 who gained **<** 2 kg within at least one month of treatment as usual (TAU) during outpatient, inpatient, or day-care treatment. Time points for assessments were at screening, baseline and at 8-, 16 weeks, 6- and 12 months. The primary feasibility parameters were the number of patients who agreed to take olanzapine and who adhered to treatment and complete study assessments. The change in body mass index (BMI) and changes in ED psychopathology were secondary feasibility parameters. **Results:** From June 2022 to May 2023, 20 participants were recruited across 10 study sites in England (of the 55 participants required). Fifty-two people were assessed at pre-screening; 17 people were ineligible (13 at pre-screening, 4 at formal screening), and another 15 declined or didn't take part for other reasons. All 20 recruited participants started olanzapine. Thirteen out of 20 participants (65%) completed a follow up assessment (either 6 or 12 months). Participants in the trial experienced, on average, a decrease over time in their EDE-Q Global scores, an increase in weight and a corresponding increase in BMI during treatment with olanzapine in addition to TAU. There was a mean BMI increase of 0.08 kg/m2 per week in the whole sample of 20 participants. **Conclusion:** Possible reasons for the recruitment difficulties and the low adherence rate are the reluctance of clinicians to prescribe olanzapine and of patients to agree to take olanzapine under the relatively strict conditions of a clinical study. These conditions include the delay of the start of treatment with olanzapine as ample time should be given to consider participation in the study, a pregnancy test before the start of treatment, the commitment to blood collection at assessments and to complete the questionnaires. However, exploratory data evaluation indicates a benefit of olanzapine regarding weight recovery and reduction of ED symptoms.

BEYOND WEIGHT GAIN: EATING COGNITIONS, EMOTIONS AND BEHAVIOUR UNDER TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS

Hubertus Himmerich**1*, *Hiba Mutwalli2, Johanna Louise Keeler2, Sevgi Bektas2, Namrata Dhopatkar3, Janet Treasure2*

[1]German Society for Biological Psychiatry, 2King's College London, 3South London and Maudsley NHS Foundation Trust

Objective: Weight gain and metabolic disturbances are frequent in people treated with second generation antipsychotics (SGA). SGAs have also been proposed as treatment option for people with anorexia nervosa (AN). We aimed to investigate the effect of SGAs on eating behaviors, cognitions and emotions.

Methods: A systematic review and a meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Original articles measuring outcomes relating to eating cognitions, behaviours and emotions, during treatment with SGAs were included in this review. A total of 92 papers with 11,274 participants were included from three scientific databases (PubMed, Web of Science and PsycInfo). Results were synthesized descriptively except for the continuous data where meta-analyses were performed and for the binary data where odds ratios were calculated.

Results: Hunger was increased in participants treated with SGAs with an odds ratio for appetite increase of 1.51. Compared to controls, our results showed that craving for fat and carbohydrates are the highest among other craving subscales. There was a small increase in dietary disinhibition and restrained eating in participants treated with SGAs compared to controls and substantial heterogeneity across studies reporting these eating traits.

Conclusion: Understanding of mechanisms associated with appetite and eating-related psychopathology changes in patients treated with SGAs is needed to inform the development of effective preventative strategies for weight gain during treatment with SGAs. Such understanding might also help to use SGAs as a treatment option for patients with AN.

THE MICROBIOME-GUT-BRAIN AXIS IN ANOREXIA NERVOSA – POTENTIAL TARGET FOR NEW TREATMENT OPTIONS?

Jochen Seitz*[1], *Lara Keller1, Stefanie Trinh1, Brigitte Dahmen1, John Baines2, Beate Herpertz-Dahlmann1*

[1]*University Hospital RWTH Aachen, 2Max-Planck-Institute for Evolutionary Biology, Plön*

Objective: The gut microbiome has been shown to influence both metabolism and weight gain, as well as brain changes and behavior. This is especially interesting in the case of Anorexia nervosa (AN), where all these areas are known to be affected. Observation studies have repeatedly shown altered gut microbiota in patients with AN – even after weight normalization, and transplantation studies of AN-patients' stool into germ-free animals have shown significant effects regarding weight gain and anxiety/compulsivity.

Methods: Longitudinal observational studies using 16S- or metagenomic shotgun analysis allow the study on which factors influence the gut microbiome in AN and which taxa are associated with good or bad outcome. Transplanting stool of patients with AN or supplementing specific taxa in the activity-based anorexia animal model can give crucial information about causal influences of the microbiome and help elucidate underlying mechanisms.

Results: We present an overview over current study results. Longitudinal studies continue to show beta diversity differences between patients with AN and healthy controls before and after weight gain and remaining differences at follow-up. Taxa belonging to the Sutterella genus helped to predict higher body weight at one year. Animal models show differing alpha- and beta diversity as well as specific taxa to be altered in semi-starvation and support a potential causal role of the gut microbiome in AN.

Conclusion: The predictive power of taxa belonging to Sutterella for clinical outcome could complement known predictors at admission, help to inform patients and clinicians and serve as a candidate for interventions such as probiotic or nutritional supplementation. Trying to generate new microbiome-targeted treatment approaches like pro- and prebiotics, nutritional interventions or even stool transplantations might be interesting options to enhance existing AN-treatment.

EFFICACY OF PSILOCYBIN AND OTHER MEDICATIONS IN THE TREATMENT OF ANOREXIA NERVOSA

Walter Kaye*[1], *Stephanie Knatz-Peck1, Samantha Shao1, Murray Susan1, Finn Daphna1*

[1]
University of California – San Diego

Objective: Anorexia nervosa (AN) is a deadly behavioral disorder with no proven treatments to reverse core symptoms and no FDA-approved medications. Novel and innovative treatments methods are urgently needed to improve clinical outcomes and reduce mortality. Research suggests that disturbances of serotonin and dopamine function occur in AN and may contribute to anxiety and other symptoms.

Methods: This is the first trial to report on the safety, tolerability, and preliminary efficacy of psilocybin therapy for AN (ClinicalTrials.gov Identifier: NCT04661514). In this open label feasibility study, 10 participants who met DSM 5 criteria for AN received a single 25mg dose of synthetic psilocybin with psychological support. We assessed safety, tolerability, acceptability, and efficacy at pre-treatment, post-treatment, 1-month and 3-month follow-up.
Results: Psilocybin treatment was safe, well tolerated, and had good acceptability. Measured changes in eating disorder psychopathology were highly variable between participants. Four participants (40% of sample) demonstrated decreases in eating disorder scores to within 1 standard deviation of community norms at 3-month follow-up, qualifying for remission from eating disorder psychopathology.
Conclusion: Results from this open-label study suggest that psilocybin therapy is safe and tolerable in participants with AN. Additionally, data suggest that a single-dose trial of psilocybin therapy may be effective at reducing ED psychopathology in a subset of participants. These preliminary results are promising given the complex physiological dangers associated with AN and the lack of effective and acceptable treatments. We will also review the literature regarding other treatment approaches for AN.

Some studies, but not all, also support the efficacy of fluoxetine in reduction of relapse in restrictor-type AN. In addition, there is limited data suggesting that some atypicals may be useful for AN.

GENETIC RISK PREDICTIONS AND BIOLOGICAL MECHANISMS IN ADHD – TOWARDS PRECISION MEDICINE

James Kennedy, Univ of Toronto

Symposium Synopsis: ADHD is one of the most common mental and behavioral disorders in children, often co-occurring with various behavioral problems. ADHD exhibits high heritability of 74% and recent genome-wide association studies (GWAS) (Demontis, 2021) have identified a number of significant hits in several genes that have implications for new drug targets. Interestingly, the heritability of ADHD changes with its comorbid disorders (CDs) where ADHD had higher heritability when comorbid with disruptive behavior disorders. The objectives of the current symposium are to explore the genetics and biomarkers of ADHD with or without CDs such as aggression, eating disorders (Eds) and autism spectrum disorder (ASD), as well as discuss the current evidence-based treatments, and pharmacogenetic guidance of medication choice for ADHD.
Symposium speakers employ research-based clinical assessment of ADHD, aggression, Eds and ASD. The genotyping employs powerful genome-wide microarray technology that interrogates millions of markers. Analyses of the associations between diagnoses, subtypes and CDs are performed using well-developed GWAS statistical methods. Polygenic risk scores (PRSs) are derived from GWAS and can be applied to behavioral phenotypes in other samples exhibiting related disorders. Genetic factors influencing the effectiveness of drugs for ADHD and its common comorbidities will be discussed, including the use of pharmacogenetics for more precise prescribing.
Overall, results show that ADHD has shared genetic architecture with its CDs. Separating ADHD into its clinical subtypes with/without CDs leads to more specific biological predictors and drug targets, that in turn have the potential to lead to better precision medicine for the treatment of ADHD.

ASSESSMENT OF POLYGENIC RISK SCORE OF ADHD AND AGGRESSION IN YOUTH: RESULTS FROM A CLINICAL AND A COMMUNITY SAMPLE

Tuana Kant*[1], *Emiko Koyama2, Clement C. Zai1, Joseph H. Beitchman1, James L. Kennedy1*

[1]Centre for Addiction and Mental Health, University of Toronto, 2Centre for Addiction and Mental Health

Objective: More than 50% of youth with ADHD exhibit clinically significant aggression, representing high comorbidity. Although this points to the common genetic risk variants for the etiology of ADHD and aggression in youth, studies understanding the common genetic variation of ADHD and clinical aggression, and their subtypes, in children are limited. The objectives of this study were to assess the genetic relationship between ADHD and aggression in children. The study tested whether 1) ADHD scores were associated with aggression polygenic risk scores (PRS), and whether 2) aggression case status was associated with ADHD PRS. **Methods:** 1) 3594 children of European ancestry were recruited as part of the Adolescent Brain Cognitive Development (ABCD) study. The sample was genotyped with the Smokescreen® Genotyping Array. Continuous measures of ADH were obtained from Child Behaviour Checklist (CBCL). 2) 232 youth of European white ancestry were recruited as a part of an ongoing study of childhood aggression in Toronto, Canada. The sample was genotyped with Illumina PsychArray Beadchip v.1.2 and v.1.3. The case status was based on the participant scoring GREATER THAN 90th %tile on aggression subscales of both the CBCL and the Teacher Report Form, and a minimum two-year history of this disruptive behavior. Two PRSs were calculated using the standard clumping and thresholding methods with the p-value thresholds from 5x10-8 to 1 in PRSice2. Data for both PRSs came from the pediatric population of the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium. The first PRS was calculated from a genome-wide association meta-analysis (GWAMA) of ADHD (n=17666), while the second PRS was calculated from a GWAMA of aggression (n=87485). Linear and logistic regressions were used to analyze the associations between aggression PRS and ADHD scores in the ABCD sample, and between ADHD PRS and aggression case/control status in the Toronto sample, respectively. **Results:** Aggression PRS significantly explained ~ 0.2% of the variance in the ADHD scores of ABCD sample ($p = 0.007$). ADHD PRS significantly explained ~ 6% of the case-control status for the Toronto Child Aggression sample ($p = 0.002$). **Conclusion:** There were significant associations between aggression PRS with ADHD, and ADHD PRS with aggression case status. Our preliminary results indicate evidence that clinical aggression and ADHD share common genetic factors based on both clinical and community youth samples. The large sample size for the ABCD sample provides increased power for the results. The results may lead to generating better prediction strategies, for example aggression acting as a biomarker for ADHD. Personalized treatment strategies based on the genetic risk score may help with early prevention efforts. We will be exploring the genetic risk underlying ADHD by analyzing the aggression PRS in clinically aggressive children with, and those without, ADHD diagnosis.

GENETICS AND CELL BIOLOGY OF READING DISABILITIES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Cathy Barr*[1], *Kaitlyn Price2, Karen G. Wigg3, Yu Feng3, Kirsten Blokland4, Margaret Wilkinson4, Elizabeth Kerr5, Sharon Guger5, Maureen W. Lovett5, Lisa Strug5, Maria Carol Marchetto6*

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Objective: Reading disabilities (RD) represent a major health, social, and educational handicap. Comorbid psychiatric disorders are common in children with RD, particularly ADHD (20%) which shares genetic risk. The high rate of ADHD further impacts academic achievement and social

development. Little is currently known of the genetic, molecular and cellular mechanisms contributing to these neurodevelopmental disorders. **Methods:** To address this gap, we performed a genome-wide association study (GWAS) for word reading. Based on the findings from that study, we then performed a Hypothesis-Driven GWAS testing the relationship between autism spectrum disorder (ASD) and genes involved in neuronal migration/axon pathfinding. We also used the results from the genetic studies, linkage disequilibrium score regression (LDSC) and single cell RNA-seq data to identify which neural cell types are enriched for genes for ADHD and RD risk. We then directly tested migration using stem cell derived neural precursor cells (NPCs) from children with RD. To understand the underlying molecular mechanisms, we investigated the transcriptome of the neurons and NPCs derived from the children. We selected one of the differentially expressed genes for further study by overexpressing the gene using CRISPR activation. **Results:** The results indicate overlap of word reading for genes previously identified for educational attainment, neurodevelopmental and psychiatric disorders, particularly ADHD and ASD. We also identified overlap with genes involved in neuronal migration. This supports the a priori hypothesis that alterations in neuronal migration during neurodevelopment contribute to the risk of RD. To test this, we created stem cells from two children with severe RD and their strong reader siblings. Derived NPCs from RD children migrated significantly faster than their siblings supporting migration alterations. Transcriptome analyses of neurons and neural precursor cells identified 44 genes that were differentially expressed between probands and their siblings in both cell types. One of these, OTX2, has been implicated in analyses of externalizing behaviour including ADHD, depression, educational attainment, and smoking initiation from GWAS studies. OTX2 is a transcription factor and our bioinformatic analyses indicates it may regulate 11 of the 44 genes. To test this, we are currently overexpressing OTX2 in NPCs, using CRISPR activation. Using LDSC, we also determined that specific subclasses of glutamatergic and GABAergic neurons are enriched with RD risk genes. Studies of ADHD identified a different glutamatergic neuron subtype. These findings indicate these cell types for stem cell derived neural models and functional studies. **Conclusion:** The results identify overlap for risk genes for ADHD, ASD and word reading. The findings of overlap for ADHD, support previous twin data showing a genetic relationship. Little is known of the overlap between ASD and RD. Our finding likely stems from shared genetic risk for neurodevelopmental disorders, particularly those contributing to language-related difficulties. Our novel, unpublished observation of altered migration in neural derived cells from RD children, supports previous evidence from neuroanatomical studies for altered neural migration and transcriptome analyses are providing information on the underlying molecular mechanisms.

PHARMACOGENETICS FOR PRESCRIBING MEDICATION TYPE AND DOSAGE IN ADHD: TOWARD PRECISION MEDICINE

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Objective: There are many promising genetic findings in terms of risk factors for ADHD. Recently a report by Demontis et al. (2021) provided an updated list of Genome Wide Association Study (GWAS) significant findings for genetic sites from across the genome that contribute to risk for ADHD.
In parallel with these hypothesis-free GWAS studies of the etiology of ADHD, we and others have been examining the application of genomic tools to help predict treatment response and side effects in ADHD. Given that current prescribing practice for ADHD consists mostly of trial-and-error approaches, there is a large unmet need to measure selected biological characteristics (biomarkers) of each patient in order to provide more precise prescribing.

Towards this goal of biomarker-guided precision medicine, Myer, Boland and Faraone (2017) have used meta-analytic methods to examine pharmacogenetic predictors of methylphenidate efficacy in childhood ADHD. They analyzed 36 studies with total n = 3647 children, examining response measures of methylphenidate treatment for association with DNA variants. Pooled data revealed significant association with single nucleotide polymorphisms (SNPs) in the alpha adrenergic 2A receptor gene ADR2A (odds ratio (OR) = 1.69); the norepinephrine reuptake transporter SLC6A2 (OR = 2.93) which is the target of atomoxetine, as well as the repeat variant in the dopamine D4 receptor gene (DRD4, OR = 1.66). Other data has shown that the drug metabolism gene cytochrome CYP2D6 plays a significant role in the liver deactivation of atomoxetine, which in turn influences clinical response. We will provide a critical assessment of these findings regarding their potential utility in clinical decision-making in ADHD. From our laboratory we will present work suggesting that a higher dosage of methylphenidate is helpful for individuals with a DRD4 7-repeat variant, due to impairments in D4 receptor trafficking to the synapse **Methods:** N/A **Results:** N/A **Conclusion:** We provide evidence that use of genetic factors to predict response and side effects, as well as separating ADHD into clinical subtypes, can lead to potential for better precision medicine for treatment of ADHD and its subtypes. Current pharmacogenomic knowledge provides a relevant amount of clinical guidance for selection of medication type and dosage. Further research is necessary for the optimization of personalized interventions in ADHD.

LEVERAGING GENETICS IN THE CLINICAL MANAGEMENT OF ADHD AND DISRUPTIVE BEHAVIOR

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Objective: Approaches to the clinical management of ADHD, disruptive behavior and other comorbidities span medication classes and psychotherapeutic techniques. Currently, treatment matching is driven by serial trial-and-error. Given the potentially serious consequences of uncontrolled symptoms, pharmacogenomic and other biomarkers of therapeutic response could represent a substantial advance in the precision treatment of these disorders.
Methods: Current evidence-based pharmacotherapy and psychotherapies for ADHD and disruptive behavior disorders (DBDs) in children and adults will be reviewed, including known predictors and moderators of response. The utility and limitations of commercially available decision support tools (DSTs) will be examined. Research questions and future directions will be suggested.
Results: Little is known about genetic factors influencing drug action at brain targets; however, many genetic variants influencing the pharmacokinetics of psychotropics are well understood. While genetic impairments in stimulant metabolism are rare, large genetic effects are seen with alternative ADHD drugs. Non-stimulant ADHD options, atomoxetine and clonidine, are affected by common CYP2D6 variation, and bupropion is a CYP2D6 inhibitor, phenocopying the CYP2D6 poor metabolizer phenotype. Medication classes used to target disruptive behaviors are broad, including ADHD drugs, antidepressants, mood stabilizers and antipsychotics. Many of these agents are also impacted by known genetic variation. Common ADHD and DBD comorbidities, most frequently mood and anxiety disorders, have the strongest evidence base for integrating genetic information. Genetic data is actionable in ADHD and DBD pharmacotherapy in a considerable proportion of patients. For example, one-third of normal metabolizers never achieve therapeutic atomoxetine levels at the FDA maximum dose and require suprathreshold dosing. The Clinical Pharmacogenomics Implementation Consortium (CPIC) recommendations for incorporating genetic results to optimize response will be summarized. Evidence-based applications of DSTs that are commercially available to guide

prescribing will be outlined. Research supporting the implementation of DSTs in adults is mixed at best, with significant concerns regarding bias. A single DST trial was negative in adolescents and trials in children are non-existent. Recent reports highlight that efficacy in pediatric populations cannot routinely be extrapolated from adult studies. **Conclusion:** Numerous therapeutic options have demonstrated benefits in the management of attention-deficit and disruptive behavior disorders and their common comorbidities. While current pharmacogenomic knowledge cannot predict which interventions are best for individual patients, some clinical guidance can be gleaned from pharmacogenomic data. As our knowledge about mechanisms of psychiatric disease and pharmacologic action expands, the use of pharmacogenomic DSTs in the practice of precision medicine will likewise mature.

INNOVATIONS IN PHARMACOGENOMIC RESEARCH: TRANSLATION AND CLINICAL UTILITY

Bernhard Baune, University of Münster

Symposium Synopsis: The role of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacotranscriptomic approaches, focusing on genetic variants and expression levels of relevant genes for pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry, but still lacking. This concept of the multi-omics foundation of response to pharmacological treatments will be presented. Examples of this approach that entails the analyses of individual omics layers as well as an integrated analysis using multiple omics in relation to response to treatment will be presented. Results on the development of a model precision psychiatry framework that integrates clinical data (wide range of symptomatology assessment, treatment side effects, presence of childhood trauma) and -omics features (genomic, transcriptomic and miRNomic) for the prediction of treatment response in MDD patients will be shown. Moreover, an overview of RCTs on pharmacogenetic-based decision support tools for antidepressant drugs will be critically assessed. Moreover, recent findings on rare genetic variation impacting important clozapine-associated adverse drug reactions as well as such variation varies across ethnicities will be discussed. Finally, results of a recent systematic review on what is currently known about common genetic variation impacting clozapine response will be shown.

NEW DEVELOPMENTS IN THE PHARMACOGENOMICS OF TREATMENT RESPONSE PREDICTION IN PSYCHIATRY

University of Münster
Bernhard Baune*[1]
[1]

Objective: As background, the overall aim of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, in the psychiatric field, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacoepigenomic approaches, focusing on genetic variants and epigenetic modification related to pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry. These two layers of omics

and their integration provide important and novel information regarding therapeutic response and side effects, contributing to optimizing pharmacological treatment in an individualized approach. The objective of this presentation is to introduce a concept of the multi-omics foundation of response to pharmacological and non-pharmacological treatments, which entails the genomics, transcriptomics and epigenomics layers of response to a pharmacological intervention and demonstrate this concept in in two case studies using randomised controlled trial (RCT) data from the PREDDICT and CERT-D trials.

Methods: The chosen approach requires the analyses of individual omics layers as well as an integrated analysis of multiple omics in relation to response to treatment. Two examples of RCTs will used to illustrate this multi-omics concept of prediction of treatment outcomes: first, the PREDDICT study, which is a randomized controlled trial to test the efficacy of an antidepressant plus augmentation with celecoxib vs antidepressant plus placebo in major depressive disorder (MDD). In a second case study, he will present multi-omics results from the randomized CERT-D study that tests the antidepressant effects of a personalised cognitive training program in MDD. In both examples, multi-omics predictions of treatment response will be presented.

Results: Results from the CERT-D study show that DNA methylation can be suitable to capture early signs of treatment response and remission following a cognitive intervention in depression. Despite not being genome-wide significant, the CpG locations and GO-terms returned by our analysis comparing patients with and without cognitive impairment, are in line with prior knowledge on pathways and genes relevant for depression treatment and cognition. Results from the PREDDICT study will be presented as well. Results on the integration of genetic and epigenetic layers for both the PREDDICT and CERT-D studies will complete this presentation.

Conclusion: The conceptual approach chosen is useful to better understand the complexity of the underlying biology of treatment response in depression treatment. Methodological developments are underway and encouraged by our findings.

THE PROMPT STUDY: REVEALING NEW KEY PLAYERS IN PREDICTING TREATMENT RESISTANCE

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Objective: Dr Júlia Perera-Bel will present results on the development of a model precision psychiatry framework that integrates clinical data and -omics features (transcriptomic and miRNomic) for the prediction of treatment response in major depression disorder (MDD) patients. This is the overall objective of the PROMPT ("Toward PrecisiOn Medicine for the Prediction of Treatment Response in major depressive disorder through Stratification of Combined Clinical and -Omics Signatures") consortium, which is funded by the European ERA PerMed funding scheme.

Methods: The overall methodology of the project is based on a two-phase design. In the first phase (training phase, retrospective design), 300 already recruited MDD patients, including 150 TRD and 150 responders considered as extreme phenotypes of response, will undergo a deep clinical and omics profiling. These data will be exploited to develop an innovative integrative algorithm for the prediction of MDD treatment outcome. Recruited patients undergo a comprehensive clinical assessment and molecular profiling (genomic, transcriptomic and miRNomic). DNA and RNA for genomic, pharmacogenetic extracted from peripheral blood samples are prepared transcriptomic and miRNomic analyses. RNA library preparation is performed following the manufacturer's recommendations. Final samples pooled library preparations are sequenced on a Novaseq 6000 ILLUMINA, at a depth of 2x30Millions of 100bases reads per sample after

demultiplexing. MiRNomic (+ other small RNA) profiling is conducted by small RNA-Seq. Sequencing yields 20-30 million single-end 50 bp reads per sample on a NextSeq2000 (Illumina). Quality assessment is done with FastQC, and reads are trimmed using Cutadapt before mapping. Sequences with length < 16 nucleotides are discarded. The reads count table is generated using featureCounts, filtered for underrepresented genes, and analyzed using linear models (limma) for differential expression analysis. Functional analysis utilizes available annotations in functional genomics resources. Network-based approaches are employed to visualize miRNA-target connections and perform gene ontology (GO) analyses. STRINGdb is used for protein-protein interaction retrieval, igraph for network analysis, and clusterProfiler for GO and pathway enrichment analyses. Differential expression of miRNAs is validated by qPCR.

Results: We have already recruited 192 patients with MDD, including 104 TRD/88 responders. This cohort is composed of 70% of females, equally represented in both groups. BMI and age are associated with TRD, as well as mental comorbidities (e.g. anxiety, personality disorders). We have identified differentially expressed genes between the two groups. We observed a downregulation of immune-related pathways in TRD patients. Importantly, the microRNA regulation explains most of the differentially expressed genes, thus indicating their causal involvement in treatment resistance, and opening new yet unexplored therapeutic avenues in MDD.

Conclusion: The projects revealed the importance of microRNA as regulators of important molecular pathways underlying treatment response in major depression. Importantly, we detected downregulation of immune-related pathways in TRD patients and deregulated gliucemia and neuroinflammatory pathways. This project will provide a new predictive tool for future use in clinical practice, enabling better prevention and management of MDD treatment resistance.

CLINICAL EFFICACY OF ANTIDEPRESSANT PHARMACOGENETIC TESTS IN CLINICAL PRACTICE: STATE OF THE ART, CHALLENGES AND FUTURE PERSPECTIVES

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Objective: Several data indicate that the success of pharmacological treatment in major depressive disorder (MDD) is still unsatisfactory, and matching a patient to his/her optimal treatment generally requires multiple trials with different treatments. It is sobering to note that the more unsuccessful therapies tried, the lower the likelihood that a successful outcome will occur, which could lead to a protracted illness, a worse long-term prognosis, more side effects, and significant medical, social, and financial costs.

Methods: Numerous environmental and biological aspects of the disease as well as medication treatments are to blame for the low response and remission rates. Pharmacogenetic (PG) testing has the potential to improve the accuracy of outcome prediction and lower the rate at which antidepressants are stopped due to adverse effects. Commercial PG tests for antidepressants have been more widely available, but there has also been rising skepticism about their usefulness. Several studies have been carried out, with intriguing but conflicting findings.

Results: Few of them currently are randomized controlled trials (RCTs), and the majority of them are observational studies without a control group. Several limitations were found concerning study design, generalization of results, duration of the trails, patients group studied, and cost-effectiveness ratio. We conducted the first study in Italy concerning the validation of a pharmacogenetic test for antidepressants in clinical daily practice with advocacy license independence. In order to provide a comprehensive view of outcomes, including symptom improvements and the emergence of negative effects, we tried to overcome the limitations of prior studies by applying a wide range of rating scales.

This allowed us to identify the true impact of the pharmacogenetic test on the various symptom phenotypes of depression. **Conclusion:** In conclusion, a number of obstacles have been identified for the widespread use of PG testing for antidepressants in clinical care for patients with MDD. The lack of overall efficacy in some prospective trials necessitates further research and indicates that there are variations between the population seen in prospective clinical trials and the real-world populations that should undergo PG testing. Attempts to gain a better understanding of the subset of people who might benefit and the time frame over which such advantages are required.

GENETICS OF CLOZAPINE RESPONSE AND ADVERSE DRUG REACTIONS: FROM RARE TO COMMON GENETIC VARIATION

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Objective: Little is known about how genetic variation impacts clozapine-related side effects and clozapine response, thus making clinicians and patients often reluctant to start clozapine. Moreover, few studies have examined ancestry-diverse populations in psychiatric genetics. We therefore examined associations of common and rare genetic variants with clozapine response and clozapine-related side effects.

Methods: Both targeted (using Taqman and Sanger sequencing) and whole-genome analyses were conducted in a sample of 800 subjects using clozapine with a diverse ancestry. Genome-wide association studies (GWASs) were conducted. Polygenic risk scores (PRS) for schizophrenia were generated. Linear models correcting for covariates were run to examine associations between clozapine response and PRS. Finally, we examined associations between genotype-predicted CYP1A2, CYP2D6, and CYP2C19 enzyme activities and clozapine response.

Results: In targeted analyses we found that rs113332494 (HLA-DQB1) was significantly associated with clozapine-associated neutropenia/agranlycytosis in the all participants (P = 3.5 × 10−8), in Caucasians (P = 9.3 × 10−6) and in Turkis (P = 2.8 × 10−5). Rs41549217 (HLA-B) was nominally significant in the Caucasian group (P = .018).

Our GWAS indicated that rs1923778 within NFIB showed a suggestive association with symptom severity while on clozapine.

PRS-schizophrenia was positively associated with low symptom severity.

Furthermore, higher genotype-predicted CYP2C19 enzyme activity was independently associated with lower symptom severity while on clozapine.

Conclusion: Ethnicity-dependent and clinically relevant effects of genetic polymorphisms on the risk to develop clozapine-induced neutropenia/agranulocytosis exist. Pharmacogenetic testing can complement clinical decision making and thus empower appropriate CLZ prescribing, but ancestry should be taken into account when performing such testing for CLZ. High schizophrenia-PRS and genotype-predicted CYP2C19 enzyme activity are independently associated with lower symptom severity among individuals treated with clozapine Although it is too early to adopt PRSs in clinical decision-making, these findings strengthen the positioning of PRS-SCZ as relevant to treatment response in psychiatry, particularly in patients with difficult-to-treat symptoms.

PARAM: A NEURODEVELOPMENTAL COHORT FROM INDIA

Vivek Benegal, National Institute of Mental Health and Neurosciences, Bangalore

Symposium Synopsis: The PATHWAYS TO RESILIENCE AND MENTAL-HEALTH [PARAM] is a longitudinal study, in India to trace the normal and deviant neurodevelopmental trajectories which underlie resilience and vulnerability to mental illnesses; and understand the impact of Genome x

Exposome interactions on these processes, across the developmental span. The PARAM seeks to extend and enrich an existing neurodevelopmental cohort (the Consortium on Vulnerability to Externalizing Disorders and Addictions) of individuals aged 6-23 years, set up between 2016-2020 to establish a database and biobank of 9000+ subjects across seven sites in India. The symposium will present data from the cohort to discuss our work in establishing normative brain (and cognitive) developmental trajectories and the impact of exposures to environmental (modifiable) risk factors such as socioeconomic status, nutrition and pollution (PM2.5, arsenic) 1. Introduction to the Indian neurodevelopmental cohort 2. Growth trajectories for executive and social cognition abilities and the impact of psychosocial determinants 3. Impact of Developmental Exposure to Air Pollution and a matrix of environmental risk on Cognitive Function in Adolescent and Young Adults 4. A neurocognitive investigation of low-level arsenic exposure with executive functions and brain structure and resting state activity.

IMPACT OF DEVELOPMENTAL EXPOSURE TO AIR POLLUTION AND A MATRIX OF ENVIRONMENTAL RISK ON COGNITIVE FUNCTION IN ADOLESCENT AND YOUNG ADULTS

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Objective: Brain development is influenced by both genetic and environmental factors and is critical for the normal growth and maturation of mental processes such as attention, memory, learning, and executive functions. It is well established that there are critical periods in the development of the brain when the environment can significantly impact neuroplasticity and cognitive development. The impact of developmental exposure to air pollution and a matrix of environmental risks on cognitive function in adolescent and young adults is a growing area of concern. The Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA) is an accelerated longitudinal cohort based in India that aims to study the impact of genes and environment on brain structure, function, and cognitive abilities. This study focuses on the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, body mass index, and psychopathology.

Methods: The participants of the cVEDA study were assessed at baseline and two follow-up times, and measures of socio-demographics, psychopathology, cognitive functions, and high-resolution ambient air PM2.5 exposure were available for n=6307 at baseline and were included for the current analyses. We performed a hierarchical confirmatory factor analysis and generated a single latent factor (g) representing general cognitive abilities. We then studied the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, BMI and psychopathology.

Results: The study found that exposure to particulate matter was significantly associated with poorer general cognitive abilities, after controlling for confounds. Further, we also found that the impact of developmental exposure to PM2.5 on overall cognitive functioning was significantly greater among people from lower socio-economic backgrounds, indicated by lower wealth scores.

Conclusion: In conclusion, the results of this study provide evidence for the impact of exposure to particulate matter on general cognitive abilities in adolescent and young adults and suggest that the presence of multiple environmental risk factors (eg., malnutrition, poverty etc) may have additive effects on cognitive development. The cVEDA cohort represents a unique opportunity to investigate the interplay between environmental exposures, psychopathology, and cognitive development in a developing country context. These findings highlight the need for further research to understand the potential implications of air pollution on cognitive development in populations exposed to high levels of particulate matter. These findings have important implications for policy and public health initiatives aimed at reducing exposure to environmental pollutants and promoting healthy cognitive development.

GROWTH TRAJECTORIES FOR EXECUTIVE AND SOCIAL COGNITION ABILITIES AND THE IMPACT OF PSYCHOSOCIALDETERMINANTS

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Objective: Structural and functional developmental reorganization of the brain manifests as motor, sensory, cognitive, social, emotional and other functional abilities. Timing and pattern of maturation follow a simple to complex order. Basic sensory and motor functions are fairly well established in early childhood; timelines for certain cognitive and socio-emotional abilities might extend into adulthood. Examining functional brain abilities could help track brain development; they also have a putative role in early risk identification for psychopathology. These abilities need to be better characterized over development, in terms of maturational patterns, implications of delay or deficits, factors that influence developmental change, etc.

Methods: The cVEDA study, an Indian developmental cohort, with data on more than 9000 youth, ages 6-23 years, enabled examination of developmental trajectories (for verbal and visuo-spatial working memory, response inhibition, set-shifting, and social cognition), and how these are influenced by gender, socio-economic status and childhood adversity. Working memory enables holding information temporarily for task performance. Response inhibition is self-regulatory, enabling appropriate inhibition of undesirable responses. Set-shifting is cognitive flexibility, enabling consideration of alternatives. Faux pas recognition that detects social blunders and emotion recognition are necessary for socio-emotional functioning. The sample represented sex, urban-rural background, and psychosocial risk (psychopathology, childhood adversity and wealth index, i.e. socio-economic status) adequately. Quantile regression was used to model developmental change. It models conditional percentiles by representing observations along with their distributions. This method allowed for examination of covariate effects on shape and location of the graph. We could examine whether covariates affected everyone similarly or were there differences in, say, high versus low performers.

Results: Development in both executive and social cognitive abilities continued into adulthood. Maturation and stabilization occurred in increasing order of complexity, from working memory to inhibitory control to cognitive flexibility. Social faux pas recognition matured by adolescence, but emotion recognition abilities continued to develop into early adulthood. Age related change was more pronounced for low quantiles in response inhibition, but for higher quantiles in set-shifting. Wealth index had the largest influence on developmental change across cognitive abilities. Sex differences were prominent in response inhibition, set-shifting and emotion recognition. Childhood adversity had a negative influence on cognitive development.

Conclusion: These findings add to the limited literature on patterns and determinants of functional brain development. They have implications for developmental vulnerabilities in youth, and need for providing conducive environments. Socio-economic status, by providing enriched environments, has the most prominent influence on development, whereas adversity negatively impacts development. Childhood performance level plays a role in adult outcomes. Interestingly, more prominent impact of determinants on lower performance levels of response inhibition and emotion recognition suggests that these abilities can be enhanced by adequate learning opportunities. This could have a cascading impact on other skill development.

A NEUROCOGNITIVE INVESTIGATION OF LOW-LEVEL ARSENIC EXPOSURE WITH EXECUTIVE FUNCTIONS AND BRAIN STRUCTURE AND RESTING STATE ACTIVITY

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Objective: Arsenic, a contaminant of groundwater and irrigated crops, is a global public health hazard. While isolated impairments of cognitive function following chronic exposure to high arsenic levels have been described, a comprehensive assessment of the scope of such impairments and their underlying brain mechanisms does not exist, especially not in the case of the much more common low-level arsenic exposure. We applied multivariate statistical modelling to (i) investigate potential arsenic-related syndromic changes across multiple cognitive domains; (ii) identify arsenic-related changes in brain structure and function; (iii) understand the relationship between arsenic-associated brain and cognitive alterations, and (iv) explore the moderating influence of other measures of environmental risk and physical health.

Methods: We analysed cross sectional data of 1014 participants aged 6 to 23 years of the Indian Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA cohort). Participants were characterised using deep phenotyping measures of behaviour, neuropsychology, psychopathology, brain neuroimaging and exposure to developmental adversities and environmental neurotoxins. Arsenic was measured in urine as an index of exposure. Executive function was measured using cVEDA neuropsychological battery, grey matter volumes were extracted from T1 weighted MRI and functional network connectivity measures were extracted from the resting state functional MRI. Our multivariate approach controls for age, gender, site, educational level and total intracranial volume. We used sparse partial least square (sPLS) analysis to determine the relationship between arsenic, cognition, brain structures and functions through the application of L1 penalization, applied under resampling. Subsequently we carried out mediation analysis. Next, we conducted moderated mediation analysis using data on participant's SES and BMI.

Results: 1014 participants aged 6 to 23 years (44.5% females) were included from 5 geographic locations. Using sparse-partial least squared analysis (sPLS) we describe a negative association of arsenic exposure with executive function (r=-0.12, p=5.4x10-4), brain structure (r=-0.2, p=1.8x10-8) and functional connectivity (within-network: r=-0.12, p=7.5x10-4, between-network: r=-0.23, p=1.8x10-10). Alterations in executive function were partially mediated by localised changes in grey-matter volume (b=-0.004, 95%CIs=-0.007 to -0.002) and within-network functional connectivity (b=-0.004, 95%CIs=-0.008 to -0.002). Socio Economic Status (SES) and Body Mass Index (BMI) moderated the link between arsenic and changes in grey-matter volume, such that the effect is strongest in participants from lower SES and with low BMI.

Conclusion: Our results indicate that low exposure to arsenic, among participants residing in areas with reported groundwater arsenic content below WHO thresholds, is correlated with aberrations in structural and functional brain regions and alterations of cognitive processes of executive function. Further, children from lower standard of living and with low BMI might be more vulnerable to environmental insults associated with arsenic and might point towards a "syndemic" relation between arsenic exposure and low SES, BMI resulting in greater health problems.

MACHINE LEARNING APPROACHES TO IDENTIFY FUNCTIONAL BRAIN NETWORKS CORRELATING WITH COGNITIVE PERFORMANCE IN ADOLESCENTS WITH ADHD

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Objective: Psychopathology is increasingly associated with impairments in cognitive, emotional and behavioural functions due to underlying alterations in distributed neural networks. Using rsfMRI, large-scale resting state networks (RSNs) have been identified consistently in healthy subjects. Connectivity within these networks correlates with cognitive and behavioural measures obtained outside the scanning environment.

Statistical machine learning methods have been successfully used to classify ADHD based on fMRI measures in previous studies. Here, we used reliefF- SVM derived methods with FSL derived ICA networks as input, to evaluate the cognitive performance of adolescents with ADHD, to identify brain networks underlying cognitive dysfunction.

Methods: The subjects in this study were from the cVEDA neurodevelopmental cohort in India. 71 subjects with a diagnosis of Attention Deficit Disorder [mean age (SD) :12.7 (±3.2)years] were included along with 71 healthy controls (HC) matched for age [mean age (SD) – 12.9 (±2.8) years], gender, head-motion profile during fMRI and scanner-site from the cVEDA imaging databank (http://cveda.org/dataset/).

Cognitive task scores from the cVEDA neuropsychological battery, included digit span test, corsi block test, trial making test, now or later test, balloon analogue risk task, stop signal task, sort the cards, emotional recognition task and social cognition rating tool in Indian setting. Scores on these tasks were scaled to a mean of 50 and standard deviation of 10 and summated to compose cognitive domains.

Resting-state functional MR imaging (EPI) scans were obtained (164 dynamics; TR/TE/FA – 2200ms, 30ms, 75°; 38 slices; 3.4x3.4x3.4 mm). Folllowing pre-processing, subject-specific network time-series were derived, using the dual regression approach of FSL. The data was decomposed into 79 components using the Fast ICA algorithm in FSL. For the purpose of machine learning classification, all the 79 components were used to regress out subject-specific time courses and spatial maps. Feature-set reconstruction was carried out and a filter based feature selection method - ReliefF was implemented

Results: The reliefF-SVM algorithm predicted 55/71 ADHD subjects and 54/71 HC correctly. 16 ADHD subjects were misclassified as HC and 17 HC were misclassified as ADHD. The ROC analysis revealed consistent performance of the algorithm across thresholds. The performance of the classifier model was evaluated using a 10-fold stratified cross validation resulting in 128 training instances and 14 test instances. The overall accuracy was 76.76% with 76.05 % specificity and 77.46 % sensitivity.

Among the 62 components there were 18 components that revealed significant group differences. These components belonged to task positive, default mode, cingulate, orbito frontal, sensory motor, temporal, and visual networks. **Conclusion:** Our study found that rsFMRI measures can be used to predict subjects with ADHD and can be used as an adjunct to phenotypic classification of ADHD. Further we found that variations in specific functional brain networks, appeared to correlate with different cognitive, emotional functions including attention, working memory, impulse control, processing speed social cognition and emotion recognition reflecting lower connectivity in these networks as an indicator of a poor performance.

TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON ANTIPSYCHOTICS

Xenia Hart, German Society for Biological Psychiatry

Symposium Symposium For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A personalization of drug treatments towards highest possible efficacy with acceptable tolerability involves titrating towards the best individual dose and dosing strategy by the use of tools implemented to support clinical decision making. Two tools have been introduced in these terms that can be used in clinical practice i) Therapeutic Drug Monitoring of antipsychotic drug levels and ii) pharmacogenetic testing. Valuable additional insights derive from in vivo brain imaging studies.

Methods: We provide details on pharmacokinetics and pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Articles were selected for inclusion and discussion by more than 40 international experts in the field of psychiatry and psychopharmacology. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. In vivo occupancy of target structures occupied by antipsychotic drugs was primarily assessed using positron emission tomography.

Results: Study findings strongly support the use of Therapeutic Drug Monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes to guide antipsychotic drug therapies. Molecular brain imaging is a strong tool to support the definition of target windows for optimal antipsychotic drug action, so called therapeutic reference ranges.

Conclusion: Therapeutic drug monitoring and genotyping are valid tools to guide individual drug therapies, far beyond the typical indications i.e. uncertain adherence, and polypharmacy.

INTRODUCING TOOLS FOR OPTIMIZING ANTIPSYCHOTIC PHARMACOTHERAPY IN PSYCHIATRY (THERAPEUTIC DRUG MONITORING, MOLECULAR BRAIN IMAGING AND PHARMACOGENETIC TESTS)

Xenia Hart**1*

[1] *German Society for Biological Psychiatry*

Objective: For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A large spectrum of antipsychotic drugs is now available in most western countries. A personalization of drug treatments aims at achieving the highest possible efficacy and acceptable tolerability at the same time. It involves not only the selection of the optimal drug for a patient but also the titration towards the best individual dose based on patients' specific characteristics.

Methods: In my talk, I will give a short introduction in to-date available tools that can be used to optimize pharmacotherapy in psychiatry. I will give an overview on how these tools can be used in order to support clinical decision making in antipsychotic drug therapies. The presented findings are

based on an international guideline initiated by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" with a contribution of more than 40 international experts. Therapeutic drug monitoring nowadays represents the most commonly used tool for personalizing drug treatments in clinical psychiatry. After determination of a drugs' blood level, this level is compared to predefined reference ranges published in relevant guidelines. Pharmacogenetic testing is predominantly used to detect genetic polymorphisms of enzymes involved in drug metabolism. However, the clinical application potential goes far beyond this. The third tool introduced in this presentation are in vivo brain imaging studies, primarily using positron emission tomography. **Results:** The guideline developed by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" provides a detailed review on pharmacokinetics, pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. The use of therapeutic drug monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes are strong tools to guide antipsychotic drug therapies for most drugs. Molecular brain imaging has been used to support the definition of valid therapeutic reference ranges. **Conclusion:** Despite the introduction of useful tools to optimize drug treatments in psychiatry, personalized drug treatment has still not become standard of care in psychiatric patients. Guidelines provide strong support for the use of therapeutic drug monitoring and pharmacogenetic testing. For example, they contain practical instruction for the interpretation of drug monitoring results.

WFSBP TASK FORCE - TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON THERAPEUTIC DRUG MONITORING OF ANTIPSYCHOTICS

Frederik Vandenberghe**1*, *Xenia Hart2, Nicolas Ansermot1, Severine Crettol1, Chin B. Eap3*

[1]Lausanne University Hospital, 2German Society for Biological Psychiatry, 3Swiss Society for Biological Psychiatry

Objective: Therapeutic drug monitoring (TDM) is an important tool to optimize pharmacotherapy, in particular for drugs with narrow therapeutic range. The clinical value of TDM during antipsychotic therapy is best established for clozapine. However, because of the wide interindividual variation of plasma levels and treatment responses, most other antipsychotics are good candidates for routine TDM.

Methods: The literature was extensively reviewed by the WFSBP task force to assess pharmacokinetics, therapeutic ranges and relations between plasma concentrations, daily doses and therapeutic responses of 43 common antipsychotics.

Results: The main conclusions of this review will be discussed, with a focus on clinically important data for the TDM of specific antipsychotics. In addition, the following important aspects of TDM will be addressed: a) specific indications (e.g., treatment resistance, evaluations of drug–drug interactions, specific comorbidities affecting drug pharmacokinetics), b) pre-analytical issues (e.g., steady-state conditions and time of blood sampling), and c) post-analytical issues (e.g., clinical interpretations of drug levels and therapeutic recommendations such as dose adjustments and antipsychotic switches).

Conclusion: To be clinically relevant, TDM should be used according to the latest available evidence and with a good knowledge of the pharmacokinetics, pharmacodynamics and safety profile of the drugs. Moreover, TDM should be associated when needed with other valid tools, such as cytochrome P450 phenotyping and/or genotyping, to optimize personalized antipsychotic therapy.

ASSOCIATION BETWEEN CYP2D6 SLOW METABOLIZER STATUS AND EXPOSURE TO ANTIPSYCHOTICS

Marin Jukic1, Céline Verstuyft**2*

[1]University of Belgrade, 2University Paris Saclay

Objective: Precise estimation of the drug metabolism capacity for individual patients is crucial for adequate dose personalization. The aim of this meta analysis was to quantify the difference in the antipsychotic exposure among patients with genetically associated CYP2D6 poor (PM), intermediate (IM), and normal (NM) metabolizers.

Methods: PubMed, Clinicaltrialsregister.eu, ClinicalTrials.gov, International Clinical Trials Registry Platform, and CENTRAL databases were screened for studies. Two independent reviewers performed study screening and assessed the following inclusion criteria: (1) appropriate CYP2D6 genotyping was performed, (2) genotype-based classification into CYP2D6 NM, IM, and PM categories was possible, and (3) 3 patients per metabolizer category were available. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for extracting data and quality, validity, and risk of bias assessments. A fixed-effects model was used for pooling the effect sizes of the included studies. Drug exposure was measured as (1) dose-normalized area under the plasma level (time) curve, (2) dose-normalized steady-state plasma level, or (3) reciprocal apparent total drug clearance. The ratio of means (RoM) was calculated by dividing the mean drug exposure for PM, IM, or pooled PM plus IM categories by the mean drug exposure for the NM category.

Results: the most profound differences were observed in the patients treated with aripiprazole (CYP2D6 PM plus IM vs NM RoM, 1.48; 95% CI, 1.41-1.57; 12 studies; 1038 patients), haloperidol lactate (CYP2D6 PM vs NM RoM, 1.68; 95% CI, 1.40-2.02; 9 studies; 423 patients), risperidone (CYP2D6 PM plus IM vs NM RoM, 1.36; 95% CI, 1.28-1.44; 23 studies; 1492 patients). Exposure differences were also observed for clozapine, quetiapine fumarate; however, these differences were marginal, ambiguous, or based on less than 3 independent studies.

Conclusion: In this systematic review and meta-analysis, the association between CYP2D6 genotype and drug levels of several antipsychotics was quantified with sufficient precision as to be useful as a scientific foundation for CYP2D6 genotype-based dosing recommendations.

THERAPEUTIC PLASMA CONCENTRATIONS OF ANTIPSYCHOTICS: LESSONS FROM PET IMAGING

Gerhard Gründer**1*, *Moritz Spangemacher1, Hiroyuki Uchida2, Xenia Hart1*

[1]German Society for Biological Psychiatry, 2Japanese Society for Biological Psychiatry

Objective: Positron emission tomography (PET) and single photon emission tomography (SPECT) of molecular drug targets (neuroreceptors and transporters) provide essential information for TDM-guided drug therapy with antipsychotic drugs. Optimal therapeutic windows for D2 antagonists and partial agonists as well as proposed target ranges are discussed based on an up-to-date literature search.

Methods: An overview of neuroimaging findings in humans and primates that after the administration of amisulpride, haloperidol, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, cariprazine, and ziprasidone will be provided. A particular focus is set on dopamine D2-like and 5-HT2A receptors. Target concentration ranges are estimated based on receptor occupancy ranges that relate to the onset of clinical effects or side effects (i.e. EPS). Findings for other relevant receptor systems complement the discussion.

Results: Reported reference ranges for aripiprazole and for clozapine are well in line with findings from PET studies. For haloperidol, risperidone and olanzapine, an adjustment of the previously

published upper limit towards lower concentrations would be indicated from PET studies' findings to decrease the risk for EPS.
Conclusion: Neuroimaging studies provide a strong tool to define target ranges for antipsychotic drug treatment and to direct TDM.

WHITE MATTER IN MENTAL ILLNESS, AS A BIOMARKER AND THERAPEUTIC TARGET

Xinmin Li, University of Alberta
Symposium Synopsis: Since the introduction of drugs used in the treatment of major psychiatric disorders in the 1950s, emphasis has been placed on classical pharmacological actions. Putative therapeutic mechanisms of focus have included effects on monoamine neurotransmitter synthesis, catabolism, release, uptake, and receptor activation. We need to identify alternative and additional targets for drug action in this context. The innovative work that we are leading has indicated possible new mechanisms of action of many of these drugs in terms of effects on neuroprotective effects on neurodegenerative processes in the brain.
Our team approaches mental health disorders as neurodegenerative disorders. We examine whether central white matter damage can produce behavioral symptoms and brain pathology in experimental animal models of schizophrenia or depression as well as neuroimaging, genetic, and clinical studies. We examine whether antipsychotic and antidepressant treatment, rTMS, and ultrasound can prevent white matter damage and/or facilitate recovery which suggests a new role for these treatments and also suggests a new target for future drug development.

RESEARCH ON MYELINATION RELATED SUSCEPTIBLE GENES OF SCHIZOPHRENIA

Weihua Yue*[1], *Hao Yan1, Yuyanan Zhang1, Yaoyao Sun1, Dongxue Chen1, Zhe Lu1, Zhewei Kang1, Tianlan Lu1, Dai Zhang1*

[1]*Insitute of Mental Health, Peking University Sixth Hospital*
Objective: The strategy of genetics has been proven to be effective and helpful to explore the mechanism of schizophrenia and the myelination related susceptible genes of antipsychotic medications. We have been committed to finding the myelination related susceptibility genes of schizophrenia in Chinese Han population.
Methods: We used the genome-wide association study (GWAS) and meta- analysis, the multi-omics approaches, and the pharmacogenomics in Chinese Han population (n = 5934).
Results: We found several myelination related susceptibility genes associated with the risk of schizophrenia (MBP, MAG, MOP, etc.). Combined clues of bioinformatics data and functional experiments by using the gene knock-out or knock-in mice models, we further explored the potential function of the novel susceptible genes. There were very important interactive effects on genetic polymorphisms or variants, on transcriptional levels or neuroimaging characters in schizophrenia patients. With a large sample size of pharmacogenomics (3 stages-design, n = 5934), the applicant reported several susceptible genes associated with individual differences in therapeutic or side effects of common antipsychotic medicines. Patients in the pharmacogenomics-guided pharmacotherapy (PGT) group had greater early-response rate (94.0% versus 80.8%), response rate (83.1% versus 60.3%) and symptomatic remission rate (68.7% versus 46.2%) compared to the treatment-as-usual (TAU) group.
Conclusion: These results will be helpful to interpret the pathogenesis of schizophrenia, as well as the pharmacological mechanism of common antipsychotic medications.

Haiyun Xu*[1]
[1]School of Mental Health, Wenzhou Medical University, China

Objective: Understanding the pathogenesis of schizophrenia involves exploring various hypotheses, including the dopamine (DA) hypothesis, mitochondrion hypothesis, oligodendrocyte (OL) hypothesis, among others. The coexistence of these hypotheses suggests a potential common neurobiological mechanism underlying schizophrenia.
Methods: This study investigates a potential neurobiological mechanism by utilizing two animal models of schizophrenia, cultured OLs, and neuron-OL co-cultures. The research employs animal behavioral tests, as well as cellular and molecular biological techniques.
Results: Adolescent C57BL/6 mice administered tolcapone (TOL) for two weeks exhibited elevated DA levels in the prefrontal cortex (PFC), mitochondrial dysfunction in brain cells, and dose-dependent hypomyelination in the PFC, hippocampus, and caudate putamen (CPu), alongside schizophrenia-related behaviors. Catechol-O-methyltransferase (COMT) gene knockout (COMT-ko) mice displayed dopaminergic dysfunctions in the PFC and CPu, mitochondrial functional deficits, reduced mature OLs, and hypomyelination in similar brain regions to TOL-treated mice. In cultured OLs, DA inhibited cell development and impaired mitochondrial function in a concentration-dependent manner. These effects were mitigated by the antioxidant N-acetyl-L-cysteine (NAC) and trans-2-phenylcyclopropylamine (TCP), a mitochondrial monoamine oxidase (MAO) inhibitor. Additionally, DA inhibited axonal myelination in neuron-OL co-cultures while impairing mitochondrial function.
Conclusion: These findings underscore the critical role of mitochondria in linking DA catabolism to axonal myelination in the brain, offering new insights into schizophrenia pathogenesis and therapeutic strategies.

MODIFICATION OF MYELINATION AS A TARGET FOR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND FLUOXETINE TREATMENT IN A MOUSE MODEL OF DEPRESSION

Jue He*[1], *Qianfa Yuan2, Lijing Chen1, Linman Wu1, Huai Li1, Mengbei Lou1, Yanlong Liu1, Yang-Huan Bao3*

[1]*Wenzhou Medical University, 2Xiamen Xian Yue Hospital, 3Precision Brain Science Biotechnology (Suzhou) Co., Ltd.*

Objective: In order to test the neurotrophic hypothesis on myelination of depression, myelin basic protein (MBP), brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (TrkB) signaling were investigated in a mouse model of depression which was applied by a physical treatment of repetitive transcranial magnetic stimulation (rTMS) or (and) by a medical treatment of fluoxetine.
Methods: After 28 days of chronic unpredictable mild stress (CUMS) exposure, mice were chronically treated with rTMS (10 Hz for 5 seconds per train, total 20 trains per day) and (or) fluoxetine (5 mg/kg/day, intraperitoneally) for 28 days targeting on the frontal cortex. After the behavioral tests, the protein expressions of MBP, BDNF and TrkB were measured by immunohistochemistry and (or) Western Blot.
Results: The results showed rTMS and (or) fluoxetine attenuated the locomotion decrease, anxiety and depressive-like behaviors in the CUMS-exposed mice. In the same time, rTMS and (or) fluoxetine attenuated MBP and BDNF-TrkB decrease in the frontal cortex of the CUMS mice. Our results suggest that rTMS and fluoxetine could both benefit the CUMS-induced abnormal behaviors including depressive-like behaviors, and the beneficial effects of rTMS as well as fluoxetine on depression might be partly related to their common effect on modulating myelination through BDNF-TrkB signaling.
Conclusion: These indicate that modulation of myelination could be a potential novel treatment target for major depressive disorder.

MATRIX METALLOPROTEINASE-9 AS A MYELINATION RELATED PROTEIN IN INTRACEREBRAL HEMORRHAGE AND DEPRESSION

Xin Yu1, Mengzhou Xue Xue*2

[1]*Peking University, Institute of Mental Health, 2The Second Affiliated Hospital of Zhengzhou University*

Objective: The zinc-dependent proteinases (MMPs) are a endopeptidases which have the capability of cleaving protein constituents of extracellular matrix. They are physiologically expressed in neurons, astrocytes and microglia, and their aberrant elevation contributes to a few central nervous system diseases.

Methods: Among the MMP members, MMP-9 has generated considerable attention because of its involvement in inflammatory responses, blood-brain barrier permeability, the regulation of perineuronal nets, demyelination, and synaptic long-term potentiation. MMP-9 is strongly detected in many cell types including endothelial cells and infiltrated neutrophils after brain injuries. It can be induced by factors such as the c-fos and c-Jun, immediate early genes and the cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).

Results: Primary hematoma expansion occurs shortly after intracerebral hemorrhage onset and appears to correlate with MMP-9 elevation. Perihematomal edema also seems to be linked to MMP-9 levels. Inhibition of MMP-9 could potentially improve clinical outcome through maintenance of BBB integrity and perihematomal edema reduction. Emerging evidence indicates an association between MMP-9 and the syndrome of depression. MMP-9 is considered to be an important factor in depression, not only as a therapeutic target but also as a biomarker in the condition. Clinical studies suggest that MMP-9 gene polymorphisms are related to depressive symptoms, and altered MMP-9 levels are observed in depressed patients and in depressive-like animal models. The serum MMP-9 may be a novel therapeutic target and biomarker for depression, although that blood level of MMP-9 may not directly correlate with brain MMP-9 content.

Conclusion: MMP-9 is likely to be a target for classical antidepressant treatments and MMP-9 inhibitors possess potential therapeutic effects for depression.

3:30 p.m. - 5:00 p.m. Debate Session III - Anthony Pelosi and Steven Hyman

DOES NATURE FAVOUR DIMENSIONAL OR CATEGORICAL DIAGNOSES? BY THEIR (CLINICAL) FRUITS SHALL YE KNOW THEM

*Anthony Pelosi*1*

[1]*University of Glasgow*

Objective: I will consider some pros and cons of categorical versus dimensional diagnoses in clinical practice and in research.

Methods: Results will be presented from epidemiological and health services research over the decades.

Results: I will argue that, on balance, a categorical diagnostic approach in psychiatry has been more useful to more patients than a dimensional approach over recent decades.

However, I will also also outline some recent worrying developments in British psychiatry that lessen the importance of Mother Nature when it comes to clinical diagnosis. These include the following.

1. Categorical and dimensional diagnoses are being used to exclude certain patients from the caseloads of highly specialised multidisciplinary clinical teams.

2. Specialist clinicians are claiming that they have special diagnostic skills and that diagnoses within their narrow area of interest are being missed by other psychiatrists (see, for example, Report by Bipolar UK 2022). 3. Certain psychiatrists and even their multidisciplinary colleagues are increasingly preoccupied with diagnostic classification. This is sometimes to help them exclude patients from their caseloads. At other times, it is to obtain access to additional resources for their patients that can only follow "an official diagnosis". Some nurses, psychologists, occupational therapists and social workers are taking this approach even though one of the strengths of these professions is that they are trained not to make diagnoses. 4. Patients are sometimes being referred to a clinic for confirmation of a particular self-diagnosis rather than for an assessment by a doctor who understands diagnosis and differential diagnosis and who is aware of their importance and their limitations. 4. Clinical and administrative preoccupation with "an official diagnosis" means that certain patients are passed from pillar to post when they present with mental ill health. Some patients, especially those with severe and complicated conditions, can end up receiving no care and treatment from mental health professionals. In the months before the conference I will be making inquiries of colleagues in other parts of the world about whether they have encountered similar situations. This is with a view to starting a good discussion of what can be done to maximise the benefit of both categorical and dimensional diagnoses and differential diagnoses. **Conclusion:** I will suggest that diagnostic categories in psychiatry remain a useful tool but, like all powerful tools, they can be misused.

DEBATE. NATURE STRONGLY FAVOURS DIMENSIONAL DIAGNOSES

*Steven Hyman*1*
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The Broad Institute

Objective: In this debate, I will present evidence that psychiatric disorders are best captured in dimensional terms that cross current diagnostic boundaries; I will also describe how the dominant DSM categorical system has become reified in a manner that thwarts scientific progress and new treatment development.
Methods: I will describe and synthesize results from epidemiology, genetics, neurobiology, and clinical research that can inform concepts and boundaries of psychiatric disorders.
Results: Psychiatric disorders are genetically and phenotypically highly complex and heterogeneous. Genetic contributions to risk involve thousands of DNA sequence variants (‘risk alleles’) segregating within populations. Each human being has a stochastic grab-bag representing some small fraction of the alleles associated with essentially all common quantitative traits. These range from disorders such as risk of schizophrenia to non-disorder traits such as adult height. Risk alleles for psychiatric disorders act additively, with degree of genetic loading (that can be measured by polygenic scores) being associated probabilistically with quantitative likelihood of unaffected, sub-threshold, or affected status. Common risk alleles are continuously distributed in populations; there are no discontinuities in distributions of polygenic risk that would support categorical distinctions between ill and well. There are also no discontinuities that would support categorical distinctions between disorders. Empirically, risk alleles are shared across psychiatric disorders (e.g., schizophrenia and bipolar disorder share approximately 65% of their common risk alleles) and importantly, some alleles that confer risk for certain disorders confer, at the same time, likelihood of beneficial cognitive and behavioral phenotypes (e.g., alleles that increase risk of obsessive-compulsive disorder, autism spectrum conditions, or anorexia nervosa are associated with greater educational attainment.)

Paralleling genetic risk, symptoms that contribute to psychiatric disorders (e.g., anxiety, social communication difficulties, dysphoric mood, inattention) are also continuously distributed in populations, differing quantitatively between unaffected and affected individuals in number and severity. The symptom counts that DSM-5 uses to define disorders (e.g., 5 of 9 listed symptoms for major depression) represent (unfortunately arbitrary) normative designations. Overall, genetic, clinical, and epidemiological findings impugn the imposition of categorical boundaries between ill and well and favor transdiagnostic dimensional measures.

Conclusion: What is the path forward? (1) Continued pursuit of large-scale unbiased psychiatric genetics and follow-on neurobiology; (2) Use of information emerging from genetics and neurobiology to perform transdiagnostic efforts at biomarker discovery; (3) Epidemiology and genetics at the level of symptoms and symptom covariation, not categorical disorders; (4) Development of quantitative scales based on symptoms and symptom clusters, genetics, and biomarkers with the properties needed for diagnostic measures; (5) Integrative efforts to develop dimensional diagnostic criteria with openness to revision.

3:30 p.m. - 5:00 p.m.
Concurrent Symposia X

WHEN RANDOMIZED TRIALS AREN'T AN OPTION: TARGET TRIAL EMULATION IN PSYCHIATRIC RESEARCH *Helene Speyer, Copenhagen Research Center for Mental Health – CORE Mental Health Center*
Copenhagen; Copenhagen University Hospital

Symposium Synopsis: Because randomized trials in psychiatry are difficult to conduct, clinical decisions may need to be guided by analyses of non-randomized (observational) data. These observational analyses need to use a methodology that appropriately emulates a (hypothetical) randomized pragmatic trial—a target trial—. These challenges are not unique to psychiatry research.

Elsewhere in medicine investigators have applied this method to provide the same answers as randomized trials when other approaches to analyze observational data had failed. Here, we will present four different applications:

First, antipsychotic discontinuation in early psychosis. A research question famous for being hard to answer with randomized trials. But as health-care professionals, we are responsible for providing evidence-based counseling to help patients make informed choices.

Second, functional interventions in patients with a recent hospitalization for major depression disorder. Attrition rates and the small sample sizes rendered existent RCT analyses inconclusive. We will apply the target trial emulation framework to Finnish Registry data.

Third, we will apply this methodology to suicide research, where the event is so rare that it is hard to

find adequate sample sizes to study in randomized trials. We will explore the comparative effectiveness of antidepressants in reducing suicide risk.

Finally, we will discuss how we can use existing randomized trials to strengthen this proposed methodology. By benchmarking observational data analyses against the results of existing randomized trials, we can more confidently extend to new questions. We will discuss this approach using as a case study the EUFEST trial and observational analyses on First Episode Psychosis.

BENCHMARKING OBSERVATIONAL ANALYSES AGAINST RANDOMIZED TRIAL RESULTS: AN APPLICATION TO FIRST EPISODE PSYCHOSIS

Alejandro Szmulewicz*[1], *Gonzalo Martínez-Alés1, Maria Ferrara2, Diane Fredrikson3, Juan Gago4, Vinod Srihari2, Lakshmi Yatham3, Sarah Conderino4, Ann Shinn5, Dost Öngür5, Miguel Hernán1*

[1]Harvard University, 2Yale School of Medicine, 3University of British Columbia, 4New York University Grossman School of Medicine, 5McLean Hospital

Objective: To increase confidence in observational analyses in first episode psychosis (FEP), we would benchmark the observational analyses against existing trial results before extending the observational analyses to answer clinical questions not originally considered in that trial.

Methods: The FEP-CAUSAL Collaboration is an international consortium of observational cohorts of individuals with FEP. We analyzed data from four FEP-CAUSAL cohorts in North America (current N=1,081) to emulate a target trial similar to the EUFEST randomized trial. EUFEST found a higher average 1-year hazard ratio (HR) of treatment discontinuation in haloperidol compared with olanzapine and quetiapine, but similar 1-year probabilities of hospitalization and mean Clinical Global Impressions-Severity (CGI-S) scores. We replicated the results from EUFEST and then extended the emulation to include aripiprazole and risperidone.

Results: Compared with haloperidol, the HR (95% confidence interval) of treatment discontinuation was 0.38 (0.24-0.59) for olanzapine and 0.24 (0.13-0.44) for quetiapine. The 1-year mean of CGI-S for haloperidol, olanzapine, and quetiapine were 3.5, 3.4 and 4.2, respectively, and the 1-year risks of hospitalization were 24.2 (16.2-35.0), 25.4 (18.8-34.0), and 28.2 (21.6-34.2), respectively. Compared with haloperidol, the HR of treatment discontinuation was 0.18 (0.12-0.26) and 0.21 (0.13-0.34) for risperidone and aripiprazole. The 1-year hospitalization risk for aripiprazole was 33.0% (24.7-43.6).

Conclusion: Our observational estimates were similar to those from the EUFEST randomized trial. After benchmarking known effect estimates, we estimated a greater 1-year hospitalization risk for aripiprazole compared with all other drugs. Our findings suggest that this observational dataset may be used to estimate treatment effects in FEP research.

COMPARATIVE EFFECTIVENESS OF ANTIDEPRESSANTS TO LOWER SUICIDE RISK AFTER A SUICIDE ATTEMPT: WHY ARE RCTS UNFEASIBLE AND HOW CAN WE LEVERAGE OBSERVATIONAL DATA TO GUIDE CLINICAL DECISIONS?

Gonzalo Martínez-Alés*[1], *Alejandro Szmulewicz2, Miguel Hernán2*

[1]Harvard TH Chan School of Public Health, 2Harvard University

Objective: Lack of evidence regarding use of commonly prescribed antidepressants (e.g., SSRIs, SNRIs, mirtazapine) for patients discharged after an attempt has important implications for clinical practice, because (i) most of such patients are diagnosed with mental health conditions potentially treatable with antidepressants and (ii) there is conflicting evidence as to whether initiation of antidepressants may temporarily increase risk of suicidal ideation and suicidal behaviors. This presentation is aimed at clarifying limitations of RCTs to examine the potential role of antidepressants for suicide prevention following an attempt, introducing the target trial emulation framework as a way forward, and presenting preliminary results of the first target trial emulation of antidepressants for post-discharge suicide prevention.

Methods: We first critically review RCTs examining use of antidepressants to prevent suicide among suicide attempters. We provide a detailed overview of the limitations of such studies. Then, we introduce the notion of target trial emulation using observational data to guide clinical decision-making for clinicians and patients choosing antidepressant agent and treatment strategy following a suicide attempt. Last, we present results from a large target trial emulation including ~67,000 suicide attempters from the US Veteran Health Administration.

Results: The scarce evidence on antidepressants and suicidality comes largely from randomized controlled trials including antidepressant initiators but excluding patients deemed acutely suicidal (or at high suicide risk, such as recent suicide attempters). Traditionally, the potential inclusion of patients discharged following a suicide attempt in antidepressant trials has raised ethical and safety concerns. In addition to potential ethical concerns, randomized trials including patients discharged following a suicide attempt are difficult to implement because of pragmatic reasons: adequately large samples are arduous to gather, and patients may be reluctant to enroll or remain engaged. Observational data can be used to evaluate the benefits and risks of clinical interventions when randomized trials are not available. In fact, many analyses of observational data are attempts to emulate a hypothetical pragmatic randomized trial. This methodological approach rests on a key idea: observational analyses need to emulate a (hypothetical) target trial as closely as possible, because the process of specifying and emulating a target trial forces the investigators to sharpen their research question in terms of actionable interventions and enhances interpretability of results. Results from the first target trial emulation of antidepressants to lower suicide risk following a suicide attempt, examining the comparative effectiveness of initiation of an SSRI, an SNRI, or mirtazapine with doses following recommendations from standard clinical guidelines, suggest this approach is feasible and can guide clinician decision-making. The outcomes of interest are nonfatal suicide re-attempt, suicide death, and death by any external cause, all measured within 1-, 3-, 6-, and 12-months following discharge. **Conclusion:** By adopting and successfully applying target trial emulation, we can use observational data to generate new avenues to guide decision-making in clinical questions such as post-discharge suicide prevention – where randomized trials are unethical, not feasible, or currently under way.

EARLY VS. DELAYED RETURN TO WORK AMONG INDIVIDUALS DIAGNOSED WITH MAJOR DEPRESSIVE DISORDER: A TARGET TRIAL EMULATION

Kaisla Komulainen*[1], *Mai Gutvilig[1], Ripsa Niemi[1], Markus Jokela[1], Marko Elovainio[1], Christian Hakulinen[1]*
[1]*University of Helsinki*

Objective: Prolonged absence from work among patients with first-episode major depression may add to depression-related functional impairment and impede recovery. The effectiveness of early return to work against adverse functional outcomes is not yet well known and conducting a randomized controlled trial to evaluate the effectiveness is not feasible. We emulate a hypothetical target trial to assess the risk of a new sick leave due to depression among persons with first-episode major depression who returned to work early vs. after a prolonged sick leave period.
Methods: Using individual-level data linked across Finnish nationwide registers, we emulate a target trial among persons who went on sick leave following a diagnosis of first-episode major depressive disorder. Persons are eligible if they received their first recorded diagnosis of major depressive disorder (ICD-10 code F32) between Jan 1, 2009 and Dec 31, 2019, were 25–50 years old at the time of the diagnosis, had no sick leave due to any mental disorder during the 4 years preceding the diagnosis and were granted sick leave for 10–84 days since the diagnosis. We compare assignment to two sick leave strategies: 1) early return to work (sick leave duration 10–28 days) and 2) delayed return to work (sick leave duration 29–84 days). We classify individuals into one of two sick leave strategies according to their records obtained from the sickness absence register of the Social Insurance Institution of Finland, which contains diagnosis-specific administrative information on all sick leaves granted by a physician for > 9 days. The assignment is assumed to be random conditional on baseline covariates including sex, age, educational level, geographical area, depression severity, psychiatric comorbidity and comorbid physical conditions. The outcome of interest is the start of a

new depression-related sick leave during the follow-up period. For each person, the follow-up starts on the first day of sick leave (baseline) and ends on the day of the outcome event of interest (a new sick leave), death, emigration, 2 years after baseline or the administrative end of follow-up on Dec 31, 2019, whichever occurs first. The causal contrast of interest is the observational analogue of the per protocol effect. We evaluate the cumulative incidence estimates of the 2-year risk of a new sick leave, risk differences and risk ratios between individuals with early and delayed return to work. **Results:** There were 114 000 eligible individuals (52 000 with early return to work; 62 000 with delayed return to work). The 2-year cumulative incidences of a new sick leave, risk differences and risk ratios will be presented. **Conclusion:** We will evaluate the implications of our findings on the effectiveness of early vs. delayed return to work among individuals with first-episode depression and discuss the application of target trial emulation using population-based register data in a real-world setting.

WHY OBSERVATIONAL DATA MAY BE THE SOLUTION TO CHALLENGES IN ANTIPSYCHOTIC MAINTENANCE TREATMENT RESEARCH

Helene Speyer*[1]

[1] *Copenhagen Research Center for Mental Health – CORE Mental Health Center Copenhagen; Copenhagen University Hospital*

Objective: Current recommendations, largely based on expert consensus or observational evidence, suggest antipsychotic maintenance treatment for 1-2 years following remission after a first episode of psychosis (FEP). The aim of this presentation is to discuss limitations of randomized controlled trials (RCTs) to address gaps in evidence. Current gaps include lack of long-term studies, limited adherence to studied interventions – and of uptake of proper per-protocol analysis methods, absence of examination of clinically important treatment strategies (e.g., different treatment durations), limited real-world generalizability of study results, and lack of power to detect relevant outcomes (e.g., mortality). We examine the potential of observational data (e.g., from electronic health records), analyzed to emulate a hypothetical (target) trial, to address these limitations and inform clinical guidelines.

Methods: The key to inform clinical decision-making (i.e., choice between available interventions) is to explicitly define the most useful causal contrast of interest for clinicians and patients. In traditional relapse prevention RCTs including participants experiencing FEP, maintenance treatment is compared to an abrupt transition to placebo, assessed in blinded design on samples fulfilling a narrow set of eligibility criteria. These have limited real-world validity. More recent trials compare maintenance treatment to open label, personalized tapering strategies. Despite mirroring real world clinical situations, these trials have low levels of adherence to assigned treatment strategies, especially after long-term follow-ups. When analyzed as intention-to-treat, confounding may lead to underestimation of both beneficial and harmful effects. Indeed, data may approximate observational data and therefore need careful adjustment for potential post-randomization confounding, while still having the limitations associated to narrow eligibility criteria and small samples sizes. Furthermore, recruitment problems have led to failed and underpowered trials, as few people can accept that medication strategy is determined by randomization. Studies using observational data have been published. While attempts have been made to adjust for confounding at baseline, these studies have typically failed to adjust for time-varying confounding, such as fluctuations in illness severity over time.

Results: There are several limitations in conducting RCTs to expand the knowledge gaps: 1) Recruitment problems lead to underpowered or failed RCTs, 2) low adherence to assigned treatment arm introduces confounding, 3) narrow eligibility criteria lead to low real-world generalizability, 4)

there are ethical concerns as superiority of maintenance treatment has already been established. Data from electronical health records with rich longitudinal information may be a feasible way forward. When observational data are used to explicitly emulate a hypothetical (target) trial, they can provide clinically useful estimates of the causal contrast of interest while securing sufficient power and real-world validity and allowing for appropriate adjustment for time-varying confounders. **Conclusion:** To develop evidence-based clinical guidelines for treatment maintenance in FEP, emulating a hypothetical (target) trial using rich observational data may be the solution.

PRECISION PSYCHIATRY APPROACH FOR MOOD DISORDERS: ROLE OF BRAIN BIOMARKERS AND DYSFUNCTIONAL IMMUNE RESPONSE

Manish Jha, University of Texas Southwestern Medical Center

Symposium Synopsis: Modest benefits of currently available treatments for mental illnesses have limited our ability to address the ongoing public health emergency of increasing rates of deaths due to suicide. In fact, over the past decade, suicide rates have increased by 178% and 76% respectively in youths aged 10-14 years and 15-19 years. Current syndromic approaches of diagnosing and investigating mental illnesses are a key barrier to developing mechanistically-guided treatments. Therefore, our proposed panel will bring together early- stage investigators and senior researchers who will present on issues relevant to precision psychiatry approach for mood disorders. The first presentation will discuss neuroimaging-predicted brain age as a novel biomarker that is associated with antidepressant response and with all-cause mortality. The second presentation will focus on how persons with depression should be elevated to be the focus of personalized medicine and improve quality of care. The third presentation will present novel data form a large observational natural-history cohort of patients where integration of brain and immune biomarkers can help in identifying distinct trajectories of depression. The final presentation will focus on the on the topic of the aggregation of marginal gains as a philosophy of care; this recognizes that there are no silver bullets, and for most people it aggregating several small-effect sized factors which are selected on the basis of clinical formulation. Together, these presentations will highlight novel approaches to identifying subgroups of individuals with mental illness and discuss issues relevant to precision approaches for mood disorders.

ACCELERATED AGING OF BRAIN: ASSOCIATION WITH ANTIDEPRESSANT TREATMENT RESPONSE AND ALL-CAUSE MORTALITY

Manish Jha*[1], Abu Minhajuddin[1], Cherise Chin Fatt[1], Madhukar Trivedi[1]
University of Texas Southwestern Medical Center

Objective: Recent reports suggest that neuroimaging-predicted brain age is higher than chronological age (or Δ brain age) in adults with major depressive disorder (MDD). In this presentation, we will discuss its reliability as a biomarker, association with antidepressant treatment response and with all-cause mortality.

Methods: Both studies: Accelerated Brain Age was estimated as difference between T1-weighted structural MRI scan-predicted brain age and individual's chronological age.

Study 1: Mixed model analyses evaluated whether accelerated brain aging at baseline (N=290) in the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study was associated with treatment-related changes in depression severity.

Study 2: Kaplan Meier survival curves and Cox proportional hazards regression were used to estimate the association between accelerated brain aging and all-cause mortality in the second-wave of Dallas Heart Study (DHS-2; N=1948).

Results: In EMBARC, greater accelerated brain aging at baseline was associated with smaller reductions in depression severity with sertraline with sertraline (p=0.019) but not with placebo (p=0.64) after controlling for age, gender, race, ethnicity, and site. In DHS-2, each additional year of accelerated brain aging was associated with 6% higher likelihood of all-cause mortality even after controlling for Framingham 10-year risk score, race, ethnicity, income, education, waist-to-hip ratio, diabetes, hypertension, and history of myocardial infarction. **Conclusion:** Accelerated brain aging was independently associated with poorer outcome to antidepressants in MDD and to higher likelihood of all-cause mortality in an epidemiological sample. Future prospective studies are needed to replicate these associations and elucidate the mechanisms that link accelerated brain aging to poor outcomes.

THE PERSON AND ITS RELATION TO PERSONALIZED MEDICINE AND DEPRESSION TREATMENT

Koen Demyttenaere*[1], *Madhukar Trivedi[2], Michael Berk[3], Manish Jha[2]*

[1]KU Leuven, University Psychiatric Center, [2]The University of Texas Southwestern Medical Center, [3]Deakin University

Objective: Psychiatry has been adopting terminology used in cancer clinics and cancer research: the concepts of remission and of quality of life have been widely adopted and more recently, the concepts of personalized medicine or of precision medicine have also getmore and more attention.
Methods: Given the limitations of currently available biomarkers, we still believe personalized medicine within the scope of depression treatment first of all has to take the 'person' into account.
Results: The poorly defined concept of major depression results in a highly heterogeneous patient population and the very non-specific scales used to assess severity and change during treatment obscure the more subtle clinical effects observed in clinical practice. Moreover, patient sociodemographic characteristics as well as patient beliefs and patient preferences play an important role in predicting outcome. One could even speculate that the currently available biomarkers are more relevant than usually believed if the 'person' would be better taken into account in the prediction models.
Conclusion: Patient preferences, illness beliefs, treatment beliefs and adherence are crucial in what we can expect from treatment modalities.

BRAIN AND IMMUNE BIOMARKER BASED TRAJECTORIES OF DEPRESSION: FINDINGS FROM THE TEXAS RESILIENCE AGAINST DEPRESSION (T-RAD) STUDY

Madhukar Trivedi*[1]

[1] *The University of Texas Southwestern Medical Center*

Objective: Major depressive disorder (MDD) is a heterogenous syndrome which affects 1 in 5 adults during their lifetime and is associated with marked impairments in social, occupational, and interpersonal functioning and reductions in quality of life. Clinical markers have proven to be of minimal benefit in predicting long-term trajectories of symptoms and functioning. Studies using biomarkers, including blood-based and brain neuroimaging, have typically focused on distinct age groups, such as those on youths, young adults, or elderly individuals, and may miss out on age-related differences in these mechanisms. Furthermore, these studies have often not included individuals who are at risk for developing depression and characterize those who are resilient in face of the risk factors and stressors.
Methods: This report is based on findings from the ongoing Texas Resilience Against Depression (T-RAD) study which has enrolled. The individuals undergo comprehensive clinical phenotyping and biomarker assessments using electroencephalogram (EEG), magnetic resonance imaging (MRI) and multiplex immune marker assays.

Results: Between September 2016 to Sep 2022, 1313 individuals aged 10-95 years who either have a diagnosis of unipolar or bipolar depression or have risk factors that predispose them to depression (such as diagnosis of depression in first degree family members) were enrolled. Three-fourths of the sample attended at least two in-person visits, and 57% had at least four in-person visits. Data for less than 6 months, 6-12 months and > 12 months was available for 519 (37.61%), 132 (9.56%), and 729 (52.83%) participants, respectively. Connectomic analyses using EEG data from 1083 individuals revealed distinct patterns of dysfunction within the executive control network. Immunometabolic analyses revealed distinct subgroups of individuals with dysregulation within innate and adaptive immune responses. Ongoing analyses are evaluating how these dysfunctions relate long-term symptom and quality of life trajectories.

Conclusion: This study of individuals with depression or at-risk for depression demonstrates the utility of comprehensively phenotyping and implementing multimodal biomarker assessment.

THE AGGREGATION OF MARGINAL GAINS AS A PHILOSOPHY OF CARE

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to discuss the construct of the aggregation of marginal gains informed by clinical formulation as a philosophy of care and a pragmatic pathway to personalised medicine.

Methods: There are no magic bullets in psychiatry and very few people respond dramatically to any one therapy. For most individuals, one needs a combination of different modalities that are tailored to individual needs. The philosophy of aggregation of marginal gains capitalises on the idea that even small improvements in multiple domains can lead to very large changes because they compound over time. Clinically, each small change can increase capacity to take on subsequent steps, leading to a virtuous cycle which with persistence and time can result in major changes.

Results: At present despite promising developmental work there are no biomarkers capable of stratifying participants to predict response to therapy that are ready for the clinic. However clinical formulation allows one to understand the individual biological psychological and social predisposing, precipitating, perpetuating and resilience factors that allows one to select from the large number of psychological, lifestyle and biological therapies that are available.

Conclusion: In conclusion the philosophies of the aggregation of marginal gains, informed by clinical formulation, supported by a solid therapeutic alliance and consistency of care have the capacity to lead to substantial improvements in clinical outcomes.

Wednesday, June 5, 2024

12:00 p.m. - 4:00 p.m.

Pre-Conference Workshops

ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA - A PRACTICAL COURSE FOR EARLY CAREER PSYCHIATRISTS *Istvan Bitter, Semmelweis University*

Overall Abstract: Antipsychotic treatment of schizophrenia - a practical course for early career psychiatrists. Course director: Prof. Istvan Bitter, Semmelweis University, Budapest, Hungary. This interactive course will summarize evidence-based knowledge based on randomized clinical trials and real-world data about the efficacy and safety of antipsychotic drugs in the acute and maintenance treatment of schizophrenia. The course will address how to individually use different antipsychotic drugs with the help of such information as their pharmacological effects on the neurotransmitter systems (e.g. dopamine D2 occupancy; D2 partial agonists), pharmacokinetic parameters (e.g. the potential roll of metabolites; elimination half-life; long acting injectable antipsychotics) and their clinical effects (use of rating scales or real world data such as time to discontinuation of taking a drug, risk of re/hospitalization and mortality). The importance of regular evaluation of extrapyramidal and metabolic side effects will be highlighted. Such specific topics as the differential diagnosis and treatment of negative symptoms and the management of treatment resistance in schizophrenia will also be discussed. The participants - who request - will receive a short list of selected literature linked to the topic of the course, that could provide help in their daily practice.

USING AI IN SYSTEMATIC REVIEW SCREENING WITH ASREVIEW

Jelle Teijema, Utrecht University

Pre-Conference Workshop Synopsis: This workshop will delve into ASReview, an innovative AI based software designed to transform the process of systematic literature review, making it faster, more accurate, and less labor-intensive. Systematic reviews are foundational to evidence-based practices across disciplines, yet they are time-consuming and prone to bias. ASReview leverages machine learning algorithms to significantly reduce the amount of time researchers spend screening titles and abstracts by prioritizing relevant studies for inclusion. The session will commence with an introduction to the challenges of traditional literature review processes, setting the stage for a detailed exploration of ASReview. Participants will gain insights into the underlying technology, including the machine learning models that power ASReview, and how these models adapt and improve through user interaction. We will address critical questions around the efficacy of ASReview, its impact on reducing researcher workload, and the quality and reliability of the results it produces. A portion of the workshop will be dedicated to hands-on activities, where attendees will have the opportunity to interact with ASReview directly, requiring a laptop. This practical experience aims to equip participants with the knowledge to set up and begin using the software for their own systematic reviews. Additionally, there will be ample time for discussion, allowing participants to raise questions, share experiences, and discuss the implications of integrating such technologies into their research practices. The workshop promises to be an engaging and informative session, offering a blend of theoretical knowledge and practical skills. By the end, participants will be well-prepared to adopt ASReview, enhancing their research efficiency and contributing to the advancement of evidence-based findings.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL *Joan Marsh, The Lancet Psychiatry* **Pre-Conference Workshop Synopsis:** The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry. The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines. The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions. The workshop will include questions and answers throughout and group discussions.

SUCCESSFUL PUBLISHING IN A QUALITY PSYCHIATRY JOURNAL

*RajivTandon*1*
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University of Michigan Medical Center

Objective: This interactive workshop is designed to learn essential steps and augment skills that will enable attendees to successfully publish their scholarship in writing for peer-reviewed journals. Information about what happens to a manuscript after submission will be summarized, with the focus on the editorial and review process.
Methods: This workshop is organized in three parts:
a)40-minute didactic introduction;
b)30-minute interactive process with participants, reviewing vignettes (or personal publishing experiences) that illustrate successful negotiation of challenges across the many steps in the publishing process; and
c)20-minute summation with 7 KEYS to SUCCESSFUL PUBLISHING IN PSYCHIATRY
Results: Participants will discover rich information and techniques for:
(i)Successfully navigating the manuscript publication process after submission;
(ii)Recognize the expectations and priorities of the multiple audiences (editor, reviewer, reader) of the manuscript;
(iii)Producing effective scientific writing that meets expectations of these audiences (specifically editor and reviewers);
(iv) Learn how to respond to reviewers
(v)Being attentive to ethical issues during publication
Conclusion: Attendees will learn specific techniques and receive a checklist that will facilitate acceptance of their manuscripts for publication in high quality scientific journals.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL

*Joan Marsh1, Yasin Hasan Balcioglu*2*
[1]The Lancet Psychiatry, 2Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery

Objective: The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry.
Methods: The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines.
Results: The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions.
Conclusion: The workshop will include questions and answers throughout and group discussions.

4:15 p.m. - 5:45 p.m.
Concurrent Symposia I

REVISING CONSTRUCT OF SCHIZOPHRENIA: RELEVANCE TO BIOLOGICAL RESEARCH

Rajiv Tandon, University of Michigan Medical Center

Symposium Synopsis: An increasing number of researchers are debating about how schizophrenia has devolved into an "inherently flawed construct". Even as we accumulate increasing amounts of new knowledge about schizophrenia, its definition gets fuzzier. It is clearly time to take stock of what is known and what remains to be known about this syndrome, seriously examine the increasingly mosaic construct/s of schizophrenia, more clearly define the contours of the multiple disease entities encompassed by this term, and identify potential future directions for better understanding and treatment of this complex and heterogeneous syndrome.
In this symposium, we will review the nature of and problems with the current construct/s of schizophrenia, discuss challenges in developing reliable and valid biological markers, and consider the implications for future biological research of ongoing efforts to redefine this entity. Wolfgang Gaebel will briefly summarize the history of schizophrenia leading up to the current ICD-11 definition and description. Rajiv Tandon will review the DSM-5 characterization and outline an ongoing international initiative at reconceptualizing this entity (Schizophrenia Research; 2022, Volume 242; and 2023, 252, 345-347). Florence Thibaut will summarize the current status of biological markers for schizophrenia, updating the WFSBP workgroup report on biological markers. Peter Falkai will discuss implications of the evolving concepts of psychosis and schizophrenia for ongoing and future biological research.

SCHIZOPHRENIA OR OTHER PRIMARY PSYCHOTIC DISORDERS: ICD-11 AND THE ROAD AHEAD

Wolfgang Gaebel*[1]
[1]*German Society for Biological Psychiatry*

Objective: ICD-11 was released by WHO in 2018 and approved by the World Health Assembly (WHA) in 2019 as a global medical classification system. Development, Concept and Structure of ICD-11 will be briefly outlined with the focus on Schizophrenia or other primary psychotic disorders, their potential for adaptation and the debated need for reconstruction in the context of neuroscientific and related developments.
Methods: The development of the new chapter 06 Mental, Behavioural or Neurodevelopmental Disorders including psychotic disorders was guided by the principles of global applicability, scientific validity, reliability, and clinical utility. At that time, neither for DSM-5 nor for ICD-11 schizophrenia spectrum or primary psychotic disorders a conceptual 'paradigm shift' by including biomarkers or other valid diagnostic criteria seemed to be justified.
Results: ICD-11 innovations of primary psychotic disorders diagnostic criteria, dimensional symptom specifiers and course indicators according to the new CDDR (Clinical Descriptions and Diagnostic Criteria) and options for complex digital coding with potential impact on diagnostics, treatment and care will be outlined. Challenges for reconceptualizing the current construct and for national implementation will be briefly summarized.
Conclusion: The presentation will inform about innovations in classifying schizophrenia and other psychosis according to ICD-11 and give an outlook on future options for modifying the construct based on innovative scientific approaches in biological psychiatry.
References: Gaebel W, Stricker J, Kerst A. Changes from ICD-10 to ICD-11 and future directions in psychiatric classification. doi:10.31887/DCNS.2020.22.1/wgaebel
Gaebel W, Salveridou-Hof E. Reinventing schizophrenia: Updating the construct – Primary schizophrenia 2021 – The road ahead. doi.org/10.1016/j.schres.2021.12.021

DSM-5 SCHIZOPHRENIA: DEFINITION AND CLINICAL AND RESEARCH IMPLICATIONS

Rajiv Tandon*[1]
[1]
University of Michigan Medical Center

Objective: Schizophrenia, as currently defined in DSM-5-TR and ICD-11, is conceptualized as a multi-dimensional singular disorder. As questions arise about the very construct of schizophrenia, it is useful to review all that we know about this disease entity and examine what these data reveal about its essential nature. Although the DSM-5 description of schizophrenia was published a decade ago, its essence is still incompletely understood.
Methods: The DSM-5 definition of schizophrenia will be summarized. The outlines of a 2-year ongoing international effort to reconceptualize schizophrenia will be presented.
Results: The DSM-5 definition of schizophrenia is categorical with dimensional elaboration- this will be discussed and its clinical and research implications will be summarized. The initial output from a 50-person international collaboration on redefining schizophrenia will be presented (Schizophrenia Research 2022; Volume 242, 1-3).
Conclusion: Collectively, "facts of schizophrenia" argue against a singular disease entity but do not explicitly elucidate the nature and number of composite disease entities. Research implications of the initial international collaboration formulation of schizophrenia and related psychotic disorders will be outlined.

BIOLOGICAL MARKERS IN PSYCHIATRY

Florence Thibaut**1*

[1]*University Paris Cité*

Objective: A biological marker is an indicator of the pathogenic process of a disease, or of the pharmacological response to a therapeutic intervention. Biological markers may be trait markers (persistent abnormalities) or state-dependent markers (episodic markers).

Methods: Some examples of biomarkers which might be used in psychiatry will be described.

Results: Markers may be used as diagnostic tools, markers of the disease progression, to study the pathophysiology of the disease (risk factors), or to monitor treatment efficacy or side effects (pharmacogenetics).

Conclusion: The sensitivity, specificity and ease-of-use of a biomarker (especially for diagnosis) are the most important factors.

References: Thibaut F, Boutros NN, Jarema M, Oranje B, Hasan A, Daskalakis ZJ, Wichniak A, Schmitt A, Riederer P, Falkai P; WFSBP Task Force on Biological Markers. Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. World J Biol Psychiatry. 2015;16(5):280-90

Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, Collier DA, Corrales A, DeLisi LE, Gallo C, Gill M, Kennedy JL, Leboyer M, Maier W, Marquez M, Massat I, Mors O, Muglia P, Nöthen MM, Ospina-Duque J, Owen MJ, Propping P, Shi Y, St Clair D, Thibaut F, Cichon S, Mendlewicz J, O'Donovan MC, Rujescu D. Genetics of schizophrenia: A consensus paper of the WFSBP Task Force on Genetics. World J Biol Psychiatry. 2017 Oct;18(7):492-505

BEYOND SCHIZOPHRENIA IN DSM-5 AND ICD-11: NEW OPTIONS FOR RESEARCH

Peter Falkai**1*

[1] _____

German Society for Biological Psychiatry

Objective: The classification of schizophrenia has a long history starting with the description of Dementia praecox and Manic-depressive insanity by E Kraepelin paving the way for a dichotomy which still influences our thinking and clinical activities today. ICD-11 and DSM-5 have modified a lot of these assumptions but research has shown that the neurobiological underpinnings of these disorders rather form clusters than sticking to the current classification systems. RDoC and HiTOP will be introduced as examples to use a dimensional approach focussing on the neurobiology and on the other hand using psychopathological dimensions organized into increasingly broad, transdiagnostic spectra.

Methods: Advances and shortcomings of DSM-5 and ICD-11 will be based on published studies.

Results: For future studies a mixture of RDoC and HiTOP might be an optimal way to characterize patients and controls from childhood to old age. New scales need to be developed optimally based on self-rating, being short and having a better validity than currently used classification systems.

Conclusion: The presentation will analyse the shortcomings of currently available classification systems for clinical research and will give an outlook what advantages new systems like RDoC and HiTOP might give to characterize healthy and diseased subjects for research.

BIOMARKERS IN INSOMNIA: EVIDENCE DERIVED FROM A WFSBP TASK FORCE CONSENSUS STATEMENT

Constantin Soldatos, National and Kapodistrian University of Athens

Symposium Synopsis: Thus far, the diagnosis of insomnia is based on purely clinical criteria. Although a broad range of altered physiological parameters has been identified in insomniacs, the evidence to establish their diagnostic usefulness is very limited. Purpose of this symposium is to present a

summary of a WFSBP Task Force consensus statement, based on a systematic evaluation of a series of biomarkers as potential diagnostic tools for insomnia. **Methods:** A newly created grading system was used for assessing the validity of various measurements in establishing the diagnosis of insomnia; these measurements originated from relevant studies selected and reviewed by experts. **Results:** The measurements with the highest diagnostic performance were those derived frompsychometric instruments. Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy, and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm, and certain neuroimaging patterns. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPAaxis, and inflammation indices were not shown to be of satisfactory diagnostic value. Most of the above findings regarding biological measurements, however, need replication as well as establishment of commonly accepted methodology and diagnostic cut-off points. **Conclusions:** Apart from psychometric instruments which are confirmed to be the gold standard in diagnosing insomnia, six biomarkers emerge as being potentially useful for this purpose. **Reference:** D.Dikeos et al. "The potential of biomarkers for diagnosing insomnia: Consensus statement of the WFSBP Task Force on Sleep Disorders" World J Biol Psychiatr (In Press) 2023.

SLEEP EEG AND ACTIGRAPHY IN THE DIAGNOSIS OF INSOMNIA

Adam Wichniak**1*

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Institute of Psychiatry and Neurology, Warsaw

Objective: Although objective assessment of sleep parameters is not necessary for the diagnosis of insomnia, polysomnography and actigraphy frequently provide information that is important for the diagnostic process. The aim of the study was to summarize the evidence on the use of polysomnography and actigraphy in the assessment of insomnia.

Methods: The presentation is based on data from a consensus paper on the diagnostic usefulness of polysomnography and actigraphy in insomnia and results of an original study in 126 insomnia patients that was aimed to assess factors contributing to differences in the assessment of sleep parameters between actigraphy and sleep diary in patients with insomnia.

Results: Polysomnography and more advanced sleep EEG evaluation methods like EEG spectral analysis favor the hypothesis of an increased CNS hyperarousal in patients with insomnia. However, polysomnographic data do not correlate very strongly with the subjective assessment of sleep in sleep diaries. The same observation is true for actigraphy. There are large and variable differences in the assessment of sleep parameters between sleep diaries and actigraphy, which are not strongly related to insomnia severity.

Conclusion: While some studies have confirmed satisfactory accuracy, especially of actigraphy for the evaluation of normal sleep quality, the use of PSG and actigraphy in the assessment of insomnia is limited and indicated only in certain cases, for example in patients with chronic therapy refractory insomnia, when sleep-disordered breathing is suspected (polysomnography) or in case of clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders (actigraphy).

LABORATORY BIOMARKERS FOR INSOMNIA OTHER THAN THOSE DERIVED FROM SLEEP EEG AND ACTIGRAPHY

Thorsten Mikoteit*[1], *Anne Eckert[2], Martin Hatzinger[3]*

[1]Swiss Society for Biological Psychiatry, 2University Clinics of Psychiatry Basel, 3Psychiatric Services Solothurn and University of Basel

Objective: Laboratory measurements are easy and mostly non-invasive to assess, and they might allow to link insomnia to more basic pathways of neuropathology like models of neuroendocrinology, neuroinflammation or neuroplasticity. Further, the advances of neuroimaging have provided findings of alterations in brain activity and connectivity in insomnia. The aim of this review was to evaluate the diagnostic possibility to identify laboratory and neuroimaging biomarkers for insomnia.

Methods: Five different laboratory biomarkers were considered: Markers of the hypothalamic-pituitary-adrenal (HPA) axis, melatonin, inflammatory markers such as C-reactive protein (CRP), and serum brain-derived neurotrophic factor (BDNF) as a proxy of neuroplasticity. Moreover, we considered five neuroimaging studies of insomnia.

Results: Findings of HPA activity patterns were inconsistent. Elevated cortisol levels in the first half of the night and in the morning were found rather in insomnia with shortened total sleep time than in insomnia with normal total sleep time. Melatonin levels revealed a more flattened circadian rhythm in individuals with insomnia, but night-time blood sampling was a limitation for itsclinical application. As reported by two independent studies, the best diagnostic accuracy was provided by measurements of low serum BDNF in insomnia. Neuroimaging studies showed that a key feature of insomnia is a corticolimbic overactivity in brain areas involved in activation, emotion regulation, cognition and conscious awareness.

Conclusion: For laboratory measurements, low serum BDNF levels had the highest diagnostic value for insomnia, linking clinical insomnia to a decreased neuroplasticity. The pattern of neuroimaging findings supported the hyperarousal hypothesis of insomnia. More research is needed to replicate findings and enlarge the body of evidence, to establish appropriate methods and diagnostic cut-offs.

PSYCHOMETRICS IN THE DIAGNOSIS OF INSOMNIA

Dimitris Dikeos*[1]

[1] National and Kapodistrian University of Athens

Objective: To evaluate the diagnostic potential for insomnia of psychometric instruments.

Methods: (a) Search for well cited original papers of scales, questionnaires and personality inventories, which reported on suitable measures of diagnostic validity for insomnia, based on a well-defined population of insomniacs versus a sample of non-insomniac controls. (b) Creation of a novel grading system for establishing diagnostic usefulness for insomnia, based on the one hand on the degree of pertinence of each study's methodology to diagnose insomnia and on the other on the level of diagnostic accuracy for insomnia of the instrument utilized in each study.

Results: Three main categories of psychometric instruments were found to be of diagnostic value for insomnia. Scales and questionnaires for diagnosing insomnia or for evaluating beliefs about sleep were proven to be the gold standard for the diagnosis of insomnia, based on established cut-off scores. Among personality inventories the potential of MMPI as a tool for diagnosing insomnia was found to be quite satisfactory.

Conclusion: Psychometric instruments are a well-proven means for the diagnosis of insomnia, reflecting its subjective nature.

OVERVIEW OF THE DIAGNOSTICS FOR INSOMNIA

Constantin Soldatos*[1]
[1]*National and Kapodistrian University of Athens*

Objective: To synthesise the systematic evaluation of biomarkers as potential diagnostic tools for insomnia based on measures of diagnostic accuracy, as well as an identical assessment of the diagnostic accuracy of psychometric instruments in diagnosing insomnia.
Methods: The findings of a large array of various instruments and methods for diagnosing insomnia, which were presented by the previous three symposium panelists will be comprehensively discussed
Results: Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm and certain neuroimaging patterns. These findings need replication, establishment of commonly accepted methodology and diagnostic cut-off points. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPA axis and inflammation indices were not shown to be of satisfactory diagnostic value. Psychometric instruments are confirmed to be the gold standard in diagnosing insomnia.
Conclusion: Various biomarkers emerge as potentially useful for the diagnosis of insomnia, although psychometric instruments remain the strongest means.

PREDICTIVE BIOMARKERS AND NEW METHODOLOGICAL APPROACHES FOR MENTAL DISORDERS

Oliver Pogarell, University Hospital, LMU Munich

Symposium Synopsis: In psychiatry, a wide spectrum of therapeutic interventions are applied to effectively improve signs and symptoms. However, individual response and remission rates are limited and to date, there are no unequivocal personalized clinical or auxiliary measures to identify responders or predict the course of symptoms under treatment.
Regarding predictive biomarkers new developments in neurophysiological research could play an important role. QEEG or fMRI at rest or under activation are tools for the investigation of different brain states under various conditions including monitoring. Novel analyses address temporal dynamics and functional connectivities that may show differences between disorders or disease states.
We will discuss the potential of neurophysiological biomarkers for the prediction of response or outcomes in psychiatric disorders. This includes novel analyses of QEEG, machine learning techniques or the extraction of treatment related neurophysiological repsonses, e.g. under non-invasive brain stimulation or neurofeedback.
Jonas Björklund will present data on brain oscillations in patients with schizophrenia. He demonstrates the viability of a biomarker predicting transition to full psychosis based on EEG connectivity disturbances. Machine learning techniques applied on physiological EEG/EOG data as demonstrated by Sebastian Olbrich, allow the generation of predictive markers from samples of large cohorts. It will be shown how automated analyses can be used for individual assessments in a clinical setting. Tomiki Sumiyoshi will report data indicating the ability of near-infrared spectroscopy to predict resonse to tDCS in schizophrenia. Finally, Max Maywald applied novel treatment interventions such as rt-fMRI neurofeedback showing that neurophysiological modulations under treatment correlate with response characteristics.

PREDICTIVE PROPERTIES OF QEEG AND OSCILLATIONS

Jonas Björklund*[1], *Moritz Haaf2, Sebastian Vauth2, Saskia Steinmann2, Jonas Rauh2, Christoph Mulert2, Gregor Leicht2*

[1]LMU, 2University Medical Center Hamburg-Eppendorf

Objective: Early detection and prediction of transition to full psychosis in high-risk individuals is crucial for early intervention and improved treatment outcomes. EEG and fMRI-based analyses provide opportunities to assess connectivity disturbances before the onset of clinical symptoms. In a previous study, we demonstrated reduced gamma response in an auditory processing network in individuals at high risk of psychosis (HRP) using EEG-informed fMRI analysis. This study aims to investigate the predictive nature of EEG connectivity disturbances in HRP individuals and explore the potential of using specific EEG-based connectivity disturbances to predict progression to psychosis based on disturbed gamma band oscillations.

Methods: We analyzed datasets of 27 HRP individuals and 26 healthy controls, including combined EEG-fMRI data recorded during an auditory reaction task. We employed Granger causality analysis, correlation analysis, and gPPI to calculate a matrix of individual connectivity values between previously identified ROIs in the dACC, DLPFC and the auditory cortices. Connectivity analysis methods were used to calculate individual connectivity values per subject. By comparing connectivity values between healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis, we aimed to predict the likelihood of developing psychosis within 12 months. Follow-up clinical data and combined EEG-fMRI recordings after 12 months were used to assess the degree of connectivity changes over time.

Results: We observed alterations in connectivity across domains when comparing healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis during the 12-month follow-up. We used data generated during the 12-month follow-up visit to verify if early changes in single-subject gamma connectivity persist and correlate with clinical disease progression.

Conclusion: By measuring gamma network disturbance using simultaneous EEG and EEG-informed fMRI, we aim to predict individual likelihoods of developing full psychosis within the next 12 months. EEG-based biomarkers are a relatively low-cost and widely available tool to aid in clinical decision making. The identification of specific EEG gamma band disturbances associated with disease progression and treatment response may enable more personalized treatment strategies for individuals with psychosis.

AUTOMATED AND MACHINE LEARNING ANALYSES OF EEG AND ECG DATA FOR TREATMENT PREDICTION IN MENTAL DISORDERS

Sebastian Olbrich*[1]

[1]Psychiatric University Hospital Zurich

Objective: Addressing the profound impact of psychiatric disorders on global health and socioeconomic systems necessitates a paradigm shift in treatment modalities. The reliance on subjective assessments in psychiatric care underlines a critical need for more objective treatment indicators to enhance patient outcomes across various mental health conditions.

Methods: This presentation will delineate the utilization of automated processing pipelines applied to electrophysiological time series data obtained from electroencephalograms (EEG) and electrocardiograms (ECG). The integration of these methodologies into routine clinical practice through comprehensive biomarker reports will be showcased. Additionally, the session will provide an update on the latest advancements in machine learning and deep learning techniques applied to EEG and ECG data, drawing from extensive datasets from the UK-Biobank and the CANBIND study.

Results: Contemporary advancements in automated electrophysiological processing and biomarker computation have reached a level of sophistication that permits their application in clinical settings. Over recent years, a plethora of biomarkers pertinent to treatment prediction—particularly within the context of major depressive disorders—have been identified, rigorously validated, and consistently replicated. **Conclusion:** The implementation of electrophysiological biomarkers in psychiatric care emerges as a compelling strategy to foster a more stratified approach to patient treatment. The clinical applicability of these biomarkers has been substantiated, with accumulating evidence indicating their potential to significantly influence the management of mental health disorders and enhance patient outcomes.

TRANSCRANIAL

AND DIRECT CURRENT STIMULATION FOR ENHANCING SYMPTOMS FUNCTIONALITY IN PATIENTS WITH SCHIZOPHRENIA; PREDICTION WITH NEUROPHYSIOLOGICAL TOOLS

Tomiki Sumiyoshi*[1], *Yuji Yamada2*
[1]National Institute of Mental Health, National Center of Neurology and Psychiatry, 2National Center Hospital, National Center of Neurology and Psychiatry

Objective: Schizophrenia is one of the most prominent causes of disease burdens worldwide. In addition to positive and negative symptoms, patients with the illness show disturbances of several types of cognitive function (e.g., neurocognition and social cognition). Importantly, cognitive impairment leads to a decline in real-world functional outcome for patients.
Methods: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that modulates neural activity by applying electric currents. tDCS (anodal stimulation) delivered to the dorsolateral prefrontal cortex (DLPFC) alleviates hallucinations and negative symptoms, and improves neurocognitive function, particularly working memory in patients with schizophrenia. Specifically, our group in National Center of Neurology and Psychiatry has reported the first data indicating the ability of neural responses, as measured by the near infra-red spectroscopy, to predict efficacy of tDCS for ameliorating psychotic symptoms in these patients.
Results: This talk will also provide the current state of endeavor to alleviate cognitive impairment and higher-level functional outcomes, by means of tDCS, in patients with schizophrenia. These findings may add to efforts to increase the chance of recovery for patients by using feasible and non-invasive brain stimulation methods.
Conclusion: References; Narita et al. J Psychiatr Res 2018; 103:5-9

PREDICTIVE BIOMARKERS IN REAL-TIME FMRI NEUROFEEDBACK

Maximilian Maywald*[1], *Marco Paolini2, Boris Rauchmann2, Christian Gerz2, Jan Heppe2, Annika Wolf2, Linda Lerchenberger2, Igor Tominschek3, Sophia Stöcklein2, Paul Reidler2, Nadja Tschentscher2, Birgit Ertl-Wagner2, Oliver Pogarell2, Daniel Keeser2, Susanne Karch2*
[1]Psychiatric Hospital of the LMU University Munich, 2University Hospital, LMU Munich, [3]Psychosomatic Day Care Unit Westend, Munich

Objective: The aim of this pilot study was to investigate whether individualized rtfMRI NF training as an adjunct to a psychotherapeutic program can increase connectivity between the insula and the dlPFC and thereby improve symptoms in patients with major depressive disorder (MDD, ICD-10). The second aim was to investigate if there are biomarkers of successful real-time fMRI neurofeedback?
Methods: Sixteen patients with MDD and 19 matched healthy controls (HC) participated in a rtfMRI NF training consisting of two sessions with three runs each, within an interval of one week. RtfMRI NF was applied during a sequence of negative emotional pictures to modulate the connectivity

between the dlPFC and the insula. The MDD REAL group was divided into a 'Responder' (N=6) and a 'Non-Responder' group (N=7). **Results:** The comparison of hemodynamic responses during the first compared to during the last NF session demonstrated significantly increased BOLD-activation in the medial orbitofrontal cortex (mOFC) in patients and HC, and additionally in the lateral OFC in patients with MDD. These findings were particularly due to the MDD Responder group, as the MDD Non-Responder group showed no increase in this region during the last NF run. There was a decrease of neural activation in emotional processing brain regions in both groups in the last NF run compared to the first (HC: insula, parahippocampal gyrus, basal ganglia, and cingulate gyrus; MDD: parahippocampal gyrus). There was no significant reduction of BDI scores after NF training in patients. **Conclusion:** The activation of the mOFC seems to be a predictive biomarker of improved control- strategies and association-learning processes. The increased lOFC activation could indicate a stronger sensitivity to failed NF attempts in MDD. Overall, the rtfMRI NF had an impact on neurobiological mechanisms, but not on psychometric measures in patients with MDD.

THE DIFFERENT FACES OF DEPRESSION ACROSS THE LIFE SPAN: FROM SOCIAL ISOLATION TO SUICIDE

Paolo Brambilla, University of Milan

Symposium Synopsis: Suicidal ideation, also known as suicidal thoughts, is a broad term used to describe a range of thoughts about death and self-harming behaviours. Rates of suicide deaths and suicidal thoughts and behaviours have risen by more than 50% among young people in the past decade, making suicide the second leading cause of death among those aged under 20. Most importantly, suicidal ideation represents a trans-diagnostic feature characterizing several psychiatric conditions (e.g., depression, psychosis) that seems to increase the risk of completed suicide. For instance, it has been shown that treatment-resistant depression (TRD) may increase an individual's likelihood of engaging in suicidal behaviours and up to 30% of people with TRD will attempt suicide at some point in their life. Although individual, environmental, and clinical risk factors (such as social isolation, social stress, apathy and elderly depression) for suicidal thoughts and behaviours have been
well established, these factors have demonstrated low predictive validity. In response, the number of studies examining neurobiological underpinnings of suicidal thoughts and behaviours, in and out of psychiatric populations, has grown exponentially. Nevertheless, understanding the neural mechanisms underlying social isolation, suicidal thoughts and behaviours and their clinical utility remains elusive. Therefore, the present symposium aims at summarizing and discussing recent evidence on the morphofunctional brain correlates of social isolation, social stress, apathy, elderly depression, and suicidal ideation, with a particular focus on their clinical implications for the development of trans-diagnostic tailored treatments.

NEUROIMAGING OF SOCIAL BRAIN

*Marcella Bellani1, Maria Gloria Rossetti*1, Paolo Brambilla2*
[1]University of Verona, 2University of Milan

Objective: According to the social brain hypothesis, the human brain includes a network designed for the processing of social information. This network includes several brain regions that elaborate social cues, interactions and contexts, i.e. prefrontal paracingulate and parietal cortices, amygdala, temporal lobes and the posterior superior temporal sulcus. While current literature suggests the importance of this network from both a psychological and evolutionary perspective, little is known about its neurobiological bases. Specifically, only a paucity of studies explored the neural

underpinnings of constructs that are ascribed to the social brain network functioning, i.e. objective social isolation and perceived loneliness. **Methods:** Overview of neuroimaging studies that investigated social isolation in healthy subjects. **Results:** Social isolation correlated with both structural and functional alterations within the social brain network and in other regions that seem to support mentalising and social processes (i.e. hippocampus, insula, ventral striatum and cerebellum). **Conclusion:** However, results are mixed possibly due to the heterogeneity of methods and study design. Future neuroimaging studies with longitudinal designs are needed to measure the effect of social isolation in experimental v. control groups and to explore its relationship with perceived loneliness, ultimately helping to clarify the neural correlates of the social brain.

SOCIAL STRESS AND SUICIDE: MECANISTIC HYPOTHESES

Aiste Lengvenyte**1*, *Emilie Olié2, Emma Sebti2, Adrian Alacreu3, Philippe Courtet2*

[1]CHU Montpellier, 2University of Montpellier, 3University of Zaragosa

Objective: To assess the biological underpinnings of social adversity that lead to suicidal behaviour.
Methods: Depressed patients are submitted to the Trier Social Stress Test (TSST) in order to examine the changes in emotional and biological markers according to their past history of suicidal behaviour.
Results: We will discuss the association of suicidal behaviour with measures of cortisol, of the autonomous nervous system and inflammatory markers during and after the TSST.
Conclusion: Objective markers of response to a social exclusion task using different kinds of parameters may help to define specific groups of patients at risk of suicide in order to foster a personalized suicide prevention.

CEREBRAL NETWORK OF APATHY AND GOAL-ORIENTED BEHAVIOURS

Jean-Charles Roy**1*, *Julie Cologner1, Gabriel Robert1*

[1] EMPENN Unit, Rennes 1 University, ERL U1228 Inserm, INRIA, CNRS

Objective: We aimed to identify the structural and functional brain subnetworks associated with apathy in LLD in the core resting-state networks (RSN) putatively underlying goal-directed behaviors.
Methods: Diffusion-weighted and Resting-state functional MRI data were collected from 39 non-demented depressed elderly and 26 healthy elderly from October 2019 to April 2022. Apathy was evaluated using the diagnostic criteria for apathy, the apathy evaluation scale and the apathy motivation index. Participants' daily activity was recorded via an accelerometer worn at the wrist for three days. Principal components were derived from accelerometer data to provide a qualitative and quantitative interpretation of daily activity. The clinical significance of these principal components in terms of apathy were assessed by regression with the apathy scales. Brain sub-networks associated with the principal components of activity were identified via the threshold-free network-based statistics. This method combines the network-based statistics approach with the threshold-free cluster enhancement algorithm, producing a powerful identification of the significant sub-networks while controlling for multiple comparisons. Structural tracts were identified via deterministic tractography. Association between the apathy and accelerometry on the diffusion metrics - derived from a multicompartment model - were evaluated by mixed-effect modelling.
Results: LLD patients had an altered intranetwork resting-state connectivity in the default-mode, the cingulo-opercular and the frontoparietal networks compared to healthy controls. The first and second principal components of daily activity were associated with apathy measures, corresponding respectively with a reduced mean diurnal activity and with a late-rise/late-bedtime. Apathy and daily activity were associated with modified intranetwork resting state connectivity in the same networks distinguishing LLD from controls. These networks involved reduced activity of the pregenual cingulate

regions, the dorsal anterior cingulate cortex, the middle insula, but increased connectivity in the dorsolateral prefrontal regions. Internetwork resting-state connectivity of cortical regions related to goal-oriented behavior showed a decoupling between pregenual and dorsal anterior cingulate cortices associated with apathy. Principal components associated with apathy were also associated with increased orientation dispersion index, a measure of inflammation, in the anterior commissure. **Conclusion:** This study suggests that accelerometry provides a proxy for an ecological evaluation of apathy in LLD. Apathy and accelerometry are consistently associated with changes in intra and inter- network connectivity of regions implied in goal-oriented behaviors.

THE FUNCTIONAL NETWORKS OF DEPRESSION IN THE ELDERLY

*Eleonora Maggioni*1, Federica Goffi1, Paolo Brambilla2*
1Politecnico di Milano, 2University of Milan

Objective: To disentangle the complex relationships among environmental risk factors, functional brain connectivity, autonomic nervous system regulation, and frailty and adult-onset depression.
Methods: Control subjects and individuals with adult-onset major depressive disorder (MDD) took part in the study. The dataset included sociodemographic, environmental, and psychopathological information, and simultaneous electrocardiographic (ECG) and functional Magnetic Resonance Imaging (fMRI) data. The ECG and fMRI data were processed to extract information on heart rate variability (HRV) and functional brain connectivity. The associations among stressful life events, frailty level, MDD diagnosis, and HRV and functional brain connectivity were extracted using integrated HRV-fMRI analyses and multivariate models.
Results: The MDD diagnosis was associated with alterations in the activity and connectivity of brain regions that are key nodes of the central autonomic network. Traumatic events and perceived stress were correlated with HRV metrics and showed interactions with depressive symptomatology and sex.
Conclusion: Evidence from our study suggests an impact of environmental risk factors on heart-brain interactions and in turn on depressive symptomatology onsetting in adulthood, and further supports the potential of HRV-fMRI analyses in providing novel information on the neurobiological bases of depression.

MANUSCRIPT WRITING WORKSHOP

Florence Thibaut, University Paris Cité

HOW TO WRITE A SCIENTIFIC PAPER

Dan Rujescu-Balcu1
1Medical University of Vienna

Objective: The World Journal of Biological Psychiatry is a major clinically oriented journal on biological psychiatry. The opportunity to educate (through critical review papers, treatment guidelines and consensus reports), publish original work and observations (original papers and brief reports) and to express personal opinions (Letters to the Editor) makes The World Journal of Biological Psychiatry an extremely important medium in the field of biological psychiatry all over the world.
The aim is to meet the Chief Editor and to discuss all steps from formulating hypotheses, study design, data generation, analysis and finally publication.
Methods: A short presentation of the Journal will be followed by a lively discussion.
Results: N/A

Conclusion: It is important to oversee the whole process from asking the scientific question to study design and generation of original data to manuscript writing, submission and finally publication in a scientific journal.

HOW TO WRITE A SCIENTIFIC PAPER

Michael Berk1
[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: Scientific Journals are a key platform for disseminating critical reviews, treatment guidelines, consensus reports, original research, and personal opinions in the field of biological psychiatry. This session aims to guide participants through the publication process, from formulating hypotheses and designing studies to generating data, analyzing results, and ultimately publishing in scientific journals. Attendees will have the opportunity to engage with the Chief Editor and gain insights into each step of the publication journey.
Methods: The session will begin with a brief presentation on the scope and significance of The World Journal of Biological Psychiatry. This will be followed by an interactive discussion, where participants can ask questions and receive practical tips on navigating the publication process.
Results: While this session does not generate experimental results, it will equip participants with valuable knowledge and strategies to enhance their chances of successfully publishing their research in peer-reviewed journals.
Conclusion: Understanding the comprehensive process of scientific publication—from formulating a research question and designing a study to writing and submitting a manuscript—can significantly increase the likelihood of acceptance in a scientific journal. By attending this session, researchers will be better prepared to contribute meaningful findings to the field of biological psychiatry, thereby advancing evidence-based practice and scientific knowledge.

HOW TO WRITE A SCIENTIFIC PAPER

Florence Thibaut1
[1]*University Paris Cité*

Objective: Publication of scientific papers is important to improve evidence-based practice or scientific knowledge. Most importantly, failure to publish important findings significantly diminishes the potential impact that your findings may have.
Methods: This educational session is intended to give you tips to help you publish in scientific journals.
Results: Most clinical studies are published in peer-reviewed journals, where author's peers, or experts in the area, evaluate the manuscript.
Conclusion: Following this review, the manuscript is recommended for publication, revision or rejection. Having an understanding of the process and structure used to produce a peer-reviewed publication will increase the likelihood that a submitted manuscript will result in a successful publication.

6:30 p.m. - 7:30 p.m.
Opening Plenary I - John Krystal

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

Lakshmi Yatham, The University of British Columbia

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

John Krystal1

[1]Yale

Objective: To review challenges that have traditionally plagued the development of medications for psychiatry indications and to highlight two areas of exciting recent developments: 1) ketamine and psychedelics and 2) antipsychotics that may work via targets other than the dopamine D2 receptor.

Methods: This presentation will focus on the advances in neuroscience that have laid the groundwork for the development of Esketamine and the recent “non-D2” antipsychotics. It will begin by tracing steps to understand the mechanisms through which ketamine produces its therapeutic effects. It will then highlight ways that this search has led to ways to optimize ketamine efficacy. It will also highlight ways that insights related to ketamine’s effects that point to other potential novel treatment mechanisms, such as psychedelics, that have convergent effects on neuroplasticity.

Results: This presentation will present a model for cortical microcircuit dysfunction that emerged from studies of ketamine effects in healthy humans and schizophrenia patients. This model highlights the potential for cortical network disinhibition, including disinhibition of projections to the striatum, to be a contributor to pathophysiology in some patients. This model sets the stage for developing a mechanistic context for recent clinical trial data suggesting that drugs enhancing muscarinic M4 receptors (KarXT, Emraclidine) and TAAR1 (Ulotorant) might be effective antipsychotic medications without blocking dopamine D2 receptors.

Conclusion: This presentation will conclude by raising remaining challenges as we grapple with the complexity of the neurobiology of psychiatric disorders, particularly the opportunities and challenges that emerge as we try to translate the genetics of psychiatric disorders to novel therapeutics.

Thursday, June 6, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session II - Nora Volkow

SUBSTANCE USE AND ABUSE: ADVANCES IN NEUROBIOLOGY AND TREATMENT OF SUBSTANCE USE DISORDERS

Allan Young, King's College

HOW HAS THE SCIENCE OF ADDICTION ILLUMINATED OUR UNDERSTANDING OF THE HUMAN BRAIN

Nora Volkow1

[1]*NIDA*

Objective: Addiction, a complex disorder linking genes, development and the social environment has, for decades, been illuminating our understanding of the human brain and is leading the way toward promising strategies for its effective treatment.

Methods: Studies employing neuroimaging technology paired with behavioral measurements, and more recently genetics, have led to remarkable progress in elucidating neurochemical and functional changes that occur in the brains of addicted subjects and the neurocircuits that modulate risk for substance use disorders.

Results: Although large and rapid increases in dopamine have been linked with the rewarding properties of drugs, the addicted state, in striking contrast, is marked by significant decreases in brain dopamine D2 receptor mediated signaling and the downstream dysfunction of circuits that it modulates through striato cortical and limbic projections. Among the most prominently affected is the prefrontal cortex (PFC), including ventral PFC implicated in salience attribution and motivation (orbitofrontal cortex, and anteroventral cingulate gyrus), and dorsal PFC including dorsolateral and medial PFC implicated in executive function and internal awareness.

Conclusion: These PFC disruptions underlie the enhanced value given to drugs and drug-related stimuli at the expense of other reinforcers and the impulsive and inflexible behaviors that lead to compulsive drug consumption. In parallel, dysfunction of limbic projections are believed to underlie the enhanced stress reactivity and negative emotional states that emerge during drug withdrawal.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia II

UNDERSTANDING BODY DYSMORPHIC DISORDER (BDD): LATEST INTERNATIONAL RESEARCH

Susan Rossell, Swinburne University

Symposium Synopsis: Body dysmorphic disorder (BDD) affects 1.7-2.4% of the population worldwide. However, until the last 20 years relatively little was known about BDD, and there was a paucity of research. The aim of this symposium is to bring together and present comprehensive data from four internationally respected research sites specialising in BDD.

Methods: The authors will provide the latest updates on epidemiology, clinical characteristics, brain mechanisms as well as novel treatment insights in relation to BDD.

Results: The four presentations will include recent data on: 1) the epidemiology of BDD using a representative, population-based sample of young people in England. 2) An update on clinical and cognitive characteristics of BDD, including some novel findings on hallucinatory experiences in BDD. 3) A discussion of recent brain imaging data in BDD involving white matter microstructure and dynamic effective brain connectivity in visual systems, and their relationships to appearance

appraisals. 4) Finally, we will review the efficacy, predictors and long-term outcomes of an app-based cognitive behavioral therapy for BDD with coach support. **Conclusion:** Given the prevalence of BDD improving clinicians understanding of this disorder is critical. The authors of this symposium hope by presenting advanced and novel data the audience will improve their awareness of BDD and how to treat it.

EPIDEMIOLOGY OF BODY DYSMORPHIC DISORDER IN YOUTH: PREVALENCE, COMORBIDITY AND PSYCHOSOCIAL IMPAIRMENT

Georgina Krebs**1*, *Bruce Clark2, Tamsin Ford3, Argyris Stringaris1*

[1]University College London, 2South London and Maudsley NHS Foundation Trust, 3University of Cambridge

Objective: Little is known about the epidemiology of body dysmorphic disorder in youth. We evaluated the prevalence, comorbidity, and psychosocial impairment associated with BDD and more broadly defined appearance preoccupation among children and adolescents.

Methods: Data were drawn from the 2017 Mental Health of Children and Young People in England survey. BDD and psychiatric comorbidity were assessed in 5-19 year olds (N = 7,654) according to DSM-5 criteria, using a clinician-rated standardised diagnostic assessment. Psychosocial impairment was measured with a quantitative scale, and also indexed by reported self-harm and suicide attempts, and service utilisation, which were assessed using structured interviews.

Results: The point prevalence of BDD was 1.0% (95% CI 0.8 – 1.3%). BDD was significantly more common among adolescents than children (1.9 vs 0.1%; OR = 22.5, $p < 0.001$), and females than males (1.8% vs 0.3%; OR = 7.3, $p < .001$). Similar age and sex effects were observed for appearance preoccupation. Approximately 70% of young people with BDD had psychiatric comorbidity, most commonly internalising disorders. BDD was associated with self- and parent-reported psychosocial impairment, self-harm and suicide attempts, and service utilisation. Appearance preoccupation was more common than full syndrome BDD, but showed similar age and sex effects, patterns of comorbidity, and associated impairment.

Conclusion: BDD and appearance preoccupation are relatively common, especially among adolescent girls, and associated with substantial co-occurring psychopathology, risk, and impairment. Improved screening is needed to increase detection and diagnosis of BDD, and to facilitate access to evidence-based treatment. Future research should seek to examine appearance preoccupation as a possible target for early intervention.

UNDERSTANDING PSYCHOTIC EXPERIENCES IN PEOPLE WITH BODY DYSMORPHIC DISORDER (BDD)

Susan Rossell**1*, *Grace Fountas1, Wei Lin Toh1*

[1] Swinburne University

Objective: Body dysmorphic disorder (BDD) is a severe mental illness characterised by a preoccupation with a perceived flaw in appearance, along with repetitive behaviours and/or mental acts that occur in response to the preoccupation. Referential delusions (people take special notice of me owing to how I look) are frequently noted in BDD. In DSM-5, there is an optional specifier “with absent insight/delusional beliefs” for patients who hold high conviction that their BDD beliefs are accurate and aligned with reality. This marks a key departure from past editions of the DSM (that is, from DSM-III-R onwards), where non-delusional and delusional variants of BDD were alleged to exist, with the latter double-coded as a delusional disorder, somatic subtype. However, there are only a handful of empirical studies which have examined the presence of delusions and insight in BDD; and no work to date to have explored the existence of hallucinations. Thus, further work is needed in BDD

to characterise the psychotic symptoms of the disorder, especially to understand the possible differences or similarities that may exist with schizophrenia. **Methods:** Data from three clinical will be presented, examining: a) delusions and insight in BDD using Peters Delusion Inventory (PDI) and the Brown Assessment of Beliefs (BABS), respectively; and b) differences in the presentation of psychotic symptoms between BDD and schizophrenia using the Questionnaire for Psychotic Experiences (QPE). **Results:** The data from the PDI and BABS established that the majority of individuals with BDD hold substantial delusional beliefs, which are a) not restricted to referential delusions in terms of delusional themes, and typically include appearance-based (somatic) delusions, and b) the vast majority (>89%) of BDD patients are classified as having absent insight. Further, an extensive examination of hallucinatory experiences using the QPE in BDD has demonstrated that only somatic hallucinations are endorsed more frequently and qualitatively different from healthy controls (there were no differences for auditory, visual, olfactory, gustatory or multimodal hallucinations). With these somatic experiences akin to those present in schizophrenia. **Conclusion:** This is the first study to have reported on hallucinatory experiences in BDD. In conclusion, this work suggests considerable similarities between BDD and schizophrenia in the somatosensory domain when examining psychotic symptoms.

MICROSTRUCTURE AND FUNCTIONAL CONNECTIVITY OF THE VERTICAL OCCIPITAL FASCICULUS IN BODY DYSMORPHIC DISORDER

Jamie Feusner**1*, *Wan Wa Wong2, Joel Diaz1, Ryan Cabeen3*

[1]Centre for Addiction and Mental Health, University of Toronto, 2Centre for Addiction and Mental Health, 3University of Southern California

Objective: Body dysmorphic disorder (BDD) is marked by preoccupations with misperceived appearance flaws, which may be due to disturbances in visual information processing. Previous studies suggest abnormally reduced global visual processing in BDD. While previous fMRI data are informative about the functional global/local visual processing imbalances, the underlying structural connections have been less explored. The vertical occipital fasciculus (VOF) is the major fibre bundle connecting the dorsal and ventral visual systems. Here, we investigated the white matter (WM) microstructure of the VOF, estimated with neurite orientation dispersion and density imaging (NODDI) and diffusion tensor imaging (DTI) metrics, and tested their associations with psychometric measures and dynamic effective connectivity (DEC) during task fMRI.
Methods: 21 unmedicated adults with BDD with face concerns and 23 healthy controls were included. Tractography was performed to obtain microstructure maps of the right and left VOF. Geometric models of WM connectivity were reconstructed from fibre orientation data estimated from diffusion MRI. Bundle-specific analysis was performed, enabling quantitative estimation of NODDI and DTI metrics of the whole bundle. For fMRI, they viewed photos of their own face naturally. Four regions of interest (ROIs) in the dorsal visual stream (DVS), and 4 ROIs in the ventral visual stream (VVS) were selected. DEC, a measure of directional connectivity, was computed using time-varying Granger causality. Linear regressions were used to test associations between NODDI/DTI metrics, psychometric measures, and DEC from DVS to VVS.
Results: In BDD, neurite density index (NDI) (R=.7, FDR-adjusted P=.0076) and fractional anisotropy (FA) (R=.63, FDR-adjusted P=.036) were positively associated with Body Image State Scale (BISS) scores. Mean diffusivity (MD) was positively associated with DEC during face viewing (R=.61, FDR-adjusted P=.046), and there was a trend for NDI negatively associated with DEC (R=-.61, FDR-adjusted P=.053). In healthy controls, no significant associations were found between the NODDI or DTI metrics and BISS scores. In controls, associations between DEC and WM microstructure were

nonsignificant, with only trends for orientation dispersion index (ODI) negatively associated with DEC (R=-.41, unadjusted P=.068), and FA positively associated with DEC (R=.45, unadjusted P=.043).
Conclusion: Those with BDD with worse evaluative body experiences have a lower proportion of axons or dendrites and a lower degree of anisotropy along the vertical occipital fasciculus, which could reflect lower tract integrity. Further, there were different function/structure relationships among those with BDD than among healthy controls. These results provide early insights into how the structural integrity of WM connections involved in the integration between global and local visual processing systems in BDD relate to subjective appraisals of their appearance.

LATEST ADVANCES IN THE TREATMENT OF BODY DYSMORPHIC DISORDER: APP BASED COGNITIVE BEHAVIORAL THERAPY WITH COACH SUPPORT

Sabine Wilhelm*[1], *Jennifer L. Greenberg[2], Hilary Weingarden[2], Susanne S. Hoeppner[2], Ivar Snorrason[2], Emily E. Bernstein[2], Thomas H. McCoy[2], Oliver Harrison[3]*

[1]Harvard Medical School, [2]Massachusetts General Hospital and Harvard Medical School, [3]Koa Health

Objective: This presentation summarizes the current state of the field of cognitive behavioral therapy (CBT) for Body Dysmorphic Disorder (BDD) and offers a vision for the future.
empirically supported psychotherapy for BDD. While this treatment has a lot of promise, we still have a long way to go. Currently, most individuals in need of treatment for BDD receive no mental health services at all, and even those who do often do not receive optimal care. New technology-enhanced therapies have the potential to expand the reach of our interventions to those for whom traditional treatments are currently unavailable. Dr. Wilhelm will present the result of a smartphone-based treatment with coach support, including predictors of treatment outcome.
Methods: A randomized waitlist-controlled trial was conducted. Adults (N = 80) with primary BDD were randomized to 12 weeks of app based CBT or waitlist. Coaches supported engagement and answered questions via in-app messaging and phone calls. BDD severity was measured at baseline, mid-treatment, and end of treatment by blinded independent evaluators. Secondary outcomes, predictors of treatment outcome and long-term outcomes were also examined.
Results: App-based CBT was associated with significantly lower BDD-YBOCS severity at end of treatment (M [SD]: 16.8 [7.5]) compared to the waitlist (26.7 [6.2]; $p < 0.001$, $d = 1.44$). App-based CBT was associated with greater improvements across all secondary measures, including BDD-related insight, depression, quality of life, and functioning. We also examined several predictors of treatment outcome as well as maintenance of treatment gains.
Conclusion: App-based CBT, supported by a bachelor's-level coach, is an efficacious, scalable treatment for adults with BDD. Our results also highlight the importance of efforts to develop stratified care models to optimize treatment allocation.

FROM DAMAGED DNA TO MORBIDITY: MITOCHONDRIAL DYSFUNCTION IN BIPOLAR DISORDER AS A NOVEL THERAPEUTIC TARGET

Aysegul Ozerdem, Mayo Clinic

Symposium Synopsis: Bipolar disorder (BD) is commonly associated with substantial medical comorbidities, premature aging, and mortality. Mitochondria, inflammation, and oxidative stress are important links in the pathogenesis of mood disorders. A crosstalk between nuclear DNA and mitochondrial DNA is needed for proper cellular functioning and homeostasis. Evidence shows alterations in the base excision repair (BER) mechanism of the oxidatively induced DNA damage in BD. Accumulation of DNA damage or mutations and mitochondrial dysfunction are theorized to contribute to the early ageing and age-related diseases which are frequently seen in BD. Reduced

mitochondrial DNA-copy number has been associated with inducing cancer progression via hypermethylation of nuclear DNA promoters. Dysregulated mitochondrial biogenesis often occurs together with other comorbidities in BD such as non-alcoholic fatty liver disease (NAFLD), diabetes and osteoporosis. Mechanism of action of lithium, the gold standard medication for treatment of BD involves regulation of mitochondrial bioenergetics and PARP, an enzyme involved in DNA repair. This symposium aims to explore the interaction between various comorbidities including breast cancer, NAFLD, osteoporosis and bipolar disorder in the context of illness progression and increased morbidity and identify novel treatment targets via regulation of mitochondrial dysfunction for better illness outcome. Another objective of the symposium is to explore if changes in mitochondrial copy numbers, and mitochondrial DNA methylation levels in response to treatment in BD can be a marker for treatment outcome. Data from large cohorts with and without comorbid BD and data from clinical trials will be presented.

MITOCHONDRIAL DNA MODIFICATIONS IN MOOD DISORDERS

Deniz Ceylan*[1], *Bilge Karaçiçek[2], Kemal Uğur Tüfekci[3], Şevin Hun Şenol[1], Şermin Genç[2]*

[1]*Koç University, 2Izmir Biomedicine and Genome Center, 3Izmir Demokrasi University*

Objective: Mood disorders are significant psychiatric conditions that result from a complex interplay of genetic and environmental factors. One intriguing avenue of research in the realm of mood disorders involves investigating alterations in mitochondrial DNA (mtDNA). In the scope of this study, our primary objective was to explore changes in mtDNA in individuals with depressive disorder (MDD) and bipolar disorder (BD).

Methods: Displacement loop methylation (D-loop-met), mitochondrial DNA copy number (mtDNA-cn), and mitochondrial DNA oxidation (mtDNA-oxi) were scrutinized in DNA samples from individuals with major depressive disorder (MDD; n = 34), bipolar disorder (BD; n = 23), and a control group of healthy individuals (HC; n = 40) using real-time polymerase chain reaction. Blood samples were collected from a subgroup of individuals with MDD (n = 15) both during a depressive episode (baseline) and after achieving remission (at the 8th week).

Results: The study groups displayed notable distinctions in D-loop-methylation (D-loop-met) ($p = 0.020$), while mitochondrial DNA copy number (mtDNA-cn) and mitochondrial DNA oxidation (mtDNA-oxi) yielded similar results. During the remission phase (8th week), there were decreased levels of mtDNA-cn ($Z = -2.783$, $p = 0.005$) and D-loop-methylation ($Z = -3.180$, $p = 0.001$) in comparison to the acute MDD baseline, with no significant alteration observed in mtDNA-oxidation levels.

Conclusion: Our findings suggest that there are distinct modifications in mtDNA associated with these conditions. Furthermore, the observed changes in mitochondrial mtDNA-cn and D-loop methylation during the remission phase suggest a potential involvement of mtDNA alterations in the underlying mechanisms of MDD.

This work was supported by TUSEB (TUSEB 20131-Deniz Ceylan) and a BAGEP award by the Science Academy of Turkey

BIPOLAR DISORDER AND BREAST CANCER: CLINICAL INSIGHTS INTO DNA DAMAGE-RELATED MECHANISMS

Mete Ercis*[1], *Melissa Solares-Bravo1, Kathryn J. Ruddy1, Fergus J. Couch1, Vanessa M. Pazdernik1, Nicole L. Larson1, Jorge A. Sanchez-Ruiz1, Mark A. Frye1, Janet Olson1, Stacey J. Winham1, Aysegul Ozerdem1*

[1]*Mayo Clinic*

Objective: Bipolar disorder (BD) is associated with an increased risk of breast cancer in women. The causality between BD and breast cancer is unclear. BD is associated with increased DNA damage and concomitant alteration in gene expression levels of the enzymes operating on base-excision repair (BER) of both nuclear and mitochondrial DNA. FEN1 and PARP1, the two genes of the BER mechanism that are involved in cancer treatment showed genome-wide significant association with BD and significant association with lithium response respectively. Given the involvement of DNA damage and repair mechanisms in both conditions, we aimed to explore the effect of having BD on clinical features of breast cancer including age at breast cancer diagnosis, presenting cancer stage, and survival.
Methods: Our sample included female patients from the Mayo Clinic Breast Disease Registry (MCBDR) with breast cancer only (BC-Only; n=9390) diagnosis and patients with breast cancer and BD comorbidity (BC+BD; n=59). All available information from electronic health records was used to ascertain the diagnosis of BD. Clinical features of breast cancer and lifestyle characteristics of individuals were obtained from the MCBDR data repository. Fisher exact tests, Wilcoxon rank sum tests, Kaplan-Meier survival curves, and Cox proportional hazards models were used to compare BC+BD and BC-Only groups. A multivariable regression on age at breast cancer diagnosis was conducted to estimate the effect of comorbid BD while adjusting for confounding variables.
Results: Age at breast cancer diagnosis was significantly earlier in the BC+BD group (52.8±10.5 years) compared to BC-Only (57.1±12.5 years, p=0.005). BD diagnosis was consistently associated with earlier age at breast cancer diagnosis after adjusting for potential confounders that differed significantly among groups, such as smoking, exercise, and BMI (β=-5.88, p=0.016). Presenting stage of breast cancer or survival did not differ between groups (both $p > 0.05$). Among BC+BD patients, lifetime lithium users had an older age at breast cancer diagnosis (n=32, 54.3±11.5 years) than non-users (n=27, 51.0±9.0 years) although the difference was not statistically significant (p=0.315). Lithium use was not associated with presenting cancer stage, or survival (both $p > 0.05$).
Conclusion: Our initial findings highlight that BD diagnosis is associated with breast cancer development approximately five years earlier than non-BD individuals even after adjusting for confounders, suggesting a possible shared mechanism between the two diseases beyond lifestyle characteristics. Examining the shared genetic mechanisms between breast cancer and BD including their
those involving mitochondrial DNA repair will provide a deeper understanding of pathophysiology toward identifying novel therapeutic targets.

MITOCHONDRIAL TARGETS FOR NOVEL THERAPY DEVELOPMENT

Michael Berk**1*, *Jee Hyun Kim2, Bruna Panizzutti2, Zoe Liu2, Olivia Dean2, Johnny Park2, Ken Walder2*
[1]Australasian Society for Bipolar and Depressive Disorders Ltd, 2Deakin University

Objective: This presentation will highlight the evidence regarding abnormal mitochondrial energy generation in bipolar disorder as a treatment target. Mitochondria are cellular organelles involved in energy production. Symptomatically, bipolar disorder is a biphasic disorder of energy generation. Mania is characterised by increased energy in mania and in depression, by decreased energy. Bipolar disorder can be seen as a biphasic dysregulation of mitochondrial energy generation, typified in depression by inability to upregulate biogenesis in response to metabolic demands, and in mania to downregulate generation when demand abates. There is preclinical, electron microscopic, and post-mortem evidence of mitochondrial changes, and evidence of altered energy generation in the disorder. Many widely used psychotropic agents have effects on mitochondrial energy generation, implying that this is a viable therapeutic target. Several agents that enhance antioxidant defences or mitochondrial functioning have been studied for the treatment of mood disorders as adjuvant

therapy to pharmacological treatments. This could be especially beneficial for treatment-resistant patients.

Methods: This presentation will summarise the evidence supporting the involvement of mitochondrial dysfunction in mood disorders, the effects of current therapies on mitochondrial functions, and highlight novel targeted therapies acting on mitochondrial pathways that might be useful for the treatment of mood disorders. In addition, this presentation will highlight a novel stem cell derived platform for drug repurposing that highlights a mitochondrial therapeutic as having potential for the treatment of bipolar disorder, trimetazidine.

Results: Trimetazidine was identified with no a-priori hypothesis. We used a gene expression signature to determine the effects of a combination of known drugs used to treat bipolar disorder. We then screened a library of off-patent drugs in cultured human neuronal-like cells, identifying trimetazidine. Trimetazidine has cytoprotective and metabolic effects, leading to improved glucose utilization for energy production. It is used to treat angina pectoris and has an excellent safety profile. The preclinical and clinical literature strongly support trimetazidine's potential to treat bipolar depression, as the agent has anti-inflammatory and antioxidant properties while normalizing compromised mitochondrial function. Preclinical models suggest antidepressant effects.

Conclusion: Trimetazidine's established safety and tolerability provide a robust rationale for clinical trials to trial its efficacy to treat bipolar depression that could progress its repurposing to address arguably the major unmet need in the disorder.

SOCIAL ISOLATION IN YOUTHS: PREVENTION AND TREATMENT STRATEGIES

Paolo Brambilla, University of Milan

Symposium Synopsis: Human nature is thought to be rooted in its social interactions and relationships, which support the development and preservation of physical and mental health. In humans, extreme cases of social isolation can lead to the complete avoidance of social contexts including work, school and those involving significant others. This condition is known as Hikikomori syndrome, a phenomenon that affects roughly 2% of the Japanese general population. The evidence to date shows that this phenomenon is growing in both Eastern and Western countries, possibly influenced by cultural and environmental factors and the recent COVID-19 pandemic, with particular regard to the most fragile subgroups such as juvenile and elderly populations. Notably, social isolation and related loneliness have been associated with increased mortality and depressive symptoms, poorer cognitive functioning, faster cognitive decline and alterations in the neuroendocrine systems in healthy individuals. Furthermore, social isolation often constitutes a prodromal symptom of severe psychiatric conditions such as social anxiety disorder, psychosis and depression. Therefore, early interventions aimed at treating social isolation could lead to a more favourable outcome for young patients and reduce the burden on the national health systems. In this symposium, we will discuss the current challenges of preventing and treating social isolation-related disorders in fragile populations in and out of psychiatric trajectories.

SOLITAIRE - DIGITAL INTERVENTIONS FOR SOCIAL ISOLATION IN YOUTHS AND THEIR FAMILIES

Maria Gloria Rossetti*[1]

[1] *University of Verona*

Objective: Social Isolation (SI) is a condition that can lead to complete withdrawal from society, with particular regard to the most fragile subgroups such as juvenile and elderly populations. It often constitutes a core symptom (often prodromal) of severe psychiatric disorders such as the Hikikomori syndrome, social anxiety disorder, psychosis, depression, mood-dysregulation and others. If not treated, SI can degenerate into a complete withdrawal from society. Therefore, early interventions

aimed at treating SI could result in a more favourable outcome for young patients. However, due to the social interaction barrier intrinsic to the condition, current treatments alone are problematic and only partially effective in treating SI. SOLITAIRE aims at implementing a multi-component digital psychiatric intervention to remotely help youths suffering from Social Isolation (SI), based on cognitive behavioural therapy (CBT), Cognitive Remediation (CR) and Psychoeducation (PE) for family members. SOLITAIRE will overcome most barriers and limitations of standard clinical interventions.
Methods: SOLITAIRE aims to test the feasibility and preliminary efficacy of two digital interventions for treating young adults and adolescents suffering from severe social isolation. Recruited participants will be randomly assigned to two arms i.e., experimental versus control. In the experimental arm, patients will undergo a brief cycle of CBT combined with computerized CR. In the control arm, patients will receive only CBT. Additionally, for all recruited patients, a psychoeducational intervention (PE) is planned for family members to alleviate the psychological burden associated with caring for socially withdrawn relatives. SOLITAIRE started in June 2023, and recruitment is ongoing.
Results: In this talk, I will present the preliminary findings of the SOLITAIRE study, with particular emphasis on the challenges encountered during the study design, the implementation of the digital interventions and the data collection.
Conclusion: Due to its multimodal digital approach, SOLITAIRE is expected to significantly impact patients' quality of life and well-being addressing previously unmet clinical needs, possibly exacerbated by the recent pandemic. Moreover, the synergistic CBT+CR intervention is thought to stimulate cognitive processes implied in social cognition and we expect that clinical improvements will be generalized to more ecological scenarios and daily life contexts.

PREDICTORS OF EARLY PSYCHOSIS AND SOCIAL ISOLATION

Stefan Borgwardt*[1]
[1] *University of Lübeck*

Objective: Social isolation has been associated with increased psychopathological symptomatology, poorer cognitive functioning and constitutes a prodromal symptom of psychosis. In this presentation, we will review predictors for early psychosis in the context of social isolation. Furthermore, current challenges of preventing and treating social isolation in people at high-clinical risk for developing severe mental disorders will be reviewed.
Methods: Review of findings from international longitudinal consortia (Psy-Scan, PRONIA, NAPLS 2) and available evidence from early psychosis studies
Results: Social isolation plays a crucial role in longitudinal clinical trajectories of people presenting with attenuated symptoms of psychosis and at clinical high risk for psychosis (CHR).
Conclusion: Further search for improved treatments for social isolation and a comprehensive prediction and prevention model for early psychosis is needed.

HIKIKOMORI: PSYCHOPATHOLOGICAL AND BIOLOGICAL UNDERSTANDING OF SOCIALLY ISOLATED PERSONS

Takahiro Kato*[1]
[1]*Graduate School of Medical Sciences, Kyushu University*

Objective: Hikikomori, a severe form of social withdrawal for more than six months, is originally observed in Japan and now becoming a global mental health issue. I have established the world-first hikikomori research clinic/system to understand/treat multidimensional aspects of hikikomori based on bio-psycho-social analyses. I introduce our hikikomori research system and also show our updated biological data.

Methods: Drug-free patients with hikikomori (n=42) and healthy controls (n=41) were recruited. The severity of hikikomori was assessed using the HQ-25. Blood biochemical tests and plasma metabolome analysis were performed. Based on the integrated information, machine-learning models were created to discriminate cases of hikikomori from healthy controls, predict hikikomori severity, stratify the cases, and identify metabolic signatures that contribute to each model. **Results:** Long-chain acylcarnitine levels were remarkably higher in patients with hikikomori; bilirubin, arginine, ornithine, and serum arginase were significantly different in male patients with hikikomori. The discriminative random forest model was highly performant, exhibiting an area under the ROC curve of 0.854. To predict hikikomori severity, a partial least squares PLS-regression model was successfully created with high linearity and practical accuracy. Additionally, blood serum uric acid and plasma cholesterol esters contributed to the stratification of cases. **Conclusion:** Our findings reveal the blood metabolic signatures of hikikomori, which are key to elucidating the pathophysiology of hikikomori. Our data have suggested the importance of biological understandings of hikikomori in addition to sociocultural aspects.

LONELINESS IN PEOPLE WITH SEVERE MENTAL ILLNESS: A DATA SCIENCE INVESTIGATION

Dulce Alarcón Yaquetto**1*, *Robert Stewart1, Mariana Pinto da Costa1*

1 Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Loneliness is prevalent and has been linked with different health outcomes.

Objective: To investigate if loneliness is associated with clinical phenotypes of psychosis in people with severe mental illness (SMI).

Methods: We used the Clinical Record Interactive Search (CRIS) platform which provides anonymised copies of the South London and Maudsley NHS Foundation Trust (SLaM) electronic health records. A previously validated natural language processing (NLP) algorithm that identifies instances of loneliness was used to assess exposure.

Results: We identified people based on their first diagnosis of SMI and assessed if loneliness was a predictor of negative, depressive, and manic symptoms during a 12 month follow-up. We will present the findings obtained, with a focus on age and other individual characteristics. The advantages and challenges of using data science and large real world health electronic records to study loneliness will be discussed.

Conclusion: Loneliness can be studied as a predictor of clinical phenotypes in SMI using electronic health records coupled with NLP. As a potentially modifiable factor, this opens up opportunities for future research and interventions aimed at improving treatment outcomes and recovery in SMI patients.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia III

DIGITAL TECHNOLOGIES AND NEW ADVANCEMENTS IN PSYCHIATRY

Oğuz Karamustafalıoğlu, İstanbul-University Cerrahpaşa

ADVANCES IN DIGITAL PHENOTYPING FOR BRIDGING BIOLOGICAL RESEARCH AND CLINICAL CARE

John Torous

State-of-the-Art Synopsis: Digital phenotyping is an increasingly popular method that takes advantage of the multiple sensors and interactions that people have with their smartphones. It enables clinicians and researchers to capture various data streams, including mobility patterns (from GPS and accelerometer sensors), social patterns (from anonymized call and text message logs), self-

reported symptoms (from on-phone surveys), cognition (assessed through response time to on-screen tasks or more formal cognitive tests), and other real-time data on individual functioning. However, like all data streams, there are limitations including patient engagement, data quality, and replicable derived features. This talk will review the state of the art for digital phenotyping with a focus on validation and verification efforts to highlight the current and future use cases for this data. Biological research targets including current ready-to-analyze digital phenotyping datasets as well as clinical use cases of the data will be reviewed to frame the translational potential. Finally, ethical and equity issues concerning digital phenotyping will be presented with action-oriented steps toward ensuring the method is used appropriately. **Objective:** To define digital phenotyping and review relevant data streams. To highlight digital phenotyping data processing pipelines (machine learning) with the goal of highlighting potential sources of bias. To review recent evidence for the use of the method in both biological research and clinical care. To also explore reasons for currently contradictory results. To discuss the ethics of digital phenotyping and present a solutions oriented approach. **Methods:** This talk will draw evidence from published research, the ongoing AMP-Schizophrenia study, and Dr. Torous personal experiences applying it in research/care. **Conclusion:** Digital phenotyping remains a promising method to advance both biological psychiatry and clinical care. However, it is not a panacea and requires thoughtful applications and careful research to yield breakthroughs. The low barriers to entry and use of digital phenotyping mean that a global consortium to advance digital phenotyping is not only possible but necessary to realize its full potential.

NEW INSIGHT AND DEVELOPMENT OF INTEGRATIVE TREATMENT IN SCHIZOPHRENIA

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: The development of integrative treatment of pharmacological and non-pharmacological treatment for people affected by schizophrenia spectrum disorders has been identified as an important and urgent priority. Due to the adverse events and limited effects of medication treatment for schizophrenia, there is a need to identify effective combined interventions that can improve functioning recovery and can be provided within routine care services. This symposium will bring together the evidence evaluating these novel interventions.

Current antipsychotic treatments do not lead to beneficial effects on primary negative symptoms and
cognitive deficits in schizophrenia. Given that these domains of the disorder contribute substantially to low recovery rates and unfavorable disease course, new treatment approaches are warranted. In recent years, different types of exercise interventions have been proposed as promising add-on treatments. L Roell summarizes all current meta-analyses targeting effects of exercise on negative symptoms and cognitive impairments in schizophrenia. He further compares the observed effects sizes to other additional treatment approaches such as cognitive remediation and provides recent evidence on the underlying neural mechanisms that may drive these improvements on the clinical level.

POTENTIAL NEURAL MECHANISMS EXPLAINING BENEFICIAL EFFECTS OF PHYSICAL EXERCISE IN SCHIZOPHRENIA

Lukas Roell**1*, *Daniel Keeser2, Andrea Schmitt3, Alkomiet Hasan3, Isabel Maurus1, Peter Falkai3*

[1]LMU, 2University Hospital, LMU Munich, 3German Society for Biological Psychiatry

Objective: As demonstrated by multiple large-scale meta-analyses, physical exercise interventions in people with schizophrenia improve negative symptoms, cognition, social and occupational functioning, and general disorder severity. However, the underlying neural mechanisms that drive

these improvements remain to be determined. Therefore, we conducted a global exploratory analysis of structural and functional neural adaptations after exercise and explored their clinical implications. **Methods:** Combining meta-analytic techniques with original data of 91 patients with schizophrenia from a large-scale multicentre randomized-controlled trial, we investigated stuctural and functional neural adaptations induced by different types of exercise based on multimodal neuroimaging acquisitions. We further linked obtained changes in the brain to several relevant clinical outcomes. **Results:** Our results indicated that physical exercise in people with schizophrenia can induce structural and functional adaptations within the hippocampal formation, the default-mode network, the cortico-striato-pallido-thalamo-cortical loop, and the cerebello-thalamo-cortical pathway. We further observed that volume increases in the right posterior cingulate gyrus as a central node of the default-mode network were linked to improvements in general disorder severity. **Conclusion:** These findings suggest a positive impact of physical exercise on several neural networks involved in the pathophysiology of schizophrenia and thus provide further insights into neural mechanisms underlying clinical improvements after exercise. A more comprehensive understanding of these mechanisms is essential to gain a deeper insight into the pathophysiology of schizophrenia which in turn may facilitate the development of treatments that specifically target respective mechanisms.

WHAT DOES NON-INVASIVE BRAIN STIMULATION CONTRIBUTE TO THE TREATMENT OF PEOPLE LIVING WITH SCHIZOPHRENIA?

Frank Padberg**1*

1

University Hospital, LMU Munich

Objective: Non-invasive brain stimulation (NIBS) approaches comprise an array neurophysiologically distinct methods, e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES). NIBS methods have been applied for treating clinical conditions within the spectrum schizophrenia syndromes, mainly predominant negative symptoms and persistent auditory hallucinations. The further implementation of NIBS interventions in clinical routines is a matter of debate.

Methods: The array of NIBS methods and their underlying mechanistic principles will be introduced. The current evidence for efficacy and safety of NIBS in schizophrenia will be critically reviewed and discussed based on the available evidence from randomized controlled trials (RCTs) and meta-analyses.

Results: Two main research lines focusing on predominant negative symptoms (target area: prefrontal cortex subregions) and persistent auditory verbal hallucinations (target area: temporoparietal cortex) have been established over the last two decades, and data from RCTs support their efficacy and safety. Across NIBS approaches and target regions, findings are nevertheless heterogeneous probably also due to different mechanisms of neuroplasticity induction. To date, there is very limited evidence how NIBS interventions could be implemented in clinical care and treatment algorithms.

Conclusion: Growing evidence supports the notion that NIBS methods (mainly rTMS and tES) are efficacious for treatment psychopathological syndroms in people with schizophrenia and could be easily implemented in combined treatment protocols due to their good safety profile and application modalities which are easily scalable for various clinical settings. Future studies should focus on gaining a deeper mechanistic understanding of the respective NIBS methods and systematically include NIBS in RCTs as active comparators to other treatment modalities.

A PILOT RANDOMIZED CONTROLLED TRIAL OF AN INTEGRATIVE INTERVENTION OF TDCS AND YOGA FOR COGNITIVE FUNCTION IN CHRONIC SCHIZOPHRENIA

Jingxia Lin*[1]
[1]*The Hong Kong Polytechnic University*

Objective: The pilot randomized controlled trial aimed to examine the feasibility and effectiveness of a 2-week combined intervention of active tDCS and yoga on cognitive function and clinical symptoms in individuals with chronic schizophrenia.

Methods: A total of 18 participants with chronic schizophrenia were recruited and randomized into two arms: (1) 2-week active tDCS + yoga (a-tDCS-Y) (n=9), and (2) 2-week sham tDCS + yoga (s-tDCS-Y) (n=9). Both interventions were conducted five sessions weekly for two weeks, with each session lasting 1 hour. Active tDCS was applied using a wearable stimulator (LifTid) with a constant stimulation intensity of 1.2mA for 20 minutes, and sham tDCS was performed using the same device but without stimulation. During the yoga training, all participants wore the device and a facilitator turned on the stimulation for participants receiving a-tDCS-Y intervention, and pretended to turn on the stimulation for participants receiving s-tDCS-Y intervention after the first 10-minute warm-up. Outcome measures were conducted at baseline and post-intervention including cognitive tests, quality of life, and clinical symptoms.

Results: There were 16 participants completed the pilot trial with an attrition rate of 11%. Mean age was 44.5 years old, and mean duration of illness was 7.5 years. There were no significant differences in the demographic characteristics between two groups at the baseline. We found a-tDCS-Y had a small-to-medium effect size in executive function measured by the Verbal Fluency Test (Cohen's d=0.39) compared with s-tDCS-Y group. We also found a significant time × group interaction effect on physical function assessed by SF-36 (Cohen's d=0.61) with superior improvements in a-tDCS-Y group. Both groups showed a trend of improving working memory and clinical symptoms (Cohen's d ranged from 0.21 to 0.55).

Conclusion: Overall, the pilot study provides preliminary evidence for the feasibility of our approach and showed encouraging findings on executive function after a 10-session active tDCS + yoga intervention in chronic schizophrenia. Further full-scale RCT to evaluate the additive and synergistic effects of tDCS and yoga on neurocognitive function and to examine the underlying neuro-mechanisms using imaging approach is highly recommended.

OPTIMIZING CARE FOR PEOPLE LIVING WITH SCHIZOPHRENIA THROUGH NON-PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS

Christoph Correll*[1]
[1]*Zucker School of Medicine at Hofstra/Northwell, Hempstead*

Objective: This presentation will focus on the effects of nonpharmacologic psychological and psychosocial treatments when added to antipsychotics across a broad range of outcomes. Additionally, data on the combination of antipsychotic treatment with healthy lifestyle education, instruction or management interventions with be presented, either alone or in conjunction with pharmacologic treatments aimed at reducing appetite, food intake and cardiometabolic risk factors or poor outcomes in people with mental illness. Finally, adaptive monitoring and management strategies will be proposed.

Methods: Review of systematic reviews and meta-analyses as well as umbrella reviews on the topics of nonpharmacologic psychological and psychosocial treatments added to antipsychotics across a broad range of outcomes for people with schizophrenia.

Results: Several meta-analyses, network meta-analyses and umbrella reviews exist regarding the effects of adjunctive nonpharmacologic psychological, psychosocial and lifestyle interventions for

mental and physical health outcomes. In patients with early-phase schizophrenia, integrated or "coordinated specialty" care seems to be the most promising approach. Otherwise, among psychological interventions, cognitive behavioral therapy and family interventions had the most data in support of their adjunctive use. For cognitive health, cognitive remediation and exercise were more effective than control groups. Regarding lifestyle interventions, coached and group interventions had the biggest effect, including on physical health and global as well as social cognition. **Conclusion:** Adjunctive nonpharmacologic psychological and psychosocial treatments as well as healthy lifestyle counseling and interventions are viable options for people with schizophrenia to improve a range of relevant mental and physical health outcomes. Ways to increase initiation of, engagement in and retention related to such interventions as well as their effects on longer-term biopsychosocial outcomes requires further study.

THE ART OF PRESCRIBING CLOZAPINE: NOVEL DEVELOPMENTS

Dragana Ignjatovbic Ristic, University of Kragujevac

Symposium Synopsis: Clozapine is a cornerstone of the management of treatment-resistant schizophrenia, presents unique challenges in clinical management and is underprescribed. Our symposium delves into three key facets of clozapine treatment: therapy adherence, blood levels, and neutrophil counts.

The first presentation explores a novel approach to monitor long-term adherence to clozapine. Utilizing data from the Utrecht Patient Oriented Database, it reveals a significant association between clozapine use and enhanced FL3 neutrophil granulocyte fluorescence. This finding opens avenues for using FL3-fluorescence as a potential biomarker for clozapine adherence, a crucial aspect in schizophrenia management.

Our second presentation shifts focus to therapeutic drug monitoring (TDM) of clozapine. The study analyzed clozapine levels in patients with treatment-resistant schizophrenia in a middle income country who were titrated without TDM. This revealed a substantial interindividual variation in clozapine levels, absence of a relationship between levels and side effects, and only a weak relationship between levels and functional outcome. These results challenge strict adherence to the conventional therapeutic range and support a more personalized approach.

The final presentation revisits the history and current practices surrounding clozapine-induced agranulocytosis. Reviewing literature from 1975-2022, it suggests a reevaluation of the mandatory intensive blood monitoring protocols, advocating for a more nuanced approach that balances the risks and benefits of clozapine treatment, especially in the initial weeks of therapy.

Together, these presentations underscore the importance of personalized, evidence-based approaches in optimizing clozapine treatment for schizophrenia. In this way this symposium hopes to contribute to the removal of hurdles to clozapine treatment.

CLOZAPINE LEVELS AND OUTCOMES IN SERBIAN PATIENTS WITH THERAPY RESISTANT SCHIZOPHRENIA PREVIOUSLY TREATED WITHOUT MEASURING CLOZAPINE LEVELS

Hans de Haas*[1], *Dan Cohen[2], Mariken de Koning[3], Geke van Weringh[4], Veroljub Petrovic[5], Lieuwe de Haan[6], Daan Touw[7], Dragana Ignatovic-Ristic[8]*

[1]Arkin Mental Health, [2]MHO North-Holland North, Amsterdam, [3]Arking Mental Health, Amsterdam, [4]Onze Lieve Vrouwe Gasthuis, Amsterdam, [5]Special Hospital for Psychiatric Disorders Kovin, [6]Amsterdam University Medical Center, [7]University Medical Center Groningen, [8]University of Kragujevac, Faculty of Medical Sciences

Objective: Clozapine remains the only pharmacological treatment option for therapy resistant schizophrenia. Therapeutic drug monitoring (TDM) of clozapine is recommended, although the evidence for the therapeutic range of 350-600 ng/ml is limited. In various countries including Serbia, TDM of clozapine is not routinely performed. This study evaluated the distribution of clozapine levels in Serbian patients who had not undergone prior TDM and investigated the relationship of clozapine levels with clinical outcomes. **Methods:** Clozapine levels were measured by dried blood spot (DBS) analysis

in patients with therapy resistant schizophrenia. DBS samples were taken in Serbia, and shipped to The Netherlands for analysis. Side effects were evaluated by GASS-c, severity of symptoms and functional impairment with WHODAS, CGI-S and GAF.

Results: Clozapine was determined for 129 of 140 enrolled patients. 51.2% had subtherapeutic levels, 24.8% were in the therapeutic window and 24% had supratherapeutic levels. Clozapine levels were not associated with side effects, and showed a weak positive association with symptom severity and functional impairment. No severe side effects were observed in patients with clozapine levels surpassing 1000 ng/ml (n=8).

Conclusion: Current findings revealed substantial interindividual variation. Especially when patients are titrated without TDM, some patients achieve high clozapine levels with apparently good tolerance and others experience side effects with relatively low clozapine levels. We propose that the upper limit of the therapeutic range should not be regarded as an absolute barrier, and guidelines should allow for a personalized approach when prescribing clozapine.

NEUTROPHIL FLUORESCENCE IN CLOZAPINE TREATMENT: THE FIRST BIOLOGICAL MARKER OF LONG-TERM DRUG ADHERENCE

Wai Hong Man**1*, *Maarten ten Berg1, Ingeborg Wilting1, Albert Huisman1, Wiepke Cahn1, Jan Willem Douma2, Hanneke den Breeijen1, Eibert Heerdink1, Toine Egberts1, Wouter van Solinge1*

[1]University Medical Center Utrecht, 2Tjongerschans Hospital, Heerenveen

Objective: Non-adherence to medication is a major issue in the treatment of schizophrenia in general and in particular for those treated with clozapine. A reliable tool to quantify patients long-term adherence to clozapine is currently unavailable. Enhanced FL3 neutrophil granulocyte fluorescence was serendipitously observed in a small population of schizophrenic patients treated with clozapine. The present study was aimed at assessing the association between clozapine use and FL3-fluorescence.

Methods: A cross-sectional study was performed using data from the Utrecht Patient Oriented Database (UPOD). A total of 38 390 inpatients were included, of which 124 (0.33%) used clozapine.

Results: FL3-fluorescence was significantly higher (U=240 179, P LESS THAN 0.001) in clozapine users (mean (SD)= 90.5 (11.8)) than in non-users (mean (SD)= 69.8 (3.3)). Observed FL3-fluorescence was found to increase with increasing clozapine dose. The area under the receiver operating characteristic curve was 0.95.

Conclusion: Our results confirm the association between use of clozapine and elevated FL3-fluorescence. Further research is needed to unravel the underlying mechanism and to investigate the true potential of FL3-fluorescence as a clozapine-adherence in clinical practice.

MODIFIED LEUKOCYTE MONITORING IN CLOZAPINE: PROPOSAL BY THE DUTCH CLOZAPINE COLLABORATION GROUP

Dan Cohen**1*, *Peter FJ Schulte1, Selene Veerman1, Jan PAM Bogers2*

[1]MHO North-Holland North, 2MHO Rivierduinen

Objective: After the introduction of clozapine in 1975 in Finland, eight Finnish patients died after developing agranulocytosis, whereupon clozapine was withdrawn from the market. Its reintroduction – from 1990 onwards – was accompanied by mandatory white blood cell monitoring if treatment lasts and strict thresholds at which clozapine must be discontinued definitively. The fear of agranulocytosis and the need for intensive blood monitoring is and remains the single most important barrier for prescribers and patients alike and leads to under prescription of the only effective and approved medication for treatment-resistant schizophrenia.
Methods: We review the literature from 1975-2022 on the incidence of clozapine-associated agranulocytosis and the relation between the occurrence of the agranulocytosis with treatment duration
Results: The risk of agranulocytosis is smaller than perceived at the time of reintroduction, b. the risk of agranulocytosis is concentrated in the first 18 weeks of treatment, c. such risk is not greater than with other antipsychotics and d. that frequent blood monitoring has not demonstrably decreased the rate of agranulocytosis.
Conclusion: 1) Restrict mandatory monitoring of the absolute neutrophil count (ANC) to the first 18 weeks of clozapine treatment, 2) the prescriber and the well-informed patient decide together about further monitoring frequency, 3) Clozapine treatment must be stopped if the ANC falls below 1.0×10^9/L. Continuation of clozapine or a rechallenge are possible if prescriber and patient together determine that the benefits outweigh the risks. 4) National registries which control hematologic monitoring are unnecessary and should be abolished.

EXPLORING CURRENT AND FUTURE DIRECTIONS IN THE MICROBIOME – A FOCUS ON NEUROPSYCHIATRIC DISORDERS

Sian Hemmings, Stellenbosch University

Symposium Synopsis: Humans have co-evolved with the trillions of microbiota that occupy every inch of our bodies, creating habitat-specific ecosystems that play a crucial role in bodily functions. Over the past decade, the interest in the role of that microbiota play in neuropsychiatric disorders, including autism spectrum disorder, posttraumatic stress disorder (PTSD), major depressive disorder and Parkinson's Disease has exploded. Recent evidence has indicated that the microbiome plays a key role in the brain and behaviour at critical windows across the lifespan, with numerous studies supporting the role of the gut microbiome in neurodevelopment. This symposium will bring together four leaders in the field of microbiome research, to discuss the current and future directions in microbiome research in neuropsychiatric disorders across the lifespan. Dr Hemmings will provide an overview of the role of the microbiome in neurodevelopmental disorders, with a focus on fetal alcohol spectrum disorders; Dr Malan-Muller will discuss the emerging role of the gut and oral microbiome in common mental disorders, such as PTSD, anxiety and depression, and Dr El-Aidy will discuss gut microbiome adaptations and implications for Parkinson's Disease treatment. Finally, Dr Walter Pirovano will provide insight into standardised and robust approaches for the identification of microbial markers in neuropsychiatric disorders.
This symposium will feature preclinical and clinical microbiome findings, and discuss the gut microbiome as a potential therapeutic target. Future considerations for holistically investigating the gut microbiome and untangling the molecular mechanisms whereby it influences the brain and behaviour, will also be discussed.

FETAL ALCOHOL SPECTRUM DISORDER: INSIGHTS FROM THE MICROBIOME

Sian Hemmings*[1], *Sian Hemmings2, Natasha Kitchin2, Lauren Martin2, Philip May3, Lindsay Hall4, Raymond Kiu5, Matthew Dalby5, Jacqueline Womersley2, Anna-Susan Marais1, Marlene de Vries1, Soraya Seedat2*

[1]Stellenbosch University, 2Stellenbosch University; Stellenbosch University/South African Medical Research Council Extramural Unit on the Genomics of Brain Disorders, 3Gillings School of Global Public Health, Nutrition Research Institute, University of North Carolina, 4Gut Microbes and Health, Quadram Institute Biosciences; Intestinal Microbiome, School of Life Sciences, ZIEL-Institute for Food and Health, Technical University of Munich; Norwich Medical School, University of East Anglia, 5Gut Microbes and Health, Quadram Institute Biosciences

Objective: Fetal alcohol spectrum disorder (FASD) is an overarching term describing four diagnoses along a severity spectrum, that occur consequential to prenatal alcohol exposure (PAE). Arguably the most profound consequences of FASD are the enduring neurodevelopmental abnormalities and cognitive deficits. In South Africa, the prevalence of FASD is reported to be higher than anywhere else in the world, with prevalences of up to 170-233 per 1,000 children reported, compared to the global prevalence of 7.7 per 1,000. Although FASD is a serious public health problem, both locally and internationally, treatment options are limited and further research is required in order to uncover novel therapeutic targets. Microbiome studies are a rapidly growing area of neuropsychiatric and neurodevelopmental research. Vertical and horizontal transfer of microbes from mother to child during and shortly after birth results in the acquisition of intestinal bacteria which, via the microbiome-gut-brain axis, have been found to play a significant role in neurodevelopment. Microbial alterations in the maternal gut and vaginal bacteriome, as well as the infant gut microbiome, may therefore increase the risk of FASD.

Methods: Participants (n=207) provided both stool and vaginal swab samples. Additionally, stool samples were collected from their infants at birth, six weeks, and nine months of age. Maternal alcohol use was assessed using AUDIT questionnaire and physiological markers of alcohol use. FASD diagnoses were made by triangulating data from dysmorphology examinations, neurodevelopmental assessments, and maternal interviews. Microbial DNA was extracted from maternal stool and vaginal samples, and infant samples at birth, 6 weeks and 9 months of age, and the V1-V2 hypervariable region of the 16S rRNA gene was sequenced. Microbial composition and diversity analyses were performed using R packages dada2, vegan, phyloseq, and MaAsLin2.

Results: Relative abundances of maternal gut Subdoligranulum and Bifidobacterium were lower in participants who birthed infants with FASD, compared to participants who birthed infants not diagnosed with FASD ($q = 0.026$; $q = 0.034$, respectively). Between the ages of 6 weeks and 9 months, Streptococcus relative abundance increased in the gut of infants without FASD, but decreased in infants diagnosed with FASD ($p = 0.023$), while the relative abundance of Bacteroides decreased in infants without FASD, but increased in those with FASD ($p = 0.073$).

Conclusion: Our research findings shed light on the nature and persistence of PAE-induced changes in the gut microbiome, and how alcohol-induced alterations in the microbiome may correlate with the development of FASD symptomology. These studies provide the first step in facilitating the identification of robust maternal and infant biomarkers of FASD, which may enable early identification of individuals most at risk for FASD, offer an early window for intervention, and contribute towards mitigating FASD-related disabilities in later life.

EXPLORING THE ORAL-GUT-MICROBIOME-BRAIN AXIS: ADVANCING FROM ASSOCIATION STUDIES TO MECHANISTIC INSIGHTS AND BEYOND

Stefanie Malan-Muller*[1], *Thomaz Bastiaanssen2, Rebeca Vidal1, Juan Carlos Leza3*
[1]Complutense University of Madrid, 2APC Microbiome Ireland, Microbiota-Gut-Brain axis, Cork, [3]Complutense University of Madrid; Biomedical Network Research Center of Mental Health (CIBERSAM), Institute of Health Carlos III; Hospital 12 de Octubre Research Institute (Imas12); Neurochemistry Research Institute UCM

Objective: Investigate the intricate interplay between the microbiomes of the oral cavity and the gut and explore the underlying molecular mechanisms that link these microbial ecosystems and their influence on anxiety, depression, and trauma-related symptoms.

Methods: In a Spanish cohort, we studied the connection between mental health and fecal and oral microbial characteristics, covering self-reported symptoms and clinical diagnoses of anxiety, depression, and PTSD.

We collected stool, saliva, and blood samples from 290 participants who completed questionnaires. Microbial communities in the gut and mouth were analyzed via 16S rRNA sequencing, examining diversity, structure, and taxonomic abundance. Linear models were used to assess associations between taxonomic abundance and variables while adjusting for covariates.

We used PICRUSt2 to identify Gut-Brain Modules (GBMs) and Gut Metabolic Modules (GMMs) and employed linear models to uncover modules significantly linked to mental health. Analysis of the oral microbiome is ongoing.

We measured plasma LPS levels with ELISA and are currently assessing levels of kynurenine, tryptophan, serotonin, and various inflammatory markers.

Results: A substantial proportion of individuals exhibited anxiety (72.41%), depression (41.38%), and PTSD symptoms (20%), often overlapping. Lower Simpson's diversity was found in those with anxiety disorders and psychiatric medication use. Microbial composition was affected by general health, depression/bipolar disorder diagnoses, childhood abuse, and neglect.

Certain microbial abundances correlated with symptoms: Duodenibacillus, Desulfovibrio, and Senegalimassilia positively correlated, while Parasutterella negatively correlated with CTQ scores. Severe/moderate childhood emotional abuse was linked to higher Prevotella and lower Parasutterella abundances. Severe/moderate childhood physical abuse correlated with higher Desulfovibrio and Senegalimassilia levels.

Individuals with depression symptoms had lower Monoglobus abundances. Those with depression symptoms, diagnosed depression, or PTSD symptoms had reduced Monoglobus and Hungatella compared to mentally healthy controls. Comorbid depression+anxiety and PTSD+depression+anxiety individuals exhibited lower Hungatella and Monoglobus levels. Desulfovibrio positively correlated, while Hungatella negatively correlated with PCL scores.

Comorbid PTSD+depression and PTSD+depression+anxiety cases showed increased glycine degradation. Individuals with depressive symptoms and childhood physical neglect had elevated plasma LPS levels.

Conclusion: In a population-based study, we've uncovered vital connections between gut microbes and mental health. Notably, lower Simpson's diversity was found in anxiety disorders, echoing generalized anxiety disorder trends. Parasutterella negatively correlates with childhood trauma and autism spectrum. Prevotella is higher in childhood emotional abuse cases. We identified lower Hungatella levels in those with multiple mental health symptoms, corrected for psychoactive drug effects. Reduced Monoglobus, linked to poorer life quality, is seen in significant depressive symptoms. Higher glycine degradation is tied to PTSD, depression, and anxiety. Elevated LPS levels

indicate increased gut permeability in individuals with childhood neglect and depressive symptoms. These findings suggest potential early-life interventions for improved mental health.

GUT MICROBIOME ADAPTATION AND TREATMENT IMPLICATIONS IN PARKINSON'S DISEASE

Sahar El Aidy*[1]

[1]*University of Groningen*

Objective: The intricate interplay of the microbiome within the human body is integral to determining overall health. Of particular significance is the dynamic nature of the gut microbiome, influenced by multifaceted factors such as nutrient availability, and interactions with the host. Disruptions in these factors have been observed in conditions like Parkinson's disease, often accompanied by discernible alterations in the microbiome profile. However, the field faces challenges in reconciling conflicting findings that assign specific roles to individual microbes in the development and progression of the disease.
Methods: In this context, research from my lab has shown how specific gut bacteria diminish the bioavailability of the primary treatment for Parkinson's disease (1, 2), and how their metabolic activities affect bowel movement and the overall microbiome profile (3, 4).
Results: Our recent investigations have brought to light the presence of distinct bacterial strains in Parkinson's patients, displaying unique genotypic and phenotypic traits (unpublished data).
Conclusion: Ultimately, these discoveries promise to provide a deeper understanding of how certain microbial community members adapt and flourish within the gut environment, thereby facilitating the development of tailored microbiome-targeted interventions.

NEUROPSYCHIATRIC DISORDERS AND THE MICROBIOME: TOWARDS STANDARDIZED AND ROBUST APPROACHES FOR THE IDENTIFICATION OF MICROBIAL MARKERS

Walter Pirovano*[1]

[1]*Vrije Universiteit Amsterdam*

Objective: In recent years, an increasing number of studies has allocated an important role to the microbiome in the proliferation of neuropsychiatric disorders. Many of these studies focus on the characterization of microbiota imbalances (dysbiosis) and the impact this may have on functioning of the central nervous system by means of the direct and indirect gut-brain axis communication pathways. The differences in sample processing and data analysis methods however result in findings which are often inconsistent and difficult to replicate. To overcome this more standardized and robust approaches are warranted, but we argue also larger and/or combined cohorts are essential to increase the statistical power.
Methods: We reviewed microbiome association studies that link microbial shifts to neuropsychiatric disorders, and summarized the findings together with the study design, lab- and data analysis procedures. The statistical power and suitability of the normalization technique used within each study was assessed as well. Next, studies that shared an overlapping setup were combined and analyzed using different analysis approaches to identify dysbiosis, to link taxa with metadata covariates and to quantify taxa-taxa interactions. The results were compared against findings obtained on the individual datasets as well as the findings of the original studies.
Results: We show that the use of different study designs, lab- and analyses methods have a profound impact on the outcomes of microbiome association studies in neuropsychiatric disorders. We show that the choice of the (biostatistical) analysis method is of particular importance to this regard. That said, the impact of the method is considerably lower when using larger and/or combined cohorts.
Conclusion: We conclude the use of different study setups and protocols for sample processing and data analysis lead to a divergent microbial landscape associated with neuropsychiatric illness. In

order to improve the coherence of studies, the use of standardized and statistically robust approaches is essential. Yet significantly larger and/or combined cohorts are needed to increase the statistical power and to gain a more comprehensive insight into the mechanisms that microbes use to trigger the development of psychiatric illnesses.

GRANT WRITING WORKSHOP

Sophia Frangou, The University of British Columbia

STRATEGIES FOR SUCCESS IN OBTAINING RESEARCH FUNDING

Sophia Frangou1
1 The University of British Columbia

Objective: Present strategies for successful grant writing in psychiatry.
Methods: The presentation will cover the following:
(a) Types of research funding available
(b) Writing a research proposal
(c) What the reviewer are looking for
(d) What the funding agencies are looking for
Results: Participants should be better equipped to apply for competitive funding.
Conclusion: Research funding is very competitive, and applicants benefit for using proven strategies.

EUROPEAN JOURNALS AND IMPACT FACTOR

Paolo Brambilla1
1 University of Milan
Paolo Brambilla, University of Milan

Objective: Young researchers often wonder whether the impact factor or the number of citations is more relevant. My very personal view is that citations become increasingly important with increasing maturity of the career of a scientists.
The older scientists get the more they will be judged for the consistency of their output (how many papers per year during the last 5 or 10 years – but also how many 'excellent' papers per year based on the impact factor and/or citations).
Young researchers often have only one or two publications which are pretty new, thus, the number of citations is limited.
Therefore, for pragmatic reasons, funding institutions and universities will use the impact factor of the journal as a proxy of their scientific excellence. To evaluate the output of more mature scientists the h-index or the m-index may be used which are both based exclusively on citations and not on impact factors.
Thus, young researchers are confronted with the problem that their scientific quality will be judged based on the impact factors of their publications – especially in contexts which are highly relevant for their early careers such as in selection committees (to get hired) and grant committees (to get funding).
Methods: How to build a CV and become an independent researcher.
Find facilities and mentor (also you got to be lucky and causality may help sometimes)
Learn a method, balance quantity and quality of publications in a 2-3 years span, start Networking with colleagues, present posters at conferences, try oral presentations, apply for congresses' awards, and start preparing proposal grants.
intramural / local / national / european-international

The following strategies are well known among senior scientists and will primarily help young researchers to look for feasible ways to improve their studies within the limits of their contract and budget.

1. Look for a mechanism not for a phenomenon
2. Address the same question with additional methods
3. Re-analyze your samples with a different or more complex method
4. Add fancy techniques
5. Develop a fancy technology
6. Collaborate with a statistician
7. Fuse smaller studies
8. Collaborate with experts in the field
9. Look for a journal with the perfect scope and check where your competitors publish
10. Submit to a journal with a much higher impact factor to get reviewers comments

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: EARLY DETECTION, INTERVENTION AND PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Symptoms related to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, loss of synaptic plasticity and nucleotide polymorphisms. Activation of the immune response can alter neurotransmission leading to transmitter deficiency, and increased production of neurotoxic substances. Aberrant levels of proinflammatory cytokines can be detected in serum, plasma, and cerebrospinal fluid. A persistent proinflammatory state, gone undetected and untreated, contributes to neuroprogression. Predicting risk and intervening to prevent and reverse a neuroprogressive course remain a challenge. This symposium will focus on assessment of the homeostatic balance of the autonomic nervous system focusing on vagal nerve activity by measuring heart rate variability. The cholinergic anti-inflammatory pathway of the vagus regulates peripheral immune response. Restoring vagal nerve activity by non-pharmacologic interventions restores normal immune response. Baseline systemic immune-inflammation index (SII) is an indicator of immune response and systemic inflammation based on peripheral blood platelet, lymphocyte, and neutrophil counts, and is a simple way to objectively assess the balance between inflammatory and immune responses. The association between elevated neutrophils (along with SII) and treatment resistance may allude to the role of oxidative stress in the pathophysiology of Bipolar Disorder. Selective genomic testing pertaining to the thyroid pathway can provide guidance in determining vulnerability to treatment resistance, and a neuroprogressive course. Mutations in deiodinase enzymes peripherally and in CNS may explain the pathophysiology and progression of the disease up to cerebral atrophy. These mutations, when addressed with high dose thyroid hormones and rTMS, yield long term stable remission.

HEART RATE VARIABILITY IS AN INDEX OF AUTONOMIC DYSFUNCTION AND A TOOL TO ASSESS NEUROPROGRESSION

Angelos Halaris**1*

[1]*Loyola University Chicago Stritch School of Medicine*

Objective: Autonomic nervous system (ANS) dysregulation is associated with various symptoms of depressive disorder. The beat-to-beat pattern of heart rate (Heart Rate Variability) (HRV) provides a noninvasive portal to ANS function through the quantification of periodic heart rate patterns. In this study we quantified two components of HRV: Respiratory Sinus Arrhythmia (RSA), and Low

Frequency HRV (LFHRV). Both of these components have been extensively reported in studies of depression and have been at least partially associated with reduction in vagal nerve tone. We quantified RSA and LF-HRV in patients with Major Depressive Disorder (MDD) and Bipolar Depression as measures of ANS regulation seeking to establish the utility of components of HRV as potential diagnostic and prognostic biomarkers for treatment outcome. Given the regulatory effect of the vagal pathway on cells of the immune system, HRV provides a non-invasive index of the peripheral inflammatory status of the individual. **Methods:** Respiratory sinus arrhythmia (RSA), low-frequency (LF) of HRV, and systolic blood pressure (SBP) were assessed in patients with bipolar depression (31) and major depressive disorder (MDD=32), and in healthy controls (HCs=32). Since bipolar depressed subjects were maintained on specific medications to manage manic/hypomanic symptoms, we explored whether mood stabilizers (atypical antipsychotics and anticonvulsants or their combinations) could independently affect the physiological parameters. **Results:** When the autonomic measures were analyzed by a multivariate analysis of variance (MANCOVA), after controlling for BMI, the combination of variables (RSA, LF, SBP) discriminated patients with bipolar depression and MDD from HC ($F(6, 178)=3.036$, $p=0.007$, $\Lambda=0.823$, partial $\eta 2=0.093$). In any case, we cannot exclude that mood stabilizers might have affected SBP values in the bipolar group. To deconstruct this multivariate effect, pairwise ANOVAs and discriminant analyses contrasted groups and documented that RSA was the primary variable distinguishing the groups. Discriminant function analyses showed that RSA had a significant discriminating weight between bipolar depressed patients and HC subjects (p LESS THAN 0.0005). By contrast, RSA showed a trend towards statistical significance in discriminating between bipolar depression and MDD patients ($p=0.06$). **Conclusion:** In conclusion, physiological parameters (e.g., RSA and SBP) can be easily assessed in outpatient settings, thus facilitating the differential diagnosis of affective disorders. In addition to other clinical tools, such as pharmacogenomic testing, history, and questionnaires, HRV analyses and BP measurement can add relevant physiological parameters to reach the final diagnosis. Components of HRV may be predictive of antidepressant response in MDD patients. Lastly, we highlight the regulatory influence the ANS exerts on the immune system. It has been shown that inflammation can increase symptomatology in affective disorders, and its modulation can reverse resistance to drug treatment.

THE ROLE OF CBC-BASED INDICES OF PERIPHERAL INFLAMMATION IN PREDICTING CLINICAL OUTCOMES AND NEUROPROGRESSION FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION

Stephen Murata*[1], *Nausheen Baig[2], Kyle Decker[2], Sakibur Hasan[3], Angelos Halaris[4]*

[1]Michigan State University, 2Loyola Stritch School of Medicine, 3Western Michigan University Stryker School of Medicine, 4Loyola University Medical Center

Objective: Dysregulation of the immune system has emerged as an important contributor to the pathophysiology neuropsychiatric illness, including bipolar disorder (BD) and its treatment-refractory depressed form (TRBDD). As we develop a wider armamentarium for treating TRBDD, there is a need for objective biomarkers for stratifying patients by their propensity to respond to treatment, including with augmentation by inflammatory modulators (Halaris et. al 2020), The objective of this study is to characterize the relationship of systemic inflammatory burden with categorical and continuous clinical outcomes in TRBDD. To that end, our specific aims are to describe the relationship of baseline systemic inflammatory indices (constructed from markers in the complete blood count, or CBC) to (1) diagnosis of TRBDD compared to healthy controls (2) pre- and post-treatment

depressive severity after adjunctive celecoxib (COX-2 inhibitor) and (3) relationship to immune-metabolic biomarkers. **Methods:** This is a secondary analysis of biomarkers from our primary study (Halaris et. al 2020), which was a randomized, double-blind, placebo-controlled clinical trial of adjunctive celecoxib for TRBDD (total N=79, HC=32, TRBDD=37). Peripheral inflammatory indices were constructed from the CBC including the systemic inflammatory index (SII = neutrophils x platelets / lymphocytes) and the systemic inflammatory response index (SIRI = neutrophils x monocytes / lymphocytes). SIRI and SII were subjected to (1) group comparisons according to diagnosis and treatment arm and (2) univariate associations with pre- and post-treatment depressive severity (HAMD-17) and biomarkers. We modelled post-treatment depression (main outcome) according to baseline SII or SIRI, adjusted by pre-treatment depression and relevant covariates. **Results:** Inflammatory indices (SII or SIRI) were not distinguished by diagnosis or treatment arm. However, SIRI ($p=0.008$) and monocytes ($p=0.04$) were independently associated with pre-treatment HAMD-17. On multivariate modelling, post-treatment HAMD-17 was associated with pre-treatment SII in older patients ($p=0.001$), and SIRI in more depressed patients at baseline ($p < 0.001$), but no interaction with treatment arm. There were several significant associations with inflammatory indices and cytokines, chemokines, neurotrophic factors, and kynurenine pathway (KP) metabolites. **Conclusion:** There is a need for objective and economical biomarkers to assist in clinical assessment/treatment of neuropsychiatric illness, including TRBDD. These preliminary findings support the potential relevance of blood-based indices of peripheral inflammatory burden (monocytes, SII, and SIRI) as candidate pre-treatment indicators of treatment response, specifically for select subsets of TRBDD patients. Further, larger studies are needed to qualify these results. Once the utility of these blood-based biomarkers has been confirmed, it can also be used to stage and treat neuroprogression.

BIPOLAR SPECTRUM DISORDERS: THYROID PATHWAY GENETIC PROGNOSTIC MARKERS: IMPLICATIONS FOR ASSESSMENT, STAGING OF NEUROPROGRESSION AND TREATMENT

Andy Zamar**[1]*

[1] *The London Psychiatry Centre*

Objective: We aim to incorporate the assessment of SNPs and blood tests specific to those SNPs as well as the management using rTMS / HDT as a standard in the management of bipolar disorders particularly subthreshold presentations. Currently there are no confirmed results for the treatment of subthreshold bipolar disorder, which constitutes 60% of bipolar disorder with a prevalence of 2.5% in the United States. Furthermore, many patients with bipolar disorder 1 and 2 also present with subthreshold symptoms in between episodes and may indeed present only with disabling subthreshold symptoms while on treatment, such as mood stabilizers and antipsychotics which as a rule fail to induce full remission. The mortality of bipolar disorders is as high as circa 60% with 4 out of 10 dying of cardiovascular disease 10 years before the general population and 2 out of 10 dying of suicide and accidents. There is a very high disability rate which a WHO global study found to be higher than cancer, depression, heart disease, and epilepsy.

Methods: We present genetic findings in a cohort of 199 patients with SNPs in Deiodinase enzymes 1 and 2 and SLCO1C1 intracerebral thyroid protein transporter, as well as treatment outcomes in 2 cohorts (20 and 55 subjects). We explore the role of thyroid hormones on mitochondrial function, and the impact of the combined induction of neuroplasticity using rTMS and supraphysiological doses of Levothyroxine (HDT) and discuss their proposed mechanism of action. We also discuss the use of genetics and blood tests to predict tolerability and response to treatment.

Results: Patients achieved a long stable remission of depressive, hypomanic and mixed symptoms in Bipolar 1, 2 and BD-NOS with very few effects or disease burden. They were assessed using the Sheehan Disability Scale, a commonly used WHO scale to measure disease burden.

Conclusion: Precision medicine targeting treatments of mitochondrial dysfunction neuroplasticity provide a valid treatment option for bipolar disorders. The combination of HDT and rTMS is promising and well tolerated. Further studies of mitochondrial function before and after treatment and a randomized Controlled trial of the protocol are warranted. This is the first-time subthreshold symptoms / bipolar disorders are treated to full stable remission of an average of 2 years. The combination of inducing neuroplasticity and use of HDT is novel and may be a valuable tool in assessing the course of neuroprogression and possibly arresting if not reversing it. We are not aware of any guidelines to treat subthreshold symptoms and not even case reports, cohort studies or RCTs.

FROM NEUROPROGRESSION TO DISEASE MODIFICATION IN BIPOLAR DISORDER

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to identify the operative elements of the process of neuroprogression in order to identify clinical targets. The other objective is to define disease modification as a potential treatment effect and therapeutic goal.

Methods: Bipolar disorder progresses from an at-risk period, to the prodrome, a first episode, recurrence then chronicity. Along this path, the illness course and response patterns change, with poorer response in later stages where a greater risk of recurrence and more easily triggered recurrence are evident. There is both evidence of both progressive neurostructural change and cognitive decline aligned with a biological process of neuroprogression that appears to mediate this process.

Results: Many psychotropic agents, especially lithium, but also antidepressants and atypical antipsychotics impact the biological elements of the neuroprogressive cascade. Several repurposed and novel agents including N-acetyl cysteine, statins and anti-inflammatory agents such as statins and metformin may have neuroprotective potential. However the agent was the greatest evidence of ability to modify the clinical course the disorder is lithium. It's also likely that a state of remission regardless of how it is achieved is neuroprotective.

Conclusion: In conclusion it is important to identify disease modification as a realistic and important clinical task and to prioritise agents and clinical strategies that facilitate that goal.

3:30 p.m. - 5:00 p.m. Debate Session I -Stephen Lawrie and Deanna Barch

WHAT HAS NEUROIMAGING DONE FOR BIOLOGICAL PSYCHIATRY?

Stephen Lawrie[1]*

[1]*University of Edinburgh*

Objective: To seek out established facts from neuroimaging studies in people with major mental illness.

Methods: A systematic review of systematic reviews, augmented by adequately powered recent studies

Results: There are highly replicated demonstrations of reduced grey and white matter, hypofrontality and increased dopamine turnover in schizophrenia. These are related to key risk factors, pathophysiologies, symptoms and outcome measures - and show potential for early detection and prognostication. Comparatively little progress has been made in other conditions or in applying these findings to benefit patients. **Conclusion:** Neuroimaging studies tend to be small, noisy and underpowered, but have advanced our understanding of schizophrenia. Co-ordinated large international studies are required in other disorders and to make progress in usefully applying neuroimaging in clinical practice.

HOW HAS NEUROIMAGING HELPED US UNDERSTAND CLINICAL PREDICTION AND TREATMENT

Deanna Barch[*1]*

[1]*Washington University in St. Louis*

Objective: The goal of this debate is to discuss the ways in which neuroimaging has or has not helped us understand effective clinical prediction or treatment outcomes or treatment selection. This will include discussion of the relatively utility of neuroimaging in predicting the development of various forms of mental illness, the magnitude of effect sizes, and what type of data are needed to enhance such predictive utility. It will also include evidence that neuroimaging metrics can help us predict who will respond to treatment and who should be offered one treatment versus another.

3:30 p.m. - 5:00 p.m.
Symposia Concurrent IV

DYSREGULATIONS OF ENDOGENOUS AMINO ACIDS AND RELATED NEUROCIRCUITS IN PSYCHIATRIC DISORDERS

Hsien-Yuan Lane, Graduate Institute of Biomedical Sciences, China Medical University

Symposium Synopsis: Antipsychotic/D2 receptor occupancy triggers multiple trans-synaptic effects. Brain connectivity analysis based on key postsynaptic density proteins' expression (i.e., Homer1) is addressed in animal modeling to disentangle antipsychotics response. Patients' brain connectivity is tackled by novel 18FDG- PET approach to explore antipsychotics' response/resistance. The role of D-amino-acids in antipsychotics-resistance is also envisioned. Animal brain connectivity, patients' in vivo connectivity and metabolic marker altogether represent a multimodal strategy to understand antipsychotics resistance and highlight putative targets for novel treatments.

D-aspartate, an atypical amino acid, acts as an NMDAR agonist. Machine learning findings suggest a link between D-aspartate dysmetabolism and schizophrenia. We investigated serum levels of L-glutamate, D-serine, glycine, L- aspartate, and D-aspartate and found that, compared to healthy controls, schizophrenia patients had decreased D-serine and altered D-aspartate levels, thus confirming abnormal NMDA signaling in schizophrenia.

In addition to lower D-serine, higher D-amino acid oxidase (DAAO) expression/activity was observed in schizophrenia patients. Inhibiting DAAO (to slow D-serine degradation and enhance NMDAR) and multi-target drugs are promising for refractory schizophrenia. Sodium benzoate, targeting DAAO activator (G72)-DAAO-NMDA pathway, antioxidants-anti-inflammatory pathway, and sex hormones, improved clozapine-resistant schizophrenia in a placebo-controlled trial.

NMDAR activation plays critical roles in preventing neurodegenerative disorders. Serum DAAO increased with cognitive decline in elderly in cross-section and prospective studies, supporting hypo-NMDAR hypothesis of Alzheimer's disease. NMDAR enhancement via inhibiting DAAO improved cognition of early-phase Alzheimer's patients. Oxidative stress also leads to neurodegeneration. Glutathione, catalase, superoxide dismutase, etc. may also be implicated in neurodegeneration. Sodium benzoate's effects on antioxidants deserves further investigation.

TRANS-SYNAPTIC AND CONNECTIVITY EFFECTS OF ANTIPSYCHOTICS: IMPLICATION FOR TREATMENT RESISTANT SCHIZOPHRENIA AND ROLE OF D-AMINO ACIDS

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Objective: Treatment-resistant schizophrenia is a severe clinical condition affecting cognition and overall patient functioning. Therefore, there is a need to better understand the molecular basis of antipsychotics' action and to unveil new strategies for TRS. Dopamine D2 receptor occupancy, the main mechanism of action shared by all the available antipsychotics, may trigger multiple trans-synaptic effects strongly associated with dopamine-glutamate interaction. Here we address antipsychotics-dependent modulation of brain connectivity in a preclinical and clinical setting by multimodal imaging and its relevance in treatment-resistant schizophrenia.

Methods: 1) Brain connectivity analysis based on change of key glutamatergic postsynaptic density proteins' expression (i.e. Homer1, PSD.95) was analyzed in animal modeling to disentangle antipsychotics response, 2) Patients' brain metabolic pattern and connectivity were addressed by a18FDG- PET approach to explore brain metabolic related response or resistance to antipsychotics. 3)Structural MRI, TDI, and brain amino-acid in vivo quantitation by MRI spectroscopy were applied for multimodal analysis in a sample of adolescents responsive or resistant to antipsychotic treatment.

Results: 1) Brain networks showed differences in global efficiency and clustering coefficient. The" haloperidol network" showed enhanced interactivity between cortical and striatal regions, and within the caudate-putamen subdivision.

2) Restricted areas of significant bilateral relative hypometabolism in the superior frontal gyrus characterized TRS compared to non-TRS patients. Reduced parietal and frontal metabolism was associated with high PANSS disorganization factor scores in TRS ($P < .001$ voxel level uncorrected, $P < .05$ cluster level FWE-corrected).

3) significant increase of glutamate (absolute integral and ratio values) was detected in the cingulate cortex in TRS patients, compared to HCs (glutamate mean value: patients = 0.95, HCs = 0.66; $p < 0,001$; glutamate/creatine ratio: patients = 0.92, HCs = 0.6; $p < 0.001$)

Conclusion: Altogether, animal modeling of brain connectivity, in vivo brain metabolic detection, and connectivity in patients may suggest that 1) antipsychotics impact trans-synaptically the expression of glutamatergic postsynaptic density proteins and brain connectivity based on postsynaptic density immediate-early gene-based network analysis. 2) the response or resistance to antipsychotics is associated with different metabolism and connectivity in discrete brain regions.
3) Brain concentration of amino acids in patients as measured in vivo by MRI spectroscopy separate normal controls from schizophrenia patients and antipsychotic non-responsive to responsive patients. These changes may support a possible role for glutamatergic-based augmentation therapy such as D-amino acids, whose concentration was demonstrated to be altered in schizophrenia patients' post-mortem brains, enhancing the response to antipsychotics in treatment-resistant schizophrenia patients.

INVOLVEMENT OF THE PRENATAL D-ASPARTATE METABOLISM IN NEURODEVELOPMENTAL DISORDERS

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Objective: The atypical amino acid D-aspartate (D-Asp) acts as an N-methyl D-aspartate receptor (NMDAR) agonist. D-Asp has a peculiar spatiotemporal pattern of occurrence in the central nervous system (CNS) of mammals. Indeed, it is abundant throughout prenatal stages and decreases dramatically after birth in concomitance with the expression onset of the catabolic enzyme, D-

aspartate oxidase (DDO) Hence, D-Asp metabolism dysfunction might represent a putative candidate involved in glutamatergic-related neurodevelopmental disorders including schizophrenia (SCZ) and autism spectrum disorders (ASD). **Methods:** This symposium reviews the involvement of D-Asp metabolism dysregulation in neurodevelopmental disorders, including SCZ and autism spectrum disorders (ASD). **Results:** In line with a possible modulatory role of this endogenous NMDA agonist in modulating SCZ related phenotypes, we found that greater D-Asp brain levels in mice are able to attenuate PCP- induced PPI deficits and cerebral activity dysfunction, measured by functional magnetic resonance imaging (fMRI). In addition, consistent with its involvement in NMDA related processes, we have also shown that D-Asp modulates CNS metabolome, as assessed by nuclear magnetic resonance (NMR)- based analysis in mice brain during development. Beyond preclinical results, recently we documented the first clinical case of a young patient with severe intellectual disability (ID) and autism spectrum disorders (ASD)-related symptoms harboring a DNA duplication of 127.8 kb on chromosome 6, including the entire DDO gene. Interestingly, we found that constitutive DDO overexpression and the resulting cerebral D-Asp depletion induce cognitive and social recognition abnormalities and smaller cortical grey-matter volume in adult Ddoov mice, associated with reduced number of dorsal pallium neurons during corticogenesis. In agreement with the involvement of D-Asp in modulating cortical phenotypes, we documented that a human DDO gene variant (rs3757351) leading to lower mRNA expression in the cortex of healthy subjects is associated with increased prefrontal grey matter and prefrontal activity during working memory tasks, as measured by fMRI. Further supporting a possible involvement of D-Asp metabolism in the modulation of cortical processes related to NMDAR signaling, we recently evidenced that a machine learning hypothesis-free algorithm included D-Asp/total Asp ratio within a stable molecular cluster discriminating SCZ patients from non-psychiatric controls in the post-mortem dorsolateral PFC. Remarkably, this observation mirrors a significant 30-40% reduction in D-Asp levels found in the PFC of two post-mortem cohorts of SCZ patients, compared with non-psychiatric subjects. **Conclusion:** Altogether, our findings unveil an intriguing influence of early D-Asp metabolism in the regulation of neurodevelopmental processes and, consequently, provide a translational significance to metabolic D-Asp deregulations as a possible signature of neurodevelopmental psychiatric disorders, including SCZ and ASD.

NOVEL TREATMENT WITH MULTI-TARGETS FOR CLOZAPINE-RESISTANT SCHIZOPHRENIA: MODULATION OF NMDA RECEPTOR, D-AMINO ACIDS, AND RELATED PATHWAYS

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Objective: NMDA receptor (NMDAR) hypofunction is implicated in schizophrenia. Compared with healthy controls, schizophrenia patients had lower D-serine levels in CSF and blood, and higher blood levels of D-amino acid oxidase (DAAO) (Lin et al., Front Bioeng Biotechnol 2020) and DAAO activator (DAOA, or named G72) (Lin et al., Mol Psychiatry 2014). For discovering novel NMDAR enhancers to improve schizophrenia treatment, D-serine and other NMDAR co-agonists were examined in randomized, double-bind, placebo-controlled clinical trials (RDCs), albeit with mixed results. The second route, inhibition of glycine transporter-I, showed promising potential in improving clinical symptoms and cognitive function of schizophrenia (Lane et al., Arch Gen Psychiatry 2005; Chang et al., J Psychopharmacol et al., 2020; Fleischhacker et al., Lancet Psychiatry 2021). However, these strategies have failed in the treatment for the most resistant (clozapine [the last-line antipsychotic agent] resistant) schizophrenia patients (Goff et al., CNS Spectr 2001; Lane et al., Biol Psychiatry 2006). For potentially better treatment, the third avenue is inhibition of DAAO for slowing D-serine

degradation and thereby enhancing NMDAR function (Kuo et al., CNS Drug 2022; Cheng et al., Neuropsychopharmacology 2023). Moreover, multi-target drugs are a promising approach against refractory schizophrenia (Lin et al., Curr Drug Targets 2020). **Methods:** This symposium reviews current status of clinical trials and related mechanisms for treatment-resistant, including, clozapine-resistant schizophrenia. We also address future directions in developing better treatments for the hardest-to-treat schizophrenia. **Results:** We are the first group to discover that sodium benzoate, a pivotal DAAO inhibitor, is more efficacious than other NMDAR enhancers (Chang et al., J Psychopharmacol et al., 2019; Lin et al., Int J Neuropsychopharmacol 2022). In initial RDCs, sodium benzoate improved cognitive function of patients with chronic schizophrenia, no matter it improved clinical symptoms or not (Lane et al., JAMA Psychiatry 2013, Lin et al., World J Biol Psychiatry 2017). Later, benzoate also improved both positive and negative symptoms of clozapine (the last-line antipsychotics)-resistant schizophrenia patients in a RDC (Lin et al., Biol Psychiatry 2018). While the underlying mechanisms require more studies (Huang et al., Neurochem Res 2023), sodium benzoate has been found to possess multi- targets on the NMDA pathway, the antioxidants-anti-inflammatory pathway, and sex hormones (Lin et al., Biol Psychiatry 2018; Lin et al., JAMA Netw Open 2021; Lane et al., Psychiatry Clin Neurosci 2023). In addition to sodium benzoate, other DAAO inhibitors are promising; for example, luvadaxistat was found to be able to improve cognitive function of schizophrenia patients (Kuo et al., CNS Drugs 2022). Furthermore, combination of benzoate and brain stimulation deserves more studies too (Lane et al., Psychiatry Res 2023). **Conclusion:** If these findings can be reconfirmed, modulation of NMDAR, D-amino acids, and related pathways may instill hope for the treatment of the most resistant schizophrenia. However, 6-week benzoate treatment (at doses of 1 and 2 gm/day) still didn't improve cognitive function of clozapine- resistant patients (Lin et al., Biol Psychiatry 2018). More novel approaches are needed to develop effective therapies for the cognitive dysfunction in clozapine-resistant patients (Lin and Lane, Schizophr Res 2023 [Invited Commentary]).

THE CHANGES OF D-AMINO ACIDS AND NMDA RECEPTOR MODULATORS IN NEURODEGENERATION

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Objective: Glutamate NMDA receptor (NMDAR) activation plays a critical role in cognitive function. Dysregulation of NMDAR is the core of neurodegenerative mental disorders (Lin et al., Curr Pharm Des 2014). As the agonist or co-agonists of NMDAR, D-glutamate, D-serine, and D-alanine differ in their roles in cognitive decline in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) (Lin et al., Pharmacol Biochem Behav 2019). The clinical implications of the changes of D-amino acids and modulators of NMDAR in neurodegeneration deserve studies.

Methods: This symposium reviews the roles of D-amino acids in neurodegeneration as well as the effects of NMDAR modulators in neurodegenerative disorders.

Results: Previously, D-serine levels have been found to be altered in the AD patients. We recently found that peripheral blood levels of D-glutamate were associated with cognitive impairment, therefore a potentially suitable peripheral biomarker for MCI and AD (Chang et al., Psychopharmacol 2021). Of note, serum D-amino acid oxidase (DAAO) levels were significantly associated with D-glutamate and D-serine levels (Lin et al., Sci Rep 2017). Further, DAAO levels increased with the severity of the cognitive deficits in elderly individuals in a cross-section study (Lin

et al., Sci Rep 2017) and a prospective study (Lin and Lane, Int J Neuropsychopharmacol 2022), thereby supporting the hypo-NMDAR hypothesis of Alzheimer's disease (AD). DAAO activator (DAOA, or G72) levels also increase in patients with early phase of AD (Lin et al., Sci Rep 2019). Combination of G72 and cystine/glutamate antiporter SLC7A11 in blood can sensitively and specifically diagnose AD (Lane and Lin, Int J Neuropsychopharmacol 2022). Glutathione, catalase, superoxide dismutase and other endogenous antioxidants may also play important roles in the process of neurodegeneration (Chiang et al., Clin Psychopharmacol Neurosci 2021; Lin and Lane, Antioxidants 2021). NMDAR enhancement via inhibiting DAAO activity by sodium benzoate can improve cognitive function of patients with early-phase AD or late-life depression (Lin et al., Biol Psychiatry 2014; Lane et al., Psychiatry Clin Neurosci 2022; Lin et al., Int J Neuropsychopharmacol 2022) and alter brain activity in MCI patients (Lane et al., Int J Neuropsychopharmacol 2021), while raising blood levels of two endogenous antioxidants, glutathione and catalase (Lane et al., Psychiatry Clin Neurosci 2022). Sodium benzoate also improved cognitive function of women with behavioral and psychological symptoms of dementia (BPSD) with increased estradiol to follicle-stimulating hormone ratios in blood (Lin et al., JAMA Netw Open 2021).

Conclusion: If these findings can be reconfirmed, several potential biomarkers can aid in the diagnoses of neurodegenerative disorders and modulation of NMDAR through inhibition of DAAO may be a novel approach for the treatment of these disorders. In addition, the effects of sodium benzoate on endogenous antioxidants and sex hormones and their roles in precision medicine deserve more studies.

IMMUNE-METABOLIC DYSFUNCTION IN MENTAL DISORDERS: AN UPDATE ON CURRENT EVIDENCE

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Symposium Synopsis: There has been increasing interest in the role of immune-metabolic dysfunction in the pathophysiology of mood and psychotic disorders. Replicating evidence suggests that individuals with mental disorders are more prone to chronic inflammatory illnesses, and metabolic syndrome. Even in the absence of physical illness, individuals with mental disorders display altered levels of peripheral inflammatory markers. Given these associations, several clinical trials have evaluated repurposed agents targeting immune-metabolic pathways in depression, bipolar disorders and psychosis, with mixed results. In order to advance the field of immunopsychiatry, it is important to identify specific subtypes of mental disorders that would benefit from these repurposed agents. Further research is needed to determine specific behavioural symptom subsets that are prevalent among patients with mental disorders and concurrent immune-metabolic dysfunction. The aim of the proposed symposium is to provide an update on evidence for immune-metabolic subtypes of mood and psychotic disorders. We will present synthesized data from observational studies that provide insights into potential pragmatic molecular and genetic biomarkers of "inflamed" subtypes of depression and psychosis. In addition we will present results from recent clinical trials of lipid lowering agents and anti-inflammatory drugs as add-on treatments for treatment-resistant depression and schizophrenia-spectrum disorders. Finally, we will make recommendations for innovative trial designs that may enhance clinical translation of transdiagnostic treatments that target immune-metabolic dysfunction across mental disorders.

UNDERSTANDING THE POTENTIAL ROLE OF INFLAMMATORY MARKERS IN NEUROPROGRESSION ACROSS THE CLINICAL STAGES OF BIPOLAR I DISORDER

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Objective: In Bipolar Disorder (BD), illness progression has been linked to worse treatment outcomes and cognitive/functional impairment. Multiple instances of the disease may have the ability to cause neuronal systems to change permanently, according to the kindling model. In contrast to the West, the clinical course of BD-I in India is mania-dominant and is linked to increased intellectual loss and poor functionality. Our study was planned to examine and compare the serum levels of immuno- inflammatory, across different clinical stages of BD-I High risk, early BD, and multiple episode BD (stage 1-3) and healthy controls (HC) **Methods:** Our research was cross-sectional and involved the following groups: high-risk participants (BD-I-Stage 1), early BD-I (First episode), established BD-I (Stage 3), and age- and gender-matched healthy controls (HC). The inflammatory markers that we compared across groups were Interleukin (IL)-1β, IL-6, and Tumor necrosis factor (TNF)-α measured on a Bioplex 200 platform utilizing a multiplex suspension array and soluble TNF receptors 1 and 2 (sTNFR-1 and 2) measured using sandwich enzyme-linked immune-sorbent assay technique. SPSS-16/R software was used to do the statistical analysis. Kruskal Wallis was used to compare the inflammatory markers. **Results:** We recruited a total of 172 subjects, with 43 in each group. In the total sample, we had 100 males and 72 females. There was no group difference in gender noted. The age at assessment there was a group difference (p LESS THAN 0.001), the ME group had a higher age than the other three, who did not differ from each other. The two BD groups did not show any difference in the age of illness onset or the onset of the first episode of mania (p=0.56), family history of psychiatric illness (p=0.11), and duration of remission (p=0.10). There was a significant difference in the duration of illness the ME group by definition had a longer duration of illness compared to FEM ($p < 0.001$). In terms of the inflammatory markers, IL-1β (p=0.66) and TNF-α (p=0.44) levels did not show any group difference. IL-6 levels were significantly higher among the ME and FE-BD groups compared to the controls (h=11.26, p=0.01). ME group also had higher levels than the HR group. sTNF- R1 levels were significantly higher among the ME group compared to the FE, HR, and control groups (h=14.35, p=0.002). These three groups did not show any difference. sTNF-R2 levels were significantly higher (h=29.87, $p < 0.001$) in the patient group (ME and FEM) compared to the non-patient group (HR and HC). **Conclusion:** The important findings of the increased levels of sTNFR-1 in ME compared to FE suggest that the higher the no of manic episodes, the higher the levels of inflammatory markers like sTNFR- 1. The high-risk group did not show any difference from the control group which suggested that probably the inflammatory pathway gets involved after the disease onset. We also noted increased levels of sTNFR-2 in the BD patients compared to high-risk and controls, but no difference between the ME and FE groups. These two are important proteins that are activated in the process of apoptosis (cell death). This is one of the mechanisms of how neuroprogressive changes occur in the brain. This study emphasizes the need for longitudinal studies to evaluate these markers across the stages of BD and establish them as biomarkers of neuroprogression and staging.

NEUTROPHIL EXTRACELLULAR TRAPS (NETS): A NOVEL CELLULAR-BASED MECHANISM IN SCHIZOPHRENIA AND THE IMPLICATIONS OF EARLY-LIFE ADVERSITIES

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Objective: Previous studies using blood cytokines to stratify patients with schizophrenia suggest that only a subset presents a low-grade inflammatory state. However, these studies have not addressed whether environmental factors such as childhood maltreatment contributed to identifying

inflammatory clusters. Moreover, a neutrophil-related mechanism (NETs) has never been investigated in the field. We investigated NETs as a novel biological mechanism in early schizophrenia and their role together with interleukin-(IL-6) and childhood maltreatment in identifying cluster subgroups. **Methods:** Clinical study: We used data available from the STREAM study, a case-sibling-control investigation conducted in the Ribeirão Preto catchment area (São Paulo, Brazil). The sample included individuals with early-stage schizophrenia spectrum (n=78), sex and age-matched controls (n=78), and unaffected siblings of patients (n=25). Childhood maltreatment was evaluated using the Childhood Trauma Questionnaire. NETs and IL-6 in plasma were evaluated using the Quant-iT PicoGreen kit and multiplex, respectively. Fresh neutrophils were isolated from healthy donors to test the effect of antipsychotic drugs (haloperidol or risperidone) on NETs release in vitro. Group differences on NETs and IL-6 were evaluated using general linear models with Bonferroni post-hoc, adjusted for sex, body mass index (BMI), tobacco smoking, and psychoactive substance use. Two-way ANOVA with Bonferroni post-hoc was used to test the effect of antipsychotics on NETs in vitro.To identify clusters, we applied unsupervised two-step clustering analyses with Bayesian Criterion to estimate the maximum number of clusters after integrating values of NETs, IL-6, and childhood maltreatment scores. Rodent model: Juvenile male Sprague-Dawley rats (postnatal day, PND 24) were exposed to an adolescent early stress protocol (a combination of daily inescapable footshock from PD31-40, and three restraint stress sessions, PD31, 32, and 40) or left undisturbed (controls). At PN51, NETs and IL-6 were evaluated in serum. We also measured levels of NETs released from fresh neutrophils isolated from rats' bone marrow. **Results:** We found increased NETs levels in patients with early schizophrenia compared to their unaffected siblings and community controls ($F=50.79, df=2, p < 0.001$). Using an in vitro assay, we showed that haloperidol and risperidone do not induce but inhibited NETs release from stimulated neutrophils. Using unsupervised two-step clustering analysis, we identified two main clusters; childhood maltreatment scores and NETs were the most important variables contributing to cluster separation (high-CL1 and low-CL2). Patients with high-CL1 (61.5%) had significantly higher childhood maltreatment scores ($F=26.23, df=5, p < 0.001$), NETs ($F=25.17,5, p < 0.001$), and IL-6 ($F=3.87, df=5, p < 0.002$) levels than the remaining groups. Using a rat model based on stress exposure, we found that adolescent stressed rats had higher NETs ($t16=5.18, p < 0.001$) and IL-6 ($t10=6.33, p < 0.001$) levels in serum compared to non-stressed rats, with a tendency to produce more NETs from the bone marrow. **Conclusion:** We demonstrate for the first time a novel cellular mechanism in schizophrenia that suggests neutrophils are in an active and functional state. We further suggest that NETs and early stress should be considered in future studies aiming to identify immune biological subgroups for more personalised treatments.

EXPLORING IMMUNE-INFLAMMATORY MARKERS IN RESPONSE TO ADJUNCTIVE MINOCYCLINE TREATMENT FOR DEPRESSION.

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Deakin University

Objective: These series of studies aimed to explore the underlying biological response reflecting the clinical improvement seen in participants who took part in a clinical trial of adjunctive minocycline. Markers in the kynurenine pathway and associated inflammatory markers were explored.

Methods: A randomised placebo-controlled trial of adjunctive minocycline (200 mg/day) for people with major depressive disorder (n=71) was conducted and blood samples were collected at baseline

and the end of the treatment phase (week 12). Serum samples were analysed by the Karolinska Institutet and Deakin University to determine levels of biological makers. **Results:** Following correction for false discovery rates, changes in complement C3, IL-1Ra, IL-8/CXCL8, and ICAM-1 were found to be associated with changes in depression scores following adjunctive minocycline treatment. We have new data available on RAGE pathways that we expect to also present at the meeting. **Conclusion:** There has been considerable exploration of individual markers of treatment response in depression. This has led to heterogenous outcomes and difficulties in understanding the specificity of markers in predicting response to treatment. This study used a multi-marker approach to explore the kynurenine pathway to provide a more comprehensive understanding of the treatment response to adjunctive minocycline treatment. These studies provide valuable information alone, but moreover are contributing to a larger study encompassing multipole markers, disorders and therapeutic agents.

EFFICACY OF METHOTREXATE POINTS TO IMMUNE DYSFUNCTION IN PSYCHOSIS

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Objective: There is growing evidence implicating inflammatory processes in the pathogenesis of schizophrenia. NMDA receptor encephalitis presenting as schizophrenia suggests the possible role of cell-mediated immune processes. Several inflammatory cytokines including IL-2, IFN-gamma, TNF-alpha and soluble IL-2 receptor may be elevated in schizophrenia relapse and reduced in remission. In this presentation we will summarise evidence for the use of novel anti-inflammatory agents in the treatment of schizophrenia with a focus on methotrexate.
Methods: We tested if low-dose methotrexate as used in the treatment of systemic autoimmune disorders would be tolerable and effective in people with schizophrenia in a feasibility double-blind randomized control trial. Ninety-two participants within 5 years of schizophrenia diagnosis were randomised to receive once weekly 10mg oral methotrexate (n = 45) or matching placebo (n = 47) both with daily 5mg folic acid, in addition to treatment as usual for 12-weeks.
Results: There were eight dropouts per group. Side effects were non-significantly more common in those on methotrexate and were not severe. One person developed leukopenia. Positive symptom scores improved more in those receiving methotrexate than placebo (β = −2.5; [95% CI −4.7 to −0.4]), whereas negative symptoms were unaffected by treatment (β = −0.39; [95% CI −2.01 to 1.23]).
Conclusion: We conclude that further studies are feasible but should be focussed on subgroups identified by advances in neuroimmune profiling. Methotrexate is thought to work in autoimmune disorders by resetting systemic regulatory T- cell control of immune signalling; we show that a similar action in the CNS would account for otherwise puzzling features of the immuno-pathogenesis of schizophrenia.

INNOVATION IN OPIOID AGONIST THERAPY AND WITHDRAWAL MANAGEMENT

Marc Vogel, Psychiatric University Clinics Basel

Symposium Synopsis: The ongoing epidemic of opioid use disorder (OUD) remains one of the biggest public health problems in the world. Recent years have brought rising numbers of opioid overdose deaths particularly in North America but also in European countries and Australia. The increasing role of ultrapotent opioids such as fentanyl challenges conventional treatment practice. Opioid agonist therapy (OAT) constitutes the treatment of choice but has often not been able to reach vulnerable

populations. Furthermore, retention rates in many parts of the world remain insufficient. The implementation of innovative and patient-centered measures is needed. **Methods:** In this symposium, we present promising new and innovative methods aiming to improve withdrawal management, induction and delivery of OAT. **Results:** Opioid agoinists have different side effect profiles which may allow a patient-centered choice of medication. Buprenorphine microdosing is an innovative approach suitable for inpatient and outpatient initiation of buprenorphine OAT without the need for preceding withdrawal symptoms as in conventional induction. Symptoms inhibited fentanyl induction is an intervention to determine opioid tolerance and rotate patients on a dose of full mu-opioid-agonists suitable for OAT in the course of one day. Nasal diacetylmorphine is a new treatment option for patients not responding to oral OAT, or patients in injectable OAT transferring to a less harmful alternative. **Conclusion:** The OUD epidemic requires an expansion and further development of treatment options. There are several promising innovations in OAT suitable to improve withdrawal symptoms, treatment induction and delivery, expanding treatment access for populations not reached with current treatment methods.

NASAL OPIOID AGONIST TREATMENT

Marc Vogel**1*

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Psychiatric University Clinics Basel

Objective: Not all patients with opioid use disorder respond to oral opioid agonist treatment (OAT). Therefore, other routes of administration have been successfully introduced, e.g. injectable or smokable diacetylmorphine. However, these routes are associated with a higher risk of adverse events. Nasal OAT is a new treatment option likely associated with fewer risks and suitable to reach patients primarily sniffing opioids but not stabilizing in oral OAT.

Methods: We present the method of nasal application and data from an ongoing multicenter prospective observational cohort study accompanying the introduction of nasal OAT in Switzerland's heroin assisted treatment (HAT) centers.

Results: As of 2023, 139 patients of 16 centers initiated nasal HAT, the majority of which were male. Main reason for switching to the nasal route were sniffing being the preferred route of administration, and patients on diacetylmorphine (heroin) tablets desiring a more rapid onset of effect. At 4 and 52 weeks, 88% and 53% respectively were still prescribed the nasal route of administration. Additional substance use remained largely unaltered. Adverse events were rare, and treatment satisfaction was high among those remaining in the nasal route.

Conclusion: Nasal OAT seems to be a viable treatment option for a subpopulation of patients in HAT. It is associated with few adverse events. With switching routes of administration being common in Swiss HAT, patients with higher satisfaction remained with the nasal route. Further research is required on optimizing the application method and to determine which subpopulaton is likely to benefit from nasal OAT.

RAPID LOW-DOSE BUPRENORPHINE INDUCTIONS & SYMPTOM-INHIBITED HYDROMORPHONE & FENTANYL INDUCTIONS

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Objective: The high prevalence of fentanyl and its analogues in the unregulated drug supply has led to tragic levels of mortality and morbidity in North America and Europe, posing challenges in the clinical management of opioid use disorder due to escalating opioid tolerances. We will share our experiences with the development, implementation, and evaluation of innovative opioid withdrawal

management and opioid agonist treatment (OAT) approaches in Vancouver, the epicentre of the overdose crisis in Canada. **Methods:** We will present our low-dose buprenorphine induction protocols, which involve the administration of small, frequent does of buprenorphine, eliminating the need for a prior period of withdrawal and opioid abstinence. We will also present our pharmacokinetically-guided protocols utilizing hydromorphone and fentanyl to manage withdrawal, facilitate rapid methadone and slow- release oral morphine initiation, and promote adherence to medical treatment. **Results:** We will teach our protocols utilizing practical real-life cases and patient testimonial videos. We will share our results from clinical trials and retrospective chart reviews, and our experiences in the implementation of our protocols. **Conclusion:** Participants will gain a comprehensive understanding of the current landscape of opioid use disorder, overdose fatalities, and withdrawal management and OAT approaches to treat patients who use unregulated fentanyl and its analogues.

SIDE EFFECTS OF DIFFERENT AGONISTS IN OPIOID AGONIST TREATMENT - SYSTEMATIC REVIEW AND META-ANALYSIS

Maximilian Meyer**1*

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Objective: Opioid agonist treatment (OAT) is the treatment of choice for opioid use disorder. Most often, methadone or buprenorphine are used. However, coverage rates are fairly low and conventional OAT does not reach large parts of the target population. In order to expand treatment access and allow a more patient-centered approach, other opioid agonists such as diacetylmorphine or slow-release morphine, and other routes of administration (injectable, depot) have been introduced. With similar retention rates, the choice of opioid agonist in the future will be guided by the side effects profile.

Methods: We present data of a meta-analysis of side effects in randomized controlled trials of different opioid agonists for treatment of opioid use disorder.

Results: We identified 181 studies, 25 of which were included for potential meta-analysis. Reported opioid agonists were methadone, LAAM, methadyl acetate, buprenorphine, buprenorphine/naloxone, slow-release morphine (SROM), diacetylmorphine, hydromorphone, opium tincture. Where groupe meta-analysis was possible, buprenorphine (all formulations combined) was associated with less risk of sedation than methadone (RR 0.68; 95% CI 0.56-0.82), SROM with higher risk (0.63; 0.58-0.69). Methadone had a lower risk of nausea (0.56; 0.37-0.85) and sweating than methadyl acetate (0.73; 0.59-0.90). Some known side effects were not systematically reported although highly relevant for clinical practice, e.g. sexual dysfunction or QTc-prolongation.

Conclusion: Overall, the quality of side effect reporting in many studies was low and insufficient. Our results challenge some traditional clinical teaching about side effects (e.g. in direct comparison, the risk for sweating was not lower for buprenorphine than for methadone). Future research should actively investigate side effects given their importance for a patient-centered treatment decision. This is particularly true for side effects such as sexual dysfunction and QTc-prolongation, which have high clinical relevance but were not systematically reported at all.

APPLYING PERSONALIZED MEDICINE TO BIPOLAR DISORDER

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: Patients with bipolar disorder (BD) urgently need personalized, data-driven treatments guided by empirically validated predictive biomarkers. In this symposium, we will provide an inspiring overview of cutting-edge, biomarker-driven approaches to precision medicine in BD.

These will include biomarkers as predictors of treatment response, and the application of cutting-edge network analysis methods. First, markers of the gut-brain axis (intestinal permeability, intestinal inflammation and microbiome) will be reviewed as potential biomarkers of treatment response to probiotics. Second, gene expression studies to evaluate CHOP, a pro-apoptotic endoplasmic reticulum stress marker, and ELISA assays to assess mesencephalic astrocyte-derived neurotrophic factor (MANF) levels in BD patients and controls will be reviewed as biomarkers of response to intranasally administered MANF. MANF is an ER resident protein that promotes cellular resilience. Third, an overview of Th17 cells as a potential target for precision medicine approaches will be reviewed. Finally, causal discovery modeling (CDM) will be introduced as a method for interrogating mania and depression symptom networks to identify high-value treatment targets and BD subtypes. CDM uses a combination of graph theory and machine learning to identify central symptoms – those with the densest causal relationships to other symptoms in symptom networks. It offers the promise of a data-driven approach to determining the richest treatment targets and identifying subgroups of patients with different network structures. The symposium will conclude with a discussion of the promise and challenges of data driven discovery of treatment biomarkers and potential future directions.

USING CAUSAL DISCOVERY MODELING TO INTERROGATE MANIC AND DEPRESSIVE SYMPTOM NETWORKS IN BIPOLAR DISORDER

David Bond**1*, *Rahul Mehta2, Kathleen Miley3, Erich Kummerfeld4*

[1]Johns Hopkins University School of Medicine, 2University of Minnesota, 3Health Partners Institute, [4]Institute for Health Informatics, University of Minnesota

Objective: Network theory proposes that psychiatric syndromes like depression and mania are networks of causally interacting symptoms. Depression and mania are triggered when the activation of one symptom leads to activation of the network via the web of causal relationships between symptoms. Feedback loops between symptoms lead to persistent network activation, making episodes self-sustaining. Persistent network activation is most likely in dense (highly interconnected) networks and when central symptoms (those with numerous connections to other symptoms) are activated.

Methods: Causal discovery modelling (CDM) combines causal modeling theory, graph theory, statistics, and machine learning to generate inferences about causal relationships between symptoms in symptom networks. We used CDM to identify causal relationships in manic and depressive symptom networks. We searched the National Database of Clinical Trials for studies that used the Young Mania Rating Scale and Montgomery-Asberg Depression Rating Scale to measure manic and depressive symptoms in bipolar disorder. We used the Greedy Fast Causal Inference (GFCI) algorithm, implemented in Tetrad 6.9, to learn a partial ancestral graph (PAG) of causal relationships.

Results: We obtained data from 19 studies (N=7269). The manic and depressive symptom networks were both densely connected, especially the depressive network. Feedback loops were identified in both networks. Irritability was an important bridge symptom with dense causal relationships to both the manic and depressive networks.

Conclusion: These findings suggest hypotheses about how causal relationships in manic and depressive symptom networks lead to the perpetuation of mania and depression; and why mania and depression can co-occur.

INTRANASAL MESENCEPHALIC ASTROCYTE-DERIVED NEUROTROPHIC FACTOR (MANF) AS A NOVEL TREATMENT FOR BIPOLAR DISORDER

Benicio Frey**1*, *Mohammad Ali2, Bianca Wollenhaupt-de-Aguiar2, Todd Hoare2, Ram Mishra2*

[1]*Canadian Network for Mood and Anxiety Treatments, 2McMaster University*

Objective: Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an endoplasmic reticulum (ER) resident protein that promotes cellular resilience through modulation of ER stress response. We have recently found that lithium promotes ER homeostasis by increasing MANF gene expression (Abu-Hijleh et al., 2021). Our objective is to develop a new treatment option for individuals with bipolar disorder (BD) using hydrogel intranasal spray to administer MANF, and to further investigate the ER stress response pathway in the blood and postmortem brain tissue of individuals with BD.

Methods: Intranasal delivery of MANF was developed using functionalized starch nanoparticle carriers integrated into a mucoadhesive nanoparticle network hydrogel spray. Intranasal MANF is being tested in an animal model of mania. Gene expression was used to evaluate CHOP, a pro-apoptotic ER stress marker, and ELISA assays to assess MANF levels in the serum of 40 individuals with BD and 55 healthy controls, as well as in postmortem hippocampus brain tissues from 20 BD and 19 controls.

Results: The intranasal delivery of MANF is currently being evaluated in animal models to determine the efficacy of nose-to-brain delivery. Serum MANF protein levels were reduced in individuals with BD in a current depressive episode when compared to individuals with BD in euthymia (p=0.013) and controls (p=0.031). CHOP expression was increased in postmortem hippocampus brain tissues of individuals with BD (P LESS THAN 0.05).

Conclusion: These findings provide further evidence of the association between ER stress and BD.

INTESTINAL MARKERS TO PREDICT THE TREATMENT OUTCOME OF PROBIOTICS IN BIPOLAR DISORDER AND PSYCHOTIC DISORDERS

Magdalini Ioannou**1*, *Jenny Borkent1, Sergio Andreu-Sánchez1, Jingyuan Fu1, Iris Sommer1, Bartholomeus C.M. Haarman1*

[1]*University Medical Center Groningen*

Objective: Abnormal immune responses have been reported in patients with bipolar disorder (BD) and psychotic disorders (PD). What lies at the root of the immune system aberrations, however, is still unclear. Intestinal permeability aberrations and inflammation, along with alterations in the intestinal microbiota, may be a significant factor driving the immune dysregulation in these disorders. Probiotics are thought to be promising candidates to improve patients' symptomatology and functioning using lifestyle interventions. What makes these interventions especially relevant is that there are rational methods to personalize their application with biomarkers that measure intestinal inflammation, microbiome, and permeability.

In a novel randomized controlled trial (RCT) (GUTS, SMRI 18T-004, ZonMw 636320010), we investigate whether intestinal permeability improving probiotics influence symptom severity and cognition in patients with BD or PD, and whether we can personalize treatment with measurements of intestinal inflammation, permeability, and microbiome.

In this presentation we will present for the first time the baseline measurements of this thought-provoking study.

Methods: For this analysis, the baseline measurements of 130 patients that participate in the GUTS RCT and 130 healthy controls matched for age, sex, BMI and income were investigated. Measurements of intestinal inflammation (fecal calprotectin, alpha-antitrypsin), intestinal permeability (LPS binding protein, soluble CD14, serum zonulin and fecal zonulin) were performed using standard ELISA procedures. Intestinal microbiome analysis was performed using metagenomic shotgun sequencing.

Results: Analysis results will be available in March 2023 and will be presented for the first time during the conference. **Conclusion:** The results will be discussed in reflection to the applicability for future treatment personalization for gut targeting treatments for BD, e.g. probiotics, prebiotics and diet interventions.

TH17 CELLS: A POTENTIAL TARGET FOR PRECISION MEDICINE APPROACHES FOR BIPOLAR DISORDER

Carmen Schiweck*[1], *Magdalini Ioannou[2], Benno Haarman[2], Hemmo Drexhage[3]*

[1]Goethe University Frankfurt, [2]University Medical Center Groningen, [3]Erasmus MC Rotterdam

Objective: Patients with Bipolar Disorder (BD) have increased numbers of the pro-inflammatory, and potentially pathogenic T helper (Th)-17 cells (1,2). Interestingly, interleukin (IL)-17A, the major cytokine produced by Th17 cells, has also been associated with suicidality and inflammation in major depressive disorder, but to our knowledge this association has not yet been explored in BD. In addition, it has been shown that short chain fatty acids such as butyrate can reduce IL-17A production by Th17 cells and thereby reduce their pathogenicity, but to date, the effect on Th17 cells of patients with BD is unknown. The aim of this research was two-fold: first, we aimed to explore the association of Th17 cells with specific symptoms of patients with BD for the first time. Second we aimed to investigate the effect of short chain fatty acids on IL-17 production in Th17 cells of patients with BD and healthy controls to their efficacy as new and innovative, potential immunomodulatory strategy.
Methods: Th17 cell numbers and suicidality were assessed in 201 patients with a diagnosis of BD and 140 controls of the MOODINFLAME and GEPRO cohorts. Th17 cells were measured using fluorescence-activated cell sorting and confirmation of BD diagnosis and suicidality was assessed with the MINI neuropsychiatric Interview. Analysis of covariance was performed on Th17 cells, with suicidality as grouping variable, age, sex and BMI as covariates. For the in-vitro experiment, peripheral blood mononuclear cells (5 patients with BD, 8 controls, data collection ongoing) were harvested using Ficoll density gradient centrifugation. Naïve CD4+ T cells were extracted, cultured and differentiated to Th17 cells. IL-17 production was measured in cells exposed to butyrate or only medium.
Results: Patients with BD had higher Th17 cells compared to controls. High risk of suicide was rare in this predominantly euthymic patient group. Results regarding stratification according to sample characteristics including suicidality are currently being analysed and will be presented at the conference for the first time. Preliminary results of cell culture experiments revealed a strong reductive effect of butyrate on IL-17 production in Th17 cells (p LESS THAN 0.05).
Conclusion: Th17 cells are higher in patients with BD, and possible associations with suicidality will be presented. Results on short chain fatty acid exposure indicate a potential beneficial role on Th17 cell pathogenicity.
References: 1. Becking K, Haarman BCM, Grosse L, Nolen WA, Claes S, Arolt V, et al. (2018): The circulating levels of CD4+ t helper cells are higher in bipolar disorder as compared to major depressive disorder. J Neuroimmunol 319: 28–36.
2. Vogels RJ, Koenders MA, van Rossum EFC, Spijker AT, Drexhage HA (2017): T Cell Deficits and Overexpression of Hepatocyte Growth Factor in Anti-inflammatory Circulating Monocytes of Middle-Aged Patients with Bipolar Disorder Characterized by a High Prevalence of the Metabolic Syndrome. from Frontiers in Psychiatry, vol. 8. Retrieved https://www.frontiersin.org/articles/10.3389/fpsyt.2017.00034

PERSONALIZED TREATMENT OF BIPOLAR DISORDER

Martin Alda, Dalhousie University

Symposium Synopsis: There is a growing recognition that management of psychiatric disorders needs to be tailored to individual patients and their clinical and biological profiles -- in contrast to the common practice of trial-and-error. To optimize treatment decisions, psychiatry needs to identify reliable markers of diagnosis, relapse risk, and treatment response. Bipolar disorder is among the conditions with perhaps the greatest need for improved management: it is relatively prevalent, affects young people and runs a lifelong course. Poorly stabilized illness leads to a high risk of suicide and functional decline. The most recent treatment guidelines by CANMAT and ISBD recommend nine first-line and seven second-line maintenance treatments. However, there are no reliable guidelines as to how to choose among these options. The treatment decisions are not easy due to the highly variable, capricious clinical course of the illness, its heterogeneity, as well as poorly understood iatrogenic effects of certain medications. In this symposium, we will present data from the most promising modalities to guide the selection of long-term treatment. These include clinical and genomic patient profiles (M. Alda), electronic digital clinical monitoring (A. Ortiz), lithium magnetic resonance spectroscopy (D. Cousins), and epigenetic and microbiome measures (C. Pisanu).

CLINICAL AND GENOMIC DATA CAN INFORM TREATMENT DECISIONS IN BIPOLAR DISORDER

Martin Alda**1*, *Abraham Nunes1, William Stone1, Paul Grof2, Mirko Manchia3, Janusz Rybakowski4, Leonardo Tondo5*
[1]Dalhousie University, 2University of Toronto, 3University of Cagliari, 4University of Poznan, 5Centro Lucio Bini

Objective: Historically, the search for predictors of response to long term treatment of bipolar disorder (BD) started with clinical variables. After more than five decades of research, the most promising data are those related to the outcome of lithium maintenance. A number of clinical and family history measures associated with the outcome of lithium treatment emerged, many supported by replication studies and meta-analyses (e.g. Hui et al. Acta Psychiatrica Scand 2020). Yet, none of these variables have been tested for their predictive power. Here, we report the results of studies assessing the predictive power of clinical and genomic features.
Methods: In a large multi-site study of lithium treated patients, we used random forest machine learning algorithm to test of out sample predictive power of more than 150 clinical, demographic and family history variables in 1266 patients with BD. A total of 321 patients had available whole-genome genotypes. Using 47,465 directly genotyped SNPs we were able to differentiate prototypical responders (R) and nonresponders (NR) to lithium. Finally, we tested the model trained on lithium response in patients with data on their response to the anticonvulsants lamotrigine and valproate.
Results: Our results showed satisfactory predictive power of the clinical data (AUC ~ 0.8) to differentiate R and NR to lithium. Completely episodic clinical course was the hallmark of lithium responsiveness; a number of additional clinical features predicted the (non)response to both lithium and anticonvulsants. Whole genome genotypes discriminated poorly the two groups of patients in general (AUC ~ 0.57) but had an excellent power to differentiate clinically prototypical R and NR (AUC ~ 0.88). Gene ontology analyses identified four gene groups contributing most of the differentiation; these include G-protein coupled receptor genes, and genes in the muscarinic, amyloid secretase, and histaminergic gene families.
Conclusion: Our results support the possibility of using a combination of clinical and genomic data for optimizing long term treatment of BD once accounting for the disease heterogeneity.

IDENTIFYING PATIENT-SPECIFIC BEHAVIORS TO UNDERSTAND ILLNESS TRAJECTORIES AND PREDICT INDIVIDUAL TRAJECTORIES IN BIPOLAR DISORDER USING PASSIVE SENSING

Abigail Ortiz*[1], *Clara Park[2], Christina Gonzalez-Torres[2], Martin Alda[3], Daniel Blumberger[1], Rachael Burnett[2], Ishrat Husain[1], Marcos Sanches[2], Benoit Mulsant[1]*

[1]University of Toronto, 2Centre for Addiction and Mental Health, 3Dalhousie University

Objective: Several studies have reported on the feasibility of electronic (e-)monitoring using computers or smartphones in patients with mental disorders, including bipolar disorder (BD). While studies on e-monitoring have examined the role of demographic factors, such as age, gender, or socioeconomic status and use of health apps, to our knowledge, no study has examined clinical characteristics that might impact adherence with e-monitoring in patients with BD. Here, we describe our results on adherence to e-monitoring in patients with BD who are participating in an e-monitoring study and evaluated whether demographic and clinical factors would predict adherence to (i) daily self-rating scales; (ii) weekly self-rating scales or (iii) wearable use.

Methods: Eighty-seven participants with BD in different phases of the illness were included. Patterns of adherence for wearable use, daily and weekly self-rating scales over 15 months were analyzed to identify adherence trajectories using growth mixture models (GMM). Multinomial logistic regression models were fitted to compute the effects of predictors on GMM classes.

Results: Overall adherence rates were 79.5% for the wearable; 78.5% for weekly self-ratings; and 74.6% for daily self-ratings. GMM identified three latent class subgroups: participants with (i) excellent; (ii) good; and (iii) poor adherence. Women, participants with a history of suicide attempt, and those with a history of inpatient admission were more likely to belong to the group with good adherence.

Conclusion: Participants with higher illness burden (e.g., history of admission to hospital, history of suicide attempts) have higher adherence rates to e-monitoring. They might see e-monitoring as a tool for better documenting symptom change and better managing their illness, thus motivating their engagement.

ESTABLISHING MULTICENTRE MULTINUCLEAR BRAIN LITHIUM IMAGING IN BIPOLAR DISORDER

David Cousins*[1], *Pete Thelwall[1], Fiona Smith[1], Karthik Chary[1], Letizia Squarcina[2], Paolo Brambilla[2], Marie Chupin[3], Emmanuelle Gourieux[3], Fawzi Boumezbeur[4], Edouard Duchesney[4], R-LiNK Group[5], Frank Bellivier[6]*

[1]Newcastle University, 2Università degli Studi di Milano, 3CATI (Centre pour l'Acquisition and le Traitement des Images), 4Neurospin, CEA, 5https://rlink.eu.com, 6Université de Paris

Objective: The R-LiNK initiate is conducting a multicentre, multinational longitudinal study seeking to identify biomarkers/biosignatures capable of predicting response to lithium treatment in bipolar disorder. Brain lithium distribution, determined using a novel multinuclear imaging techniques (7Li-MRI), was identified as a potential marker but prior to the study initiation, its use was restricted to a small number of expert centres. Here we describe the steps taken to establish, coordinate and harmonise data acquisition and analysis in multiple sites.

Methods: Centres in the R-LiNK network were identified based on imaging platform capabilities and commonalities. Dual tuned 1H/7Li volume RF coils were procured and installed in each centre, together with bespoke test-objects (lithium phantoms) representative of the human brain. Acquisition sequences were optimised based on those previously published by our group, with harmonisation work conducted using the standardised phantoms. Data collection from enrolled patients proceeded in accordance with study protocol, supported by centralised sanity and quality

control checks. Acquisition processes were collated into standard operating procedures for Siemens and Philips MRI platforms. **Results:** The application of standard operating procedures enabled the collection of 7Li-MRI data (n**>** 45) from six centres as part of a longitudinal treatment study. Implementation of this novel imaging technique presented challenges, but these were surmountable and did not delay the project objectives. Close coordination between the lithium imaging and standard proton MRI work-package teams within R-LiNK, together with clear and responsive communication from participating sites was central to this success. Centralisation of data collection has proved to be advantageous in the development of novel processing pipelines. **Conclusion:** The R-LiNK initiative has established a network of centres capable of implementing 7Li-MRI as a potential marker for response to lithium as well as for future studies investigating the actions of lithium in various neuropsychiatric conditions. The development of standardised procedures and test-objects for harmonisation paves the way for an expansion of this imaging network to better understand this most important of medications.

MULTIOMICS ANALYSIS OF BLOOD METABOLOME, GUT MICROBIOTA AND GENOME-WIDE METHYLATION TO IDENTIFY BIOLOGICAL SIGNATURES OF RESPONSE TO LITHIUM IN BIPOLAR DISORDER

Claudia Pisanu*****[1], *Raffaella Ardau[2], Luigi Atzori[1], Bernardo Carpiniello[1], Donatella Congiu[1], Caterina Chillotti[2], Maria Del Zompo[1], Mirko Manchia[1], Aldo Manzin[1], Anna Meloni[1], Vanessa Palmas[1], Pasquale Paribello[1], Marco Pinna[1], Cristina Piras[1], Giovanni Severino[1], Martina Spada[1], Alessio Squassina[1]*

[1]*University of Cagliari, 2University Hospital Agency of Cagliari*

Objective: Bipolar disorder (BD) is among the major determinants of disability worldwide, with a very high socio-economic burden. The complex underlying neurobiology and the high heterogeneity in clinical response to the first-line treatments for BD, including lithium, severely impact on the management of this disorder, strongly calling for innovative integrated precision approaches. We will present results from two studies aimed at applying integrative analyses of different types of omics profiles (plasma metabolome, gut microbiota and genome-wide methylation) that represent important players in the relationship between genetic and environmental factors predisposing to psychiatric disorders and clinical response to psychotropic drugs.
Methods: In the first study we explored the role of gut microbiota and its possible interactions with the host metabolome in response to lithium in BD. To this end, we selected 50 patients with BD under lithium treatment at the time of recruitment and characterized as responders or non-responders using the “Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder” (Alda scale) and 50 patients treated with other mood stabilizers. The characterization of the blood metabolome (with nuclear magnetic resonance spectroscopy) and the gut microbiota composition (sequencing of the V3 and V4 hypervariable regions of bacterial 16S rRNA) are undergoing. In the second study, whole blood genome-wide methylation is being assessed with Infinium MethylationEPIC arrays in an extended sample of 70 patients with BD under lithium treatment and 30 controls. Data are analyzed to identify differentially methylated regions between diagnostic and lithium response groups. In addition, we will present data on differences in epigenetic age among studied groups and integrate them with other aging hallmarks measured in the same patients (leukocyte telomere length and mitochondrial DNA copy number), to explore the hypothesis of accelerated cellular aging in BD and of a potential protective effect of lithium treatment.
Results: We expect to find distinctive profiles of the gut microbial community, the host metabolome and methylation in patients exposed to lithium compared to patients treated with other mood

stabilizers or controls, as well as to identify specific biosignatures correlated with the clinical response. In addition, by applying integrative approaches to this multi-omics dataset using the Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO) method, we expect to identify multi-omics biomarker panels predictive of lithium response. **Conclusion:** By taking advantage of a multiomic approach applied to a deeply phenotyped sample of longitudinally followed-up patients, our studies aim to identify biological signatures underlying the clinical response to lithium.

5:00 p.m. - 6:30 p.m.
Symposia Concurrent V

UPDATE ON TREATMENT RESISTANT DEPRESSION

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: Treatment-resistant depression (TRD) is common and associated with multiple serious public health implications. A consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist. Instead, a plethora of definitions have been proposed, which vary significantly in their conceptual framework. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted the most used definition of TRD (i.e., inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment). Evidence indicates that a subset of MDD patients presenting with TRD may exhibit a failed antidepressant response as a consequence of a suboptimal bioavailability of the administered antidepressant, due to rapid metabolizer status. Identifying biomarkers and biosignatures associated with TRD as well as treatment response is an important future research vista. Intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) are established as efficacious in the management of TRD. Several second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine XR) are proven effective as antidepressant augmentation treatments in partial responders, but only the olanzapine-fluoxetine combination has been studied in FDA-defined TRD. The next decade can reasonably expect the regulatory approval of innovative pharmacological treatments targeting systems implicated in the pathophysiology of depression. Non-üphasrmacological treatment options are also available including both psychotherapy as well as ECt or TMS. There is as yet no clear distinction in the algorithm when to place these treatment modalities.

TREATMENT RESISTANT DEPRESSION: TREATMENT CONSIDERATIONS

Roger McIntyre**1*

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University of Toronto

Objective: To discuss the definition of treatment-resistant depression, the limitations of current definitions of treatment resistant depression, and to discuss treatment options used in major depressive disorder.

Methods: Methods are through a Delphi method and review of the literature.

Results: The results are treatment resistant depression does not have a consensus definition. Multiple definitions exist. Moreover, not a large number of treatments are available for major depressive disorder that is treatment resistant. In this program we are going to review the treatments for treatment resistant depression. **Conclusion:** A consensus definition of treatment resistant depression is required. Additionally, multiple treatment strategies are being evaluated which will be presented at this conference.

GENETIC BASIS OF TREATMENT RESISTANT DEPRESSION

Alessandro Serretti1, Chiara Fabbri1, Dan Rujescu**2*

[1]University of Bologna, 2German Society for Biological Psychiatry

Objective: Treatment resistant depression is largely modulated by genetic factors.

Methods: Several antidepressants already have a pharmacogenetic precaution/warning in their labeling for risk of side effects or interactions in CYP2D6 poor metabolizers. Conversely, rapid metabolizers may need higher doses. Other pharmacodynamic gene variants have been suggested, and, based on those evidence, over 40 commercially available pharmacogenetic assays have been implemented and their clinical applicability. While CYP polymorphisms are likely to inform about response/tolerability rates and reduce costs, single pharmacodynamic variants have little or no clinically relevant effects.

Results: More recently, the combined effect of polygenic risk scores has shown much more promising results in terms of reliability and possible drug choice and repurposing, but still explaining a relatively low variance of treatment resistant depression.

The integration of genetic information with clinical data and other biomarkers is a possible strategy to develop future more effective predictive algorithms.

Conclusion: Genetic factors are therefore at present already explaining a part of treatment resistant depression, but integrated models including further genetic and clinical predictors are needed.

DEVELOPMENT OF FAST ACTING ANTIDEPRESSANTS FOR TRD

Siegfried Kasper**1*

[1]Center for Brain Research

Objective: The development of fast acting antidepressants, specifically for treatment of so-called "TREatment resistant depression" will be presented, starting from clinical observations via randomised trials and underlying biological mechanisms

Methods: A literature overview will be given including own findings as part of Multicenter trials as well as own neuroimaging findings on esketamine.

Results: Since this is an overview, the available results published in the literature will be given

Conclusion: By the conclusion of the lecture the audience will be able to understand the development of rapid acting antidepressants with a specific focus on TRD.

NON-PHARMACOLOGICAL AND LONG-TERM TREATMENTS FOR TRD

Johan Saelens1, Anna Gramser1, Victoria Watzal1, Rupert Lanzenberger1, Christoph Kraus**1*

[1]Medical University of Vienna

Objective: Treatment strategies for treatment resistant depressions converge in repetitive trials of pharmaceutical substances with unclear maintenance treatments. Despite the successful establishment of novel rapid acting substances, several disadvantages such as adherence, side-effect profiles or long-term efficacy in relapse prevention remain. In addition, efficacious neuromodulatory treatments such as electroconvulsive therapy have their place in acute and maintenance treatment. However, in the treatment pathway for TRD, the position for other brain stimulation treatments such as transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) and vagus nerve stimulation

(VNS) remain unclear. The central aim of this talk is to present existing evidence on efficacy of neuromodulatory treatments in TRD and to compare efficacy to pharmaceutical treatment strategies. **Methods:** To compare efficacy of existing antidepressant treatments for TRD, we conducted a systematic literature research and network meta-analysis on all existing treatment modalities in TRD (as defined by non-response to two antidepressant treatment trials). Analysis was conducted in R with the netmeta package. **Results:** For the comparative network meta-analysis, 6698 abstracts were screened and 64 randomized, sham- or placebo-controlled trials with a total of 9976 patients were included. Six out of 28 antidepressant therapies in TRD had a significant higher response rate compared to placebo (ECT (OR = 13.78), minocycline (OR = 6.5), theta-burst stimulation (OR = 5.02), rTMS (OR = 4.48), ketamine (OR = 3.31) and aripiprazole (OR = 1.9). Treatments are ranked based on their probability of being the treatment with the highest response rate, with ECT ((p = .85) and theta-burst (p = .84) leading the field. **Conclusion:** In this study, we demonstrate comparative and ranked efficacy of currently available and investigational antidepressant treatments in TRD. Neuromodulatory interventions such as ECT and TMS ranked highest as far as treatment response of acute episodes are concerned. The results of this trial together with a second comparative meta-analysis on efficacy of DBS will be presented in the talk. These novel results will be placed into the context of the current treatment pathway in TRD. The audience will learn about acute and maintenance treatment strategies with neuromodulatory techniques and treatment selection in the daily clinical practice.

INTERNATIONAL STUDIES ON BRAIN MATURATION AND DEVELOPMENTAL PSYCHOPATHOLOGY: FROM BIRTH TO ADULTHOOD

Paolo Brambilla, University of Milan

Symposium Synopsis: Adolescence represents a period of increased opportunity and vulnerability, during which a complex confluence of genetic and environmental factors influences brain growth trajectories, cognition, emotion regulation and mental health outcomes.
In this symposium, international studies focusing on the link between environment, genes, disease-related behaviour and the brain, using a multidisciplinary perspective bridging epidemiology, genetic, neuroimaging and psychopathology will be presented.
Specifically, we will discuss how genetic and environmental risks for developmental disorders translate to brain function, structure and connectivity and how this in turn – ultimately- translated to emotion regulation and behavioural development. In addition, we will explore examples of the long-term psychological and behavioural sequelae in individuals with typical and atypical development, particularly focusing on clinical phenotypes associated with emotional dysregulation and major psychiatric disorders such as schizophrenia, bipolar disorders, major depression and anxiety disorders. Ultimately, we will discuss potential origins transdiagnostically characterising these disorders, associating early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
In addition, while most treatment studies focus on recovery within weeks or months, the long-term course of the above-mentioned disorders remains less established. In this symposium it will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.
Finally, the key role of genetic and neurobiological markers to improve the early detection and personalised treatment of developmental disorders will be analysed, mentioning the role of machine learning techniques and AI.

LONGITUDINAL NEONATAL BRAIN DEVELOPMENT AND ENVIRONMENTAL CORRELATES OF INFANT OUTCOMES FOLLOWING PRETERM BIRTH

Lucy Vanes1, Sunniva Fenn-Moltu1, Laila Hadaya1, Sean Fitzgibbon1, Lucilio Cordero- Grande1, Anthony Price1, Andrew Chew1, Shona Falconer1, Tomoki Arichi1, Serena J. Counsell1, Joseph V. Hajnal1, Dafnis Batalle1, A. David Edwards1, Chiara Nosarti**1*

[1]King's College London

Objective: To characterise longitudinal development of neonatal regional brain volume and functional connectivity in the first weeks following preterm birth, sociodemographic factors, and their respective relationships to psychomotor outcomes and psychopathology in toddlerhood.

Methods: We studied 121 infants born preterm (i.e., before 37 completed weeks of gestation) who underwent magnetic resonance imaging shortly after birth, at term-equivalent age, or both. Longitudinal regional brain volume and functional connectivity were modelled as a function of psychopathology and psychomotor outcomes at 18 months.

Results: Better psychomotor functioning in toddlerhood was associated with greater relative right cerebellar volume and a more rapid decrease over time of sensorimotor degree centrality in the neonatal period. In contrast, increased 18-month psychopathology was associated with a more rapid decrease in relative regional subcortical volume. Furthermore, while socio-economic deprivation was related to both psychopathology and psychomotor outcomes, cognitively stimulating parenting predicted psychopathology only.

Conclusion: Our study highlights the importance of longitudinal imaging to better predict toddler outcomes following preterm birth, as well as disparate environmental influences on separable facets of behavioural development in this population.

INTERNALIZING AND EXTERNALIZING SYMPTOMS TRAJECTORIES FROM CHILDHOOD TO EARLY ADULTHOOD, THROUGH ADOLESCENCE, IN CLINICAL AND GENERAL POPULATION SAMPLES: RESULTS FROM THE REMIND PROJECT

Maria Nobile**1*, *Maddalena Mauri1, Silvia Grazioli1, Federica Tizzoni1, Laura Camillo1, Maurizio Bonati2, Antonio Clavenna2, Alessandra Frigerio1, Carolina Bonivento3, Paolo Brambilla4*

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Objective: The REMIND project aimed at identifying specific clusters of symptom trajectories in internalizing and externalizing areas and evaluating their different exposure to risk factors in a developmental perspective.

The involved subjects from a general and a help-seeking population were evaluated at pre-adolescence (T0), adolescence (T1) and young adulthood (T2).

Methods: Psychopathological symptoms were measured through ASEBA questionnaires at the 3 time points, also neurobiological markers were collected. A Multivariate Finite Mixture Model (MFMM) was used to estimate specific developmental clusters considering T1 and T2 symptoms. We evaluated whether belonging to a specific developmental cluster was associated with sociodemographic characteristics, environmental risks (i.e., perinatal complications and stressful life events) and psychopathological symptoms measured at T0.

Results: Anxious-Depressed and Somatic scales showed 3 developmental clusters (“stable high”, “stable low”, “low-to-high”), Withdrawn-Depressed scale showed 2 developmental clusters (“stable high”, “stable low”). Individuals belonging to the ‘stable high’ internalizing developmental clusters,

presented higher emotional/behavioral dysregulation during preadolescence, with the co-occurrence of higher internalizing and externalizing problems.
Conclusion: The longitudinal perspective suggested the presence of specific manifestations trajectories from adolescence to adulthood. The presence of clinical level of psychopathology during preadolescence is a strong predictor of its persistence through lifespan, highlighting both homotypic and heterotypic continuities. These data strongly suggest the importance of accounting for both homotypic and heterotypic continuity in psychopathological traits when planning interventions.

TRAJECTORIES OF BRAIN STRUCTURE IN THE MAJOR MENTAL DISORDERS: FINDINGS FROM LONGITUDINAL STUDIES IN MDD, BD AND SZ

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Objective: Major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder (schizophrenia and schizoaffective disorder) overlap in symptomatology, risk factors, genetics, and other biological measures. It remains unclear whether there are shared regional grey matter volume alterations across these disorders, which past and current phenotypic factors and what course of illness moderate these alterations. We wanted to identify shared but also distinct grey matter volume alterations across patients compared to age- and sex-matched healthy controls.
Methods: Age- and sex matched healthy controls (n=110), DSM-IV-TR diagnosed major depressive disorder (n=110), bipolar disorder (n=110), and schizophrenia spectrum disorder patients (n=110), drawn from a sample of N=1927 were included. Grey matter volume (3T magnetic resonance imaging) was compared between HC and patients. We applied a conjunction analysis to identify shared grey matter volume alterations across the disorders. To identify potential origins of transdiagnostic GMV clusters, we associated them with early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
Results: Common to all diagnoses (vs. healthy controls), we identified grey matter volume reductions in the left hippocampus. This cluster was associated with stressful life events, the neuropsychology factor working memory/executive functioning, and with global assessment of functioning. Differential effects between groups were present in the bilateral frontal operculae and left insula, with volume variances across groups highly overlapping.
Conclusion: There are shared grey matter volume alterations in the left hippocampus across the major mental disorders. The hippocampus is a central network hub, orchestrating a wide range of mental functions. Our findings underscore the need for a novel stratification of mental disorders, besides categorical diagnoses.

COURSE PREDICTION OF DEPRESSION AND ANXIETY DISORDERS IN THE NESDA PROJECT

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Objective: While most treatment studies focus on recovery within weeks or months, the long-term course of depression and anxiety disorders remains less established. We examined the 2-6 year course trajectories of a large cohort of persons with depression and anxiety disorders, and evaluate whether we can predict chronicity by sociodemographic, clinical and biological data
Methods: Using 9-year longitudinal data from the Netherlands Study of Depression and Anxiety (NESDA, n=2981, 66% female, baseline mean age=42 yrs), we examined the naturalistic course of depression and anxiety disorders.

Results: 58% of the persons with a current depressive and/or anxiety disorder at baseline reported chronic episodes (24 months with symptoms without remission) over 6 years of follow-up (Verduijn et al. BMC Med 2018). Also switching between disorders was frequent. This is despite the fact that many persons in the study did receive pharmacotherapy, psychotherapy or a combination of these. For instance, after 6 year, also, when examining 9-year patterns in symptom severity reports, it appears that 63% of the sample belongs to the symptom cluster group that showed only a minimal improvement (Solis et al. J Affect Dis 2021). Machine learning analyses in which we considered basic clinical, psychological, lifestyle and biological predictors of course, yielded a significant prediction but with only moderate prediction value (accuracy 68%, Dinga et al. Transl Psychiatry 2018). Adding epigenetic or proteomic data did further improve predictive value (accuracy 75-75%, Clarck et al. Mol Psychiatry 2019; Habets et al. in progress). **Conclusion:** Unfortunately, chronicity appeared more the rule than the exception. Strongest predictors of chronicity of depressive and anxiety disorders are clinical baseline characteristics (including severity indicators). However, certain biological parameters did add additional predictive value. It will be presented what these findings tell us about the underlying biological mechanisms of chronicity. It will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.

NEUROSCIENCE BASED NOMENCLATURE

Oğuz Karamustafalıoğlu, İstanbul-University Cerrahpaşa

Symposium Synopsis: Symposium synopsis: neuroscience based nomenclature: a country experience:
Neuroscience based Nomenclature is a new classification system for psychotropic agents and now it (neuroscience based nomenclature), many years spent for introduction. It is now time for using NbN for clinical purposes. There is not clear information about how NbN is relevant in clinical use and will guide the clinicians, how different dosing and different pharmacology will change our clinical practice and use of NbN in psychosis and giving guidance for the clinicians. The implementation of NbN is an issue and the experience about implementation of NbN in specific country will be shared. The psychiatrists will be separated into two groups: child and adolescent and adult groups. Regarding the use of NbN the groups will differ in awareness, knowledge, use in practice and perspectives on NbN.

NBN IN THE TREATMENT OF PSYCHOSIS

Christoph Correll*[1]

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Objective: For the last seven decades, medications used to treat psychosis with regulatory approval based on randomized controlled efficacy studies have been dopamine receptor blockers. These medications have been called “antipsychotics”. However, this class of medications has also been used for and received regulatory approval for mania, bipolar depression, unipolar depression, tic disorders, indications that have nothing to do with psychosis. This indication-based nomenclature (is confusing for all stakeholders.

Methods: Review of the principles and procedures of neuroscience-based nomenclature (NbN) and how this approach pertains to treatments for psychosis. This presentation will outline the classification of dopamine blockers and partial agonists, as well as of other, emerging medications for psychosis in NbN.

Results: NbN proposes to categorize treatments for psychosis mechanistically based on the proximal effects as either blockers or enhancers with each of these proximal effects being able to lead to either

excitation or inhibition downstream. Examples of existing and emerging mechanisms of action for the treatment of psychosis are given.

Conclusion: Neuroscience-based nomenclature is a neuroscience and mechanism-based classification system of psychotropic drugs that will help with educating clinicians, patients and families about distinct actions of medications that map onto pharmacological mechanisms and thereby expected indications, benefits and adverse effect risks. Given that agents without dopamine receptor blocking effects are close to regulatory approval for schizophrenia, this NbN-based classification system is even more important for drugs for psychosis. This classification system will need to incorporate in a simple and straightforward way the complexities of proximal postsynaptic as well as presynaptic activity that can lead to either similar or opposite downstream effects.

IMPLEMENTATION NEUROSCIENCE BASED NOMENCLATURE IN TURKEY

Oğuz Karamustafalıoğlu*[1]

[1] *İstanbul-University Cerrahpaşa*

Objective: Neuroscience Based Nomenclature has been introduced more than a decade and even a second revision is published. The use of Neuroscience based Nomenclature is still limited both by adult psychiatrists and child and adolescent psychiatrists. The aim of the study is to understand the use of Neuroscience based Nomenclature among both adult psychiatrists and child and adolescent psychiatrists.

Methods: The questionnaire is prepared to give both adult psychiatrists and children and adolescents to understand the familiarity, purpose of use, their evaluations on various aspects are measured. Both groups are also compared.

Results: The knowledge of Neuroscience Based Nomenclature is limited among both groups. Both groups were not clear about the purpose of use of Neuroscience based Nomenclature .There are not enough information about how NbN is relevant in clinical use and will guide the clinicians how different dosing and different pharmacology will change our clinical practice and use of NbN in psychiatric disorders and giving guidance for the clinicians

Conclusion: The Knowledge of Neuroscience Based Nomenclature and Use of Neuroscience Based Nomenclature especially in clinical practice is very limited among both adult psychiatrists and child and adolescent psychiatrists. The barriers in the use of Neuroscience Based Nomenclature needs clear guidelines to overcome them.

NEUROSCIENCE-BASED NOMENCLATURE (NBN) - INTRODUCTION

Joseph Zohar*[1]

[1] *Post-Trauma Center, Sheba Medical Center; Tel Aviv University*

Objective: Psychopharmacology has advanced remarkably since the emergence of the first psychotropics in the 1950s. However, the pharmacological "language" still lags behind the new advances, leaving clinicians and patients with a disease-based terminology ("antipsychotics", "anxiolytics", "antidepressants'', etc) that is noninformative, stigmatizing and at times misleading. Neuroscience-based Nomenclature (NbN) is a pharmacologically-driven nomenclature, aiming to describe psychotropics through their neurobiological profile. Its main goal is to encourage more precise prescribing, help clinicians make rational and informed treatment choices and decrease patient stigma.

Methods: Chairing the symposium, Prof. Zohar will introduce the NbN concept, demonstrating the need for a new nomenclature amongst clinicians, trainees and patients. He will describe NbN's unprecedented development which was led by 5 major neuropsychiatric organizations (ECNP [European College of Neuropsychopharmacology], CINP [International], ACNP [American], AsCNP

[Asian], and IUPHAR [International Union of Basic and Clinical Pharmacology]), and will present its scope and coverage so far.

Results: NbN describes psychotropics through their mechanism, allowing for a broader understanding of treatment rationale, allowing a clearer view of the similarities and differences between medications and helping better planning of the "next pharmacological steps".

Conclusion: Neuroscience-based Nomenclature is an alternative classification system that strives to create a more scientific and precise pharmacological "language". This terminology might encourage a better understanding of psychopharmacology, help maximize the use of the current pharmacological tools available, and finally incorporate the vast knowledge available to day-to-day practice.

DIFFERENT DOSAGE DIFFERENT PHARMACOLOGY (DDDP)

Sasson Zemach*[1]

[1] *Hadassah-Hebrew University Medical Center*

Objective: Viewing medications through the "lens" of pharmacology, rather than indication, enables us to understand the underlying mechanism of each drug in a deeper level. The NbN way of thinking reveals that some medications act in differently in the pharmacodynamic level, depending on dosage, and therefore might serve different clinical uses at low dose and at full dose.

Methods: The talk will present some examples of using a medication at low dose for a certain purpose (e.g., low dose aripiprazole for the augmentation of depression), and full dose for an entirely different indication (e.g., aripiprazole for psychosis), while illuminating the pharmacological difference between low vs. full dose, and the clinical importance of distinguishing between these differences.

Results: Looking at the DDDP (Different Dose Different Pharmacology) concept illustrates how taking into consideration the dose of the medication has profound relevance, and how this difference might contribute to clinical practice and the research field alike.

Conclusion: Since continuous NbN contributes to a deeper understanding of psychopharmacology. the more precise our "language" is, the better is our ability to use the pharmacological tools available. DDDP is an example to where this understanding might extend.

TRANSLATING PSYCHIATRIC GENETICS TO CLINICAL APPLICATIONS WITH NOVEL STATISTICAL AND MACHINE LEARNING APPROACHES

Ole Andreassen, University of Oslo

Symposium Synopsis: With the advent of large-scale datasets, the field of psychiatric genetics is moving forward to an era of precision medicine to make individualized predictions. This is becoming possible with the development of novel statistical methods and machine learning techniques, leading to rapid new discoveries, and advancing the field towards clinical applications. In this symposium, we will present and discuss novel statistical methods and applications of machine learning principles in the context of precision medicine and psychiatric genetics that pave the way forward to clinical applications. Specifically, we will showcase a series of methods that we have developed for statistical genetics – boosting genetic discovery using an empirical Bayes approach, development of subject-specific trajectories using longitudinal genome-wide association studies, discovery of underlying biologically-relevant gene sets, and multimodal hazard analysis framework for predicting age of onset of different disorders. Using these novel statistical methods, we will not only present the conceptual foundations of these tools, but ground these in a clinically relevant framework and showcase how using these tools can lead to clinically relevant translational science. Speakers from Asia, Europe and North-America will cover new findings in relevant topics, including clozapine metabolism and clozapine-induced agranulocytosis, identification of gene-sets with greater biological specificity

associated with mental illness, providing new insights into the pathobiology of complex polygenic disorders, improvements in prediction performance of polygenic hazard score models, and longitudinal findings highlighting how the effect of SNPs change with time to reveal factors relevant for development of mental illness applying longitudinal cohorts.

SHARED GENETIC ARCHITECTURE BETWEEN CLOZAPINE METABOLISM, WHITE BLOOD CELL COUNTS, AND AGRANULOCYTOSIS

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Objective: Clozapine is the most effective antipsychotic drug, but its use is limited due to hematological side effects, characterized by a reduction of white blood cells (WBC) including potential life-threatening agranulocytosis. Clozapine´s adverse effect on WBC is likely related to its metabolism. Still, it is not possible to predict or prevent the risk of agranulocytosis with current therapeutic clozapine monitoring methods. Genome-wide association studies (GWAS) of clozapine metabolism and clozapine-induced agranulocytosis have identified only a few genetic loci. However, applying novel statistical genetics approaches could reveal more of the shared genetic etiology of clozapine metabolism and clozapine-induced agranulocytosis. We utilized the conditional false discovery rate (condFDR) method to increase power for genetic discovery of clozapine metabolism and clozapine-induced agranulocytosis, by conditioning on WBC counts.

Methods: We used the largest available GWAS summary statistics for clozapine metabolism (clozapine-to-norclozapine ratio), clozapine-induced agranulocytosis, and WBC counts. To boost discovery of genetic variants associated with clozapine metabolism as well as clozapine-induced agranulocytosis, we applied the condFDR method to identify overlapping single nucleotide polymorphism (SNP) associations across traits. The test statistics of separate GWAS is re-ranked in a primary trait (clozapine metabolism or clozapine-induced agranulocytosis) conditional on the associations in a secondary trait (WBC counts), thereby increasing discovery of trait-associated SNPs. For replication analyses in an independent sample, we used summary statistics from a GWAS on WBC counts in an East Asian sample. For SNPs identified to be significantly (condFDR < 0.01) associated with clozapine metabolism or clozapine-induced agranulocytosis, we tested for association with measures of clozapine metabolism and granulocyte levels in a Norwegian sample of 392 clozapine-treated individuals.

Results: After conditioning on WBC counts, we identified three novel loci associated with clozapine metabolism (condFDR), and six novel loci associated with clozapine-associated agranulocytosis. The majority of the identified loci replicated using the independent WBC count GWAS, and they were associated with clozapine-related measures in the sample of clozapine-treated individuals.

Conclusion: Our findings of shared genetic variants influencing clozapine metabolism, WBC counts, and clozapine-induced agranulocytosis may form the basis for developing prediction models for severe adverse effects of clozapine.

THE MIXER TOOLBOX FOR UNRAVELING GENETIC ARCHITECTURE OF COMPLEX TRAITS

Oleksandr Frei*[1], *Guy F. L. Hindley2, Nadine Parker2, Alexey A. Shadrin2, Dennis Van der Meer3, Bayram Akdeniz2, Espen Hagen2, Kevin S. O'Connell2, Shahram Bahrami2, Olav B. Smeland1, Ole Andreassen2, Anders M. Dale4*

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Objective: Genome-wide association studies (GWAS) are increasingly successful in discovering genomic loci associated with complex human traits and disorders, yet biological interpretation of these results and their translation into accurate and actionable polygenic prediction tools remains challenging. Based on GWAS results, the MiXeR framework has previously allowed us to quantify the polygenicity of complex traits, and the degree of polygenic overlap between traits. In this talk I will give an overview of these methods and introduce two new extensions: (1) GSA-MiXeR, allowing the quantification of partitioned heritability and fold enrichment for small gene-sets, and (2) MiXeR-Pred, a tool for calculating polygenic risk scores that leverage polygenic overlap between traits for improved prediction accuracy.

Methods: GSA-MiXeR applies stochastic gradient-based log-likelihood optimization to fit a model of gene-set heritability, evaluating its fold enrichment over a comprehensive baseline model to account for MAF- and LD-dependency of genetic effects, and for differential enrichment of functional categories, thus taking into account the unique genetic architecture of each trait, while also controlling for linkage disequilibrium (LD) between variants. MiXeR-Pred tool computes enhanced polygenic risk scores, building on the cross-trait MiXeR model to compute the posterior effect size for each trait. This approach differentiates between shared and trait-specific genetic variates using the bivariate distribution of GWAS z-scores, and the estimated pattern of genome-wide overlap between the traits.

Results: In both simulated and real data, we show GSA-MiXeR's capability to reorder gene-sets in a way that promotes smaller gene-sets (with 10 genes or less) while yielding an equivalent or higher replication rate compared to current standards in the field. For schizophrenia, we show that calcium channel function gene-sets had greater fold enrichment than larger gene-sets related to post-synaptic functioning; additionally, the top two most fold enriched gene-sets implicated in GSA-MiXeR analysis were related to dopaminergic neurotransmission, the leading theory of schizophrenia pathogenesis. Using MiXeR-Pred, we show how the latest GWAS of schizophrenia can improve the accuracy of predicting the onset of bipolar disorder in an independent sample, while at the same time reducing the number of SNPs used for prediction.

Conclusion: Our findings illustrate that GSA-MiXeR provides the granularity required to map GWAS tested findings to potentially more informative neurobiological processes which can be experimentally, thus facilitating better characterization of the pathobiology of schizophrenia with potential for identifying new druggable targets and clinical sub-groups. Improved prediction accuracy of the MiXeR-Pred tool is an important step in towards incorporating more accurate polygenic prediction into the MiXeR framework.

POLYGENIC HAZARD SCORE MODEL TO PREDICT AGE OF ONSET OF ALZHEIMER'S DISEASE IN EUROPEAN POPULATIONS

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Objective: Polygenic hazard score (PHS) models are being used to estimate age-dependent genetic risk of various diseases including Alzheimer's disease (AD). The original PHS model for predicting the age of AD onset included 31 common variants and APOE ε2/ ε4 alleles [1]. Here, our aim is to the predictive ability of the PHS model and validate the updated model using genotyping data from

the European Alzheimer and Dementia Biobank (EADB) which includes cohorts from several countries across different regions of Europe. **Methods:** EADB samples whose age of onset (for cases) or age of last follow-up (for controls) are lower than 60 years are excluded resulting in N= 14195 cases, 16956 controls. We split this data into 80% for training and 20% for test data. For developing EADB model we applied genome-wide filtering using existing genome-wide association study (GWAS) of EADB data for AD [2]. We have eliminated single-nucleotide polymorphisms (SNPs) with p-value >10-5. The remaining 12631 candidate SNPs were used for the development of the new PHS model. Training for developing the new model was done via stepwise regression framework as proposed in [1]. As a result, 94 candidate SNPs (including APOE 2/4 alleles) were identified and then incorporated into the Cox proportional hazards model. **Results:** We have evaluated the performance of the new model using the test data. We have plotted corresponding Kaplan Meier curves and Cox regression estimates of the risk groups classified using PHS calculated using both models (for both the original model and the new model). We then calculated the Hazard ratio (HR) between risk groups such as HR of the samples who are in the highest 20 percent with respect to PHS to the lowest 20 percent (HR80/20) and similarly, we calculated HR98/50. The new EADB model surpassed the original model in prediction performance: HR80/20 increased to 3.22 from 2.42 in the original model, and HR98/50 increased to 4.59 from 3.41 in the original model. Furthermore, in the new model, the concordance index of PHS scores increased to 0.65, compared to 0.62 for the original model. **Conclusion:** Preliminary results showed increased prediction performance with the new EADB PHS model compared to the original PHS model. The performance may be further improved by using Lasso Regression, and sex-dependent data. Together, the presented findings indicate that the PHS model for predicting AD has the potential for clinical utility. **References:** [1] Desikan, Rahul S., et al. "Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score." PLoS medicine 14.3 (2017): e1002258. [2] Bellenguez, Céline, et al. "New insights into the genetic etiology of Alzheimer's disease and related dementias." Nature genetics 54.4 (2022): 412-436.

FAST AND EFFICIENT MIXED-EFFECTS ALGORITHM (FEMA) FOR GENOME-WIDE ASSOCIATION STUDIES (GWAS) OF LONGITUDINAL PHENOTYPES

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Objective: Longitudinal data are critical for advancing our understanding of causal mechanisms of complex human diseases. Compared to cross-sectional data, longitudinal dataset provides a wealth of information on subject-specific temporal trajectories of different phenotypes and development of diseases, like psychiatric disorders. While large longitudinal population data have recently become available, there are numerous challenges in performing genome wide association studies (GWAS) for trajectories of phenotypes. We have developed the FEMA-GWAS, a novel analytical tool that allows nuanced analyses of longitudinal phenotypes as well as linear and non-linear interaction with age/time and show results from different phenotypes highlighting how we can leverage trajectories of phenotypes to make subject-specific predictions in mental disorders.
Methods: FEMA-GWAS builds upon FEMA, a recently developed computationally efficient solution to performing mixed effects analyses, enabling the analysis of non-independent observations. For

FEMA-GWAS, we extend FEMA to perform linear and non-linear interaction of each single nucleotide polymorphism (SNP) with time and sex, thereby revealing novel associations of different SNPs with longitudinal phenotypes. We have applied FEMA-GWAS to height, weight, and BMI from the Norwegian mother, father and child cohort study (MoBa), and cortical thickness from the Adolescent Brain Cognitive Development (ABCD) and the UK Biobank datasets.
Results: Our results reveal novel loci that are associated with longitudinal trajectories of height, weight, and BMI in children (from birth to adolescence), with change in cortical thickness during adolescence (ABCD), and with change in cortical thickness during mid-life (UK Biobank). Importantly, we discovered novel loci that show significant SNP×age interaction effect, highlighting how the effect of SNPs change in different periods of time. Further, using these discoveries, we present data on constructing subject-specific precision norms, which can help make predictions on susceptibilities to developing psychiatric illnesses.
Conclusion: We have developed a powerful new tool that can be used for the analysis of genetics of non-independent observations. Using FEMA-GWAS, we discovered promising genetic leads that can help identify individuals who deviate from the normative genetically determined developmental trajectories. This method of identifying individuals at risk for various psychiatric disorders can open up possibilities of early intervention targeting modifiable environmental factors. It also opens up the possibilities of clinical translation by leveraging longitudinal clinical information and genetics in making subject-specific genetically adjusted predictions, thereby bringing us closer to precision psychiatry.

PSYCHIATRIC ELECTROPHYSIOLOGY AS ADD-ON TOOL IN THE MANAGEMENT OF ADDICTION DISORDERS

Oliver Pogarell, University Hospital, LMU Munich

Symposium Synopsis: Addiction is a worldwide health problem, still presenting large relapse rates despite decades of research and treatment programs including withdrawal, medication and psychosocial support. Neurophysiological tools (such as qEEG, cognitive event-related potentials, the neuroimaging-guided neurofeedback) are tools to offer new perspectives regarding pathophysiological mechanisms triggering diverse forms of addictions, to monitor states of the disorder and to develop new add-on tools for treatment as well as for prevention. In this symposium, we will furnish up-to-date evidence about new and complementary neurophysiological ways to face with addictive disorders. QEEG studies point at altered brain electric states in subjects with addictions. The investigation of differences and similarities across disorders provide insight into differential pathophysiological aspects that may be relevant for the treatment of dual diagnoses. Cognitive potentials are used to monitor patients during addiction treatment programs and may be such as helpful for predicting treatment outcomes. Neurophysiology based treatments neurofeedback are novel options to augment and improve standard care of patients with addiction including related neurophysiological parameters that may serve as biomarkers to predict clinical short and long-term effects. In summary psychiatric electrophysiology is of increasing relevance not only for basic brain research but also as a contribution to diagnostic and treatment decisions, complementing treatment options in psychiatry.

QEEG CORRELATES OF ADDICTION IN BIPOLAR DISORDER

Mehmet Kemal Arıkan*[1]
[1]
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Objective: High rates of alcohol and substance abuse have been found in patients diagnosed with bipolar disorder. This study aims to explore the electrophysiological differences in addicted bipolar

patients using quantitative electroencephalography as a technique to measure cerebral cortical activity. **Methods:** Retrospective screening was used to obtain data from patients admitted to a private psychiatry clinic. In the initial stage, the prevalence of alcohol and substance abuse was compared among the most common diagnoses. In the second phase, bipolar patients were compared to healthy individuals in terms of electrophysiology. Within this comparison, alcohol dependent and substance dependent bipolars were studied separately in contrast to the healthy group. Alongside the healthy control, bipolar patients deprived of substance or alcohol abuse were examined in both cases. Statistical analysis involved MANOVA and gender and age were taken into account. **Results:** 1) In the initial analysis of common psychiatric diagnoses (depression, anxiety, OCD, schizophrenia, and bipolar disorder), the percentage of alcohol or substance abuse was significantly higher than otherdiagnoses. 2) Electrophysiological comparison revealed distinct electrophysiological profiles between bipolar patients with addiction and those without, as well as the healthy control group. Specifically, individuals with bipolar disorder and without alcohol dependence exhibited higher general theta, beta, and temporal alpha power compared to those with dependence and healthy individuals. Additionally, the former group demonstrated higher occipital alpha power compared to the healthy control group only. 3) Patients with bipolar disorder, both with and without substance abuse, exhibited higher overall beta power than the healthy control group. **Conclusion:** It can be concluded that alcohol dependence led to significant alterations in brain activity in patients with bipolar disorder compared to non-addicted and healthy patients. In contrast, no such differences were observed in substance dependence, possibly due to the stimulant properties of the substance used. Future research could investigate the changes to the electrophysiological profile within this patient group, depending on the substance type with more detail.

COGNITIVE ERPS IN THE MANAGEMENT OF ADDICTIVE DISORDERS

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Objective: Despite withdrawal, psychotherapy, social support and anti-craving medication, the relapse rate remains tremendous among addicted patients. Cognitive ERPs may be considered as an add-on tool in the management of these patients.
Methods: Different ERP studies dealing with the management of addictive disorders will be reviewed.
Results: Different ERP parameters, such as the oddball P300, the Nogo P3d and the ERN, were identified as interesting biomarkers of abstinence vs. relapse in addictive disorders.
Conclusion: It is time to include ERPs in the management of addictions in order to monitor the evolution of different neurocognitive functions that may subtend relapse.

RTFMR-NEUROFEEDBACK IN ADDICTION PSYCHIATRY - SHORT AND LONG TERM EFFECTS

Oliver Pogarell**1*, *Susanne Karch1, Daniel Keeser1, Maximilian Maywald1*

1 University Hospital, LMU Munich

Objective: Psychosocial therapies are first line treatments in addictions, but long-term abstinence rates are limited to 40 to 60 %, even if extensive inpatient treatment and rehab has been offered. One risk factor of relapse is craving, that can be induced by alcohol related cues. Neuroimaging studies have revealed evidence for the association of craving with ACC and medial frontal areas during cue exposure. The activity in these regions can be modified by neurofeedback techniques.

Aim of the studies is to investigate neurofeedback in patients with substance use disorders in terms of feasibility, short and long-term effects. **Methods:** We implemented a real-time fMRI design in patients with alcohol and tobacco use disorders. Subjects received fMRI with a paradigm presenting substance related cues to elicit individual brain activations and were asked to modulate the cue induced brain responses. **Results:** There were significant modulations of addiction related brain activities along with slight reductions in craving. Due to small samples long-term data did not show increased abstinence rates so far. Differences between abstainers and relapsers point at predictive properties. **Conclusion:** Neurofeedback is a promising tool to augment treatments in substance use disorders. Larger samples in prospective studies are required to further improve the technique and assess long- term clinical effects.

NEUROFEEDBACK FOR ALCOHOL ADDICTION: CHANGES IN RESTING STATE NETWORK ACTIVITY

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Objective: The aim of this study was to investigate whether neurofeedback training can alter resting state fMRI activity in brain regions that play a crucial role in addiction disorders in patients with alcohol dependence.

Methods: For this purpose, a total of 52 patients were recruited for the present study, randomized, and divided into an active and a sham group. Patients in the active group received three sessions of neurofeedback training. A random sample (N=16) remained for the data analysis. We compared the resting state data in the active group as part of the NF training on six measurement days.

Results: When comparing the results of the active group from neurofeedback day 3 with baseline 1, a significant reduction in activated voxels in the ventral attention network area was seen. This suggests that reduced activity over the course of therapy in alcohol-dependent subjects may lead to greater independence from external stimuli. Overall, a global decrease in activated voxels within all three analysed networks compared to baseline was observed in the study.

Conclusion: The use of resting-state data as potential biomarkers in further studies may hold promise, as activity changes within these networks, may help restore cognitive processes and alcohol abuse-related craving and emotions.

THE ROLE OF REWARD SYSTEM IN PSYCHIATRIC DISORDERS: A TRANSDIAGNOSTIC APPROACH

Esin Erdogan, University of Health Sciences, Izmir Faculty of Medicine

Symposium Synopsis: The Diagnostic and Statistical Manual of Mental Disorders categorically classifies various neurodevelopmental and psychiatric disorders, despite their sharing common features in terms of symptoms, causes, and abnormal brain processes. In fact, there are numerous instances where different disorders exhibit similar underlying pathological mechanisms. This overlap suggests the potential benefits of investigating shared patterns of disrupted brain function and associated characteristics. The ultimate objective is to more accurately link these pathological processes to well-founded and targeted interventions. One area that has received growing research attention in both nonclinical and clinical settings is the development of reward-processing systems. This approach revolves around the identification of malfunctioning mechanistic processes that are common to disorders with seemingly distinct symptom profiles. This strategy represents a specific implementation of the endophenotypic approach to uncovering the underlying pathophysiological mechanisms of these diseases. In this symposium, we aim to discuss preclinical models and clinical

research addressing reward circuit dysfunction in various neurodevelopmental and psychiatric disorders such as schizophrenia, mood disorders, eating disorders, and ADHD.

REWARD PROCESSING DYSFUNCTION IN SCHIZOPHRENIA

Aslihan Bilge Bektas*[1]

[1]*İzmir Bozyaka Training and Research Hospital*

Objective: Schizophrenia is a heterogeneous clinical disease with symptoms classified as positive, negative, disorganized, neurocognitive. It is thought that dysfunctional cortico-striatal interactions that worsen the prognosis in schizophrenia, reduce the social functionality of patients, play a role in the formation of negative symptoms that are resistant to treatment prevent the decision-making processes to create goal-directed behavior and cause disruption in the reward processing system.
Methods: Various components of reward processing have been shown to be impaired in schizophrenia. These components include reinforcement learning, the calculation of reward value, effort estimation, action selection, and reward expectation. These impairments are associated with changes in the cortico-striatal pathway. Various models have been proposed in the literature to explain motivation deficits in schizophrenia.
Results: A common assumption in most of these models is that the hedonic response is preserved in schizophrenia. Strauss et al. have proposed an approach that suggests impairments in hedonic systems in schizophrenia.
While individuals diagnosed with schizophrenia have hedonic responses similar to those of healthy individuals, they are less engaged in activities aimed at obtaining rewards. According to Barch and Dowd, this is because these individuals have difficulty using internal representations of emotional experiences, previous rewards, and motivational goals. It is believed that these difficulties in individuals with schizophrenia result from impairments in the components of reward processing, such as reward expectation, representation of reward value, calculation of effort required for rewards, and the ability to plan goal-directed activities.
Similarly, Gold and colleagues have argued that the fundamental problem in reward processing in schizophrenia lies in the creation and maintenance of mental representations of reward value. The model proposed by Kring and Elis in 2013 takes a different approach to explaining reductions in reward seeking and goal-directed behavior.
Conclusion: These models are supported by neuroimaging studies. Previous studies have revealed that anhedonia in patients with schizophrenia is attributed to the dysregulation of the frontostriatal circuit and mesocortical and mesolimbic circuit systems. Reduced OFC and putamen/ventral striatum activity during reward anticipation is linked to greater anhedonia and depressive symptoms in patients with schizophrenia. The motivational deficits of schizophrenia are thought to result from a reduced ability to differentiate between signal gains and instances of loss-avoidance, which are associated with the dysfunction of the frontostriatal pathway, including the vmPFC, dorsal ACC, anterior insula, and ventral striatum. Furthermore, patients with schizophrenia exhibit an inverse correlation between anhedonia-associality and posterior cingulate and precuneus activity, a key part of the DMN, during an auditory oddball task. Dysfunction of the striatum, cortex, and limbic regions and impaired integration of the reward networks may also lead to anhedonia in patients with schizophrenia.
In this session, we planned to discuss the differences in the reward processing process in schizophrenia and its relationship with the clinic in the light of current developments.

REWARD DEFICIT AND ANHEDONIA IN MOOD DISORDERS

Merve Babalioglu*[1]

[1]*Health Sciences University İzmir Tepecik Training and Research Hospital*

Objective: To explain the clinical and behavioral presentation of anhedonia and reward deficit in mood disorders, as well as the differences and commonalities in the underlying neurocircuitry.
Methods: A selective literature search including both human and rat studies were conducted using PubMed and PsychINFO to identify anhedonia and reward deficit in mood disorders.
Results: Mood disorders are common and debilitating conditions characterized in part by profound deficits in reward-related behavioural domains. Evidence suggests that depression is characterized by hypofunction of the reward-related brain structures such as the nucleus accumbens, prefrontal cortex, amygdala and hippocampus, while bipolar disorder manifests dysregulation of the behavioral activation system that increases goal-directed reward behavior. Importantly, strong evidence does not exist to suggest significant differences in anhedonia severity between depressed unipolar and bipolar patients, suggesting that there are more nuanced fluctuations in reward processing deficits in bipolar patients depending on their state. Both euthymic unipolar and bipolar patients frequently report residual reward dysfunction, which highlights the potential of reward processing deficits that give rise to the clinical symptom of anhedonia to be trait factors of mood disorders.
Conclusion: Reward processing represents a potential diagnostic and treatment marker for mood disorders. Further research should systematically explore the facets of reward processing in at-risk, affected, and remitted patients.

WHICH COMES FIRST: ALTERED BRAIN REWARD CIRCUITS IN EATING DISORDERS?

Vefa Erbasan**1*

[1]*İzmir Tepecik Training and Research Hospital*

Objective: It was aimed to examine the role of changes in the brain reward system in eating disorders.
Methods: Eating disorders are multifaceted psychopathologies, and the transdiagnostic approach is currently considered a useful framework to understand their complexity. The transdiagnostic model of eating disorders represents a dimensional approach that cuts across traditional categorical diagnoses and goes beyond them by considering the processes that are relevant to both eating pathology and other psychological disorders. With this approach, reward processing systems were thought to be effective in the development of eating disorders.
Results: Recent evidence has proposed neurobiological and behavioral similarities between substance dependence and excessive consumption of highly processed foods. These findings led to the recognition of food addiction as a key trigger in eating disorders. There is now considerable evidence that food and drug addiction share similar pathways in dopaminergic, opioid, and cannabinoid systems. In fact, dopamine has been associated with the reward mechanism in both food and psychoactive substances. The more rewarding the food or drug evaluated, the greater the release of extracellular dopamine into the nucleus accumbens. Also, pharmacological blockage of dopamine receptors may reduce the reward of both high-sugar foods and drugs of abuse. Studies based on positron emission tomographic imaging have also shown that both obese and drug-dependent individuals have significantly lowered the levels of dopamine receptors.
Conclusion: All this information suggests that the changing brain reward system has an important role in the pathophysiology of eating disorders, and more research should be done in this field to better understand eating disorders.

NEURAL MECHANISMS UNDERLYING REWARD PROCESSING IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Esin Erdogan**1*

[1] *University of Health Sciences, Izmir Faculty of Medicine*

Objective: The prevailing view is that ADHD is characterized by deficits in different cognitive domains. In addition to executive functions, deficits are observed in reward processing, temporal processing and timing, speech and language, memory span, processing speed, response time variability, arousal/activation, and motor control tasks. The aim of this presentation is to enhance our understanding of the behavioral and neural factors associated with reward processing in adults with ADHD and to reconcile discrepancies found in the existing literature. **Methods:** Neuroimaging studies of reward processing (structural imaging studies, functional imaging studies, and imaging of the brain at rest) in ADHD have been examined. **Results:** Various imaging techniques have consistently shown that ADHD is linked to alterations in the neural system responsible for reward processing. Structural studies have identified volume reductions in the Ventral Striatum (VS) and Prefrontal Cortex (PFC). While the precise functional implications of these volumetric differences remain unclear, researchers have initiated functional investigations into reward processing. These efforts have consistently revealed functional changes in adults with ADHD, primarily characterized by reduced brain responses during the anticipation of rewards in the VS and anomalous signaling during the receipt of rewards in the Orbitofrontal Cortex (OFC). The signaling in the VS during reward anticipation has been proposed to reflect either the predicted value of an expected reward (Schultz 2010) or the incentive salience (Berridge and Robinson 2003). Responses in the OFC have been associated with signaling the value of stimuli in our environment, indicating that adults with ADHD may exhibit an exaggerated response to rewarded stimuli, potentially leading to imbalanced decision-making. The evidence regarding neural alterations linked to reward processing in young individuals with ADHD is less conclusive when compared to adults. There are several factors contributing to this uncertainty. Firstly, there have been fewer studies conducted in young participants, and the reported findings exhibit a high degree of inconsistency. These discrepancies pertain to the locations within neural structures where changes occur and the direction of these effects, whether they involve increases or decreases. Secondly, studies involving young participants with ADHD have generally worked with smaller sample sizes. In comparison, the largest study in adults included 136 participants (Hoogman et al. 2011), while studies in adolescents typically involved only 68 participants (Paloyelis et al. 2012). Thirdly, the majority of studies focusing on young participants with ADHD have concentrated solely on the aspect of reward anticipation. **Conclusion:** Hence, it is imperative to conduct further research involving young participants with ADHD, encompassing crucial elements of reward processing, including both anticipation and receipt of rewards. Additionally, the reported alterations in functional connectivity among young individuals with ADHD suggest that viewing brain reward processing from a network perspective could offer additional insights into the neural changes associated with this disorder. Given the absence of research on endophenotypic traits in neural measures associated with reward processing, familial studies are crucial for understanding the hereditary contributions to these neural characteristics.

Friday, June 7, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session III - Catherine Mummery

A NEW ERA IN AD DRUG TRIALS: TRANSLATING HOPE INTO IMPACT

Catherine Mummery1

[1]*University College London*

Objective: The search for treatments for Alzheimer's disease has been a long and arduous one with many negative trials and heated debate on what we should be targeting, and how. However, recent results on anti-amyloid immunotherapies have shown for the first time that we can alter the course of the disease and, while modest, have given us a foundation on which to build.

Methods: In this talk, I will summarise the results we have so far, and what they teach us in terms of next steps; I will then explore the novel targets and mechanisms that are developing and how we are using these in patients with earlier and genetic forms of disease to inform us about the future of treatments.

Results: I will outline some initial results from new genetic therapies as well as other novel therapies.

Conclusion: We are now in a position where we can be more than hopeful; we can be optimistic about the future. We are at the beginning of an era where we will build better disease modifying therapies and develop precision based medicines. We are at a real cornerstone - we are moving towards an ability to treat dementias as chronic diseases, not just offer palliative care for a terminal disease.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VI

THE ROLE OF DOPAMINE IN BIPOLAR DISORDER MOOD CYCLING AND DYSREGULATED CIRCADIAN CYCLES: A DOPAMINERGIC RHYTHMOPATHY? *Sameer Jauhar, King's College, London*

Symposium Synopsis: Mood cycling in bipolar disorders is a complex phenomenon driven by multiple
internal and external factors. We will present brain imaging data implicating Dopamine in this phenomenon, particularly, in mania and psychosis. We will also present data showing how a disrupted circadian cycle, especially by light and other factors, impacts sleep/activity and is associated with many mood symptoms from suicidal ideas to disrupted eating patterns. We will describe methods developed for quantitative ambulatory measurement of patterns in sleep and eating rhythms as well as associations between the two rhythms. Finally, we will integrate these phenomena into a coherent model integrating the role of a group of midbrain dopaminergic neurons
working as a non-circadian oscillator interacting with the circadian timer.

TESTING THE DOPAMINE HYPOTHESIS OF BIPOLAR DISORDER USING PET IN HUMANS

Sameer Jauhar*1, *Oliver Howes1*

[1]*King's College, London*

Objective: Delineate the role of the pre-synaptic dopamine system in bipolar disorder.

Methods: Case-control Positron Emission Tomography study in people with bipolar disorder and controls, using 18F-DOPA.

Results: Converging lines of evidence have implicated changes in the dopamine system in people with bipolar disorder, at trait and state levels. In this proposal I will present our data in first episode

mania psychosis, comparing it to schizophrenia psychosis, as well as newly acquired data in psychotic depression, addressing whether there is a transdiagnostic role for dopamine across these disorders. **Conclusion:** There does appear to be elevation in dopamine synthesis capacity in mania, with psychosis, and a probable reduction in dopamine synthesis capacity in the deprewssive pole of the illness, compared to this. Further longitudinal studies will shed further light on this.

DYSREGULATED RHYTHMS AND SYMPTOMATOLOGY IN BIPOLAR AND EATING DISORDERS

Outi Linnaranta**1*, *Serge Beaulieu2, Clement Bourguignon3, Elaine Tian4, Howard Steiger3, Kai-Florian Storch3*

[1]Finnish Institute for Health and Welfare, 2Canadian Network for Mood and Anxiety Treatments, [3]Douglas Mental Health University Institute, 4University of Hong Kong

Objective: To describe associations between sleep and eating rhythms in cohorts with patients with a diagnosis of a bipolar disorder (n=75) or an eating disorder (n=29).
Methods: Patients in both cohorts completed hourly charts of mood and eating occasions for two weeks. Locomotor activity was recorded continuously by wrist actigraphy for a minimum of 10 days, and sleep was calculated based on periods of inactivity. We computed the center of daily inactivity (CenDi) as a measure of sleep phasing and consolidation of the daily inactivity (ConDI) as a measure of daily sleep rhythm strength. We assessed interday irregularities in the temporal structure of food intake using the standard deviation (SD) of frequency (IFRQ), timing (ITIM), and interval (IINT) of food intake.
Results: In bipolar disorders, sleep timing and fragmentation were robustly associated with eating irregularity. In eating disorders, the phasing and rhythmic strength of sleep showed a moderate, positive correlation with the degree of eating irregularity. The similarity of findings despite several potential confounding factors and differences between the samples strengthen the notion of a potential shared rhythmopathy.
Conclusion: Two cohort studies showed shared rhythmopathy of sleep and circadian rhythms and eating rhythms. The presented methods are valid for descriptive studies on circadian rhythms in humans and deserve further development for use in clinical settings and in intervention studies.

A ROLE FOR MIDBRAIN DOPAMINE NEURONS IN BD CYCLICITY

Kai-Florian Storch**1*, *Pratap S. Markam1, Clement Bourguignon1, Lei Zhu2, Martin Darvas3, Bruno Giros1, Serge Beaulieu1, Outi Linnaranta1*
[1]McGill University2Douglas Mental Health University Institute, 3University of Washington

Objective: The mechanistic basis of cycling in bipolar disorder is poorly understood. Here we aimed to identify the neuronal substrate of cyclicity employing the mouse as a model.
Methods: Chronic treatment with methamphetamine in mice results in the emergence of a second rhythmic locomotor component that can reach periods of 48hrs, a frequency also found in bipolar disorder subjects exhibiting ultra-rapid cycling. We used genetic and pharmacological approaches to ablated or manipulate dopamine (DA) neurons in mice and then tested the resulting animals for deficits in second component emergence.
Results: We found that ablation of the DA neurons of the ventral tegmental area (VTA) abolished the ability of methamphetamine to induce the second component. Selective disruption of the tyrosine hydroxylase gene across the VTA equally led to a loss of second component emergence, while disruption of the gene for the vesicular monoamine transporter 2 in the VTA did not impede second component induction.

Conclusion: Our findings indicate that DA neurons of the VTA or their ability to produce DA are necessary for the emergence of a second rhythmic component regulating sleep-wake, likely harboring the oscillator that drives it. As the period of this component often reaches 48hrs, we suggest that DA neurons of the VTA also drive 48hr cycling in BD, where sleep length rhythmically alters alongside with mood.

DECODING MENTAL DISORDERS - DECIPHERING THE GENETIC BASIS AND EXPLORING ANIMAL AND IPSC MODELS

Florian Raabe, Max Planck Institute of Psychiatry

Symposium Synopsis: The goal of this symposium is to highlight the genetic basis of mental illness and advanced modeling with animal models and induced pluripotent stem cells (iPSCs).

Recent breakthroughs in genetic research have identified numerous risk genes associated with mental illness, and cutting-edge techniques have explored the functional implications of these identified risk genes.

By applying animal models that partially mimic the phenotypic characteristics of psychiatric conditions, researchers can investigate environmental factors that contribute to the development of mental illness and study gene-environment interactions.

The emerging field of induced pluripotent stem cells (iPSCs) enables the generation of various personalized neural subtypes, allowing for the dissection of cellular and molecular mechanisms in patient-derived neurobiological test systems.

The speakers of this symposium will discuss advancements in genetics, animal models, and iPSC technology, highlighting their strengths and limitations on the road towards personalized psychiatry.

PSYCHIATRIC GENETIC DISCOVERIES IN BIPOLAR DISORDERS - NEW INSIGHT IN UNDERLYING BIOLOGY

University of Oslo
Ole Andreassen[1]*, *Kevin O'Connell1, Bipolar Disorders PGC Working Group1*

Objective: We aimed to discover more of the the genetic architecture of bipolar disorders by applying a large transancestry sample.

Methods: Genome-wide association study of bipolar disorder with functional follow up of genetic loci. We analysed 158,036 bipolar disorders cases (including clinical, biobank and self-report cohorts) including diverse samples of European, East Asian, African American and Latino ancestries.

Results: We identified 337 independent genome-wide significant variants mapping to 298 loci. Exploratory enrichment analyses using the novel GSA-MiXeR tool highlighted enrichment of dopamine- and calcium-related biological processes and molecular functions, as well as GABAergic interneuron development, suggesting interesting molecular mechanisms and pathways to consider as targets for drug-repurposing. Genes fine-mapped to associated loci were also shown to be enriched for ultra rare damaging missense and protein-truncating variation in sequenced datasets, respectively, highlighting convergence of common and rare variant signals. We mapped genes to the 298 GWS loci using seven complementary approaches and identified a subset of 47 credible genes that were mapped to loci by at least three of these approaches.

Conclusion: Our findings highlight that increasing ancestral diversity in genetic studies of bipolar disorders improves discovery and ensures equitable benefit from genetic discoveries across ancestry groups.

EXCESS GDNF DEFINES SUBSET OF SCHIZOPHRENIA WITH ENHANCED STRIATAL DOPAMINE

JO Andressoo*[1]
[1]*University of Helsinki*

Objective: Recent evidence shows that only those schizophrenia (SCZ) patients who show striatal elevation in dopamine (DA) metabolism respond to DA blocking drugs. We investigated what mechanism can be responsible for the pathologically high DA metabolism in the striatum.
Methods: We analyzed post-mortem striatal gene expression in SCZ followed by analysis of targeted proteins in the CSF of first episode psychosis patients (FEP). We then analyzed the hit in mouse models.
Results: We found that glial cell line-derived neurotrophic factor (GDNF) mRNA levels are increased in post-mortem striata of SCZ patients. GDNF is among the strongest DA function enhancing proteins known. Similar increase in GDNF protein was found in first episode psychosis (FEP) patients CSF. In mice similar increase in brain endogenous GDNF expression starting from mid-pregnancy resulted in avolition, polydipsia, pre-pulse inhibition defect, enhanced striatal and reduced prefrontal DA metabolism thus resembling striatally DA elevated patients (Mätlik et al Andressoo Mol Psych 2022). Further post-mortem analysis of individual patients striata revealed “GDNF response” gene expression pattern in about 20% of patients which aligned with data from GDNF treated human DA neurons and with data from mice where endogenous brain GDNF expression was doubled at mid-pregnancy.
Conclusion: Our data suggest that excessive GDNF signaling may explain a subset of SCZ with elevated striatal DA. Ongoing work by ERANET NEURON Consortia GDNF UpReg focuses on patient stratification based on GDNF levels and explores options for pharmacological intervention.

MITOCHONDRIA PLAY A KEY ROLE IN THE GENESIS OF SCHIZOPHRENIA-LIKE CELLULAR, MOLECULAR AND BEHAVIORAL PATHOLOGIES IN HIPSCS AND RAT MODELS

Dorit Ben-Shachar*[1], *Hila Ene1, Rachel Karry1*
[1]*Technion, Israel Institute of Technology*

Objective: Ample evidence implicate mitochondria in psychiatric disorders in general and in schizophrenia in particular. Here we will show a causative role for mitochondria in neuronal development and in behavior. We will further suggest a molecular potential target to manipulate mitochondrial function.
Methods: Isolated active normal mitochondria (IAN-Mit) were transplanted into SZ and healthy subjects-derived lymphocyte cell lines (hLCLs) and iPSCs as well as into the medial prefrontal cortex (mPFC) of the Poly I:C SZ-model and healthy rats in adolescence. Cellular, structural, molecular, mitochondrial and behavioral alterations were assessed.
Results: IAN-Mit transplantation into SZ-iPSCs ameliorated mitochondrial function, neuronal sprouting and synaptic connectivity. In rats, IAN-MIT transplantation in adolescence significantly improvement mitochondrial function, neuronal sprouting and activity, enriched proteome metabolic in and neuronal development pathways, consequently restoring mPFC-regulated behaviors adulthood. Opposite effects in all parameters were induced by IAN-Mit in healthy rats. A similar disparate phenomenon was observed in schizophrenia and healthy subjects-derived LCLs. The possibility to mimic the effect of transplanted mitochondria in LCLs by molecular means will be discussed.
Conclusion: This study demonstrates the essential role of adolescent mitochondrial homeostasis in the development of a normal functioning adult brain. In addition, in order to ameliorate mitochondrial function in SZ, we suggest an alternative molecular tool to the transplantation of the double edge sword mitochondria.

IPSC TECHNOLOGY REVEALS COMMON MECHANISMS DESPITE DISTINCT INDIVIDUAL POLYGENIC RISK PROFILES

Florian Raabe*[1]

[1]*Max Planck Institute of Psychiatry*

Objective: Genetic studies have provided correlative evidence suggesting that distinct combinations of genetic risk factors in each patient converge onto common molecular mechanisms.

Methods: To validate this notion on a functional level, a cellular model system was employed, differentiating induced pluripotent stem cells (iPSCs) from 104 individuals with high polygenic risk load and controls into cortical glutamatergic neurons (iNs).

Results: Comprehensive multi-omics profiling revealed widespread differences of numerous synaptic transcripts between iNs derived from SCZ patients and healthy donors. Moreover, omics-based analysis highlights molecular mechanisms that regulate the neuronal transcriptomes that highly correlate with SCZ polygenic risk, and the affected genes were significantly enriched for common genetic variations associated with SCZ.

Conclusion: In summary, the results highlight that iPSC technology offers great potential for deciphering molecular mechanisms in SCZ and demonstrates that distinct individual polygenic risk profiles converge in common downstream signaling pathways.

POTENTIAL CLINICAL TOOLS ACROSS PSYCHIATRIC DISORDERS: FROM BIOMARKERS TO CLINICAL MARKERS

Bo Cao, University of Alberta

Symposium Synopsis: A major goal of translational psychiatry is to develop and identify effective clinical tools that can aid in the diagnosis, prognosis, and outcome prediction of mental illnesses. These tools can be developed from a variety of sources, including cross-species biomarker findings obtained through brain imaging, clinical markers obtained through clinical and behavioral assessments, or data obtained from clinical trials about the placebo effect in mental disorders. Additionally, innovative statistical and computational techniques, such as machine learning, can be leveraged to enhance the predictive power of these tools.

In this symposium, we have invited experts from a range of disciplines to present their latest research on the diagnosis and health outcomes of depression, bipolar disorder, schizophrenia, violence, and suicide. These investigations are all aimed at developing translational tools that can improve the delivery of mental health services.

We hope that this symposium will facilitate a lively discussion on the biological and clinical foundations of these tools, as well as the challenges and concerns associated with their translation into clinical practice. We believe that this symposium will provide a unique opportunity for attendees to explore new ideas and approaches in translational psychiatry for improving mental health services. Ultimately, we hope that this symposium will contribute to the ongoing efforts to provide better mental health care for all individuals, from innovation to practice.

CROSS-SPECIES NEUROIMAGING INTERMEDIATE PHENOTYPES DEEPEN OUR UNDERSTANDING OF DEPRESSION

Huiling Guo1, Shuai Dong1, Yao Xiao1, Jingyu Yang1, Pengfei Zhao1, Tongtong Zhao1, Aoling Cai1, Hui Wang2, Ruifang Hua2, Rongxun Liu2, Yange Wei2, Dandan Sun3, Zhongchun Liu4, Mingrui Xia5, Yong He5, Yankun Wu6, Tianmei Si6, Fay Womer7, Fuqiang Xu8, Jie Wang8, Weixiong Zhang9, Xizhe Zhang10, Fei Wang*[1]

[1]*Affiliated Nanjing Brain Hospital, Nanjing Medical University., 2School of Laboratory Medicine, Xinxiang Medical University., 3The People's Hospital of China Medical University and the People's*

Hospital of Liaoning Province, 4Renmin Hospital of Wuhan University, 5Beijing Normal University, 6Peking University Sixth Hospital, Peking University, 7Saint Louis University, 8Chinese Academy of Sciences-Wuhan National Laboratory for Optoelectronics, 9The Hong Kong Polytechnic University, 10School of Biomedical Engineering and Informatics, Nanjing Medical University.

Objective: Multiple genetic variants and their interplay with environmental factors have hindered the progress of mental disease research and the development of effective markers of neuropsychiatric disorders. Intermediate phenotypes like neuroimaging brain patterns offer unique opportunities to understand multifaceted etiologies of neuropsychiatric diseases such as depression. This study identified neuroimaging intermediate phenotypes bridging etiologic differences and disease behavioral features cross species.

Methods: We established rodent genetic (P11 knockout mice, N=11) and chronic unpredictable mild stress (CUMS, N=15) models of depression to illustrate the effects of different etiologies on neuroimaging patterns of the amplitude of low-frequency fluctuations (ALFF). To identify ALFF patterns in depressed individuals that correspond to the two rodent models, we used t-Distributed Stochastic Neighbor Embedding method and an agglomerative clustering algorithm to delineate two ALFF subtypes of depression in two independent datasets (N=438). Linear regression was performed to identify which ALFF alterations predicted core symptoms of depression across species.

Results: Compared to controls, opposite ALFF patterns in subcortical and sensorimotor regions were found between P11 knockout mice and CUMS. Similarly, two ALFF subtypes with opposite patterns in frontal-subcortical, and sensorimotor regions were clustered and validated in two independent depressed cohorts. Importantly, anhedonia was significantly increased across all rodent models and human subtypes when compared to controls, despite differences in ALFF patterns. Further, anhedonia correlated with subcortical-sensorimotor ALFF in rodent models and human cohorts.

Conclusion: Overall, subcortical-sensorimotor ALFF may serve as an intermediate phenotype that bridges etiologic differences and anhedonia in depression. These results deepened our knowledge of disease mechanisms underlying depression which may facilitate translational applications of animal models to humans with depression other psychiatric disorders.

DIFFERENTIAL POWER OF PLACEBO ACROSS MAJOR PSYCHIATRIC DISORDERS

Bo Cao*[1], *Yang Liu[2], Alessandro Selvitella[1], Diego Librenza-Garcia[2], Ives Passos[3], Jeffrey Sawalha[1], Pedro Ballester[4], Jianshan Chen[1], Shimiao Dong[1], Fei Wang[5], Flavio Kapczinski[2], Serdar Dursun[1], Xin-Min Li[1], Russell Greiner[1], Andrew Greenshaw[1]*

[1]University of Alberta 2McMaster University, 3Hospital de Clínicas de Porto Alegre; Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul, 4School of Technology, Pontifícia Universidade Católica do Rio Grande do Sul, 5China Medical University

Objective: The placebo effect across psychiatric disorders is still not well understood. In the present study, we conducted meta-analyses including meta-regression, and machine learning analyses to investigate whether the power of the placebo effect depends on the types of psychiatric disorders.

Methods: We included 108 clinical trials (32,035 participants) investigating pharmacological intervention effects on major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ). We developed measures based on clinical rating scales and Clinical Global Impression scores to compare placebo effects across these disorders. We performed meta-analysis including meta-regression using sample-size weighted bootstrapping techniques, and machine learning analysis to identify the disorder type included in a trial based on the placebo response.

Results: Consistently through multiple measures and analyses, we found differential placebo effects across the three disorders, and found lower placebo effect in SCZ compared to mood disorders. The

differential placebo effects could also distinguish the condition involved in each trial between SCZ and mood disorders with machine learning. **Conclusion:** Our study indicates differential placebo effect across MDD, BD, and SCZ, which is important for future neurobiological studies of placebo effects across psychiatric disorders and may lead to potential therapeutic applications of placebo on disorders more responsive to placebo compared to other conditions.

A CLINICAL RISK PREDICTION TOOL FOR IDENTIFYING THE RISK OF VIOLENT OFFENDING IN SEVERE MENTAL ILLNESS: A RETROSPECTIVE CASE-CONTROL STUDY

Xiaoping Wang**1*

1

Chinese Society of Neuroscience and Psychiatry

Objective: Individuals with severe mental illness are at higher risk of violence than the general population. However, there is a lack of available tools to assess the risk of violence in clinical settings. We aimed to develop an easy-to-use tool to identify risk of violent offences to assist decision-making in Chinese clinical settings.

Methods: We identified 1157 patients with severe mental illness who conducted violent offending and 1304 patients who were not suspected of violent offending in the matched living areas. We used stepwise regression and Lasso's method to screen for predictors, built a multivariate logistic regression model, and performed internal validation with the K-fold method to develop the final prediction model.

Results: The risk prediction model for violence in severe mental illness included age (beta coefficient, b=0.05), male sex (b=2.03), education (b=1.14), living in rural areas (b=1.21), history of homeless (b=0.62), history of previous aggression (b=1.56), parental history of mental illness (b=0.69), diagnosis of schizophrenia (b=1.36), episodes (b=-2.23), duration of illness (b=0.01). The area under curve (AUC) for the predictive model for risk of violence in severe mental disorder was 0.93 (95% CI: 0.92-0.94).

Conclusion: A predictive tool of violent offending containing 10 items that can be easily used for individuals with severe mental illness was constructed in this study. The model was internally validated to have good discrimination and high accuracy and have potential for assessing the risk of violence in patients with severe mental illness in routine care.

PROPHYLACTIC BLUE LIGHT THERAPY IMPROVES DEPRESSION: A STUDY OF LIGHT THERAPY WITH DIFFERENT PARAMETERS

Lingli Cheng1, Ying Yan1, Yang Yu1, Ni Fan1, Hongbo He**1*

1The Affiliated Brain Hospital of Guangzhou Medical University

Objective: Previous studies have demonstrated the therapeutic value of blue light therapy for treating depression. Yet the ideal light therapy parameters are not consistent. In the present study, blue light was prophylactically used to test the antidepressant effects of different light therapy parameters. This experiment explored the antidepressant effect of different duration（2 weeks or 3 weeks, or 4 weeks）, daily exposure time（2 hours or 3 hours or 4 hours）, and frequencies (0 Hz or 8 Hz or 40 Hz) of blue light therapy on improving depression-like behaviors.

Methods: Adult male C57/BL6 mice at the ages of 7–8 weeks were used in the present study. (Corticosterone was
Corticosterone-chronic restraint stress (Cort-Crs) depression model
administered subcutaneously at a dose of 20 mg/ kg , Restraint of 2 hours/day, over 4 weeks) was performed as a stress model to study depression along with blue light therapy. The light sources in this experiment are blue light sources with three different frequencies, Its details are as follows: LED, wavelength = 462.8 nm, Tc ≥ 25,000 K, flicking frequency = 0 Hz or 8 Hz or 40 Hz, irradiation power

density = 0.3 mW/cm2. Behavioral experiments including sucrose preference, open field, and tail suspension tests were assessed to evaluate the antidepressive effects of blue light therapy. **Results:** Cort-Crs procedure induced depression like behaviors. Prophylactic blue light therapy improves improved behavioral results. The optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters. **Conclusion:** The results showed that 40 Hz light therapies are the most effective. The antidepressant effect of blue light at various durations was examined for the first time in this study. We found that three weeks of blue light therapy had the greatest antidepressant effect. Moreover, we also found that three hours of blue light therapy per day had the best efficacies. Our results reconfirmed blue light is the effective component of light therapy for treatment of depression. And we determined the optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia VII

OLIGODENDROCYTE PATHOLOGY AND COGNITION IN SEVERE MENTAL DISORDERS

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: Cognitive deficits are a hallmark of severe mental disorders and remain after the acute treatment period. These symptoms respond only limited to treatment with psychotherapy or antipsychotics and cause disability in everyday life, including functional impairments that prevent social and professional reintegration. In this symposium we add to the new view that disturbed myelin plasticity, more precisely “dysmaturation of oligodendrocyte precursor cells (OPCs)”, is a critical pathophysiological substrate of cognitive disturbance in severe mental disorders and represents an unexplored target for treatment. OPCs generate oligodendrocytes that are capable of myelination. Their dysfunction leads to disturbances in myelination, connectivity, metabolic support of neurons and – on the functional level – cognitive deficits. Recent replicated findings of decreased oligodendrocyte number in the hippocampal subregion CA4 and new data from a postmortem study of OPCs in Schizophrenia will be provided. The relation to cognitive deficits and alterations in Major Depression and Bipolar Disorder will be discussed. Insight in molecular changes related to oligodendrocytes, synaptic plasticity and energy metabolism from proteomic studies in postmortem brains, hiPSCs and organoids in Schizophrenia will be given. An overview on cognitive deficits in Schizophrenia with emphasis on different cognitive domains will be provided. Finally, recent genome-wide association studies (GWAS) in in Major Depression, their relation to the neurobiological background of cognition and an introduction on the clinical relevance of cognition in Major Depression will be discussed.

LOSS OF OLIGODENDROCYTES IN SCHIZOPHRENIA AND ITS RELATION TO COGNITIVE DEFICITS

Peter Falkai*[1], *Andrea Schmitt2, Florian Raabe2, Isabel Maurus2, Sergi Papiol2, Anna Kessel3, Konstantin Schlaaff3, Johann Steiner3*

[1]German Society for Biological Psychiatry, 2LMU Munich, 3University of Magdeburg

Objective: In a diffusion tensor imaging (DTI) study, oligodendrocyte (OL)-related gene variants, such as myelin-associated glycoprotein (MAG), were related to white matter tract integrity and cognitive performance in schizophrenia patients. Interestingly, a single nucleotide polymorphism of the OL lineage transcription factor 2 (OLIG2), which is necessary for maturation of OPCs, was also associated

with reduced white matter fractional anisotropy, indicating impaired myelination in schizophrenia. Therefore in our studies we focused on oligodendrocyte numbers in brains of schizophrenia patients and their relation to cognitive deficits. **Methods:** Using unbiased design-based stereology in postmortem brains from schizophrenia patients, we estimated total number of oligodendrozytes, neurons and astrocytes in hippocampal subregions. In an independent postmortem sample in the hippocampus we tried to replicate these findings and extended the area of interest to the white matter of the cingulum. We applied immunohistochemical staining of breast carcinoma amplified sequence 1 (BCAS1) to identify and quantify density of early myelination oligodendrocyte precursor cells in the hippocampus. **Results:** Our stereological post-mortem findings demonstrated that a reduction in the number of OLs in the cornu ammonis 4 (CA4) subregion of the hippocampus was related to cognitive dysfunction in schizophrenia patients and has impact on the neuronal Papez Circuit. In an independent sample we replicated the finding of reduced OLs in CA4 and found a reduced number of OLs in white matter of the Cingulum. Results from immunohistochemical studies will be presented. **Conclusion:** Targeting the DLPFC in schizophrenia a previous stereological study revealed a loss of OLs, pointing to a network problem involving fronto-temporal regions. Taken together, these findings show that dysconnectivity in schizophrenia is likely related to oligodendrocyte deficits. New treatment strategies are needed that target deficits in OL-related pathological processes, for example by improving differentiation of OPCs to myelinating OLs, thereby promoting myelination and optimally abolishing cognitive symptoms.Physical exercise is so far the only existing means to enhance myelin plasticity and consequently improve cognition in schizophrenia. Accumulating evidence suggests that stimulating myelin plasticity (OPC differentiation and unidentified OL-based molecular mechanisms) represents a promising and thus far unexplored mechanism to enhance cognition.

OLIGODENDROCYTES AS TARGETS FOR SCHIZOPHRENIA TREATMENT

Valéria Almeida**1*, *Daniel Martins-de-Souza2*

[1]University of Muenster, 2University of Campinas (Unicamp)

Objective: Several studies have implicated oligodendrocyte dysfunction and myelin abnormalities, including altered expression of myelin-related genes, with schizophrenia. However, the molecular mechanisms subjacent of these alterations could still benefit of more studies.

Methods: Our group aimed at characterizing the biochemical profiles of different in vitro oligodendrocyte models when treated with the classical antipsychotics such as haloperidol and clozapine as well as with novel treatments such as D-serine and different cannabinoids. For that, we mostly employed shotgun proteomics, using 2DLC–HDMSe and label-free quantitation besides cellular validation assays.

Results: Biochemical pathways commonly affected by the classical antipsychotics were mainly associated to ubiquitination, proteasome degradation, lipid metabolism and DNA damage repair. In turn, metabolic processes, especially the metabolism of nitrogenous compounds, were a predominant target of modulation of clozapine + d-serine treatment. The modulation of cannabinoid signaling in cultured oligodencrocytes was found to affect pathways linked to cell proliferation, migration, and differentiation of oligodendrocyte progenitor cells. Additionally, we found that carbohydrate and lipid metabolism, as well as mitochondrial function, were modulated by different endo- and phytocannabinoids.

Conclusion: Our results open new roads of opportunities, suggesting that cannabinoid signaling in oligodendrocytes might be relevant in the context of demyelinating and neurodegenerative diseases.

COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

Siegfried Kasper**1*

[1]*Center for Brain Research*

Objective: Cognitive dysfunction in schizophrenia has been considered as a main component of the disease in numerous publications

Methods: A summary of the literature is given including recently available data

Results: Cognitive dysfunction in schizophrenia has been shown to be a main component of the disease and can be influenced by second generation antipsychotics but not for the older types of medication called typical neuroleptics. Newer psychopharmacological approaches have been taken which will be summarised.

Conclusion: There is considerable literature and data available to address cognition in schizophrenia and the influence of specific antipsychotic medication

CLINICAL IMPORTANCE AND GENETIC UNDERPINNINGS OF COGNITIVE DYSFUNCTION IN DEPRESSION

Bernhard Baune**1*

[1]*University of Münster*

Objective: Major Depressive Disorder (MDD) often is associated with significant cognitive dysfunction, both during a current episode of depression as well as a trait before onset or between episodes of depression. The biological underpinnings of cognitive function have been explored in healthy individuals, but remains elusive in severe mental illness, such as major depressive disorder (MDD) Here investigated the genetic foundations of cognitive function in MDD.

Methods: To this end, we conducted a meta-analysis of genome-wide interaction of MDD and cognitive function using data from four large European cohorts in a total of 3510 MDD cases and 6057 controls. In addition, we conducted analyses using polygenic risk scores (PRS) based on data from the Psychiatric Genomics Consortium (PGC) on the traits of MDD, Bipolar disorder (BD), Schizophrenia (SCZ), and mood instability (MIN). Functional exploration contained gene expression analyses and Ingenuity Pathway Analysis (IPA®).

Results: We identified a set of significantly interacting single nucleotide polymorphisms (SNPs) between MDD and the genome-wide association study (GWAS) of cognitive domains of executive function, processing speed, and global cognition. Several of these SNPs are located in genes expressed in brain, with important roles such as neuronal development (REST), oligodendrocyte maturation (TNFRSF21), and myelination (ARFGEF1). IPA® identified a set of core genes from our dataset that mapped to a wide range of canonical pathways and biological functions (MPO, FOXO1, PDE3A, TSLP, NLRP9, ADAMTS5, ROBO1, REST). Furthermore, IPA® identified upstream regulator molecules and causal networks impacting on the expression of dataset genes, providing a genetic basis for further clinical exploration (vitamin D receptor, beta-estradiol, tadalafil). PRS of MIN and meta-PRS of MDD, MIN and SCZ were significantly associated with all cognitive domains.

Conclusion: Our results suggest several genes involved in physiological processes for the development and maintenance of cognition in MDD, as well as potential novel therapeutic agents that could be explored in patients with MDD associated cognitive dysfunction.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Arun Ravindran, Canadian Network for Mood and Anxiety Treatments

Symposium Synopsis: Background: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing

subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.
Methods: Strength of evidence was rated based on published literature and clinical expertise. The systematic evaluation focused on the domains of CAM therapies: lifestyle interventions, physical therapies, nutraceuticals and herbal remedies.
Results: The first presentation will focus on lifestyle interventions, including diet and smoking cessation etc., and will outline evidence and recommendations. The second presentation will provide an update on the evidence for the benefit of physical therapies, nutraceuticals and herbal remedies for the treatment of MDD, followed by two presentations on the therapeutic benefit and the proposed neurobiological mechanisms of exercise and yoga. Recent publications confirm the benefit of exercise and yoga reported in previous guidelines, which recommended its use as adjunctive treatment in mild to moderate major depression.
Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

CLINICAL GUIDELINES FOR THE USE OF LIFESTYLE-BASED MENTAL HEALTH CARE IN MAJOR DEPRESSIVE DISORDER: WORLD FEDERATION OF SOCIETIES FOR BIOLOGICAL PSYCHIATRY (WFSBP) TASKFORCE

*Wolfgang Marx1, Sam Manger2, Mark Blencowe3, Greg Murray4, Fiona Yan-Yee Ho5, Sharon Lawn6, James Blumenthal7, Felipe Schuch8, Brendon Stubbs9, Anu Ruusunen10, Hanna Demelash Desyibelew11, Timothy G. Dinan12, Felice Jacka*1, Arun Ravindran13, Michael Berk1, Adrienne O'Neil1*
Deakin University, 2James Cook University, 3Australasian Society of Lifestyle Medicine, 4Swinburne University of Technology, 5The Chinese University of Hong Kong, 6Flinders University, 7Duke University Medical Center, 8Federal University of Santa Maria, 9King's College London, 10University of Eastern Finland, 11Bahir Dar University, 12University College Cork, 13University of Toronto

Objective: The primary objectives of these international guidelines were to provide a global audience of clinicians with (a) a series of evidence-based recommendations for the provision of lifestyle-based mental health care in clinical practice for adults with Major Depressive Disorder (MDD) and (b) a series of implementation considerations that may be applicable across a range of settings.
Methods: Recommendations and associated evidence-based gradings were based on a series of systematic literature searches of published research as well as the clinical expertise of taskforce members. The focus of the guidelines was eight lifestyle domains: physical activity and exercise, smoking cessation, work-directed interventions, mindfulness-based and stress management therapies, diet, sleep, loneliness and social support, and green space interaction.
Results: Nine recommendations were formed. The recommendations with the highest ratings to improve MDD were the use of physical activity and exercise, relaxation techniques, work-directed interventions, sleep, and mindfulness-based therapies (Grade 2). Interventions related to diet and green space were recommended, but with a lower strength of evidence (Grade 3). Recommendations regarding smoking cessation and loneliness and social support were based on expert opinion. Key implementation considerations included the need for input from allied health professionals and support networks to implement this type of approach, the importance of partnering such recommendations with behaviour change support, and the need to deliver interventions using a biopsychosocial-cultural framework.

Conclusion: Lifestyle-based interventions are recommended as a foundational component of mental health care in clinical practice for adults with Major Depressive Disorder, where other evidence-based therapies can be added or used in combination. Further work is also needed to develop innovative approaches for delivery and models of care, and to support the training of health professionals regarding lifestyle-based mental health care.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Brendon Stubbs*[1]
[1]*King's College London, Institute of Psychiatry*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Kaviraja Udupa*[1]
[1]*National Institute of Mental Health and Neurosciences (NIMHANS) Hosur Road, Bangalore*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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EARLY INTERVENTION FOR BIPOLAR DISORDER: FROM CUTTING EDGE SCIENCE TO TRANSFORMATIVE CLINICAL PRACTICE

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: The success of early psychosis programs has shown that early intervention for serious mental illnesses is feasible, effective, and scalable. For example, building on the Recovery After an Initial Schizophrenia Episode (RAISE) study, a nationwide network of first episode psychosis programs called NAVIGATE was created in the United States to provide coordinated specialty care for people with schizophrenia. Early intervention is also important for bipolar disorder (BD) but early intervention efforts for BD are less advanced. This symposium will highlight scientific advances in identifying people with, and even at risk for, early-stage BD and the development of evidence based clinical interventions to treat them. We will show early results from cutting edge work using endophenotypes to identify people in the prodromal or early stages of BD. The endophenotypes of interest include cortical inhibition and mirror neuron system activity during transcranial magnetic stimulation (TMS), functional near infra-red spectroscopy (fNIRS), eye-movement tracking findings, abnormalities in retinal vasculature, and neurocognitive functioning. We will describe novel intervention programs for early-stage BD patients being developed in the United States and Canada. STRIDE, based at the University of Minnesota, adapts the NAVIGATE early psychosis model for early-stage BD. We will also show key aspects of a novel manualized psychological intervention for prodromal and early-stage BD based at the University of British Columbia. The presenters will highlight opportunities and challenges for early intervention in BD, including possibilities for harmonizing clinical research and treatment.

STRIDE: A BLUEPRINT FOR TAILORING COORDINATED SPECIALTY CARE FOR EARLY INTERVENTION IN BIPOLAR DISORDER

David Bond**1*, *Kathleen Miley2, Carissa Coudray3, Piper Meyer-Kalos3*

[1]Johns Hopkins University School of Medicine, 2Health Partners Institute, 3University of Minnesota

Objective: Early intervention for bipolar disorder (BD) has the potential to improve clinical and functional outcomes. Comprehensive clinical programs are needed. Coordinated specialty care (CSC) models such as NAVIGATE are evidence-based interventions for first episode psychosis that were widely implemented in the US and internationally following results from the Recovery After an Initial Schizophrenia Episode (RAISE) trial. We sought to adapt NAVIGATE to meet the unique needs of people with BD.

Methods: Adaptations to the NAVIGATE model for BD were determined through literature review, international expert consultation, and focus groups with stakeholders including patients, family members, and clinicians.

Results: A detailed model for CSC for BD, called STRIDE, was created based on this iterative process. Strengths of NAVIGATE, including shared decision making and a recovery focus, were maintained. Key adaptations for BD included 1) modification of psychotherapy modules to address prevention

and treatment of mood episodes, 2) new modules on circadian and social rhythms, affective regulation, and comorbidities common in BD, 3) creation of an early-stage BD prescribers manual, 4) broadened focus on health and wellbeing, 5) increased attention to co-occurring substance use disorders; 6) tailored family supports, and 7) incorporation of supported education and employment services. **Conclusion:** NAVIGATE has many strengths and can be adapted to meet the needs of people with BD. Next steps include evaluation of the feasibility of the STRIDE model.

CAN ENDOPHENOTYPES HELP IN EARLY IDENTIFICATION AND INTERVENTION PLANNING IN BIPOLAR DISORDER?

Muralidharan Kesavan**1*, *Sanjay Naik1, Ramkumar Segar1, Daniel Ritish Paul Kavati1, Abhishek Ramesh1, Nandhini Bojappen1, Shivani Sivaramkrishnan1, Preethi Reddy1, Rakshathi Basavaraju1, VijayaKumar KG1, Rajakumari P Reddy1, Urvakhsh Mehta1, Naren Rao1, Venkatasubramanian Ganesan1*

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National Institute of Mental Health and Neurosciences

Objective: The role of first-episode mania (FEM) in the progression of bipolar disorder (BD) is well studied, with reported brain structural and neuropsychological deficits soon after FEM, very early in the course of the disorder. This has been linked to poor clinical and functional outcomes. Hence, there is a need to study biological risk markers for BD, which may be present in individuals at risk for BD, even before disease onset.

Methods: about a series of investigations - in individuals very early in the course of the disorder (BD I- FEM in remission) and in individuals who are yet to develop this disorder (matched healthy individuals with family history of BD I) as compared to healthy subjects (no personal or family history of psychiatric disorders). The three groups of subjects were investigated for (1) cortical inhibition, social cognition and mirror neuron system activity using transcranial magnetic stimulation (TMS), (2) functional near infra-red spectroscopy (fNIRS) during facial emotion recognition and cognitive task performance, (3) eye-movement tracking - saccades and smooth pursuit during facial emotion processing tasks (4) abnormalities in retinal vasculature using nonmydriatic fundus camera and (5) neuropsychological functioning. They were also examined using bedside tests of neurological soft-signs, minor physical anomalies.

Results: TMS markers of cortical inhibition, inteleukin-6, executive functions, emotion processing and eye movement tracking had endophenotypic potential while the other investigations were more of a disease marker rather than risk marker. Interestingly, on all investigations, the FEM subjects differed significantly from healthy subjects indicating that these investigations have tremendous potential in differentiating remitted early bipolar disorder from healthy subjects.

Conclusion: The endophenotypic and diagnostic potential of each of these investigations as well as its translational applications in clinical practice will be discussed.

COGNITIVE ENDOPHENOTYPES AND NEUROPSYCHOLOGICAL INTERVENTIONS IN EARLY BIPOLAR DISORDER

Rajakumari Reddy**1*, *Muralidharan Kesavan1, Ivan Torres2, Nandini Bhojappa1, Shyam Sundar1, Preethi Reddy1, Jayasree Basivireddy2, Lakshmi Yatham2*

[1]National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, 2University of British Columbia

Objective: Bipolar disorder (BD) is characterized by recurrent depressive and manic episodes. First episode of mania (FEM) determines bipolarity and is universally recognized as the onset of BD. The staging model of BD proposes early intervention to be more effective, which could mitigate clinical

and neurobiological consequences of the illness. Meta-analyses have shown that euthymic BD exhibit impairment on attention/working memory, verbal memory, speed and executive functions. Unaffected siblings of BD probands tend to show impairment in executive function and verbal learning and memory suggestive of potential endophenotype markers for BD. An understanding of the course of BD from the onset or even prior, may contribute to the development of early interventions. **Methods:** Site: 1 Cross sectional study using convenient sampling method (India) Remitted First episode mania patients (FEM; n=25), first-degree relatives of patients with BD (HR; n=25) and healthy subjects (HC) Site 2: Longitudinal Study, baseline, 1-year, and 3-year time points (Canada) (FEM, n= 91, 61 healthy subjects) Assessment tools: Cognitive domains assessed using neuropsychological battery, mood scales **Results:** Visual Memory and Verbal Fluency (Executive function) have endophenotypic potential thereby emphasising need for early cognitive screening and institution of early interventions. Patients showed deficits in all domains at baseline, and longitudinal trajectories compared to healthy participants with some gains with time. Cross sectional study indicates the impairment prior to onset, longitudinal study indicates impairment but suggests changes in trajectory. Both studies indicate cognitive deficits which could have cascading effects on course and functional outcome of the patients. **Conclusion:** Integrated approach might be beneficial which in turn could have an impact on the course and outcome of the illness. The intervention initiated early may have more benefits. Components of integrated neuropsychological intervention will be discussed in this context.

A NOVEL MANUALIZED PSYCHOEDUCATION AND RESILIENCE ENHANCEMENT PROGRAM FOR INDIVIDUALS AT HIGH RISK FOR BIPOLAR DISORDER: FINDINGS FROM A FEASIBILITY STUDY

Kamyar Karamatian*[1]

[1]

The University of British Columbia

Objective: Bipolar Disorder (BD) typically emerges during adolescence and early adulthood and is associated with significant cognitive impairment and functional disability. Despite the high prevalence and large disability burden, BD often goes unrecognized and untreated for several years leading to serious consequences including greater severity and frequency of mood episodes, higher number of hospitalizations, and elevated risk of suicide. However, no evidence-based intervention program aimed at early identification of BD has yet been developed. We have recently developed a prototype manualized telehealth-based group Psychoeducational and Resilience Enhancement Program for individuals at high risk for BD (PREP-BD). The overarching objective of our study is to determine whether PREP-BD can be feasibly and effectively implemented to increase knowledge of BD, reduce self-stigma, improve help-seeking and enhance resilience in individuals who are at high risk of developing BD.

Methods: Recruitment for this study started in May 2023 and is expected to be completed in March 2024. Participants, aged 15 to 24 years, who meet the Bipolar At-Risk (BAR) criteria (Bechdolf et al., 2010) are recruited into a single-arm before-and-after pilot study to examine the feasibility and acceptability of PREP-BD. The intervention consisted of 8 weekly group sessions, each 60 minutes in duration. Participants complete the following questionnaires before and after the intervention: Help-Seeking Questionnaire, Bipolar Disorders Knowledge Scale, Self-Stigma of Mental Illness Scale-Short Form, and Connor Davidson Resilience Scale. Following the completion of the intervention, a focus group is conducted after the final intervention session to elicit rich, detailed, and first-person accounts of participants' experiences and their suggestions for improving the intervention. In

addition, participants complete a Client Satisfaction Questionnaire (CSQ-8) and the sum of the individual CSQ-8 item scores are calculated as a measure of the intervention's acceptability.
Results: To date, all participants who were deemed eligible (N=14) signed up to participate in PREP-BD. Preliminary findings from this pilot study confirmed the feasibility and acceptability of PREP-BD.
Conclusion: Although preliminary, our results suggest that a telehealth-based psychoeducational intervention can be feasibly implemented to improve help-seeking and enhance resilience in individuals who are at high risk of developing BD. Directions for future research and clinical implications will be discussed.

TRANSLATIONAL ADDICTION STUDIES OF NOVEL PSYCHOACTIVE SUBSTANCES

Aviv Weinstein, Ariel University
Symposium Synopsis: During the last decade, there has been a worldwide increase in the use and consumption of Novel Psychoactive Substances (NPS) worldwide. NPS are becoming a major health issue because of rising consumption and increasing numbers every. The acute effects of NPS and their long-term side effects are not always known, and safety data regarding their toxicity are often unavailable. Given the rapid increase in the use of NPS, their potential for dependence and abuse, and harmful medical and psychiatric effects, there is a need for pre-clinical and clinical research. The aim of this symposium is to provide an overview on pre-clinical and clinical studies of two of the major classes of NPS, synthetic cannabinoids (SCs) and synthetic cathinones. Results from preclinical studies (behavioral and neurochemical) will be presented. Dr. Maria De Luca who will start by presenting novel findings on repeated exposure to JWH-018 (a major synthetic cannabinoid) in adult and adolescent rats and mice. Dr. Matteo Marti will present studies on the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of the SCs JWH-018 and 5F-PB22 in mice. Prof. Magi Farré will present human clinical studies on Pharmacological effects and toxicity of the synthetic cathinones methylone and clephedrone (4-CMC), and after intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP) evaluating acute pharmacological effects and pharmacokinetics in plasma and oral fluid. Finally, Prof. Weinstein will discuss cognitive and brain imaging studies in regular users of synthetic cannabinoids, with a special focus on mental health.

NEUROBIOLOGICAL SEQUELAE OF THE PASSIVE OR VOLUNTARY ADMINISTRATION OF THE SYNTHETIC CANNABINOID RECEPTOR AGONIST JWH-018

Maria De Luca*[1]
[1] *University of Cagliari*

Objective: The use of Synthetic Cannabinoid Receptor Agonist (SCRA) is growing among adults and adolescents, posing major medical and psychiatric risks. JWH-018 represents the reference compound of SCRA-containing products. Our preclinical studies were performed to evaluate the enduring effects of repeated JWH-018 passive or voluntarily exposure.
Methods: Studies were performed by both passive intraperitoneal (0.25 mg/kg ip for 14 days) or vaping administration (0.3 mg/ml vapor by LJARI vapor chambers for 21 consecutive days) in adult and adolescent rats, respectively. Additional studies were performed by intravenous self-administration (lever pressing, Fixed Ratio 1–3; 7.5 µg/kg/inf) in adolescent mice.
Results: Main results, obtained 24 hours and 7 days after drug discontinuation, showed that repeated JWH-018 exposure in adult rats: (i) induced anxious/aversive behaviors; (ii) decreased spontaneous activity and number of dopamine neurons in the VTA; and (iii) decreased dopamine sensitivity in the NAc shell and core, but not in the mPFC, to a first chocolate exposure; conversely, after a second exposure, dialysate dopamine fully increased in the NAc shell and core but not in the mPFC.

Moreover, passive JWH-018 induced: (iv) astrogliosis (mPFC, NAc shell/core, VTA), microgliosis (NAc shell/core), and downregulation of CB1 receptors (mPFC, NAc shell/core). In addition, we characterized the pharmacokinetic profile of JWH-018 in adolescent male and female rat plasma after passive JWH-018 inhalation. Other studies showed that adolescent JWH-018 IVSA induced at adulthood: (i) repetitive/compulsive-like behaviors; (ii) microgliosis (CPu, NAc) and astrocytopathy (CPu), as revealed by a decreased GFAP expression; (iii) increased of the chemokines MPC1 (striatum) and RANTES (cortex), and a decrease of the cytokines IL2 and IL13 (cortex). **Conclusion:** Taken together, these data suggest that the long-lasting behavioral and neurochemical effects of JWH-018 exposures may not differ substantially as a function of passive or voluntary administration except for some specific aspects of the brain immune response, that deserve further clarification. Nevertheless, this study provides results with high translational value in the field of psychiatric disorders by examining the interaction among environmental factors that are linked to increased psychiatric risk in humans, but also shedding light on the psychiatric risk associated with SCRA vaping, a habit that is becoming increasingly popular.

SEROTONINERGIC SYSTEM IS INVOLVED IN THE PHARMACO-TOXICOLOGICAL EFFECTS INDUCED BY SYNTHETIC CANNABINOIDS IN MICE: PRECLINICAL STUDIES ON JWH-018, 5F-PB22 AND AKB-48

Matteo Marti*[1], *Giorgia Corli[1], Sabrine Bilel[1], Marta Bassi[1], Fabrizio De Luca[2], Elisa Roda[3], Carlo Alessandro Locatelli[3]*

[1]University of Ferrara, [2]University of Milan, [3]Istituti Clinici Scientifici Maugeri, IRCCS Pavia

Objective: Since their first appearance on the illicit drugs market, Synthetic Cannabinoids (SCs) have been frequently detected in biological samples from patients involved in several intoxication and death cases. Consumption of these drugs has been related with the induction of psychotic symptoms, the underlying mechanisms of which are still to be clarified.

Methods: This study primarily investigated the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of indole-based SCs JWH-018 and 5F-PB22. Secondly, changes induced by the repeated administration of the indazole-based compound AKB48 in mice and neuroplasticity at CB1 and 5HT2A receptor and SERT adaptation have been evaluated.

Results: The present results pointed out that the tested substances deeply alter sensorimotor responses, nociceptive threshold, core temperature, and motor activity in mice. Pretreatment with the selective 5HT2A receptors antagonist MDL100907 at least partially prevented acute sensorimotor disruption, as well as antinociceptive and hypothermic effects induced by both JWH-018 and 5F-PB22. On the other hand, the effects of AKB48 have been significantly influenced by the repeated treatment, as the impairment induced by the third injection was strongly reduced in respect to that of previous administration. Alongside, repeated AKB48 injection caused a rapid downregulation of CB1 receptors and SERT expression, while 5HT2A were upregulated in cerebellar areas.

Conclusion: This evidence states for the first time the relevance of serotoninergic 5HT2A receptors in mechanisms underlying pharmaco-toxicological effects of SCs that may also significantly vary with recurrent use, thus suggesting the emergence of tolerance. Ultimately, the present findings suggest the high-risk profile of SCs as drugs of abuse with reference to the embedding of a possible increased vulnerability for psychotic-like symptoms, further related to mental disorders such as schizophrenia.

SYNTHETIC CATHINONES: ACUTE EFFECTS IN HUMANS

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Objective: Cathinones are derivatives of phenylethylamine, the basic structure of amphetamines, which include a keto group, with cathinone being the most important active substance of the Catha edulis or khat shrub. In recent years, many cathinones of synthetic origin have appeared on the market, forming a relevant part of the so-called new psychoactive substances. The most important are mephedrone, methylone, methylenedioxypyrovalerone (MDPV) or eutylone, among others. These substances are consumed as alternatives to 3,4-methylenedioxymethamphetamine (ecstasy or MDMA). The information available on these substances in humans came from surveys, online description of effects and cases of intoxications. There are few published experimental studies on the pharmacokinetics and pharmacological effects associated with the administration of synthetic cathinones in humans (mephedrone, methylone).

The objective was to evaluate acute pharmacological effects and pharmacokinetics of three synthetic cathinones in humans.

Methods: This paper presents original results of the acute human pharmacology of three different synthetic cathinones. Studies were observational in a recreational setting. A group of 24 volunteers (men and women) were included. Substances include oral doses of clephedrone (4-CMC), and intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP). Vital signs and subjective effects were evaluated repeatedly along time. Samples of oral fluid, sweat and urine were collected.

Results: Results showed prototypical effects of psychostimulants in vitals and subjective effects (euphoria, well-being, empathy). The time course of effects/concentrations in saliva were faster after intranasal administration and delayed after oral administration.

Conclusion: The three new synthetic cathinones showed similar effects of other derivatives as methylone and mephedrone. Time course of effects and pharmacokinetics parameters showed some differences that can explain the preference for some substances.

THE EFFECTS OF SYNTHETIC CANNABINOIDS ON EXECUTIVE FUNCTION AND RELATED BRAIN ACTIVITY IN FMRI

Aviv Weinstein*[1], *Koby Cohen[1]*

[1]

Ariel University

Objective: The aims of our studies were to investigate the effects of chronic use of synthetic cannabinoids on the brain's structure and function, cognitive and emotional function and schizotypal personality disorder and big 5 personality traits.

Methods: Cognitive tasks measuring executive function (N-back, WCST, Go-No-GO, Stroop) Structural and functional brain imaging studies in fMRI measuring gray matter and brain activation. Questionnaires assessing depresion, anxiety, Big 5 Personality traits and schizotypal personality disorder.

Results: Synthetic cannabinoid users have exhibited overall smaller grey matter volume than control participants, and in specific regions: insula, the inferior frontal gyrus, the anterior cingulate cortex and the precuneus. These brain regions are rich with cannabinoid CB1-receptors and are associated with addictive behaviors, cannabis use and abstinence. Secondly, SC users were less accurate and showed longer reaction times on the 2-back and 1-back task than control participants. On the high the working memory load, control participants showed additional activation in both parahippocampal gyrus and the precuneus, areas associated with the default mode network. We have further found impairments in mental flexibility (WCST task), impulsivity (Go No Go task) and

response to emotional words (Stroop) in SC users. Furthermore, SC users were more depressed, had higher scores of schizotypal personality disorder and were more introverted, neurotic and less conscientious on the big five questionnaire compared with regular cannabis users and control participants. **Conclusion:** These findings may have major implications for our understanding of the long-term consequences of synthetic cannabis on cognitive and brain function. We currently run a study using F-DOPA in PET MR to assess dopamine function and neural networks in SC users which we hope to report.

PRESENTATION SKILLS WORKSHOP

Peter Falkai, German Society for Biological Psychiatry

PRESENTATION SKILLS WORKSHOP

David Castle1, Peter Falkai2, Susan Rossell3

[1]University of Tasmania, 2German Society for Biological Psychiatry, 3Swinburne University

Objective: To outline a set of strategies to enhance scientific presentations, with a view specifically to upskill more junior colleagues such that they refine and hone their presentation skills to ensure they are engaging, focussed and effective.

Methods: After a brief introduction to the topic, with basic 'do's and don'ts' of presenting skills, the three presenters will deliver examples of what they think are good and not-so-good elements and techniques, augmented by video footage of effective and not-so-effective communication styles from media, including movies and television. The presenters will then discuss amongst themselves and engage the audience in a discussion about what elements of each presentation were effective, and what was not. Tips and strategies will be provided, as well as role play opportunities provided to the audience (nobody will be forced to do anything they don't wish to do!). A particular component will be dedicated to the fine art of how to pose a 'question from the audience' in a succinct and circumscribed manner, as well as how to answer such questions politely and effectively.

Results: We will seek to deliver an interactive presentation skills workshop which will hopefully be both fun and instructive, and show numerous examples to illustrate strategies and techniques to enhance participants' skill set.

Conclusion: Presenting one's research is a key requirement for all researchers. Learning early in one's career can enhance effective skills and hopefully make the experience of future audiences better.

WHAT ARE THE SECRETS TO A GREAT CONFERENCE PRESENTATION?

Susan Rossell1
[1]Swinburne University

Objective: Presenting at conferences is a critical part of science communication for any researcher or academic. Developing a conference presentation is no different to developing any other presentation: you need to be well prepared, consistent throughout and ensure you're able to resonate with your audience. The aim of this workshop presentation will be to provide some important strategies to help deliver a great conference presentation.

Methods: One of the biggest challenges to giving a great presentation is managing your nerves. The current talk will provide some important dos and don'ts' to help you with your anxieties and deliver a professional talk.

Results: I will work through an important checklist, which will include: be prepared and map out what you are going to talk about; make sure that you work within your time constraints; use visuals appropriately; keep things simple and consistent; know your audience; rehearse, rehearse, rehearse; prepare, prepare, prepare; back up your backup; and breathe.

Conclusion: Once you have mastered these tips you will be all set to give a great presentation at any conference big or small.

HOW TO GIVE A TALK AND PRESENT MY SCIENCE AND MYSELF

Peter Falkai1, Florian Raabe2
[1]German Society for Biological Psychiatry, 2Max Planck Institute of Psychiatry
Objective: To show evidence to improve your presentation skills to give a presentation.
Methods: Narrative review of the literature and presenting own experience.
Results: Five tips are given to present yourself and your science successfully.
Conclusion: Taking some time to prepare a talk is a good investment into your career and future.

3:30 p.m. - 5:00 p.m.
Concurrent Workshop I

SEXUAL VIOLENCE AND WOMEN

Florence Thibaut, University Paris Cité

SEXUAL VIOLENCE IN ECUADOR, LATIN AMERICA

Victoria Valdez1
[1]Catholic University of Guayaquil Ecuador, Ecuadorian Society of Biological Psychiatry
Objective: Latin America has the highest rates of gender-based violence in the world, according to the Wilson Center.
Methods: This lecture will focus on gender-based violence, sexual violence concepts, societal factors, drug trafficking industry and present statistical research on this issue.
Results: Sexual violence reveals many areas that need to be explored such as migratory transit violence, migratory consequences, wars and gender-based violence.
INEC (Ecuadorian Statistics) established a total amount of gender-based violence 64.9%, sexual violence 32.7% CEPAM (ONG) complaints 8.682 (2006).
Conclusion: It is important to understand gender violence from a women's rights perspective and not merely as a criminal problem. This way, public policies on gender violence can be designed to include a more comprehensive and effective approach to prevention and treatment.

BEHAVIORAL AND NEURAL FACTORS IN GENDER-RELATED ASPECTS OF VIOLENCE AND ADDICTIONS

Marc Potenza
Objective: Males and females differ with respect to tendencies to engage in and experience violence and aggression as well as in substance and behavioral addictions that may often co-occur with violence and aggression. Understanding better such relationships and the etiological factors could help reduce the effects of aggression, violence and addictions.
Methods: Multiple methods including surveys and neuroimaging involving adolescents and adults have been used to assess and understand gender-related considerations relating to violence, aggression, and addictive behaviors. Factors related to these constructs (e.g., stress and trauma) have also been investigated using these methods, and findings from such studies will be presented.
Results: Gender-related differences exist in relationships between addictive behaviors and violence and aggression. Tendencies such as impulsivity/sensation-seeking appear particularly relevant in males, including at relatively early developmental stages. Women as compared to men tend to experience more stress and trauma in multiple domains (e.g., social, sexual) but not all (e.g., occupational), with stronger links between stress and addictive behaviors seen in women versus men. Sexual trauma is more frequently reported in females versus males, with associated adverse

effects. Gender-related differences in brain responses to stress in women versus implicate multiple cortical brain regions, resonating with gender-related responses to stress and drug cues in people with substance addictions. These findings also resonate with those from studies of youth with higher versus lower levels of childhood trauma, suggesting potential mechanisms for transgenerational cycles of risk for addictions and other poor outcomes. **Conclusion:** Understanding gender-related factors linked to violence, aggression, and addictive behaviors is important for improving the health and well-being of females and males across developmental stages. Neuroimaging approaches are being used to investigate relevant brain- behavior relationships in this regard. Translating an improved biological understanding into improved prevention, treatment and public health interventions is an important next step.

CHEMICAL SUBMISSION AND SEXUAL VIOLENCE

Florence Thibaut1

[1] *University Paris Cité*

Objective: The term chemical submission refers to a substance administration to a person without his/her knowledge to cause him/her a change in the state of consciousness and judgment. This state might be used to perpetrate sexual violence against the victim.

Methods: We will review the main characteristics of the chemical substances consumed and the profiles of victims and aggressors.

Results: It was estimated that up to 17% of sexual assaults could be classified as chemical submission due to the involuntary exposure of the victim to a psychoactive substance. Women under 20 are particularly vulnerable to this form of sexual offence.

Conclusion: Specific prevention programs and training of health personnel is crucial to make the diagnosis (Folgar et al. 2017).

In a changing world (social interactions, dating methods, new technologies) and with the increasing use of new synthetic drugs (designer benzodiazepines, GHB...), the modus operandi of the perpetrators themselves is changing and require increased vigilance at all levels (Chaouachi 2023).

WFSBP TASK FORCE TREATMENT GUIDELINES UNIPOLAR DEPRESSIVE DISORDERS

Michael Bauer, Technische Universität Dresden

RAPID-ACTING ANTIDEPRESSANT TREATMENTS: WHERE IS THEIR PLACE IN THE TREATMENT PATHWAY

Allan Young, King's College London

Background: Mood disorders impose the largest disease related burden related to mental ill-health in adults. Although effective treatments exist, many patients are treatment resistant. New rapidly acting antidepressant treatments (RAATS) are becoming available but their place in the treatment pathway remains to be fully determined.

Objectives: To review the evidence base and science related to RAATS (psychedelics, (s)ketamine).

Methods: Evidence and literature-based workshop.

Findings: Discussion about RAATS in the treatment pathway for mood disorders.

Conclusion: Conclusions: RAATS will play a part in our future treatment pathways.

TREATMENT-RESISTANT DEPRESSION (TRD)

Anthony Cleare1

[1] *Institute of Psychiatry, King's College London*

Objective: To discuss the definitions and epidemiology of TRD

To discuss latest evidence regarding pharmacological and other augmentation strategies in TRD

Methods: Synthesis of literature.
Results: Key findings in TRD include: (1) The need for continued refining of how we diagnose, stage and stratify patients with TRD; (2) Extensive treatment gaps, where few patients are getting optimal treatment (3) accumulating evidence that augmentation strategies are an effective option in TRD and (4) evidence that the poor naturalistic prognosis for many with TRD can be improved using optimised treatment. Data on comparative efficacy of augmentation strategies will be discussed.
Conclusion: TRD remains a key clinical problem. Synthesis of the latest evidence helps us understand the important, pharmacological, role that augmenting antidepressant therapy (with psychotherapeutic and/or neurostimulatory add-on treatments) can play in improving long term outcomes in TRD.

MODERN TREATMENT GUIDELINES: METHODOLOGICAL AND TECHNICAL ASPECTS

*Andrea Pfennig*1, Michael Bauer2, Bettina Soltmann1*

[1]University of Technology Dresden, 2German Society for Biological Psychiatry; University of Technology Dresden

Objective: Methodological and technical aspects of the development of modern treatment guidelines will be presented and discussed. Propositions for the future WFSBP guideline development will be deduced.
Methods: International standards for guideline development will be briefly summarized. The methods applied in the current version of the WFSBP treatment guidelines will be presented.
Results: Challenges in the developmental process of the current version of the WFSBP treatment guidelines will be discussed.
Conclusion: Strategies for the further development of WFSBP treatment guidelines will be presented and discussed including propositions to implement processes of living guideline concepts.

ESTABLISHED AND NOVEL ANTIDEPRESSANT APPROACHES IN THE TREATMENT OF MOOD DISORDERS

Philipp Ritter1

[1]Technische Universität Dresden

Objective: Pharmacological compounds targeting neural components of the monoaminergic signalling system remain the mainstay of treatment for mood disorders. Comparative efficacy, differing side effects profiles and special indications will be reviewed. These classical approaches have more recently been augmented by novel neurostimulatory techniques such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS). The heterogenous landscape of implementation protocols and current evidence base for antidepressant efficacy will be reviewed.
Methods: Evidence and literature-based workshop.
Results: Discussion on the pharmacological and neurostimulatory treatment of mood disorders.
Conclusion: Traditional pharmacological approaches in the treatment of depressive episodes may in future be augmented or in some cases superseded by neurostimulatory approaches to accelerate response and reduce side effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Peter Fried, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Mouhsin Shafi1

[1]Beth Israel Deaconess Medical Center

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.

Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.

Applications Across Neuroscience and Clinical Practice: The workshop will explore the diverse applications of NIBS techniques, including cognitive enhancement, neurophysiologic assessments, treatment of neuropsychiatric disorders, and neurorehabilitation. In-depth discussions will revolve around case studies and ongoing research projects.

Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).

Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions.

Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.

Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF CONCURRENT TRANSCRANIAL ELECTRICAL STIMULATION AND MAGNETIC RESONANCE IMAGING

Shirley Fecteau1

[1]Universite Laval Faculty of Medicine

Objective: We will discuss the use of Transcranial Electrical Stimulation (tES) in patients with neuropsychiatric disorders. We will first describe the main stimulation parameters to consider and the choice of study designs to optimize scientific rigor and clinical responses. We will also address concerns of negative results and the importance of including neuroimaging in tES studies in order to understand its clinical efficacy (or lack of).

When developing neuropsychiatric interventions, it is recommended to measure the hypothesized mechanisms of therapeutic change. Here, the hypothetical mechanism underlying the reduction of a given set of neuropsychiatric symptoms is that tES will modulate brain activity associated with these symptoms. In previous studies, we aimed to reduce symptoms or improve cognition, without identifying the effects of tES on brain activity. A limit of this approach is that when we get null results,

we do not know if they are because tES did not modulate brain activity associated with the targeted symptoms. Also, when the goal is to induce lasting clinical benefits, several tES sessions must be delivered, for example daily sessions for 4 weeks. The effects of a single tDCS session are short-lived. Therefore, before conducting long-term clinical trials, it is important to know whether the proposed tES parameters will likely modulate brain activity relevant to the targeted symptoms.
Methods: We conducted a series of concurrent tES-MRI studies. Specifically, we performed functional and spectroscopic MRI before, during and after tES in groups of healthy adults and adults with substance-related and addictive disorders. Our main questions were: 1) Does tES reach the cortex sufficiently to modulate brain activity? These patients often have cortical abnormalities that may prevent the current from sufficiently reaching the cortex. 2) If tES reaches the cortex, are these effects on brain activity relevant to the targeted symptoms? In this workshop, we will also discuss and demonstrate the technical aspects of how to concurrently use tES and MRI.
Results: Main findings indicate that tES can modulate functional connectivity and neurotransmitters levels. Some of these effects are significant during and/or after stimulation. Some are observed in healthy adults but not in patients, and vice versa. Further, some morphometric properties such as smaller frontal volume in patients correlate with changes induced by tES on functional connectivity and neurotransmitter levels. Functional connectivity of some networks prior to tES can predict tES changes on functional connectivity. Interestingly, none of the published studies from various teams (e.g., delivering tES on both frontal regions found functional connectivity changes inhibitory/excitatory effects) between these frontal regions, despite knowing that the current travels from the anode to the cathode electrodes. The effects are proximal or/and distal to the electrodes (e.g., fronto-parietal network).
Conclusion: Concurrent use of tES and neuroimaging can greatly contribute at understanding the mechanisms of tES and its clinical benefits. Findings from such study designs also contribute at building and developing more specific hypotheses of tES effects, such as potential effects during and after stimulation and how functional connectivity, and priming such connectivity, might influence tES effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Paula Davila Pérez1
1
Hospital Universitario Rey Juan Carlos

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.
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Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).
Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision

targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions. Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development. **Conclusion:** Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Asli Demirtas-Tatlidede1
1

Bahcesehir University, Faculty of Medicine, Istanbul

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.
Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.
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Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.
Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

BIG DATA APPROACHES TO DISCOVER DISEASE MECHANISMS OF MENTAL ILLNESS *Ole Andreassen, University of Oslo*

Symposium Synopsis: The last decade has marked a period of growth in psychiatric genetics with new insights into the genetic etiology of psychiatric disorders. As the heritability and the extensive polygenicity of psychiatric disorders are now recognized, gaining a better understanding of the genetic architecture of each disorder is important. Driven by the discoveries of large consortia and big data efforts, large-scale genetic studies have uncovered many common and rare genetic variants associated with psychiatric disorders and related traits. However, there is still much unknown about the underlying disease mechanisms and potential for clinical utility.

As the field progresses and the datasets get larger, there is a need for advanced mathematical approaches. Such big data methodology for translating genetic findings into biological and clinical interpretations are critical to understand the disease mechanisms of psychiatric disorders. We will discuss new big data approaches in psychiatric genetics, to improve discovery, fine-mapping strategies, imaging genetics and clinical utility.

Dr. Nadine Parker (Canada) will present brain imaging genetics results. Dr. Bayram C. Akdeniz (Cypres) will introduce the MiXeR; a causal mixture model tool for estimating the number of causal variants. Naz Karadag (Turkey) will show how the (ConjFDR) tool identifying genetic overlap between neurological disorders and psychiatric disorders. Dr. Shahram Bahrami (Iran) will present the Multivariate Omnibus Statistical Test (MOSTest) and discuss the genetic architecture of hippocampal formation across brain disorders.

These four speakers will highlight the importance of big data approaches in psychiatry, enabling a better understanding of psychiatric disorders and their underlying brain mechanisms.

GENETIC OVERLAP BETWEEN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

*Naz Karadag1, Shahram Bahrami1, Guy F. L. Hindley2, Ole Kristian Drange3, Alexey A. Shadrin1, Srdjan Djurovic4, Anders M. Dale5, Oleksandr Frei1, Ole A. Andreassen6, Olav B. Smeland6, Guy Hindley*7*

1University of Oslo, 2University of Oslo; King's College London, 3Norwegian University of Science and Technology; St. Olavs Hospital, Trondheim University Hospital, 4Oslo University Hospital; University of Bergen, 5University of California, 6University of Oslo; Oslo University Hospital, 7NORMENT, Centre for Mental Disorders ResearchOslo University Hospital, Institute of Clinical Medicine, University of Oslo

Objective: Neurological disorders and psychiatric disorders are heritable brain disorders with overlapping clinical features and high comorbidity. However, the etiological mechanisms underlying the relationships between these disorders are poorly understood. In a series of projects we have aimed to identify overlapping genetic loci between specific neurological and psychiatric disorders to gain a better understanding of their comorbidity and shared clinical features.

Methods: We analyzed non-overlapping genome-wide association study (GWAS) data in over a million participants for neurological disorders epilepsy, migraine, Parkinson's disease and Alzheimer's disease; and for psychiatric disorders schizophrenia, bipolar disorder and depression. We analyzed GWAS summary data using the conjunctional false discovery rate (conjFDR) statistical tool to increase power for locus discovery. Identified genetic loci were then functionally annotated using FUMA.

Results: We find cross-trait genetic enrichment in neurological disorders conditional on associations with psychiatric disorders, and vice-versa, which indicates genetic overlap between these disorders. Several genomic loci have been identified between neurological disorders and psychiatric disorders.

Many of these loci show mixed effect directions, in line with the absent or weak genetic correlations previously reported between these disorders. **Conclusion:** The genetic overlap with mixed effect directions between neurological disorders and psychiatric disorders demonstrates a complex genetic relationship between these disorders and indicates that overlapping genetic risk may contribute to shared pathophysiological and clinical features between brain disorders.

DISTRIBUTED GENETIC ARCHITECTURE ACROSS THE HIPPOCAMPAL FORMATION IMPLIES COMMON NEUROPATHOLOGY ACROSS MAJOR BRAIN DISORDERS

Shahram Bahrami**1*, *Kaja Nordengen1, Alexey A. Shadrin1, Oleksandr Frei1, Dennis Van der Meer2, Anders M. Dale3, Lars T. Westlye1, Ole A. Andreassen1, Tobias Kaufmann4*

[1]University of Oslo, 2University of Oslo; Maastricht University, 3University of California, 4University of Oslo; University of Tübingen

Objective: The hippocampal formation on each side of the medial temporal lobes of the brain plays critical roles in spatial and episodic memory, navigation, emotions, and other complex human behaviours, yet is unexplored about the genetic architecture of the hippocampal formation and its involvement in psychiatric and neurological disorders.

Methods: First, we used multivariate genome-wide association analysis in volumetric data from 35,411 individuals from the UK Biobank (age range: 45–82 years, mean: 64.4 years, s.d.: 7.5 years, 51.7% females) for the main analysis, and of 5262 individuals with non-white ethnicity (age range: 45–81, mean: 62.9, s.d.: 7.6 years, 53.6% females) for the replication in independent data. Second, we used summary statistics from recent large-scale GWAS of total hippocampus volume to identify genetic overlap with eight major developmental and degenerative brain disorders (autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), schizophrenia (SCZ) and bipolar disorder (BIP), migraine (MIG), major depression (MD), Parkinson's disease (PD) and Alzheimer's disease (AD)) by conjunctional FDR statistics (FDR < 0.05).

Results: We revealed 173 unique genetic loci with distributed associations across the hippocampal formation including 153 loci that had not been previously identified. Also, Conjunctional FDR analysis allowed us to test for shared loci between the hippocampus and each of the disorders. We identified 8 loci significantly overlapping with ADHD, 4 loci with ASD, 77 with BIP, 161 with SCZ, 41 with MD, 80 with MIG, 19 with AD and 10 loci significantly overlapping with PD.

Conclusion: Our results suggest a polygenic architecture of the hippocampal formation, distributed across its subregions. The genetic overlap with various brain disorders with typical onset at different stages of life implicated genes, where common genes suggest partly age- and disorder-independent mechanisms underlying hippocampal pathology and it may be relevant targets for future studies.

GENETIC OVERLAP BETWEEN PSYCHIATRIC DISORDERS AND WHITE MATTER MICROSTRUCTURE IMPLICATE DEVELOPMENTAL AND NEURAL CELL BIOLOGY

Nadine Parker**1*, *Weiqiu Cheng1, Pravesh Parekh1, Guy F. L. Hindley2, Alexey A. Shadrin1, Anders M. Dale3, Oleksandr Frei1, Ole A. Andreassen1*

[1]University of Oslo, 2University of Oslo; King's College London, 3University of California San Diego

Objective: Many psychiatric disorders are associated with variations in brain white matter microstructure. A better understanding of the shared genetic basis of psychiatric disorders and white matter microstructure may provide insights into the biological underpinnings of these reported associations. This study aims to characterize the shared genetic architecture between three psychiatric disorders [bipolar disorder (BIP), major depressive disorder (MDD), and schizophrenia (SCZ)] and white matter fractional anisotropy (FA) as well as uncover potential underlying biology.

Methods: Summary statistics were acquired from genome-wide association studies (GWAS) of BIP, MDD, and SCZ from the Psychiatric Genomics Consortium as well as a GWAS of FA performed with UK Biobank participants. Genetic architecture (polygenicity and discoverability) and genetic overlap (genetic correlations and overlapping trait-influencing variants) were estimated along with identification of shared loci. Shared variants were mapped to genes and tested for enrichment among neurodevelopmental, cellular, and molecular gene-sets. The main analyses used average FA across brain white matter while secondary analyses assessed genetic overlap for 21 white matter tracts. **Results:** The polygenicity of BIP, MDD, and SCZ were at least seven-times greater than average FA, although, average FA was more genetically discoverable. Average FA shared an estimated 42.53%, 42.99%, and 90.68% of trait-influencing variants with BIP, MDD, and SCZ, respectively. Additionally, 12, 4, and 28 shared loci were identified for average FA with BIP, MDD, and SCZ, respectively. Enrichment analyses implicated neurodevelopmental gene expression, astrocytes, microglia, myelin, and cell adhesion molecules. The degree of these gene-level associations varied across each psychiatric disorder implicating differing underlying biology. For BIP and SCZ, case vs control tract- level differences in FA correlated with genetic correlations between those same tracts and the respective disorder. Tract-level analyses recapitulated a similar pattern of greater genetic overlap for SCZ followed by BIP and MDD. **Conclusion:** This study shows that BIP, MDD, and SCZ exhibit a polygenic overlap with white matter FA. This supports theories suggesting some psychiatric patients have impaired integration between brain regions while providing potential biological underpinnings.

FINEMAPPING CAUSAL VARIANTS IN HUMAN GENOME USING MIXER MODEL: CURRENT RESULTS AND FUTURE DIRECTIONS

Bayram Akdeniz*[1], *Oleksandr Frei[1], Alexey Shadrin[1], Dmitry Vetrov[2], Dmitry Kropotov[3], Eivind Hovig[4], Ole Andreassen[1], Anders Dale[5]*

[1] NORMENT Centre, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, [2]National Research University Higher School of Economics, Moscow, [3]Lomonosov Moscow State University, [4]Centre for Bioinformatics, University of Oslo, [5]Center for Multimodal Imaging and Genetics, University of California San Diego

Objective: Discoveries from genome-wide association studies can be hard to interpret especially due to the highly correlated genetic variants. Finemapping studies, which aim to identify causal SNPs associated with a trait at a given locus after controlling for correlation among genetic variants, become important in such cases. There are many proposed finemapping methods in the literature that focused on this problem using different approaches [1]. Among these methods, Bayesian methods demonstrated their effectiveness. FINEMAP [2] and SuSiE [3] methods can be considered some of those successful Bayesian methods in terms of accuracy and computational complexity. Our aim in this work is to develop a new finemapping method using a variational Bayesian approach and MiXeR model [4].

Methods: We propose a variational Bayesian approach for finemapping genomic data based on the optimization of Evidence Lower Bound (ELBO) of the likelihood function obtained from MiXeR model. Particularly, we derived the likelihood function of summary statistics using MiXeR model and then ELBO of this likelihood function is determined for optimization. The optimization is done by Adaptive Moment Estimation Algorithm by using the first derivatives of ELBO and corresponding posterior probabilities of being causal are obtained accordingly.

Results: We have tested our method on synthetic data (N=10.000) and UK Biobank (UKB) genome data (N=337.145) with standing height as the phenotype by comparing with FINEMAP and SuSiE. According to the results in both scenarios, our method has given promising results in terms of

accuracy to pinpoint actual causal variants and estimate the phenotype. In the extensive number of experiments both on synthetic data and UKB data, our method gives superior results compared to other methods in the majority of these experiments. **Conclusion:** We have developed a novel finemapping method using the MiXeR model to detect actual causal variants and estimate phenotype. The initial experiments gave promising results compared to the existing methods in the literature. Our next aim is to apply our method to mental disorders to identify underlying causal variants. Furthermore, we are focusing on expanding our mathematical model for cross-trait and trans-ethnic analysis. Another future work is integrating our approach with GSA-MiXeR gene set enrichment analysis to use enriched priors which leads to potential performance improvement [5].

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Saturday, June 8, 2024
8:00 a.m. - 9:00 a.m.
Plenary Session IV- Guy Goodwin

CAN WE RE-MEDICALISE THE PSYCHEDELIC EXPERIENCE?

Guy Goodwin1
[1]University of Oxford

Objective: Despite the widespread availability of multiple antidepressant treatments, depression remains a common and oftentimes debilitating disorder. A proportion of patients with major depressive disorder fail two or more antidepressant treatments and are considered to have treatment-resistant depression (TRD). Recent attention has turned to psilocybin and other psychedelic compounds as potential rapidly acting and durable episodic treatments for psychiatric disorders including depression.

Methods: COMP 001 was the first large, multinational, randomized controlled trial to evaluate the investigational drug COMP360, a proprietary pharmaceutical-grade synthetic psilocybin formulation, optimized for stability and purity, developed by the sponsor COMPASS Pathfinder Ltd in patients with TRD. This was a dose-ranging study that randomized 233 participants equally to 25mg or 10mg, or the 1mg control treatment. Participants down-tapered and washed out any previous antidepressant medications, and received a single administration of COMP360 as monotherapy, after which they were followed for 12 weeks.

Results: On the primary efficacy measure, large dose-dependent reductions from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) scores were evident starting from Day 2. Clinically meaningful differences in MADRS score improvements between the 25mg and 1mg doses were statistically significant through week 6 and remained numerically evident at week 12. Results of secondary and additional efficacy measures were consistent with MADRS results.

Conclusion: COMP360 was generally well-tolerated; in both studies over 90% of adverse events were either mild or moderate in severity. Suicidality remains a concern in TRD studies. These results suggest that COMP360 has potential to become an important contribution to the treatment for TRD and warrant the further clinical development of COMP360 in rigorous, large, randomized controlled studies.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VIII

PREVENTING AND AMELIORATING TREATMENT-RESISTANT DEPRESSION: BEST PRACTICE AND BEYOND

Allan Young, King's College London

Symposium Synopsis: Depression is the leading cause of disability worldwide, despite the many effective pharmacological and non-pharmacological treatment options available. Treatment-resistant depression (TRD), which is often defined as an insufficient response to two or more adequate treatment trials, affects up to 50% of those with depression. TRD is associated with poorer prognosis, higher mortality, and higher healthcare utilisation costs. With every additional treatment step for depression comes a decreased likelihood of response, and therefore it is critical to optimise care at the earliest possible stage of illness. This symposium will focus on avenues to improving best practice care for depression, with a focus on reducing treatment resistance. Our speakers will cover their work focused around best practice augmentation options for TRD, probiotics as potential novel augmentation options, the potential use of inflammatory markers for treatment stratification and

optimising response through pharmacogenetic-informed treatment selection. All four avenues could provide hope for enhancing the future care of people with depressive illness.

PHARMACOLOGICAL AUGMENTATION STRATEGIES FOR TREATMENT RESISTANT DEPRESSION

Anthony Cleare**1*

[1]*Institute of Psychiatry, King's College London*

Objective: Pharmacological augmentation is one of the most effective interventions for treatment resistant depression (TRD), with accumulating evidence that it may be more effective than antidepressant-switching strategies. However, very few patients with TRD receive augmentation treatment (between 0.2% and 11% depending on setting). The most often recommended first line therapies are lithium, quetiapine and aripiprazole, with other well supported options including thyroid hormone, risperidone, olanzapine, (es)ketamine, mirtazapine, buspirone, lamotrigine and bupropion (British Association for Psychopharmacology/Maudsley Guidelines).

Methods: Despite a relative paucity of RCTs, network metanalyses have helped gain a broad feel for the relative efficacy of the available augmentation strategies, at least in the acute phase. However, relatively few studies directly comparing augmentation treatments head-to-head have been undertaken, and none have looked at longer term outcomes. The LQD Study is a pragmatic RCT that directly compared two of the first line augmentation treatments, lithium and quetiapine, in patients who had failed to respond to at least two adequate antidepressant treatment trials. Clinical and health economic outcomes were collected over 1 year of treatment to address the lack of knowledge regarding longer term effects. Additionally, as TRD response is highly variable with patients often moving between response/remission, partial response and relapse, longitudinal assessment was undertaken using weekly depression ratings.

Results: Detailed results from the LQD study will be presented, including comparative clinical outcomes with lithium versus quetiapine, cost-effectiveness analyses and differential predictors of treatment response.

Conclusion: Pharmacological augmentation strategies for TRD remain underused yet effective treatments. Results from the LQD study add further evidence for their long term efficacy, and will help clinicians in the choice of first line treatment options.

PROBIOTICS AS PUTATIVE AUGMENTATION STRATEGY IN DEPRESSION

Viktoriya Nikolova**1*, *Anthony Cleare2, Allan Young2, James Stone3*

[1]*ADM Protexin, 2King's College London, 3Brighton and Sussex Medical School*

Objective: Research over recent years has outlined a clear role for the microbiota-gut-brain axis in the pathophysiology of depression and has given rise to the development of novel intervention strategies, such as probiotics. However, clinical trials of probiotics are still scarce and further safety and efficacy data are needed to support this treatment approach. Further, their underlying mechanisms of action in clinical populations remain largely unknown.

Methods: Data from meta-analyses identifying the most appropriate mode of administration of probiotics and the gut microbial alterations associated with depression will be presented. Then, this talk will focus on novel findings from a double-blind placebo-controlled pilot trial (RCT) that examined the effects of an 8-week adjunctive multi-strain probiotic intervention in adults with depression taking antidepressants. In addition to psychiatric and safety data, stool and blood samples were collected and a computer-based emotion recognition task was performed.

Results: 49 participants (18-55 years, n=38 female, residing in London, UK) were included in intent-to-treat analyses (n=24 probiotic, n=25 placebo) in the RCT. The intervention was acceptable and well-tolerated with 8% attrition rate (n=3 placebo, n=1 probiotic), 97% adherence rate and no serious

adverse reactions. Standardised effect sizes (SES) from linear mixed models demonstrated that the probiotic group attained greater improvements in depressive (IDS week 8: SES [95%CI]= 0.64 [0.03, 0.87]) and anxiety symptoms (HAMA week 8: SES [95%CI]= 0.79 [0.06, 1.05]), compared to the placebo group. 16SrRNA sequencing of stool samples indicated the probiotic was able to positively modulate the gut microbiota: (i) there was an increase in richness only in the probiotic group ($p < 0.05$); and (ii) post-treatment, only the placebo, but not the probiotic group, had significantly decreased alpha diversity compared to demographically matched healthy controls ($p < 0.05$). The probiotic increased levels of several bacteria, of which Bacilleceae and genus Bacillus remained significant post-FDR correction and correlated with anxiety improvement (rho=-0.43,$p < 0.05$). There was no impact on inflammatory cytokines (CRP, TNFα, IL-1β, IL-6, IL-17) or BDNF; however, probiotics showed a tendency to increase positive affective bias. **Conclusion:** Our research indicated that, compared to placebo, 8-week adjunctive probiotic intake resulted in greater and clinically meaningful improvement in depressive and anxiety scores. The beneficial effects of probiotics were partially mediated by modification of gut microbiota composition. The acceptability, tolerability and estimated effect sizes on key clinical outcomes encourage further investigation of probiotics as augmentation strategy in depression in large-scale clinical trials, with an expanded evaluation of mechanisms.

OPTIMISING RESPONSE THROUGH PHARMACOGENETIC-INFORMED TREATMENT SELECTION

Roos van Westrhenen*[1]

[1] *Parnassia Psychiatric Insitute, Amsterdam*

Objective: Pharmacogenetics is a discipline that investigates genetic factors that affect the absorption, metabolism, and transport of drugs, thereby affecting therapy outcome. These genetic factors can, among other things, lead to differences in the activity of enzymes that metabolize drugs. Studies in depressed patients show that genotyping of drug-metabolizing enzymes can increase the effectiveness of treatment, which could benefit millions of patients worldwide. The audience will be updated on the potential of pharmacogenetics for psychiatry.

Methods: The current status quo of pharmacogenetics in psychiatry will be provided, by presenting an overview of relevant studies, available guidelines and also ongoing projects.

Results: The European guideline on clinical implementation of pharmacogenetics in psychiatry will be shortly discussed, as well as the other available guidelines on pharmacogenetics from the Dutch Pharmacogenetic Working group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). An overview of currently performed clinical studies in psychiatry will be provided, including the recently published Dutch PREPARE trial and the current ongoing Horizon2020-funded PSY-PGx project (www.psy-pgx.org).

Conclusion: Pharmacogenetics can be used to fine-tune medication prescription by assisting in selecting medication type and dosage, for indivdual patients. Guidelines are available for prescribing antidepressants and clinical application will be discussed. The actual implementation of pharmacogenetics in psychiatry is ongoing work and in this lecture potential ways forward will be suggested.

References:

1. Editorial: From Trial and Error to Individualised Pharmacogenomics-Based Pharmacotherapy in Psychiatry R. van Westrhenen and M. Ingelman-Sundberg Frontiers in Pharmacology, 2021 doi: 10.3389/fphar.2021.725565

2. Policy and practice review: A First guideline on the use of pharmacogenetics in clinical psychiatry. R. van Westrhenen e.a. Frontiers in Pharmacology, 2021 doi.org/10.3389/fphar.2021.640032

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CAN WE USE INFLAMMATORY MARKERS TO PERSONALISE TREATMENT FOR TREATMENT-RESISTANT DEPRESSION?

Rebecca Strawbridge**1*, *Estefany Izurieta2, Allan Young2, Anthony Cleare2*

[1]Institute of Psychiatry, King's College, 2King's College London

Objective: It is now established that a subgroup of individuals with depressive illness have immune dysregulations. Treatment-resistant depression is frequently associated with elevated pro-inflammatory biomarkers, and it is likely that some recommended treatments for TRD have downregulatory effects on inflammation. This symposium will consider the effects of TRD treatments on inflammation and inflammatory biomarkers as putative predictors of (differential) treatment responses in TRD.

Methods: The symposium will present findings from naturalistic observational treatment studies in populations with (treatment resistant) depression and systematic review of the effects of recommended TRD treatments on peripheral inflammatory biomarkers across populations of patients.

Results: Ketamine and aripiprazole may reduce pro-inflammatory states. Despite mechanistic and preclinical support for ECT and lithium as anti-inflammatory, evidence of these effects in humans is mixed. Quetiapine may have less anti-inflammatory effects and be more suitable for patients without an apparent inflammatory component to TRD illness. More evidence is required for other therapies with potential anti-inflammatory effects, such as bupropion. Although overall, elevated inflammatory states precede a poor response to treatments in depression, there are some agents which appear to be more beneficial for patients with inflammatory dysregulations.

Conclusion: Inflammatory markers could be used to stratify individuals to optimised treatment. Particular treatments with anti-inflammatory mechanisms may be recommended for those with high inflammation, whereas others may be more suitable for patients without. This avenue of research has the potential to enhance TRD care by directing patients to the 'right' treatment earlier in the course of illness.

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: BIOMARKERS FOR STAGING AND INTERVENTIONS FOR PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Neuroprogression subsumes the progressive, recurrent and relapsing course of a specific disorder. In some instances, it is possible to ‘stage’ the course of the disorder based on clinical manifestations, and, to the extent that morphological, biochemical, neurochemical, immunological, physiological and genetic aspects have been established, such parameters as well. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, and loss of synaptic plasticity.

The presenters will discuss the potential utility of specific methods and biomarkers that may assist in identifying vulnerability, determining the stage of the neuroprogressive course, and arrest neuroprogression by utilizing appropriate interventions. Better endophenotypes for affective

disorders are needed to study their neurobiological correlates. Results from a GWAS study on affective temperaments will be presented to demonstrate how polygenic risk scores help understand their association with depressive phenotypes and in interaction with stressors. Development of biomarker profiles to predict mood disorders may also contribute to their staging. Depression with increased inflammation is associated with neurodegenerative changes in corticostriatal and corticolimbic structures and default mode circuitry, affective, and cognitive symptoms – predicting the risk of development of MCI and a neuroprogressive dementia course. Electrical brain activity and the its course in recurrent affective disorders assist in staging and possibly predicting neuroprogressive of course. Lastly, lithium has been associated with neuroprotective or neurotrophic effects. Using neuroimaging and preclinical studies, the model that lithium acts as a synaptic modulator and thus slows neuroprogression in affective disorder will be presented.

POLYGENIC RISK SCORES FOR AFFECTIVE TEMPERAMENTS MAY HELP PREDICT THE ROUTE TOWARDS DEVELOPMENT OF MOOD DISORDERS AND MAY AID STAGING

Xenia Gonda*[1], *Dorka Gyorik1, Zsofia Gal2, Gyorgy Bagdy2, Gabriella Juhasz2*

[1]*Semmelweis University, 2Semmelweis University; NAP-2-SE Neurochemistry Research Group*

Objective: Affective disorders show a moderate-to-high heritability depending on their severity. Furthermore, they are also characterised by remarkable heterogeneity which is paralleled by an equally divergent neurobiological and genetic background. Different subtypes of depression also differ in the relative weight of contributing genetic-internal and environmental-external factors, with the majority of genes playing a role in depression mediating the effects of stress. It is in part due to this large etiological heterogeneity that we still do not fully understand the biological background and genetic determinants of affective disorders. Identifying clinically relevant endophenotypes thus would aid research, and, consequentially, help us find better genetic and other biomarkers for screening, prediction and intervention. Affective temperaments, considered the subclinical manifestation of mood disorders and when present in a dominant form. In the present study we carried out a GWAS of affective temperaments, generated polygenic risk scores (PRS) and investigated their effect on depressive phenotypes in interaction with early traumas and recent life stressors.

Methods: Results of our previous GWAS on affective temperaments as measured by TEMPS-A in a general population was used as a discovery sample. The NewMood database containing 1820 European general population subjects' data on current depression measured by the BSI, as well as data on early childhood traumas and recent severe negative life events occurring in the past 12 months was used as the target sample. We calculated polygenic risk scores for the five affective temperaments (depressive, cyclothymic, irritable, anxious and hyperthymic) using PRSice and adjusting all models for age, gender and the first ten principal components. To calculate the empirical p-value, 10000 permutations were run. In the next step, we analysed the interaction of the five PRS-s with early traumas and recent stress using linear regression models.

Results: Polygenic risk scores calculated for anxious, cyclothymic, depressive and irritable temperaments had a significant effect on severity of current depressive symptoms explaining 0.26-0.71% of variance. In interaction with early childhood traumas, anxious, depressive and hyperthymic temperaments had a significant effect on current depression explaining approximately 10% of variance. Considering a combined effect of early childhood traumas and recent life stress, depressive temperament had a significant effect explaining 13.95% of the variance of current depression severity.

Conclusion: Our findings support the genetic and neurobiological role of affective temperaments in the development of affective disorders and may be useful for prediction and risk screening, as well

as for identifying both psychotherapeutic and pharmacological targets for intervention and possibly for prevention. The next step is to analyse the association of affective temperament PRS-s with different neuroprogressive stages in depression.

INFLAMMATION AND NEURODEGENERATION IN DEPRESSION

Ebrahim Haroon*[1], *Xiangchuan Chen1, Diana Beltran1, Deqiang Qiu1, Felicia Goldstein1, Blaine Roberts1, Jennifer Felger1, Andrew Miller1*

[1]*Emory University School of Medicine*

Objective: Depressed patients experience a 2-5 times higher risk of neurodegenerative disorders, including Alzheimer's dementia. However, predisposing risk factors that enable clinicians to stratify risk and initiate preventive measures are unclear. We propose that chronic inflammatory activation in depression promotes and sustains this risk. Our previous data have demonstrated that increased inflammation in depression increases the risk of glutamate toxicity and leads to toxic disorganization of neural systems linked to emotional and cognitive functions. Herein, we examined if increased inflammation in the brain as measured in cerebrospinal fluid (CSF) was associated with increases in both CSF and neuroimaging makers of neurodegeneration in depressed (with and without cognitive dysfunction) versus controls.

Methods: 54 subjects (35 depressed and 19 non-depressed control subjects) participated in the study and provided CSF samples and clinical and demographic information. Study participants were aged 35-65 and unmedicated with psychotropic medications. Depression was confirmed using SCID-5 for DSMV, and a standardized neurocognitive battery was used to measure psychomotor slowing and executive dysfunction. The immune marker panel included c-reactive protein (CRP), tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1beta, and their circulating receptors [type 2 TNF (TNFR2), IL-6 (IL6sr), and IL-1 receptor antagonist (IL1ra). The neurodegeneration panel included neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), hyperphosphorylated tau-181 (Tau), abeta-(ab)42, and ab40. Diffusion tensor imaging (DTI) and Neurite Orientation Dispersion Density Imaging (NODDI)-based diffusion measures were used to identify regions of interest (ROI) correlated with CSF immune biomarkers after multiple test corrections. The ROIs located in white matter space were identified using an automated probabilistic tractography atlas in the XTRACT toolbox in FSL. Extended instrumental variables regressions were used to compare groups. Linear models were used to examine biomarker/DTI associations.

Results: Of the inflammatory markers, CSF TNFR2 was differentially associated with neurodegeneration markers as a function of depressed group status. Indeed, there was a significant CSF TNFR2 by depressed group interaction that was positively associated with CSF NFL (p-corr=0.002) and CSF GFAP (p-corr < 0.001). CSF TNFR2/NFL association was significant in the DCD+ (pcorr=0.018) but not with DCD- (p=NS) and control (p=NS) groups. Similarly, CSF TNfR2/GFAP association was significant in the DCD+ (pcorr=0.006) and DCD- (p-corr=0.024) but not in the control (p=NS) groups. CSF NFL and GFAP were associated with decreased fractional anisotropy of the right frontal aslant tract (p-corr=0.02 and 0.03, respectively) and increased mean diffusivity of right anterior thalamic radiation (p-corr=0.047 and 0.008, respectively); and CSF NFL was associated with an increased orientation dispersion index (p-corr=0.04) in the left arcuate fasciculus only among depressed groups. No associations between DTI measure with CSF NFL and GFAP were noted in the control group.

Conclusion: Our data indicate that depressed subjects with increased inflammation may have a higher risk of cognitive decline and neurodegeneration. Treatment with immune-modulating or neuroprotective agents and well-known antidepressants may be useful in this group.

ELECTRICAL BRAIN ACTIVITY AND ITS COURSE IN RECCURENT AFFECTIVE DISORDERS

Dimitris Dikeos*[1], *Gerasimos Konstantinou2*
[1]*National and Kapodistrian University of Athens, 2University of Toronto*

Objective: Brain electrical activity is commonly used to assess certain neurofunctional aspects of psychiatric illness. This presentation will focus on relevant findings in mood disorders.
Methods: Search in pubmed and other databases for original papers, reviews and meta-analyses.
Results: In both major depressive disorder (MDD) and bipolar disorder (BD), electroencephalography (EEG) has revealed abnormalities in resting-state EEG and evoked-related potentials (ERPs); the latter are the result of averaging EEG activity time-locked to the onset of the presentation of a stimulus that leads to a stereotyped electrophysiological response consisting of a series of positive and negative voltage deflections.
Conclusion: The validity of the findings as potential biomarkers will be discussed, as well as their contribution to the theory of neuroprogression in affective illness, and the possibility of their use in treatment prediction.

ASSOCIATION OF IMMUNOPSYCHIATRY, TREATMENT RESISTANCE AND NEUROPROGRESSION

Dominique Endres*[1]
[1]*Medical Center - University of Freiburg,*

Objective: Immunopsychiatry is a transdiagnostic, multidisciplinary, and translational field. From a clinical perspective, the discovery of NMDA-R encephalitis has played a vital role in the development of immunopsychiatric research as it was found that neuronal autoantibodies can be associated with both neurological signs and psychotic symptoms. Several other central nervous system autoantibodies have also been described, and international consensus criteria for autoimmune psychosis have been derived from these findings. In addition, other autoimmune-mediated severe mental illnesses, such as autoimmune obsessive–compulsive disorder (OCD) and autoimmune affective syndromes, are also discussed.
Methods: The talk will provide an overview of the controversial field of clinical immunopsychiatry, focusing on autoantibody-associated syndromes.
Results: Case studies, first case series, and retrospectively analyzed groups of patients with psychoses, affective syndromes, and OCD will be presented. The underlying pathophysiological autoantibody mediated processes and relevant biomarkers using electroencephalography, brain imaging, and cerebrospinal fluid analyses will also be addressed.
Conclusion: Red-flag signs will be summarized, and the current immunopsychiatric experience will be discussed in the context of treatment resistance and neuroprogression.

UPDATES IN ECT PRACTICE AND RESEARCH: NEW APPLICATIONS

Georgios Petrides, Robert Wood Johnson Medical School

Symposium Synopsis: In this symposium we will review new data in clinical research of Electroconvulsive therapy (ECT) and discuss new clinical applications.
Dr. Stella Rosson will summarize the meta-analytical evidence and safety of ECT and discuss data from a comprehensive umbrella review of the literature for randomized control trials of non-pharmacologic somatic treatments such as Deep Brain Stimulation, Transcranial magnetic stimulation (TMS), transcranial Direct current stimulation (tDCS) and others.
Dr. Søren Dinesen Østergaard will present unpublished results from a study investigating clinical and sociodemographic characteristics associated with relapse following ECT for bipolar disorder, based on data from more than 1400 Danish patients. He will discuss identified markers indicating high risk for relapse.

Dr. Brent Forester will discuss evidence for the use of ECT for the treatment of agitation in patients with severe dementia, as well as the design and implementation of a multicenter study funded by the National Institute of Mental Health in United States. Dr. Sohag Sanghani will report on the novel use of ECT in patients with autoimmune encephalitis, including ant-NMDA receptor encephalitis, and medication resistant catatonia.

EFFICACY AND SAFETY OF ECT AND OTHER BIOLOGICAL TREATMENTS IN PSYCHIATRIC DISORDERS: RESULTS FROM AN UMBRELLA REVIEW

Stella Rosson*[1]

[1]*East London NHS Foundation Trust*

Objective: To provide a comprehensive overview of the extant evidence of efficacy and safety of electroconvulsive therapy and other biological non-pharmacological treatments in psychiatric disorders.

Methods: We conducted an umbrella review selecting the largest meta-analyses of randomised controlled trials reporting on efficacy and safety of biological non-pharmacological treatments. These were electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and light therapy.

Results: We collected evidence from 102 including meta-analyses. Biological non-pharmacological treatments were found effective in a variety of mental disorders. In depressive disorders, interventions superior to inactive treatment were, in order of magnitude of improvement, ECT (SMD=0.91), TMS (SMD=0.51), tDCS (SMD=0.46), DBS (SMD=0.42) and light therapy (SMD=0.41). In schizophrenia spectrum disorders, effective interventions compared to sham were ECT (SMD=0.88), tDCS (SMD=0.45), and TMS (SMD=0.42-0.58). Other disorders with evidence of efficacy were substance use disorder (TMS, SMD=0.77-1.16), obsessive-compulsive disorder (DBS, SMD=0.89, and TMS, SMD=0.64), post-traumatic stress disorder (TMS, SMD=0.46), generalised anxiety disorder (TMS, SMD=0.68), attention deficit-hyperactivity disorder (tDCS, SMD=0.23), and autism (tDCS, SMD=0.97).
In no case the acceptability of biological treatments was lower than inactive treatment.

Conclusion: There is a large body of evidence in the medical literature regarding efficacy and safety of biological non-pharmacological treatments in a broad array of mental disorders. Among treatments, ECT had the largest effect size in depressive disorders and schizophrenia spectrum disorders. These techniques can be considered as therapeutic tools in an increasing number of psychiatric conditions.

CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH RELAPSE FOLLOWING ELECTROCONVULSIVE THERAPY IN BIPOLAR DISORDER

Soren Dinesen Ostergaard*[1]

[1]*Aarhus University Hospital - Psychiatry*

Objective: Electroconvulsive therapy (ECT) is an effective treatment of severe episodes of bipolar disorder (BD), but relapse in the months following ECT is common. In the present study we aimed to identify clinical and sociodemographic characteristics associated with relapse following ECT in BD.

Methods: Using data from the Danish nationwide registers, we identified all patients receiving their first ECT series with an indication diagnosis of BD in the period from 2006 to 2019. These patients were followed for six months after ECT where relapse was defined as either psychiatric hospital admission or reinitiation of an ECT series. The association between clinical and sociodemographic characteristics and relapse was examined via multivariable Cox proportional hazards regression (survival analysis).

Results: A total of 1498 patients with bipolar disorder will be included in the data analyses, which are ongoing. The results will be shown at the 2024 WFSBP Congress.
Conclusion: The identified characteristics associated with relapse may guide targeted monitoring of patients with bipolar disorder following ECT.

THE SAFETY AND EFFICACY OF ECT FOR THE TREATMENT OF AGITATION IN DEMENTIA

Brent Forester*[1]
[1]*Tufts University School of Medicine*

Objective: We aim to determine the effect, tolerability, and safety of up to 9 Electroconvulsive Therapy (ECT) treatments plus usual care (ECT+UC) on severe agitation in participants with moderate to severe dementia including Alzheimer's Disease, Vascular dementia, Frontotemporal dementia, and Dementia with Lewy Bodies.
Methods: Subject enrollment is limited to individuals admitted to inpatient psychiatry or medical care units with a diagnosis of moderate to severe dementia. Cohen-Mansfield Agitation Inventory (CMAI) cut-off scores are used as the agitation and aggression standard for inclusion. ECT treatment consists of up to 9 ECT sessions administered up to 3 times per week.
Results: The primary outcome is agitation as measured by CMAI score. Secondary outcome measures include Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC), Neuropsychiatric Inventory – Clinician (NPI-C), and the Pittsburgh Agitation Scale (PAS). Participant safety is monitored by assessing cognitive function as measured by the 8-item Severe Impairment Battery (SIB-8), delirium as measured by the Confusion Assessment Method (CAM) and the Family-CAM (FAM-CAM), and routine medical monitoring.
Conclusion: Recruitment challenges, protocol modifications, recommendations for future research and clinical implications will be discussed.

ELECTROCONVULSIVE THERAPY FOR CATATONIC SYNDROME ASSOCIATED WITH AUTOIMMUNE ENCEPHALITIS AND NEW-ONSET PSYCHOSIS OF SUSPECTED IMMUNE ORIGIN: A RETROSPECTIVE CASE-SERIES

Sohag Sanghani*[1], *Georgios Petrides[2], Jason Andrus[1], Heela Azizi[1], Amy Mastrangelo[1], Marc Gordon[1], Cristina Fernandez-Carbonell[1], Simona Proteasa[1], Humaira Shoaib[1], Joanna Drucker[1], Samuel Greenstein[1], Xavier Jimenez[1], Robert Dicker[1], Sanjeev Kothare[1], Souhel Najjar[1]*

[1]*Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 2Robert Wood Johnson Medical School*

Objective: To determine efficacy and safety of ECT in management of catatonia associated with autoimmune encephalitis (AIE) and psychosis of suspected immune origin.
Methods: Medical records of all patients with catatonia and suspected autoimmune encephalitis, who were referred for ECT in the period of Jan 2017 to Dec 2022 at our health system were reviewed. Demographic, clinical characteristics, laboratory and outcome data were recorded. Catatonia symptoms were measured using Bush Francis Catatonia Rating Scale (BFCRS).
Results: Twelve cases that met the inclusion criteria were identified. Of them 4 were cases of anti-NMDA receptor encephalitis and 6 were seronegative cases of probable (n=4) and possible (n=2) origin as per the criteria described by Pollak et al. in 2020. Mean age of the patients was 26 years and about 58% were females. Their mean initial BFCRS score was 18.2 (range: 5-25). All patients showed some response within 3 ECT treatments. On average, patients required 11 (range: 3-21) ECT treatments to achieve maximum improvement. All patients (n=12) responded well to the combination of ECT and immunomodulatory treatments. Eleven of twelve patients (92%) had

complete resolution of catatonia. Introduction of ECT earlier in the course was associated with a relatively lower number of days spent with catatonia. **Conclusion:** To the best of our knowledge, this is the largest case series from a single institution, where ECT was used in the treatment of catatonia associated with autoimmune encephalitis and psychosis of suspected immune origin. Autoimmune Encephalitis is a severe condition that can have varying psychiatric presentations. The possibility of AIE should be considered in the event of new- onset catatonia or psychosis, especially in young individuals. ECT is a safe and effective treatment for catatonia and psychosis associated with AIE. It is not a substitute for immunomodulatory treatments. In the event of non-response to first line immunomodulatory treatments, early initiation of ECT may help to prevent a protracted medical course and may have a synergistic effect with concomitant immunomodulator administration.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Niall Boyce, Wellcome

Symposium Synopsis:
In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence helps to reduce waste and improve efficiency in research. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. This symposium provides a concise, comprehensive introduction to the project, presenting highlights of its work to date. The focus is on the innovative aspects of the project, including hypothesis-generating systematic reviews, meta-analyses aiming to measure effects of interventions and the role of risk factors, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

METHODOLOGY FOR LIVING SYSTEMATIC REVIEWS IN GALENOS

Georgia Salanti**1*

[1] *University of Bern*

Objective: The innovative nature of GALENOS requires methodological developments in the field of systematic reviews. The aim of this presentation is to give an overview of the novel methodological aspects underpinning the GALENOS living systematic reviews.

Methods: To answer the research questions asked in GALENOS, we have developed two types of reviews. Hypothesis testing reviews collect evidence from studies examining mechanisms of action of interventions on mental health outcomes. Then, the role of various biological or psychological mechanisms is evaluated in association evaluation reviews.

We have developed template protocols that describe the review and synthesis methodology from human and non-human studies, include instructions about how to evaluate the confidence in the evidence that these two study designs provide, and describe the planning of evidence triangulation. **Results:** The methodology will be exemplified via three systematic reviews: two association evaluation reviews (Trace amine-associated receptor 1 agonists for psychosis and pro-dopaminergic pharmacological interventions for anhedonia in depression) and one hypothesis-generating review (mechanisms through which exercise reduces symptom severity in posttraumatic stress disorder). **Conclusion:** Several sources of evidence from human and non-human studies and novel methods are required to make sense of the rapidly evolving literature.

LIVING EVIDENCE IN PURSUIT OF A STEP-CHANGE IN NOVEL INTERVENTIONS FOR ANXIETY AND TRAUMA-RELATED DISORDERS

Soraya Seedat**1*

[1]*South African Society of Biological Psychiatry*

Objective: This presentation will highlight the unique process adopted by GALENOS to identify and prioritise research questions for living systematic reviews (LSR) through a rigorous process entailing public private involvement, using an exemplar of a living systematic review on mechanisms of exercise as an intervention for posttraumatic stress disorder. The living systematic reviews produced by GALENOS focus on the most promising scientific findings (from basic laboratory and animal research to clinical studies in humans)

Methods: For the LSR on exercise for PTSD, independent searches were conducted in multiple electronic databases to identify non-human and human studies investigating the biopsychosocial mechanisms through which exercise facilitates extinction learning, memory regulation, and emotional regulation in PTSD. Ontologies were developed to facilitate study identification and data extraction. Two reviewers independently conducted the study selection, data extraction using piloted forms, and risk of bias assessment using relevant tools based on the study design. We extracted data on PTSD-related outcomes and variables that can act as mediators of the effect of exercise or as effect modifiers.

To explain the biopsychosocial mechanisms through which exercise affects the outcome of interest, we extracted effects that relate to the impact of exercise on potential mediating variables and the effect of the later outcomes. We will synthesise study results (total effects of exercise, indirect and direct effects) using meta-analyses, where appropriate.

Results: The results are currently being analysed and will be presented. Data from other living systematic reviews on PTSD/anxiety disorders undertaken by GALENOS until mid-2024 will also be presented.

Conclusion: Elucidating the potential mechanisms underlying the beneficial effects of exercise for PTSD is firstly important for fundamental knowledge; secondly, it can shed light on individual-level differences in the effectiveness of exercise for PTSD; and thirdly, it can inform the discovery of other interventions to target these mechanisms.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Tatenda Kambeu**1*, *Soraya Seedat2, Georgia Salanti3, Niall Boyce4, Andrea Cipriani5*

[1]*Global Experiential Advisory Board for The Global Alliance for Living Evidence on Anxiety, Depression and Psychosis, 2Stellenbosch University; Stellenbosch University/South African Medical Research Council Extramural Unit on the Genomics of Brain Disorders, 3Institute of Social and Preventive Medicine (ISPM), University of Bern, 4Wellcome, 5Oxford University*

Objective: In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence is one way to reduce waste and improve efficiency in research towards these ends. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) aims to provide openly accessible co-produced living systematic reviews to tackle the abovementioned challenges. **Methods:** The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. It is important for GALENOS that we coproduce everything we create with people with lived experience of mental illnesses. Hence, we have set up the GLEAB, a Global Experiential Advisory Board, to provide strategic oversight to the project. In practical terms, people with lived experience will be involved with: choosing the topics of the reviews, developing the review protocols and contributing to conducting them, helping with data analysis and the writing up of the findings. People with lived experience will also be involved in developing the mental health ontology as that develops and identifying research questions that should be prioritised in the future. **Results:** This symposium provides a concise but comprehensive introduction to the project and presents highlights of its work to date. **Conclusion:** The focus of the symposium will be on the innovative aspects of the project, including co-production with lived experience experts, hypothesis-testing meta-analyses, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

HETEROGENEITY IN PSYCHOTIC DISORDERS ACROSS LEVELS OF RESEARCH

Dost Ongur, McLean Hospital/Harvard Medical School

Symposium Synopsis: This symposium will focus on heterogeneity in psychotic disorders across multiple levels of research. The first presenter is Dr. Michael Benros who will present evidence from blood and CSF studies as well as epidemiology for an "inflammatory" subtype of psychosis linked to early life exposures that may trigger molecular mechanisms in the developing brain and lead to persistent neuroinflammation and ultimately emergence of psychosis. The second presenter is Dr. Tao Li who will present the results of her team's neuroimaging studies examining dynamic connectivity over time in psychotic and mood disorders. Next, Dr. Sinan Guloksuz will present data on lifetime exposures, clinical presentation, and treatment response which reveal significant heterogeneity within psychotic disorders. He will discuss concepts of subtyping vs. dimensional variation in the context of empirical data. Finally, Dr. John Hsu will present evidence from large population-based insurance claims databases which demonstrate highly variable pathways to care, treatment histories, and linkage to various outcomes such as hospitalization among patients diagnosed with psychotic disorders. Dr. Dost Ongur is the discussant, and he will summarize approaches to heterogeneity in psychotic disorders and propose next steps for the field.

IMMUNE-RELATED SUBTYPE OF PSYCHOTIC DISORDERS – EVIDENCE FROM LARGE-SCALE STUDIES TO DETAILED CLINICAL STUDIES

Michael Benros*[1]
[1]*Mental Health Centre Copenhagen*

Objective: The underlying causes of psychotic disorders are likely very heterogeneous with multiple biological underpinnings that are still not fully illuminated. Within the recent decades, the immune system has been shown to be implicated in an increasing number of medical diseases and immunemodulating treatments are one of the areas currently moving fastest within medicine. In this presentation the current evidence for an immune-related subtype of psychotic disorders will be summarized and perspectives for immunemodulating treatments in subgroups of patients with psychotic disorders will be discussed.

Methods: The presentation will include data from large-scale studies to detailed clinical studies within the immunopsychiatric field of psychotic disorders, including nationwide Danish registers and biobanks, large-scale genetic studies, preclinical studies, clinical studies with sampling of the cerebrospinal fluid, meta-analyses of clinical studies and RCTs of immunemodulating treatments for psychotic disorders.

Results: Utilizing Danish nationwide registers we have consistently displayed that infections and autoimmune diseases increases the risk of developing psychotic disorders in a dose-response relationship, where the risk of severe mental disorders particularly increases with the number of infections exposed to and in a temporal manner. Utilizing large national biobank data, we have shown a small immunogenetic contribution with moderate correlation between the genetic susceptibility for infections and mental disorders. Moreover, at diagnosis there are elevated levels of inflammatory markers in the blood, and studies on the cerebrospinal fluid surrounding the brain have shown some evidence for elevated immune markers in the CSF and signs of disrupted blood-brain barrier in some of the patients, making them more vulnerable to potential detrimental effects of immune components. Interestingly, our meta-analyses of randomized clinical trials have shown that anti-inflammatory treatment seems to some extent show promise for the treatment of psychotic disorders. However, studies identifying subgroups that would be most likely to respond to immune modulating add-on treatment are still warranted to pave the field forward.

Conclusion: Although there is compelling evidence for at least a smaller subgroup of psychotic disorders having immune-related underpinnings, it will be discussed what is lacking in the current evidence base, how do we best advance the current knowledge and what should be prioritized within future research to make immunopsychiatry even more clinically relevant for psychotic disorders.

DYNAMIC STRUCTURE–FUNCTION COUPLING ACROSS THREE MAJOR PSYCHIATRIC DISORDERS

Zhe Zhang1, Wei Wei2, Yu Sun1, Tao Li*[2]
[1]*, Zhejiang University, 2Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine*

Objective: Major psychiatric disorders have both similar and distinct patterns of manifestations and cognitive impairments, yet the underlying common and/or unique neural substrates are not well understood.

Methods: We perform a comprehensive brain structure–function coupling analysis to characterize the transdiagnostic and illness-specific neuroimaging patterns across major depressive disorder, bipolar disorder, and schizophrenia.

Results: We find similar abnormalities in the general dynamic structure–function coupling of the rich–club organization across the 3 disorders, and shared and specific regional coupling alterations in

the visual, cognitive control, and default mode regions. Additionally, disorder-dependent atypical associations between structure–function coupling and topological properties of functional networks are mainly dominated by two distinct functional configuration states. **Conclusion:** Our findings demonstrate brain abnormalities across 3 major psychiatric disorders from a perspective of dynamic structure–function relationships, thus opening new avenues for investigating the neurobiological mechanisms underlying these disorders.

INVESTIGATING THE UTILITY OF EXPOSOME SCORE FOR SCHIZOPHRENIA TO UNDERSTAND OUTCOME HETEROGENEITY IN PSYCHOSIS SPECTRUM DISORDER

Sinan Guloksuz**1*

[1]*University Hospital of Maastricht*

Objective: By using a predictive modeling approach, we have recently estimated the exposome score for schizophrenia (ES-SCZ), a cumulative environmental exposure score for schizophrenia, consisted of cannabis use, winter-birth, hearing impairment, bullying, and five domains of childhood adversities (emotional and physical neglect, along with emotional, sexual, and physical abuse)., The ES-SCZ successfully differentiated individuals with schizophrenia, explaining 28% of the variance in an independent case-control sample and showed a good discriminative function for schizophrenia (AUC = 0.84) in an epidemiologically representative general population cohort. Here we tested the performance of ES-SCZ for dissecting the functional and symptomatic outcome heterogeneity in psychosis.

Methods: Our analyses used data from three independent cohorts: the “vulnerability and severity” Work Package 6 of the EUGEI study including 1,261 patients with schizophrenia spectrum disorder, 1,282 unaffected siblings of these patients, and 1,525 healthy controls collected in Turkey, Spain, and the patient population of the GROUP study including 1,119 patients with schizophrenia spectrum disorder collected in the Netherlands; and the Athens First Episode Psychosis Research Study collected in Greece including 225 individuals with first episode psychosis. We investigated the cross-sectional and longitudinal associations of ES-SCZ with functioning and symptom severity assessed using the Global Assessment of Functioning (GAF), the Personal and Social Performance Scale (PSP), and the Positive and Negative Syndrome Scale (PANSS).

Results: Our analyses revealed that ES-SCZ was associated with both the GAF symptom and disability domains in the EUGEI across three groups (patients, their siblings and healthy controls), also after adjusting for polygenic risk score for schizophrenia. We were able to replicate these findings in the GROUP dataset. In the Athens FEP cohort, we replicated these findings. ES-SCZ was associated with the overall scores of GAF and PSP at the baseline and 1-month assessments. Even after adjusting for various other relevant explanatory variables such as environmental factors (ethnic minority status, obstetric complications, migration history), clinical features (symptom severity, antipsychotic use history, duration of untreated psychosis), and family history, these results remained significant. The evaluation of the explained variance (R2) of functioning further supported these findings. Specifically, ES-SCZ was found to be the greatest contributor to the explained variance for the total PSP score, as well as for PSP subscales that measure socially useful activities and personal/social relationships. ES-SCZ was also temporally associated with symptomatic improvement from baseline to 1-month assessment, particularly the negative symptom dimension.

Conclusion: Our findings indicate that ES-SCZ might be a marker for poor functioning and symptomatic improvement in patients diagnosed with schizophrenia spectrum disorder. In addition, the results obtained from the models that took into account polygenic risk score for schizophrenia and clinical features indicate that the links between ES-SCZ and functional outcomes cannot be explained solely by genetic and clinical risk indicators.

THE ROLE OF POLYGENIC SCORES IN STUDYING PHENOTYPIC AND ENVIRONMENTAL HETEROGENEITY OF PSYCHOSIS

Evangelos Vassos*[1]
[1]King's College London
Evangelos Vassos, King's College London

Objective: Psychotic disorders show high heritability and genome-wide association studies have been successful in identifying variants associated with the disease. These variants are combined to estimate polygenic scores, which provide a single measure of genetic predisposition to a disorder or trait. Polygenic scores have been used for risk prediction either in contrast to or in combination with environmental risk factors in studies aiming to explain the heterogeneity of psychotic disorders. In this session, I will present our studies using polygenic scores to predict the development of schizophrenia or affective psychosis among individuals with first episode psychosis and I will explore the limitations of the use of polygenic scores alongside environmental factors in risk prediction.
Methods: We studied two samples of First Episode Psychosis (FEP) patients and controls for association between polygenic scores and psychosis outcome (schizophrenia or affective psychosis). The first sample (Genetics and Psychosis; GAP) was collected in South London consisting of 445 cases and 265 controls and the second (Work Package 2 of the EUGEI study) in six different countries including the UK, Italy, France, Spain, Netherlands and Brazil, including 573 cases and 1005 controls of European ancestry. Environmental risk factors were tested alongside polygenic scores in prediction of affective and non-affective psychosis. Finally, to explore whether polygenic scores and environmental risk factors can be used as independent predictors, we performed a study in the UK Biobank, testing the association of polygenic scores for 8 psychiatric disorders with urbanicity, once of the most replicated risk factors for schizophrenia.
Results: In the GAP study we observed that in addition to the expected association between polygenic score for schizophrenia and case-control status in European ancestry individuals, the former also separated FEP patients who developed schizophrenia from those who developed other psychotic disorders (R2=9.2%, p=0.002). This finding was replicated in a second sample of patients with chronic psychosis.
In the EUGEI study, we found that not only schizophrenia but also depression polygenic scores have a role in separating affective from non-affective psychosis. Furthermore, we found that adding polygenic and poly-environmental risk scores further improves the predictive ability of our model.
In the UK Biobank study, we found evidence supporting the hypothesis of genetic selection of the environment we live in, which intersects the traditional gene-environment dichotomy.
Conclusion: When patients present with first episode psychosis, it is difficult to establish a definite diagnosis and predict the course of illness and optimal treatment. To that effect, better understanding and explaining the heterogeneity of psychosis has important clinical implications. In our studies we find that polygenic scores have a significant yet small effect in separating schizophrenia from affective psychoses and that adding non-genetic risk factors improves prediction. Finally, gene by environment correlation needs to be considered when adding both genetic and environmental factors in prediction models.

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDERS

Allan Young, King's College London

Symposium Synopsis: Cognitive impairment in bipolar disorders.

Impairment in processing speed, attention, verbal memory, and executive functions may be present in up to 50% of young and middle-aged euthymic patients with bipolar disorders. However, our

knowledge in elderly people with bipolar disorder is limited although cognitive impairment is likely more prevalent and severe in elderly patients with mood disorders. Furthermore, compared to healthy older adults, those with mood problems have a higher risk of dementia. In contrast to research on younger patients, clinical correlates of cognitive decline in geriatric patients with bipolar disorder have not been studied systematically. Cognitive impairment worsens psychosocial functioning and treatment response in mood disorders. Therefore, it is essential to prevent and treat cognitive impairment in these people. Few treatment options effectively treat persistent cognitive impairment in remitted phases of bipolar disorders. Cognitive remediation therapy (CRT) may improve cognitive and non-cognitive functioning and recent studies have shown CRT's efficacy. However, its long-term effects are still unknown, therefore additional studies are needed. Also, limited understanding of neurocircuitry characteristics in bipolar disorders hinders search for new treatments and improving current treatment methods, leaving it unclear if proposed treatments can effectively correct cognitive impairments. This symposium aims to address the common problem of bipolar disorder-related cognitive impairment, including the cognitive decline of older patients. Additionally, treatment guidelines and options—including CRT—will be discussed considering neuroimaging, which can be used to identify neural targets for the development of new treatments or the improvement of existing ones for bipolar disorders-related cognitive decline.

COGNITIVE IMPAIRMENT IN BD: IS IT TREATABLE?

Lakshmi Yatham*[1]

[1] *The University of British Columbia*

Objective: 1. To review evidence on magnitude of cognitive impairment in BD

2. To review new data on therapeutic strategies for managing cognitive impairment

Methods: This presentation will review new data on cognitive impairment in BD and present the results of new studies that assessed the efficacy of pharmacological and psychological interventions for treating cognitive impairment in BD.

Results: About two thirds of patients with BD have cognitive impairment even during euthymic periods, which impacts functioning. New clinical trial designs allow testing for efficacy of pharmacological and psychological treatments in improving cognition. The results of these new and novel studies will be presented in this session.

Conclusion: Cognitive impairment in BD can be treated with pharmacological and psychological strategies.

COGNITION IN GERIATRIC BIPOLAR DISORDER

Nese Direk*[1]

[1]*Istanbul University*

Objective: Mood disorders are common and complex, accounting for one of the leading causes of disability. Approximately half of adults with mood disorders have cognitive impairment, which has an impact on their occupational and social functioning as well as their life quality. Cognitive impairment is well-known in younger and middle-aged euthymic adults with mood disorders, with the most impairment reported in processing speed, attention, verbal memory, and executive functions. Cognitive impairment is more common and severe in geriatric patients with mood disorders. It is also known that the prevalence of dementia in patients with mood disorders is higher than in healthy geriatric people. The causes of cognitive impairment in elderly patients with mood disorders are still unknown. Some clinical features, such as the prevalence of previous psychotic episodes, the number of manic episodes, and cardiovascular risk factors, are linked to an increased

risk of cognitive impairment, but the results are mixed. This talk is aimed at elucidating the cognitive profiles and clinical correlates of cognition in geriatric bipolar patients. **Methods:** The Bipolar Disorder in Old Age (BipOld) Study is a longitudinal, open cohort study including bipolar patients aged 50 years and over, aiming to explore progress of bipolar disorder in elderly. Several cognitive domains such as attention, memory, executive functions, social cognition, neurological soft signs and retrospective clinical data was collected. In this talk, baseline results of the BipOld Study will be presented, and results will be discussed in the light of current studies in this field. **Results:** In total 70 bipolar patients aged 50 years and over and 70 healthy controls are compared in terms of cognition. Bipolar patients had worse cognition scores in all domains when compared to healthy controls. Number of psychotic episodes, baseline cognitive impairment, family history of bipolar disorder, number of hospitalizations were related with worse cognition. Even though numbers are limited, patients on lithium monotherapy had better cognitive profile. **Conclusion:** Cognition in elderly patients with bipolar disorder is worse than people with no psychiatric disorder. Associations of clinical characteristics with worse cognition may indicate toxic effects of episodes resulting in neurodegeneration in these patients.

THE PURSUIT OF TREATING COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: CAN MRI BE A USEFUL TOOL IN FINDING NEW TREATMENTS?

Nefize Yalin*[1], *Dimos Tsapekos[2], David Lythgoe[3], Peter Hawkins[3], Rebecca Strawbridge[2], Allan Young[2], Steve Williams[3], James Stone[4]*

[1]National Institute of Mental Health, [2]Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, [3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, [4]Brighton and Sussex Medical School

Objective: Cognitive remediation (CR) is one of the treatment modalities that may address cognitive impairment in bipolar disorder (BD). We recently showed that 12-week CR improves working memory and executive functioning in euthymic patients with BD when compared to the treatment as usual (TAU) group. In this study, we aimed to investigate the potential changes in structural magnetic resonance imaging (MRI), task-based functional MRI, and proton-magnetic resonance spectroscopy (1H-MRS) accompanying the cognitive improvement with CR in comparison to TAU.

Methods: We recruited 24 euthymic BD participants (CR: n = 12, TAU: n = 12). Neuroimaging data was collected using a 3T General Electric MRI at baseline and week 13. For T1 structural MRI images, cortical thickness (CT) and surface area (SA) measures were obtained with FreeSurfer version 7.1.1. Caudal and rostral middle frontal cortex and three subparts of inferior frontal cortex (pars opercularis, triangularis, and orbitalis) were chosen as regions of interest. Repeated measures and general linear models were used to compare CT and SA between groups. For 1H-MRS, glutamate and GABA levels were quantified from the dorsomedial prefrontal cortex (DMPFC) using the PRESS and MegaPRESS sequences, respectively. LC Model 6.3-1N was used for the analysis of spectral data, and the metabolite levels were corrected for cerebrospinal fluid, gray, and white matter fractions in the spectroscopy voxel obtained using Gannet 3.1. We assessed changes in glutamate and GABA levels using a general linear model with repeated measures.For functional MRI, the attentional-capture version of the Stop Signal Reaction-Time (SSRT) task was used to evaluate response inhibition. Regions-of-interest (ROIs) data were extracted with the MarsBaR toolbox for SPM-12. ROIs were cortical areas previously linked to response inhibition in BD, including the right inferior frontal gyrus (rIFG). Activation changes in selected ROIS were compared between groups using repeated measures general linear models.

Results: The mean age was 39.3 ± 12.6 for the CR group and 39.8 ± 14.1 for the TAU group (p = 0.93), and 66.7% of both CR and TAU groups were female (p = 1.0). In structural MRI, there was a significant change in left pars triangularis CT (p = 0.048) and a trend toward change in left rostral middle frontal CT (p = 0.069) and right caudal middle frontal SA (p = 0.054) from baseline to follow-up between groups. All changes showed an increase in CT in the CR group and a decrease in the TAU group from baseline to week 13. In 1H-MRS, we found DMPFC glutamate levels to be increased in the CR group following CR, whereas in the TAU group, glutamate levels were reduced (p = 0.037). We did not find any effect of CR on changes in GABA levels (p = 0.269). In functional MRI, CR relative to TAU was not significantly associated with SSRT-related changes in neural activity of pre-defined ROIs (all p > 0.05). For SSRT behavioral measures, there was only a trend for CR vs. TAU in the accuracy of the stop signal condition (p = 0.06). **Conclusion:** Cognitive improvement related to CRT may be mediated by structural changes and increases in DMPFC glutamate neurotransmission. MRI has a potential in identifying brain-based efficacy markers.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia IX

THE PHARMACOLOGICAL TREATMENT OF EATING DISORDERS: NEW GUIDELINES, INSIGHTS, AND PERSPECTIVES

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: This symposium on novel guidelines, insights, and perspectives for the pharmacological treatment of eating disorders is organized by the WFSBP Task Force Eating Disorders and consists of speakers with a broad range of scientific experience from Germany, Israel, the United Kingdom, and the United States of America and a Chair from Austria.
Over the last three years, the task force has worked on an update of the pharmacological treatment guidelines for eating disorders which will be presented first in this symposium. The new guidelines include several innovations such as a recommendation for lisdexamfetamine in the treatment of binge-eating disorder (BED) and an analysis of pharmacological research in avoidant restrictive food intake disorder (ARFID), rumination disorder and pica. The second presentation will display the results of meta-analytic research regarding the effect of second-generation antipsychotics (SGAs) on appetite and eating behavior which is clinically relevant for the use of SGAs in anorexia nervosa (AN), but also with respect to the resulting weight gain as a side effects of SGA treatment in schizophrenia or bipolar disorder. The second half of the symposium is dedicated to innovative and future treatments for AN. Thus, the third speaker will expound on the microbiome-gut-brain axis as a potential target for new treatment options by presenting new data on altered microbiota in patients with AN and the results from stool transplantation studies; and the fourth speaker will present and explain the study design and the results from studies testing psilocybin therapy in people with AN.

OLANZAPINE FOR YOUNG PEOPLE WITH ANOREXIA NERVOSA (OPEN): RESULTS OF A FEASIBILITY STUDY

Ece Sengun Filiz*[1], *Olena Said[2], Dominic Stringer[3], Ulrike Schmidt[4], Dasha Nicholls[1], Hubertus Himmerich[2]*

[1]Imperial College London, , 2Centre for Research in Eating and Weight Disorders (CREW), Institute of Psychiatry, Psychology and Neuroscience, King's College London, 3Institute of Psychiatry, Psychology and Neuroscience, King's College London, 4 King's College London

Objective: Despite evidence-based treatments for anorexia nervosa (AN), the remission rates are low, and the mortality is high. The atypical antipsychotic olanzapine is often used for the treatment of AN even though the evidence is limited to weight gain. The effect of olanzapine on eating disorders (ED) psychopathology, its efficacy and tolerability in children and young people, and its acceptability and adherence rate are unclear. **Methods:** We assessed the feasibility of a future definitive trial on olanzapine in young people with AN in an open-label, one-armed feasibility study, that aimed to include 55 patients with AN or atypical AN) aged 12-24 who gained **<** 2 kg within at least one month of treatment as usual (TAU) during outpatient, inpatient, or day-care treatment. Time points for assessments were at screening, baseline and at 8-, 16 weeks, 6- and 12 months. The primary feasibility parameters were the number of patients who agreed to take olanzapine and who adhered to treatment and complete study assessments. The change in body mass index (BMI) and changes in ED psychopathology were secondary feasibility parameters. **Results:** From June 2022 to May 2023, 20 participants were recruited across 10 study sites in England (of the 55 participants required). Fifty-two people were assessed at pre-screening; 17 people were ineligible (13 at pre-screening, 4 at formal screening), and another 15 declined or didn't take part for other reasons. All 20 recruited participants started olanzapine. Thirteen out of 20 participants (65%) completed a follow up assessment (either 6 or 12 months). Participants in the trial experienced, on average, a decrease over time in their EDE-Q Global scores, an increase in weight and a corresponding increase in BMI during treatment with olanzapine in addition to TAU. There was a mean BMI increase of 0.08 kg/m2 per week in the whole sample of 20 participants. **Conclusion:** Possible reasons for the recruitment difficulties and the low adherence rate are the reluctance of clinicians to prescribe olanzapine and of patients to agree to take olanzapine under the relatively strict conditions of a clinical study. These conditions include the delay of the start of treatment with olanzapine as ample time should be given to consider participation in the study, a pregnancy test before the start of treatment, the commitment to blood collection at assessments and to complete the questionnaires. However, exploratory data evaluation indicates a benefit of olanzapine regarding weight recovery and reduction of ED symptoms.

BEYOND WEIGHT GAIN: EATING COGNITIONS, EMOTIONS AND BEHAVIOUR UNDER TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS

Hubertus Himmerich**1*, *Hiba Mutwalli2, Johanna Louise Keeler2, Sevgi Bektas2, Namrata Dhopatkar3, Janet Treasure2*

[1]German Society for Biological Psychiatry, 2King's College London, 3South London and Maudsley NHS Foundation Trust

Objective: Weight gain and metabolic disturbances are frequent in people treated with second generation antipsychotics (SGA). SGAs have also been proposed as treatment option for people with anorexia nervosa (AN). We aimed to investigate the effect of SGAs on eating behaviors, cognitions and emotions.

Methods: A systematic review and a meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Original articles measuring outcomes relating to eating cognitions, behaviours and emotions, during treatment with SGAs were included in this review. A total of 92 papers with 11,274 participants were included from three scientific databases (PubMed, Web of Science and PsycInfo). Results were synthesized descriptively except for the continuous data where meta-analyses were performed and for the binary data where odds ratios were calculated.

Results: Hunger was increased in participants treated with SGAs with an odds ratio for appetite increase of 1.51. Compared to controls, our results showed that craving for fat and carbohydrates are the highest among other craving subscales. There was a small increase in dietary disinhibition and restrained eating in participants treated with SGAs compared to controls and substantial heterogeneity across studies reporting these eating traits.

Conclusion: Understanding of mechanisms associated with appetite and eating-related psychopathology changes in patients treated with SGAs is needed to inform the development of effective preventative strategies for weight gain during treatment with SGAs. Such understanding might also help to use SGAs as a treatment option for patients with AN.

THE MICROBIOME-GUT-BRAIN AXIS IN ANOREXIA NERVOSA – POTENTIAL TARGET FOR NEW TREATMENT OPTIONS?

Jochen Seitz*[1], *Lara Keller1, Stefanie Trinh1, Brigitte Dahmen1, John Baines2, Beate Herpertz-Dahlmann1*

[1]*University Hospital RWTH Aachen, 2Max-Planck-Institute for Evolutionary Biology, Plön*

Objective: The gut microbiome has been shown to influence both metabolism and weight gain, as well as brain changes and behavior. This is especially interesting in the case of Anorexia nervosa (AN), where all these areas are known to be affected. Observation studies have repeatedly shown altered gut microbiota in patients with AN – even after weight normalization, and transplantation studies of AN-patients' stool into germ-free animals have shown significant effects regarding weight gain and anxiety/compulsivity.

Methods: Longitudinal observational studies using 16S- or metagenomic shotgun analysis allow the study on which factors influence the gut microbiome in AN and which taxa are associated with good or bad outcome. Transplanting stool of patients with AN or supplementing specific taxa in the activity-based anorexia animal model can give crucial information about causal influences of the microbiome and help elucidate underlying mechanisms.

Results: We present an overview over current study results. Longitudinal studies continue to show beta diversity differences between patients with AN and healthy controls before and after weight gain and remaining differences at follow-up. Taxa belonging to the Sutterella genus helped to predict higher body weight at one year. Animal models show differing alpha- and beta diversity as well as specific taxa to be altered in semi-starvation and support a potential causal role of the gut microbiome in AN.

Conclusion: The predictive power of taxa belonging to Sutterella for clinical outcome could complement known predictors at admission, help to inform patients and clinicians and serve as a candidate for interventions such as probiotic or nutritional supplementation. Trying to generate new microbiome-targeted treatment approaches like pro- and prebiotics, nutritional interventions or even stool transplantations might be interesting options to enhance existing AN-treatment.

EFFICACY OF PSILOCYBIN AND OTHER MEDICATIONS IN THE TREATMENT OF ANOREXIA NERVOSA

Walter Kaye*[1], *Stephanie Knatz-Peck1, Samantha Shao1, Murray Susan1, Finn Daphna1*

[1]
University of California – San Diego

Objective: Anorexia nervosa (AN) is a deadly behavioral disorder with no proven treatments to reverse core symptoms and no FDA-approved medications. Novel and innovative treatments methods are urgently needed to improve clinical outcomes and reduce mortality. Research suggests that disturbances of serotonin and dopamine function occur in AN and may contribute to anxiety and other symptoms.

Methods: This is the first trial to report on the safety, tolerability, and preliminary efficacy of psilocybin therapy for AN (ClinicalTrials.gov Identifier: NCT04661514). In this open label feasibility study, 10 participants who met DSM 5 criteria for AN received a single 25mg dose of synthetic psilocybin with psychological support. We assessed safety, tolerability, acceptability, and efficacy at pre-treatment, post-treatment, 1-month and 3-month follow-up.
Results: Psilocybin treatment was safe, well tolerated, and had good acceptability. Measured changes in eating disorder psychopathology were highly variable between participants. Four participants (40% of sample) demonstrated decreases in eating disorder scores to within 1 standard deviation of community norms at 3-month follow-up, qualifying for remission from eating disorder psychopathology.
Conclusion: Results from this open-label study suggest that psilocybin therapy is safe and tolerable in participants with AN. Additionally, data suggest that a single-dose trial of psilocybin therapy may be effective at reducing ED psychopathology in a subset of participants. These preliminary results are promising given the complex physiological dangers associated with AN and the lack of effective and acceptable treatments. We will also review the literature regarding other treatment approaches for AN.

Some studies, but not all, also support the efficacy of fluoxetine in reduction of relapse in restrictor-type AN. In addition, there is limited data suggesting that some atypicals may be useful for AN.

GENETIC RISK PREDICTIONS AND BIOLOGICAL MECHANISMS IN ADHD – TOWARDS PRECISION MEDICINE

James Kennedy, Univ of Toronto

Symposium Synopsis: ADHD is one of the most common mental and behavioral disorders in children, often co-occurring with various behavioral problems. ADHD exhibits high heritability of 74% and recent genome-wide association studies (GWAS) (Demontis, 2021) have identified a number of significant hits in several genes that have implications for new drug targets. Interestingly, the heritability of ADHD changes with its comorbid disorders (CDs) where ADHD had higher heritability when comorbid with disruptive behavior disorders. The objectives of the current symposium are to explore the genetics and biomarkers of ADHD with or without CDs such as aggression, eating disorders (Eds) and autism spectrum disorder (ASD), as well as discuss the current evidence-based treatments, and pharmacogenetic guidance of medication choice for ADHD.
Symposium speakers employ research-based clinical assessment of ADHD, aggression, Eds and ASD. The genotyping employs powerful genome-wide microarray technology that interrogates millions of markers. Analyses of the associations between diagnoses, subtypes and CDs are performed using well-developed GWAS statistical methods. Polygenic risk scores (PRSs) are derived from GWAS and can be applied to behavioral phenotypes in other samples exhibiting related disorders. Genetic factors influencing the effectiveness of drugs for ADHD and its common comorbidities will be discussed, including the use of pharmacogenetics for more precise prescribing.
Overall, results show that ADHD has shared genetic architecture with its CDs. Separating ADHD into its clinical subtypes with/without CDs leads to more specific biological predictors and drug targets, that in turn have the potential to lead to better precision medicine for the treatment of ADHD.

ASSESSMENT OF POLYGENIC RISK SCORE OF ADHD AND AGGRESSION IN YOUTH: RESULTS FROM A CLINICAL AND A COMMUNITY SAMPLE

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Objective: More than 50% of youth with ADHD exhibit clinically significant aggression, representing high comorbidity. Although this points to the common genetic risk variants for the etiology of ADHD and aggression in youth, studies understanding the common genetic variation of ADHD and clinical aggression, and their subtypes, in children are limited. The objectives of this study were to assess the genetic relationship between ADHD and aggression in children. The study tested whether 1) ADHD scores were associated with aggression polygenic risk scores (PRS), and whether 2) aggression case status was associated with ADHD PRS. **Methods:** 1) 3594 children of European ancestry were recruited as part of the Adolescent Brain Cognitive Development (ABCD) study. The sample was genotyped with the Smokescreen® Genotyping Array. Continuous measures of ADH were obtained from Child Behaviour Checklist (CBCL). 2) 232 youth of European white ancestry were recruited as a part of an ongoing study of childhood aggression in Toronto, Canada. The sample was genotyped with Illumina PsychArray Beadchip v.1.2 and v.1.3. The case status was based on the participant scoring GREATER THAN 90th %tile on aggression subscales of both the CBCL and the Teacher Report Form, and a minimum two-year history of this disruptive behavior. Two PRSs were calculated using the standard clumping and thresholding methods with the p-value thresholds from 5x10-8 to 1 in PRSice2. Data for both PRSs came from the pediatric population of the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium. The first PRS was calculated from a genome-wide association meta-analysis (GWAMA) of ADHD (n=17666), while the second PRS was calculated from a GWAMA of aggression (n=87485). Linear and logistic regressions were used to analyze the associations between aggression PRS and ADHD scores in the ABCD sample, and between ADHD PRS and aggression case/control status in the Toronto sample, respectively. **Results:** Aggression PRS significantly explained ~ 0.2% of the variance in the ADHD scores of ABCD sample ($p = 0.007$). ADHD PRS significantly explained ~ 6% of the case-control status for the Toronto Child Aggression sample ($p = 0.002$). **Conclusion:** There were significant associations between aggression PRS with ADHD, and ADHD PRS with aggression case status. Our preliminary results indicate evidence that clinical aggression and ADHD share common genetic factors based on both clinical and community youth samples. The large sample size for the ABCD sample provides increased power for the results. The results may lead to generating better prediction strategies, for example aggression acting as a biomarker for ADHD. Personalized treatment strategies based on the genetic risk score may help with early prevention efforts. We will be exploring the genetic risk underlying ADHD by analyzing the aggression PRS in clinically aggressive children with, and those without, ADHD diagnosis.

GENETICS AND CELL BIOLOGY OF READING DISABILITIES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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Objective: Reading disabilities (RD) represent a major health, social, and educational handicap. Comorbid psychiatric disorders are common in children with RD, particularly ADHD (20%) which shares genetic risk. The high rate of ADHD further impacts academic achievement and social

development. Little is currently known of the genetic, molecular and cellular mechanisms contributing to these neurodevelopmental disorders. **Methods:** To address this gap, we performed a genome-wide association study (GWAS) for word reading. Based on the findings from that study, we then performed a Hypothesis-Driven GWAS testing the relationship between autism spectrum disorder (ASD) and genes involved in neuronal migration/axon pathfinding. We also used the results from the genetic studies, linkage disequilibrium score regression (LDSC) and single cell RNA-seq data to identify which neural cell types are enriched for genes for ADHD and RD risk. We then directly tested migration using stem cell derived neural precursor cells (NPCs) from children with RD. To understand the underlying molecular mechanisms, we investigated the transcriptome of the neurons and NPCs derived from the children. We selected one of the differentially expressed genes for further study by overexpressing the gene using CRISPR activation. **Results:** The results indicate overlap of word reading for genes previously identified for educational attainment, neurodevelopmental and psychiatric disorders, particularly ADHD and ASD. We also identified overlap with genes involved in neuronal migration. This supports the a priori hypothesis that alterations in neuronal migration during neurodevelopment contribute to the risk of RD. To test this, we created stem cells from two children with severe RD and their strong reader siblings. Derived NPCs from RD children migrated significantly faster than their siblings supporting migration alterations. Transcriptome analyses of neurons and neural precursor cells identified 44 genes that were differentially expressed between probands and their siblings in both cell types. One of these, OTX2, has been implicated in analyses of externalizing behaviour including ADHD, depression, educational attainment, and smoking initiation from GWAS studies. OTX2 is a transcription factor and our bioinformatic analyses indicates it may regulate 11 of the 44 genes. To test this, we are currently overexpressing OTX2 in NPCs, using CRISPR activation. Using LDSC, we also determined that specific subclasses of glutamatergic and GABAergic neurons are enriched with RD risk genes. Studies of ADHD identified a different glutamatergic neuron subtype. These findings indicate these cell types for stem cell derived neural models and functional studies. **Conclusion:** The results identify overlap for risk genes for ADHD, ASD and word reading. The findings of overlap for ADHD, support previous twin data showing a genetic relationship. Little is known of the overlap between ASD and RD. Our finding likely stems from shared genetic risk for neurodevelopmental disorders, particularly those contributing to language-related difficulties. Our novel, unpublished observation of altered migration in neural derived cells from RD children, supports previous evidence from neuroanatomical studies for altered neural migration and transcriptome analyses are providing information on the underlying molecular mechanisms.

PHARMACOGENETICS FOR PRESCRIBING MEDICATION TYPE AND DOSAGE IN ADHD: TOWARD PRECISION MEDICINE

James Kennedy**1*

1 Univ of Toronto

Objective: There are many promising genetic findings in terms of risk factors for ADHD. Recently a report by Demontis et al. (2021) provided an updated list of Genome Wide Association Study (GWAS) significant findings for genetic sites from across the genome that contribute to risk for ADHD.
In parallel with these hypothesis-free GWAS studies of the etiology of ADHD, we and others have been examining the application of genomic tools to help predict treatment response and side effects in ADHD. Given that current prescribing practice for ADHD consists mostly of trial-and-error approaches, there is a large unmet need to measure selected biological characteristics (biomarkers) of each patient in order to provide more precise prescribing.

Towards this goal of biomarker-guided precision medicine, Myer, Boland and Faraone (2017) have used meta-analytic methods to examine pharmacogenetic predictors of methylphenidate efficacy in childhood ADHD. They analyzed 36 studies with total n = 3647 children, examining response measures of methylphenidate treatment for association with DNA variants. Pooled data revealed significant association with single nucleotide polymorphisms (SNPs) in the alpha adrenergic 2A receptor gene ADR2A (odds ratio (OR) = 1.69); the norepinephrine reuptake transporter SLC6A2 (OR = 2.93) which is the target of atomoxetine, as well as the repeat variant in the dopamine D4 receptor gene (DRD4, OR = 1.66). Other data has shown that the drug metabolism gene cytochrome CYP2D6 plays a significant role in the liver deactivation of atomoxetine, which in turn influences clinical response. We will provide a critical assessment of these findings regarding their potential utility in clinical decision-making in ADHD. From our laboratory we will present work suggesting that a higher dosage of methylphenidate is helpful for individuals with a DRD4 7-repeat variant, due to impairments in D4 receptor trafficking to the synapse **Methods:** N/A **Results:** N/A **Conclusion:** We provide evidence that use of genetic factors to predict response and side effects, as well as separating ADHD into clinical subtypes, can lead to potential for better precision medicine for treatment of ADHD and its subtypes. Current pharmacogenomic knowledge provides a relevant amount of clinical guidance for selection of medication type and dosage. Further research is necessary for the optimization of personalized interventions in ADHD.

LEVERAGING GENETICS IN THE CLINICAL MANAGEMENT OF ADHD AND DISRUPTIVE BEHAVIOR

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University of California, Los Angeles

Objective: Approaches to the clinical management of ADHD, disruptive behavior and other comorbidities span medication classes and psychotherapeutic techniques. Currently, treatment matching is driven by serial trial-and-error. Given the potentially serious consequences of uncontrolled symptoms, pharmacogenomic and other biomarkers of therapeutic response could represent a substantial advance in the precision treatment of these disorders.
Methods: Current evidence-based pharmacotherapy and psychotherapies for ADHD and disruptive behavior disorders (DBDs) in children and adults will be reviewed, including known predictors and moderators of response. The utility and limitations of commercially available decision support tools (DSTs) will be examined. Research questions and future directions will be suggested.
Results: Little is known about genetic factors influencing drug action at brain targets; however, many genetic variants influencing the pharmacokinetics of psychotropics are well understood. While genetic impairments in stimulant metabolism are rare, large genetic effects are seen with alternative ADHD drugs. Non-stimulant ADHD options, atomoxetine and clonidine, are affected by common CYP2D6 variation, and bupropion is a CYP2D6 inhibitor, phenocopying the CYP2D6 poor metabolizer phenotype. Medication classes used to target disruptive behaviors are broad, including ADHD drugs, antidepressants, mood stabilizers and antipsychotics. Many of these agents are also impacted by known genetic variation. Common ADHD and DBD comorbidities, most frequently mood and anxiety disorders, have the strongest evidence base for integrating genetic information. Genetic data is actionable in ADHD and DBD pharmacotherapy in a considerable proportion of patients. For example, one-third of normal metabolizers never achieve therapeutic atomoxetine levels at the FDA maximum dose and require suprathreshold dosing. The Clinical Pharmacogenomics Implementation Consortium (CPIC) recommendations for incorporating genetic results to optimize response will be summarized. Evidence-based applications of DSTs that are commercially available to guide

prescribing will be outlined. Research supporting the implementation of DSTs in adults is mixed at best, with significant concerns regarding bias. A single DST trial was negative in adolescents and trials in children are non-existent. Recent reports highlight that efficacy in pediatric populations cannot routinely be extrapolated from adult studies. **Conclusion:** Numerous therapeutic options have demonstrated benefits in the management of attention-deficit and disruptive behavior disorders and their common comorbidities. While current pharmacogenomic knowledge cannot predict which interventions are best for individual patients, some clinical guidance can be gleaned from pharmacogenomic data. As our knowledge about mechanisms of psychiatric disease and pharmacologic action expands, the use of pharmacogenomic DSTs in the practice of precision medicine will likewise mature.

INNOVATIONS IN PHARMACOGENOMIC RESEARCH: TRANSLATION AND CLINICAL UTILITY

Bernhard Baune, University of Münster

Symposium Synopsis: The role of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacotranscriptomic approaches, focusing on genetic variants and expression levels of relevant genes for pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry, but still lacking. This concept of the multi-omics foundation of response to pharmacological treatments will be presented. Examples of this approach that entails the analyses of individual omics layers as well as an integrated analysis using multiple omics in relation to response to treatment will be presented. Results on the development of a model precision psychiatry framework that integrates clinical data (wide range of symptomatology assessment, treatment side effects, presence of childhood trauma) and -omics features (genomic, transcriptomic and miRNomic) for the prediction of treatment response in MDD patients will be shown. Moreover, an overview of RCTs on pharmacogenetic-based decision support tools for antidepressant drugs will be critically assessed. Moreover, recent findings on rare genetic variation impacting important clozapine-associated adverse drug reactions as well as such variation varies across ethnicities will be discussed. Finally, results of a recent systematic review on what is currently known about common genetic variation impacting clozapine response will be shown.

NEW DEVELOPMENTS IN THE PHARMACOGENOMICS OF TREATMENT RESPONSE PREDICTION IN PSYCHIATRY

University of Münster
Bernhard Baune*[1]
[1]

Objective: As background, the overall aim of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, in the psychiatric field, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacoepigenomic approaches, focusing on genetic variants and epigenetic modification related to pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry. These two layers of omics

and their integration provide important and novel information regarding therapeutic response and side effects, contributing to optimizing pharmacological treatment in an individualized approach. The objective of this presentation is to introduce a concept of the multi-omics foundation of response to pharmacological and non-pharmacological treatments, which entails the genomics, transcriptomics and epigenomics layers of response to a pharmacological intervention and demonstrate this concept in in two case studies using randomised controlled trial (RCT) data from the PREDDICT and CERT-D trials.

Methods: The chosen approach requires the analyses of individual omics layers as well as an integrated analysis of multiple omics in relation to response to treatment. Two examples of RCTs will used to illustrate this multi-omics concept of prediction of treatment outcomes: first, the PREDDICT study, which is a randomized controlled trial to test the efficacy of an antidepressant plus augmentation with celecoxib vs antidepressant plus placebo in major depressive disorder (MDD). In a second case study, he will present multi-omics results from the randomized CERT-D study that tests the antidepressant effects of a personalised cognitive training program in MDD. In both examples, multi-omics predictions of treatment response will be presented.

Results: Results from the CERT-D study show that DNA methylation can be suitable to capture early signs of treatment response and remission following a cognitive intervention in depression. Despite not being genome-wide significant, the CpG locations and GO-terms returned by our analysis comparing patients with and without cognitive impairment, are in line with prior knowledge on pathways and genes relevant for depression treatment and cognition. Results from the PREDDICT study will be presented as well. Results on the integration of genetic and epigenetic layers for both the PREDDICT and CERT-D studies will complete this presentation.

Conclusion: The conceptual approach chosen is useful to better understand the complexity of the underlying biology of treatment response in depression treatment. Methodological developments are underway and encouraged by our findings.

THE PROMPT STUDY: REVEALING NEW KEY PLAYERS IN PREDICTING TREATMENT RESISTANCE

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Objective: Dr Júlia Perera-Bel will present results on the development of a model precision psychiatry framework that integrates clinical data and -omics features (transcriptomic and miRNomic) for the prediction of treatment response in major depression disorder (MDD) patients. This is the overall objective of the PROMPT ("Toward PrecisiOn Medicine for the Prediction of Treatment Response in major depressive disorder through Stratification of Combined Clinical and -Omics Signatures") consortium, which is funded by the European ERA PerMed funding scheme.

Methods: The overall methodology of the project is based on a two-phase design. In the first phase (training phase, retrospective design), 300 already recruited MDD patients, including 150 TRD and 150 responders considered as extreme phenotypes of response, will undergo a deep clinical and omics profiling. These data will be exploited to develop an innovative integrative algorithm for the prediction of MDD treatment outcome. Recruited patients undergo a comprehensive clinical assessment and molecular profiling (genomic, transcriptomic and miRNomic). DNA and RNA for genomic, pharmacogenetic extracted from peripheral blood samples are prepared transcriptomic and miRNomic analyses. RNA library preparation is performed following the manufacturer's recommendations. Final samples pooled library preparations are sequenced on a Novaseq 6000 ILLUMINA, at a depth of 2x30Millions of 100bases reads per sample after

demultiplexing. MiRNomic (+ other small RNA) profiling is conducted by small RNA-Seq. Sequencing yields 20-30 million single-end 50 bp reads per sample on a NextSeq2000 (Illumina). Quality assessment is done with FastQC, and reads are trimmed using Cutadapt before mapping. Sequences with length < 16 nucleotides are discarded. The reads count table is generated using featureCounts, filtered for underrepresented genes, and analyzed using linear models (limma) for differential expression analysis. Functional analysis utilizes available annotations in functional genomics resources. Network-based approaches are employed to visualize miRNA-target connections and perform gene ontology (GO) analyses. STRINGdb is used for protein-protein interaction retrieval, igraph for network analysis, and clusterProfiler for GO and pathway enrichment analyses. Differential expression of miRNAs is validated by qPCR.

Results: We have already recruited 192 patients with MDD, including 104 TRD/88 responders. This cohort is composed of 70% of females, equally represented in both groups. BMI and age are associated with TRD, as well as mental comorbidities (e.g. anxiety, personality disorders). We have identified differentially expressed genes between the two groups. We observed a downregulation of immune-related pathways in TRD patients. Importantly, the microRNA regulation explains most of the differentially expressed genes, thus indicating their causal involvement in treatment resistance, and opening new yet unexplored therapeutic avenues in MDD.

Conclusion: The projects revealed the importance of microRNA as regulators of important molecular pathways underlying treatment response in major depression. Importantly, we detected downregulation of immune-related pathways in TRD patients and deregulated gliucemia and neuroinflammatory pathways. This project will provide a new predictive tool for future use in clinical practice, enabling better prevention and management of MDD treatment resistance.

CLINICAL EFFICACY OF ANTIDEPRESSANT PHARMACOGENETIC TESTS IN CLINICAL PRACTICE: STATE OF THE ART, CHALLENGES AND FUTURE PERSPECTIVES

Alessandra Minelli**1*

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Alessandra Minelli, Brescia University School of Medicine

Objective: Several data indicate that the success of pharmacological treatment in major depressive disorder (MDD) is still unsatisfactory, and matching a patient to his/her optimal treatment generally requires multiple trials with different treatments. It is sobering to note that the more unsuccessful therapies tried, the lower the likelihood that a successful outcome will occur, which could lead to a protracted illness, a worse long-term prognosis, more side effects, and significant medical, social, and financial costs.

Methods: Numerous environmental and biological aspects of the disease as well as medication treatments are to blame for the low response and remission rates. Pharmacogenetic (PG) testing has the potential to improve the accuracy of outcome prediction and lower the rate at which antidepressants are stopped due to adverse effects. Commercial PG tests for antidepressants have been more widely available, but there has also been rising skepticism about their usefulness. Several studies have been carried out, with intriguing but conflicting findings.

Results: Few of them currently are randomized controlled trials (RCTs), and the majority of them are observational studies without a control group. Several limitations were found concerning study design, generalization of results, duration of the trails, patients group studied, and cost-effectiveness ratio. We conducted the first study in Italy concerning the validation of a pharmacogenetic test for antidepressants in clinical daily practice with advocacy license independence. In order to provide a comprehensive view of outcomes, including symptom improvements and the emergence of negative effects, we tried to overcome the limitations of prior studies by applying a wide range of rating scales.

This allowed us to identify the true impact of the pharmacogenetic test on the various symptom phenotypes of depression. **Conclusion:** In conclusion, a number of obstacles have been identified for the widespread use of PG testing for antidepressants in clinical care for patients with MDD. The lack of overall efficacy in some prospective trials necessitates further research and indicates that there are variations between the population seen in prospective clinical trials and the real-world populations that should undergo PG testing. Attempts to gain a better understanding of the subset of people who might benefit and the time frame over which such advantages are required.

GENETICS OF CLOZAPINE RESPONSE AND ADVERSE DRUG REACTIONS: FROM RARE TO COMMON GENETIC VARIATION

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Objective: Little is known about how genetic variation impacts clozapine-related side effects and clozapine response, thus making clinicians and patients often reluctant to start clozapine. Moreover, few studies have examined ancestry-diverse populations in psychiatric genetics. We therefore examined associations of common and rare genetic variants with clozapine response and clozapine-related side effects.

Methods: Both targeted (using Taqman and Sanger sequencing) and whole-genome analyses were conducted in a sample of 800 subjects using clozapine with a diverse ancestry. Genome-wide association studies (GWASs) were conducted. Polygenic risk scores (PRS) for schizophrenia were generated. Linear models correcting for covariates were run to examine associations between clozapine response and PRS. Finally, we examined associations between genotype-predicted CYP1A2, CYP2D6, and CYP2C19 enzyme activities and clozapine response.

Results: In targeted analyses we found that rs113332494 (HLA-DQB1) was significantly associated with clozapine-associated neutropenia/agranlycytosis in the all participants (P = 3.5 × 10−8), in Caucasians (P = 9.3 × 10−6) and in Turkis (P = 2.8 × 10−5). Rs41549217 (HLA-B) was nominally significant in the Caucasian group (P = .018).

Our GWAS indicated that rs1923778 within NFIB showed a suggestive association with symptom severity while on clozapine.

PRS-schizophrenia was positively associated with low symptom severity.

Furthermore, higher genotype-predicted CYP2C19 enzyme activity was independently associated with lower symptom severity while on clozapine.

Conclusion: Ethnicity-dependent and clinically relevant effects of genetic polymorphisms on the risk to develop clozapine-induced neutropenia/agranulocytosis exist. Pharmacogenetic testing can complement clinical decision making and thus empower appropriate CLZ prescribing, but ancestry should be taken into account when performing such testing for CLZ. High schizophrenia-PRS and genotype-predicted CYP2C19 enzyme activity are independently associated with lower symptom severity among individuals treated with clozapine Although it is too early to adopt PRSs in clinical decision-making, these findings strengthen the positioning of PRS-SCZ as relevant to treatment response in psychiatry, particularly in patients with difficult-to-treat symptoms.

PARAM: A NEURODEVELOPMENTAL COHORT FROM INDIA

Vivek Benegal, National Institute of Mental Health and Neurosciences, Bangalore

Symposium Synopsis: The PATHWAYS TO RESILIENCE AND MENTAL-HEALTH [PARAM] is a longitudinal study, in India to trace the normal and deviant neurodevelopmental trajectories which underlie resilience and vulnerability to mental illnesses; and understand the impact of Genome x

Exposome interactions on these processes, across the developmental span. The PARAM seeks to extend and enrich an existing neurodevelopmental cohort (the Consortium on Vulnerability to Externalizing Disorders and Addictions) of individuals aged 6-23 years, set up between 2016-2020 to establish a database and biobank of 9000+ subjects across seven sites in India. The symposium will present data from the cohort to discuss our work in establishing normative brain (and cognitive) developmental trajectories and the impact of exposures to environmental (modifiable) risk factors such as socioeconomic status, nutrition and pollution (PM2.5, arsenic) 1. Introduction to the Indian neurodevelopmental cohort 2. Growth trajectories for executive and social cognition abilities and the impact of psychosocial determinants 3. Impact of Developmental Exposure to Air Pollution and a matrix of environmental risk on Cognitive Function in Adolescent and Young Adults 4. A neurocognitive investigation of low-level arsenic exposure with executive functions and brain structure and resting state activity.

IMPACT OF DEVELOPMENTAL EXPOSURE TO AIR POLLUTION AND A MATRIX OF ENVIRONMENTAL RISK ON COGNITIVE FUNCTION IN ADOLESCENT AND YOUNG ADULTS

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Objective: Brain development is influenced by both genetic and environmental factors and is critical for the normal growth and maturation of mental processes such as attention, memory, learning, and executive functions. It is well established that there are critical periods in the development of the brain when the environment can significantly impact neuroplasticity and cognitive development. The impact of developmental exposure to air pollution and a matrix of environmental risks on cognitive function in adolescent and young adults is a growing area of concern. The Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA) is an accelerated longitudinal cohort based in India that aims to study the impact of genes and environment on brain structure, function, and cognitive abilities. This study focuses on the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, body mass index, and psychopathology.

Methods: The participants of the cVEDA study were assessed at baseline and two follow-up times, and measures of socio-demographics, psychopathology, cognitive functions, and high-resolution ambient air PM2.5 exposure were available for n=6307 at baseline and were included for the current analyses. We performed a hierarchical confirmatory factor analysis and generated a single latent factor (g) representing general cognitive abilities. We then studied the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, BMI and psychopathology.

Results: The study found that exposure to particulate matter was significantly associated with poorer general cognitive abilities, after controlling for confounds. Further, we also found that the impact of developmental exposure to PM2.5 on overall cognitive functioning was significantly greater among people from lower socio-economic backgrounds, indicated by lower wealth scores.

Conclusion: In conclusion, the results of this study provide evidence for the impact of exposure to particulate matter on general cognitive abilities in adolescent and young adults and suggest that the presence of multiple environmental risk factors (eg., malnutrition, poverty etc) may have additive effects on cognitive development. The cVEDA cohort represents a unique opportunity to investigate the interplay between environmental exposures, psychopathology, and cognitive development in a developing country context. These findings highlight the need for further research to understand the potential implications of air pollution on cognitive development in populations exposed to high levels of particulate matter. These findings have important implications for policy and public health initiatives aimed at reducing exposure to environmental pollutants and promoting healthy cognitive development.

GROWTH TRAJECTORIES FOR EXECUTIVE AND SOCIAL COGNITION ABILITIES AND THE IMPACT OF PSYCHOSOCIALDETERMINANTS

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Objective: Structural and functional developmental reorganization of the brain manifests as motor, sensory, cognitive, social, emotional and other functional abilities. Timing and pattern of maturation follow a simple to complex order. Basic sensory and motor functions are fairly well established in early childhood; timelines for certain cognitive and socio-emotional abilities might extend into adulthood. Examining functional brain abilities could help track brain development; they also have a putative role in early risk identification for psychopathology. These abilities need to be better characterized over development, in terms of maturational patterns, implications of delay or deficits, factors that influence developmental change, etc.

Methods: The cVEDA study, an Indian developmental cohort, with data on more than 9000 youth, ages 6-23 years, enabled examination of developmental trajectories (for verbal and visuo-spatial working memory, response inhibition, set-shifting, and social cognition), and how these are influenced by gender, socio-economic status and childhood adversity. Working memory enables holding information temporarily for task performance. Response inhibition is self-regulatory, enabling appropriate inhibition of undesirable responses. Set-shifting is cognitive flexibility, enabling consideration of alternatives. Faux pas recognition that detects social blunders and emotion recognition are necessary for socio-emotional functioning. The sample represented sex, urban-rural background, and psychosocial risk (psychopathology, childhood adversity and wealth index, i.e. socio-economic status) adequately. Quantile regression was used to model developmental change. It models conditional percentiles by representing observations along with their distributions. This method allowed for examination of covariate effects on shape and location of the graph. We could examine whether covariates affected everyone similarly or were there differences in, say, high versus low performers.

Results: Development in both executive and social cognitive abilities continued into adulthood. Maturation and stabilization occurred in increasing order of complexity, from working memory to inhibitory control to cognitive flexibility. Social faux pas recognition matured by adolescence, but emotion recognition abilities continued to develop into early adulthood. Age related change was more pronounced for low quantiles in response inhibition, but for higher quantiles in set-shifting. Wealth index had the largest influence on developmental change across cognitive abilities. Sex differences were prominent in response inhibition, set-shifting and emotion recognition. Childhood adversity had a negative influence on cognitive development.

Conclusion: These findings add to the limited literature on patterns and determinants of functional brain development. They have implications for developmental vulnerabilities in youth, and need for providing conducive environments. Socio-economic status, by providing enriched environments, has the most prominent influence on development, whereas adversity negatively impacts development. Childhood performance level plays a role in adult outcomes. Interestingly, more prominent impact of determinants on lower performance levels of response inhibition and emotion recognition suggests that these abilities can be enhanced by adequate learning opportunities. This could have a cascading impact on other skill development.

A NEUROCOGNITIVE INVESTIGATION OF LOW-LEVEL ARSENIC EXPOSURE WITH EXECUTIVE FUNCTIONS AND BRAIN STRUCTURE AND RESTING STATE ACTIVITY

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Objective: Arsenic, a contaminant of groundwater and irrigated crops, is a global public health hazard. While isolated impairments of cognitive function following chronic exposure to high arsenic levels have been described, a comprehensive assessment of the scope of such impairments and their underlying brain mechanisms does not exist, especially not in the case of the much more common low-level arsenic exposure. We applied multivariate statistical modelling to (i) investigate potential arsenic-related syndromic changes across multiple cognitive domains; (ii) identify arsenic-related changes in brain structure and function; (iii) understand the relationship between arsenic-associated brain and cognitive alterations, and (iv) explore the moderating influence of other measures of environmental risk and physical health.

Methods: We analysed cross sectional data of 1014 participants aged 6 to 23 years of the Indian Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA cohort). Participants were characterised using deep phenotyping measures of behaviour, neuropsychology, psychopathology, brain neuroimaging and exposure to developmental adversities and environmental neurotoxins. Arsenic was measured in urine as an index of exposure. Executive function was measured using cVEDA neuropsychological battery, grey matter volumes were extracted from T1 weighted MRI and functional network connectivity measures were extracted from the resting state functional MRI. Our multivariate approach controls for age, gender, site, educational level and total intracranial volume. We used sparse partial least square (sPLS) analysis to determine the relationship between arsenic, cognition, brain structures and functions through the application of L1 penalization, applied under resampling. Subsequently we carried out mediation analysis. Next, we conducted moderated mediation analysis using data on participant's SES and BMI.

Results: 1014 participants aged 6 to 23 years (44.5% females) were included from 5 geographic locations. Using sparse-partial least squared analysis (sPLS) we describe a negative association of arsenic exposure with executive function (r=-0.12, p=5.4x10-4), brain structure (r=-0.2, p=1.8x10-8) and functional connectivity (within-network: r=-0.12, p=7.5x10-4, between-network: r=-0.23, p=1.8x10-10). Alterations in executive function were partially mediated by localised changes in grey-matter volume (b=-0.004, 95%CIs=-0.007 to -0.002) and within-network functional connectivity (b=-0.004, 95%CIs=-0.008 to -0.002). Socio Economic Status (SES) and Body Mass Index (BMI) moderated the link between arsenic and changes in grey-matter volume, such that the effect is strongest in participants from lower SES and with low BMI.

Conclusion: Our results indicate that low exposure to arsenic, among participants residing in areas with reported groundwater arsenic content below WHO thresholds, is correlated with aberrations in structural and functional brain regions and alterations of cognitive processes of executive function. Further, children from lower standard of living and with low BMI might be more vulnerable to environmental insults associated with arsenic and might point towards a "syndemic" relation between arsenic exposure and low SES, BMI resulting in greater health problems.

MACHINE LEARNING APPROACHES TO IDENTIFY FUNCTIONAL BRAIN NETWORKS CORRELATING WITH COGNITIVE PERFORMANCE IN ADOLESCENTS WITH ADHD

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Objective: Psychopathology is increasingly associated with impairments in cognitive, emotional and behavioural functions due to underlying alterations in distributed neural networks. Using rsfMRI, large-scale resting state networks (RSNs) have been identified consistently in healthy subjects. Connectivity within these networks correlates with cognitive and behavioural measures obtained outside the scanning environment.

Statistical machine learning methods have been successfully used to classify ADHD based on fMRI measures in previous studies. Here, we used reliefF- SVM derived methods with FSL derived ICA networks as input, to evaluate the cognitive performance of adolescents with ADHD, to identify brain networks underlying cognitive dysfunction.

Methods: The subjects in this study were from the cVEDA neurodevelopmental cohort in India. 71 subjects with a diagnosis of Attention Deficit Disorder [mean age (SD) :12.7 (±3.2)years] were included along with 71 healthy controls (HC) matched for age [mean age (SD) – 12.9 (±2.8) years], gender, head-motion profile during fMRI and scanner-site from the cVEDA imaging databank (http://cveda.org/dataset/).

Cognitive task scores from the cVEDA neuropsychological battery, included digit span test, corsi block test, trial making test, now or later test, balloon analogue risk task, stop signal task, sort the cards, emotional recognition task and social cognition rating tool in Indian setting. Scores on these tasks were scaled to a mean of 50 and standard deviation of 10 and summated to compose cognitive domains.

Resting-state functional MR imaging (EPI) scans were obtained (164 dynamics; TR/TE/FA – 2200ms, 30ms, 75°; 38 slices; 3.4x3.4x3.4 mm). Folllowing pre-processing, subject-specific network time-series were derived, using the dual regression approach of FSL. The data was decomposed into 79 components using the Fast ICA algorithm in FSL. For the purpose of machine learning classification, all the 79 components were used to regress out subject-specific time courses and spatial maps. Feature-set reconstruction was carried out and a filter based feature selection method - ReliefF was implemented

Results: The reliefF-SVM algorithm predicted 55/71 ADHD subjects and 54/71 HC correctly. 16 ADHD subjects were misclassified as HC and 17 HC were misclassified as ADHD. The ROC analysis revealed consistent performance of the algorithm across thresholds. The performance of the classifier model was evaluated using a 10-fold stratified cross validation resulting in 128 training instances and 14 test instances. The overall accuracy was 76.76% with 76.05 % specificity and 77.46 % sensitivity.

Among the 62 components there were 18 components that revealed significant group differences. These components belonged to task positive, default mode, cingulate, orbito frontal, sensory motor, temporal, and visual networks. **Conclusion:** Our study found that rsFMRI measures can be used to predict subjects with ADHD and can be used as an adjunct to phenotypic classification of ADHD. Further we found that variations in specific functional brain networks, appeared to correlate with different cognitive, emotional functions including attention, working memory, impulse control, processing speed social cognition and emotion recognition reflecting lower connectivity in these networks as an indicator of a poor performance.

TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON ANTIPSYCHOTICS

Xenia Hart, German Society for Biological Psychiatry

Symposium Symposium For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A personalization of drug treatments towards highest possible efficacy with acceptable tolerability involves titrating towards the best individual dose and dosing strategy by the use of tools implemented to support clinical decision making. Two tools have been introduced in these terms that can be used in clinical practice i) Therapeutic Drug Monitoring of antipsychotic drug levels and ii) pharmacogenetic testing. Valuable additional insights derive from in vivo brain imaging studies.

Methods: We provide details on pharmacokinetics and pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Articles were selected for inclusion and discussion by more than 40 international experts in the field of psychiatry and psychopharmacology. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. In vivo occupancy of target structures occupied by antipsychotic drugs was primarily assessed using positron emission tomography.

Results: Study findings strongly support the use of Therapeutic Drug Monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes to guide antipsychotic drug therapies. Molecular brain imaging is a strong tool to support the definition of target windows for optimal antipsychotic drug action, so called therapeutic reference ranges.

Conclusion: Therapeutic drug monitoring and genotyping are valid tools to guide individual drug therapies, far beyond the typical indications i.e. uncertain adherence, and polypharmacy.

INTRODUCING TOOLS FOR OPTIMIZING ANTIPSYCHOTIC PHARMACOTHERAPY IN PSYCHIATRY (THERAPEUTIC DRUG MONITORING, MOLECULAR BRAIN IMAGING AND PHARMACOGENETIC TESTS)

Xenia Hart**1*

[1] *German Society for Biological Psychiatry*

Objective: For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A large spectrum of antipsychotic drugs is now available in most western countries. A personalization of drug treatments aims at achieving the highest possible efficacy and acceptable tolerability at the same time. It involves not only the selection of the optimal drug for a patient but also the titration towards the best individual dose based on patients' specific characteristics.

Methods: In my talk, I will give a short introduction in to-date available tools that can be used to optimize pharmacotherapy in psychiatry. I will give an overview on how these tools can be used in order to support clinical decision making in antipsychotic drug therapies. The presented findings are

based on an international guideline initiated by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" with a contribution of more than 40 international experts. Therapeutic drug monitoring nowadays represents the most commonly used tool for personalizing drug treatments in clinical psychiatry. After determination of a drugs' blood level, this level is compared to predefined reference ranges published in relevant guidelines. Pharmacogenetic testing is predominantly used to detect genetic polymorphisms of enzymes involved in drug metabolism. However, the clinical application potential goes far beyond this. The third tool introduced in this presentation are in vivo brain imaging studies, primarily using positron emission tomography. **Results:** The guideline developed by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" provides a detailed review on pharmacokinetics, pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. The use of therapeutic drug monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes are strong tools to guide antipsychotic drug therapies for most drugs. Molecular brain imaging has been used to support the definition of valid therapeutic reference ranges. **Conclusion:** Despite the introduction of useful tools to optimize drug treatments in psychiatry, personalized drug treatment has still not become standard of care in psychiatric patients. Guidelines provide strong support for the use of therapeutic drug monitoring and pharmacogenetic testing. For example, they contain practical instruction for the interpretation of drug monitoring results.

WFSBP TASK FORCE - TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON THERAPEUTIC DRUG MONITORING OF ANTIPSYCHOTICS

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Objective: Therapeutic drug monitoring (TDM) is an important tool to optimize pharmacotherapy, in particular for drugs with narrow therapeutic range. The clinical value of TDM during antipsychotic therapy is best established for clozapine. However, because of the wide interindividual variation of plasma levels and treatment responses, most other antipsychotics are good candidates for routine TDM.

Methods: The literature was extensively reviewed by the WFSBP task force to assess pharmacokinetics, therapeutic ranges and relations between plasma concentrations, daily doses and therapeutic responses of 43 common antipsychotics.

Results: The main conclusions of this review will be discussed, with a focus on clinically important data for the TDM of specific antipsychotics. In addition, the following important aspects of TDM will be addressed: a) specific indications (e.g., treatment resistance, evaluations of drug–drug interactions, specific comorbidities affecting drug pharmacokinetics), b) pre-analytical issues (e.g., steady-state conditions and time of blood sampling), and c) post-analytical issues (e.g., clinical interpretations of drug levels and therapeutic recommendations such as dose adjustments and antipsychotic switches).

Conclusion: To be clinically relevant, TDM should be used according to the latest available evidence and with a good knowledge of the pharmacokinetics, pharmacodynamics and safety profile of the drugs. Moreover, TDM should be associated when needed with other valid tools, such as cytochrome P450 phenotyping and/or genotyping, to optimize personalized antipsychotic therapy.

ASSOCIATION BETWEEN CYP2D6 SLOW METABOLIZER STATUS AND EXPOSURE TO ANTIPSYCHOTICS

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Objective: Precise estimation of the drug metabolism capacity for individual patients is crucial for adequate dose personalization. The aim of this meta analysis was to quantify the difference in the antipsychotic exposure among patients with genetically associated CYP2D6 poor (PM), intermediate (IM), and normal (NM) metabolizers.

Methods: PubMed, Clinicaltrialsregister.eu, ClinicalTrials.gov, International Clinical Trials Registry Platform, and CENTRAL databases were screened for studies. Two independent reviewers performed study screening and assessed the following inclusion criteria: (1) appropriate CYP2D6 genotyping was performed, (2) genotype-based classification into CYP2D6 NM, IM, and PM categories was possible, and (3) 3 patients per metabolizer category were available. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for extracting data and quality, validity, and risk of bias assessments. A fixed-effects model was used for pooling the effect sizes of the included studies. Drug exposure was measured as (1) dose-normalized area under the plasma level (time) curve, (2) dose-normalized steady-state plasma level, or (3) reciprocal apparent total drug clearance. The ratio of means (RoM) was calculated by dividing the mean drug exposure for PM, IM, or pooled PM plus IM categories by the mean drug exposure for the NM category.

Results: the most profound differences were observed in the patients treated with aripiprazole (CYP2D6 PM plus IM vs NM RoM, 1.48; 95% CI, 1.41-1.57; 12 studies; 1038 patients), haloperidol lactate (CYP2D6 PM vs NM RoM, 1.68; 95% CI, 1.40-2.02; 9 studies; 423 patients), risperidone (CYP2D6 PM plus IM vs NM RoM, 1.36; 95% CI, 1.28-1.44; 23 studies; 1492 patients). Exposure differences were also observed for clozapine, quetiapine fumarate; however, these differences were marginal, ambiguous, or based on less than 3 independent studies.

Conclusion: In this systematic review and meta-analysis, the association between CYP2D6 genotype and drug levels of several antipsychotics was quantified with sufficient precision as to be useful as a scientific foundation for CYP2D6 genotype-based dosing recommendations.

THERAPEUTIC PLASMA CONCENTRATIONS OF ANTIPSYCHOTICS: LESSONS FROM PET IMAGING

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Objective: Positron emission tomography (PET) and single photon emission tomography (SPECT) of molecular drug targets (neuroreceptors and transporters) provide essential information for TDM-guided drug therapy with antipsychotic drugs. Optimal therapeutic windows for D2 antagonists and partial agonists as well as proposed target ranges are discussed based on an up-to-date literature search.

Methods: An overview of neuroimaging findings in humans and primates that after the administration of amisulpride, haloperidol, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, cariprazine, and ziprasidone will be provided. A particular focus is set on dopamine D2-like and 5-HT2A receptors. Target concentration ranges are estimated based on receptor occupancy ranges that relate to the onset of clinical effects or side effects (i.e. EPS). Findings for other relevant receptor systems complement the discussion.

Results: Reported reference ranges for aripiprazole and for clozapine are well in line with findings from PET studies. For haloperidol, risperidone and olanzapine, an adjustment of the previously

published upper limit towards lower concentrations would be indicated from PET studies' findings to decrease the risk for EPS.
Conclusion: Neuroimaging studies provide a strong tool to define target ranges for antipsychotic drug treatment and to direct TDM.

WHITE MATTER IN MENTAL ILLNESS, AS A BIOMARKER AND THERAPEUTIC TARGET

Xinmin Li, University of Alberta
Symposium Synopsis: Since the introduction of drugs used in the treatment of major psychiatric disorders in the 1950s, emphasis has been placed on classical pharmacological actions. Putative therapeutic mechanisms of focus have included effects on monoamine neurotransmitter synthesis, catabolism, release, uptake, and receptor activation. We need to identify alternative and additional targets for drug action in this context. The innovative work that we are leading has indicated possible new mechanisms of action of many of these drugs in terms of effects on neuroprotective effects on neurodegenerative processes in the brain.
Our team approaches mental health disorders as neurodegenerative disorders. We examine whether central white matter damage can produce behavioral symptoms and brain pathology in experimental animal models of schizophrenia or depression as well as neuroimaging, genetic, and clinical studies. We examine whether antipsychotic and antidepressant treatment, rTMS, and ultrasound can prevent white matter damage and/or facilitate recovery which suggests a new role for these treatments and also suggests a new target for future drug development.

RESEARCH ON MYELINATION RELATED SUSCEPTIBLE GENES OF SCHIZOPHRENIA

Weihua Yue*[1], *Hao Yan1, Yuyanan Zhang1, Yaoyao Sun1, Dongxue Chen1, Zhe Lu1, Zhewei Kang1, Tianlan Lu1, Dai Zhang1*

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Objective: The strategy of genetics has been proven to be effective and helpful to explore the mechanism of schizophrenia and the myelination related susceptible genes of antipsychotic medications. We have been committed to finding the myelination related susceptibility genes of schizophrenia in Chinese Han population.
Methods: We used the genome-wide association study (GWAS) and meta- analysis, the multi-omics approaches, and the pharmacogenomics in Chinese Han population (n = 5934).
Results: We found several myelination related susceptibility genes associated with the risk of schizophrenia (MBP, MAG, MOP, etc.). Combined clues of bioinformatics data and functional experiments by using the gene knock-out or knock-in mice models, we further explored the potential function of the novel susceptible genes. There were very important interactive effects on genetic polymorphisms or variants, on transcriptional levels or neuroimaging characters in schizophrenia patients. With a large sample size of pharmacogenomics (3 stages-design, n = 5934), the applicant reported several susceptible genes associated with individual differences in therapeutic or side effects of common antipsychotic medicines. Patients in the pharmacogenomics-guided pharmacotherapy (PGT) group had greater early-response rate (94.0% versus 80.8%), response rate (83.1% versus 60.3%) and symptomatic remission rate (68.7% versus 46.2%) compared to the treatment-as-usual (TAU) group.
Conclusion: These results will be helpful to interpret the pathogenesis of schizophrenia, as well as the pharmacological mechanism of common antipsychotic medications.

Haiyun Xu*[1]
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Objective: Understanding the pathogenesis of schizophrenia involves exploring various hypotheses, including the dopamine (DA) hypothesis, mitochondrion hypothesis, oligodendrocyte (OL) hypothesis, among others. The coexistence of these hypotheses suggests a potential common neurobiological mechanism underlying schizophrenia.
Methods: This study investigates a potential neurobiological mechanism by utilizing two animal models of schizophrenia, cultured OLs, and neuron-OL co-cultures. The research employs animal behavioral tests, as well as cellular and molecular biological techniques.
Results: Adolescent C57BL/6 mice administered tolcapone (TOL) for two weeks exhibited elevated DA levels in the prefrontal cortex (PFC), mitochondrial dysfunction in brain cells, and dose-dependent hypomyelination in the PFC, hippocampus, and caudate putamen (CPu), alongside schizophrenia-related behaviors. Catechol-O-methyltransferase (COMT) gene knockout (COMT-ko) mice displayed dopaminergic dysfunctions in the PFC and CPu, mitochondrial functional deficits, reduced mature OLs, and hypomyelination in similar brain regions to TOL-treated mice. In cultured OLs, DA inhibited cell development and impaired mitochondrial function in a concentration-dependent manner. These effects were mitigated by the antioxidant N-acetyl-L-cysteine (NAC) and trans-2-phenylcyclopropylamine (TCP), a mitochondrial monoamine oxidase (MAO) inhibitor. Additionally, DA inhibited axonal myelination in neuron-OL co-cultures while impairing mitochondrial function.
Conclusion: These findings underscore the critical role of mitochondria in linking DA catabolism to axonal myelination in the brain, offering new insights into schizophrenia pathogenesis and therapeutic strategies.

MODIFICATION OF MYELINATION AS A TARGET FOR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND FLUOXETINE TREATMENT IN A MOUSE MODEL OF DEPRESSION

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Objective: In order to test the neurotrophic hypothesis on myelination of depression, myelin basic protein (MBP), brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (TrkB) signaling were investigated in a mouse model of depression which was applied by a physical treatment of repetitive transcranial magnetic stimulation (rTMS) or (and) by a medical treatment of fluoxetine.
Methods: After 28 days of chronic unpredictable mild stress (CUMS) exposure, mice were chronically treated with rTMS (10 Hz for 5 seconds per train, total 20 trains per day) and (or) fluoxetine (5 mg/kg/day, intraperitoneally) for 28 days targeting on the frontal cortex. After the behavioral tests, the protein expressions of MBP, BDNF and TrkB were measured by immunohistochemistry and (or) Western Blot.
Results: The results showed rTMS and (or) fluoxetine attenuated the locomotion decrease, anxiety and depressive-like behaviors in the CUMS-exposed mice. In the same time, rTMS and (or) fluoxetine attenuated MBP and BDNF-TrkB decrease in the frontal cortex of the CUMS mice. Our results suggest that rTMS and fluoxetine could both benefit the CUMS-induced abnormal behaviors including depressive-like behaviors, and the beneficial effects of rTMS as well as fluoxetine on depression might be partly related to their common effect on modulating myelination through BDNF-TrkB signaling.
Conclusion: These indicate that modulation of myelination could be a potential novel treatment target for major depressive disorder.

MATRIX METALLOPROTEINASE-9 AS A MYELINATION RELATED PROTEIN IN INTRACEREBRAL HEMORRHAGE AND DEPRESSION

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Objective: The zinc-dependent proteinases (MMPs) are a endopeptidases which have the capability of cleaving protein constituents of extracellular matrix. They are physiologically expressed in neurons, astrocytes and microglia, and their aberrant elevation contributes to a few central nervous system diseases.

Methods: Among the MMP members, MMP-9 has generated considerable attention because of its involvement in inflammatory responses, blood-brain barrier permeability, the regulation of perineuronal nets, demyelination, and synaptic long-term potentiation. MMP-9 is strongly detected in many cell types including endothelial cells and infiltrated neutrophils after brain injuries. It can be induced by factors such as the c-fos and c-Jun, immediate early genes and the cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).

Results: Primary hematoma expansion occurs shortly after intracerebral hemorrhage onset and appears to correlate with MMP-9 elevation. Perihematomal edema also seems to be linked to MMP-9 levels. Inhibition of MMP-9 could potentially improve clinical outcome through maintenance of BBB integrity and perihematomal edema reduction. Emerging evidence indicates an association between MMP-9 and the syndrome of depression. MMP-9 is considered to be an important factor in depression, not only as a therapeutic target but also as a biomarker in the condition. Clinical studies suggest that MMP-9 gene polymorphisms are related to depressive symptoms, and altered MMP-9 levels are observed in depressed patients and in depressive-like animal models. The serum MMP-9 may be a novel therapeutic target and biomarker for depression, although that blood level of MMP-9 may not directly correlate with brain MMP-9 content.

Conclusion: MMP-9 is likely to be a target for classical antidepressant treatments and MMP-9 inhibitors possess potential therapeutic effects for depression.

3:30 p.m. - 5:00 p.m. Debate Session III - Anthony Pelosi and Steven Hyman

DOES NATURE FAVOUR DIMENSIONAL OR CATEGORICAL DIAGNOSES? BY THEIR (CLINICAL) FRUITS SHALL YE KNOW THEM

*Anthony Pelosi*1*

[1]*University of Glasgow*

Objective: I will consider some pros and cons of categorical versus dimensional diagnoses in clinical practice and in research.

Methods: Results will be presented from epidemiological and health services research over the decades.

Results: I will argue that, on balance, a categorical diagnostic approach in psychiatry has been more useful to more patients than a dimensional approach over recent decades.

However, I will also also outline some recent worrying developments in British psychiatry that lessen the importance of Mother Nature when it comes to clinical diagnosis. These include the following.

1. Categorical and dimensional diagnoses are being used to exclude certain patients from the caseloads of highly specialised multidisciplinary clinical teams.

2. Specialist clinicians are claiming that they have special diagnostic skills and that diagnoses within their narrow area of interest are being missed by other psychiatrists (see, for example, Report by Bipolar UK 2022). 3. Certain psychiatrists and even their multidisciplinary colleagues are increasingly preoccupied with diagnostic classification. This is sometimes to help them exclude patients from their caseloads. At other times, it is to obtain access to additional resources for their patients that can only follow "an official diagnosis". Some nurses, psychologists, occupational therapists and social workers are taking this approach even though one of the strengths of these professions is that they are trained not to make diagnoses. 4. Patients are sometimes being referred to a clinic for confirmation of a particular self-diagnosis rather than for an assessment by a doctor who understands diagnosis and differential diagnosis and who is aware of their importance and their limitations. 4. Clinical and administrative preoccupation with "an official diagnosis" means that certain patients are passed from pillar to post when they present with mental ill health. Some patients, especially those with severe and complicated conditions, can end up receiving no care and treatment from mental health professionals. In the months before the conference I will be making inquiries of colleagues in other parts of the world about whether they have encountered similar situations. This is with a view to starting a good discussion of what can be done to maximise the benefit of both categorical and dimensional diagnoses and differential diagnoses. **Conclusion:** I will suggest that diagnostic categories in psychiatry remain a useful tool but, like all powerful tools, they can be misused.

DEBATE. NATURE STRONGLY FAVOURS DIMENSIONAL DIAGNOSES

*Steven Hyman*1*
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The Broad Institute

Objective: In this debate, I will present evidence that psychiatric disorders are best captured in dimensional terms that cross current diagnostic boundaries; I will also describe how the dominant DSM categorical system has become reified in a manner that thwarts scientific progress and new treatment development.
Methods: I will describe and synthesize results from epidemiology, genetics, neurobiology, and clinical research that can inform concepts and boundaries of psychiatric disorders.
Results: Psychiatric disorders are genetically and phenotypically highly complex and heterogeneous. Genetic contributions to risk involve thousands of DNA sequence variants (‘risk alleles’) segregating within populations. Each human being has a stochastic grab-bag representing some small fraction of the alleles associated with essentially all common quantitative traits. These range from disorders such as risk of schizophrenia to non-disorder traits such as adult height. Risk alleles for psychiatric disorders act additively, with degree of genetic loading (that can be measured by polygenic scores) being associated probabilistically with quantitative likelihood of unaffected, sub-threshold, or affected status. Common risk alleles are continuously distributed in populations; there are no discontinuities in distributions of polygenic risk that would support categorical distinctions between ill and well. There are also no discontinuities that would support categorical distinctions between disorders. Empirically, risk alleles are shared across psychiatric disorders (e.g., schizophrenia and bipolar disorder share approximately 65% of their common risk alleles) and importantly, some alleles that confer risk for certain disorders confer, at the same time, likelihood of beneficial cognitive and behavioral phenotypes (e.g., alleles that increase risk of obsessive-compulsive disorder, autism spectrum conditions, or anorexia nervosa are associated with greater educational attainment.)

Paralleling genetic risk, symptoms that contribute to psychiatric disorders (e.g., anxiety, social communication difficulties, dysphoric mood, inattention) are also continuously distributed in populations, differing quantitatively between unaffected and affected individuals in number and severity. The symptom counts that DSM-5 uses to define disorders (e.g., 5 of 9 listed symptoms for major depression) represent (unfortunately arbitrary) normative designations. Overall, genetic, clinical, and epidemiological findings impugn the imposition of categorical boundaries between ill and well and favor transdiagnostic dimensional measures.

Conclusion: What is the path forward? (1) Continued pursuit of large-scale unbiased psychiatric genetics and follow-on neurobiology; (2) Use of information emerging from genetics and neurobiology to perform transdiagnostic efforts at biomarker discovery; (3) Epidemiology and genetics at the level of symptoms and symptom covariation, not categorical disorders; (4) Development of quantitative scales based on symptoms and symptom clusters, genetics, and biomarkers with the properties needed for diagnostic measures; (5) Integrative efforts to develop dimensional diagnostic criteria with openness to revision.

3:30 p.m. - 5:00 p.m.
Concurrent Symposia X

WHEN RANDOMIZED TRIALS AREN'T AN OPTION: TARGET TRIAL EMULATION IN PSYCHIATRIC RESEARCH *Helene Speyer, Copenhagen Research Center for Mental Health – CORE Mental Health Center*
Copenhagen; Copenhagen University Hospital

Symposium Synopsis: Because randomized trials in psychiatry are difficult to conduct, clinical decisions may need to be guided by analyses of non-randomized (observational) data. These observational analyses need to use a methodology that appropriately emulates a (hypothetical) randomized pragmatic trial—a target trial—. These challenges are not unique to psychiatry research.

Elsewhere in medicine investigators have applied this method to provide the same answers as randomized trials when other approaches to analyze observational data had failed. Here, we will present four different applications:

First, antipsychotic discontinuation in early psychosis. A research question famous for being hard to answer with randomized trials. But as health-care professionals, we are responsible for providing evidence-based counseling to help patients make informed choices.

Second, functional interventions in patients with a recent hospitalization for major depression disorder. Attrition rates and the small sample sizes rendered existent RCT analyses inconclusive. We will apply the target trial emulation framework to Finnish Registry data.

Third, we will apply this methodology to suicide research, where the event is so rare that it is hard to

find adequate sample sizes to study in randomized trials. We will explore the comparative effectiveness of antidepressants in reducing suicide risk.

Finally, we will discuss how we can use existing randomized trials to strengthen this proposed methodology. By benchmarking observational data analyses against the results of existing randomized trials, we can more confidently extend to new questions. We will discuss this approach using as a case study the EUFEST trial and observational analyses on First Episode Psychosis.

BENCHMARKING OBSERVATIONAL ANALYSES AGAINST RANDOMIZED TRIAL RESULTS: AN APPLICATION TO FIRST EPISODE PSYCHOSIS

Alejandro Szmulewicz*[1], *Gonzalo Martínez-Alés1, Maria Ferrara2, Diane Fredrikson3, Juan Gago4, Vinod Srihari2, Lakshmi Yatham3, Sarah Conderino4, Ann Shinn5, Dost Öngür5, Miguel Hernán1*

[1]Harvard University, 2Yale School of Medicine, 3University of British Columbia, 4New York University Grossman School of Medicine, 5McLean Hospital

Objective: To increase confidence in observational analyses in first episode psychosis (FEP), we would benchmark the observational analyses against existing trial results before extending the observational analyses to answer clinical questions not originally considered in that trial.

Methods: The FEP-CAUSAL Collaboration is an international consortium of observational cohorts of individuals with FEP. We analyzed data from four FEP-CAUSAL cohorts in North America (current N=1,081) to emulate a target trial similar to the EUFEST randomized trial. EUFEST found a higher average 1-year hazard ratio (HR) of treatment discontinuation in haloperidol compared with olanzapine and quetiapine, but similar 1-year probabilities of hospitalization and mean Clinical Global Impressions-Severity (CGI-S) scores. We replicated the results from EUFEST and then extended the emulation to include aripiprazole and risperidone.

Results: Compared with haloperidol, the HR (95% confidence interval) of treatment discontinuation was 0.38 (0.24-0.59) for olanzapine and 0.24 (0.13-0.44) for quetiapine. The 1-year mean of CGI-S for haloperidol, olanzapine, and quetiapine were 3.5, 3.4 and 4.2, respectively, and the 1-year risks of hospitalization were 24.2 (16.2-35.0), 25.4 (18.8-34.0), and 28.2 (21.6-34.2), respectively. Compared with haloperidol, the HR of treatment discontinuation was 0.18 (0.12-0.26) and 0.21 (0.13-0.34) for risperidone and aripiprazole. The 1-year hospitalization risk for aripiprazole was 33.0% (24.7-43.6).

Conclusion: Our observational estimates were similar to those from the EUFEST randomized trial. After benchmarking known effect estimates, we estimated a greater 1-year hospitalization risk for aripiprazole compared with all other drugs. Our findings suggest that this observational dataset may be used to estimate treatment effects in FEP research.

COMPARATIVE EFFECTIVENESS OF ANTIDEPRESSANTS TO LOWER SUICIDE RISK AFTER A SUICIDE ATTEMPT: WHY ARE RCTS UNFEASIBLE AND HOW CAN WE LEVERAGE OBSERVATIONAL DATA TO GUIDE CLINICAL DECISIONS?

Gonzalo Martínez-Alés*[1], *Alejandro Szmulewicz2, Miguel Hernán2*

[1]Harvard TH Chan School of Public Health, 2Harvard University

Objective: Lack of evidence regarding use of commonly prescribed antidepressants (e.g., SSRIs, SNRIs, mirtazapine) for patients discharged after an attempt has important implications for clinical practice, because (i) most of such patients are diagnosed with mental health conditions potentially treatable with antidepressants and (ii) there is conflicting evidence as to whether initiation of antidepressants may temporarily increase risk of suicidal ideation and suicidal behaviors. This presentation is aimed at clarifying limitations of RCTs to examine the potential role of antidepressants for suicide prevention following an attempt, introducing the target trial emulation framework as a way forward, and presenting preliminary results of the first target trial emulation of antidepressants for post-discharge suicide prevention.

Methods: We first critically review RCTs examining use of antidepressants to prevent suicide among suicide attempters. We provide a detailed overview of the limitations of such studies. Then, we introduce the notion of target trial emulation using observational data to guide clinical decision-making for clinicians and patients choosing antidepressant agent and treatment strategy following a suicide attempt. Last, we present results from a large target trial emulation including ~67,000 suicide attempters from the US Veteran Health Administration.

Results: The scarce evidence on antidepressants and suicidality comes largely from randomized controlled trials including antidepressant initiators but excluding patients deemed acutely suicidal (or at high suicide risk, such as recent suicide attempters). Traditionally, the potential inclusion of patients discharged following a suicide attempt in antidepressant trials has raised ethical and safety concerns. In addition to potential ethical concerns, randomized trials including patients discharged following a suicide attempt are difficult to implement because of pragmatic reasons: adequately large samples are arduous to gather, and patients may be reluctant to enroll or remain engaged. Observational data can be used to evaluate the benefits and risks of clinical interventions when randomized trials are not available. In fact, many analyses of observational data are attempts to emulate a hypothetical pragmatic randomized trial. This methodological approach rests on a key idea: observational analyses need to emulate a (hypothetical) target trial as closely as possible, because the process of specifying and emulating a target trial forces the investigators to sharpen their research question in terms of actionable interventions and enhances interpretability of results. Results from the first target trial emulation of antidepressants to lower suicide risk following a suicide attempt, examining the comparative effectiveness of initiation of an SSRI, an SNRI, or mirtazapine with doses following recommendations from standard clinical guidelines, suggest this approach is feasible and can guide clinician decision-making. The outcomes of interest are nonfatal suicide re-attempt, suicide death, and death by any external cause, all measured within 1-, 3-, 6-, and 12-months following discharge. **Conclusion:** By adopting and successfully applying target trial emulation, we can use observational data to generate new avenues to guide decision-making in clinical questions such as post-discharge suicide prevention – where randomized trials are unethical, not feasible, or currently under way.

EARLY VS. DELAYED RETURN TO WORK AMONG INDIVIDUALS DIAGNOSED WITH MAJOR DEPRESSIVE DISORDER: A TARGET TRIAL EMULATION

Kaisla Komulainen*[1], *Mai Gutvilig[1], Ripsa Niemi[1], Markus Jokela[1], Marko Elovainio[1], Christian Hakulinen[1]*
[1]*University of Helsinki*

Objective: Prolonged absence from work among patients with first-episode major depression may add to depression-related functional impairment and impede recovery. The effectiveness of early return to work against adverse functional outcomes is not yet well known and conducting a randomized controlled trial to evaluate the effectiveness is not feasible. We emulate a hypothetical target trial to assess the risk of a new sick leave due to depression among persons with first-episode major depression who returned to work early vs. after a prolonged sick leave period.
Methods: Using individual-level data linked across Finnish nationwide registers, we emulate a target trial among persons who went on sick leave following a diagnosis of first-episode major depressive disorder. Persons are eligible if they received their first recorded diagnosis of major depressive disorder (ICD-10 code F32) between Jan 1, 2009 and Dec 31, 2019, were 25–50 years old at the time of the diagnosis, had no sick leave due to any mental disorder during the 4 years preceding the diagnosis and were granted sick leave for 10–84 days since the diagnosis. We compare assignment to two sick leave strategies: 1) early return to work (sick leave duration 10–28 days) and 2) delayed return to work (sick leave duration 29–84 days). We classify individuals into one of two sick leave strategies according to their records obtained from the sickness absence register of the Social Insurance Institution of Finland, which contains diagnosis-specific administrative information on all sick leaves granted by a physician for > 9 days. The assignment is assumed to be random conditional on baseline covariates including sex, age, educational level, geographical area, depression severity, psychiatric comorbidity and comorbid physical conditions. The outcome of interest is the start of a

new depression-related sick leave during the follow-up period. For each person, the follow-up starts on the first day of sick leave (baseline) and ends on the day of the outcome event of interest (a new sick leave), death, emigration, 2 years after baseline or the administrative end of follow-up on Dec 31, 2019, whichever occurs first. The causal contrast of interest is the observational analogue of the per protocol effect. We evaluate the cumulative incidence estimates of the 2-year risk of a new sick leave, risk differences and risk ratios between individuals with early and delayed return to work. **Results:** There were 114 000 eligible individuals (52 000 with early return to work; 62 000 with delayed return to work). The 2-year cumulative incidences of a new sick leave, risk differences and risk ratios will be presented. **Conclusion:** We will evaluate the implications of our findings on the effectiveness of early vs. delayed return to work among individuals with first-episode depression and discuss the application of target trial emulation using population-based register data in a real-world setting.

WHY OBSERVATIONAL DATA MAY BE THE SOLUTION TO CHALLENGES IN ANTIPSYCHOTIC MAINTENANCE TREATMENT RESEARCH

Helene Speyer*[1]

[1] *Copenhagen Research Center for Mental Health – CORE Mental Health Center Copenhagen; Copenhagen University Hospital*

Objective: Current recommendations, largely based on expert consensus or observational evidence, suggest antipsychotic maintenance treatment for 1-2 years following remission after a first episode of psychosis (FEP). The aim of this presentation is to discuss limitations of randomized controlled trials (RCTs) to address gaps in evidence. Current gaps include lack of long-term studies, limited adherence to studied interventions – and of uptake of proper per-protocol analysis methods, absence of examination of clinically important treatment strategies (e.g., different treatment durations), limited real-world generalizability of study results, and lack of power to detect relevant outcomes (e.g., mortality). We examine the potential of observational data (e.g., from electronic health records), analyzed to emulate a hypothetical (target) trial, to address these limitations and inform clinical guidelines.

Methods: The key to inform clinical decision-making (i.e., choice between available interventions) is to explicitly define the most useful causal contrast of interest for clinicians and patients. In traditional relapse prevention RCTs including participants experiencing FEP, maintenance treatment is compared to an abrupt transition to placebo, assessed in blinded design on samples fulfilling a narrow set of eligibility criteria. These have limited real-world validity. More recent trials compare maintenance treatment to open label, personalized tapering strategies. Despite mirroring real world clinical situations, these trials have low levels of adherence to assigned treatment strategies, especially after long-term follow-ups. When analyzed as intention-to-treat, confounding may lead to underestimation of both beneficial and harmful effects. Indeed, data may approximate observational data and therefore need careful adjustment for potential post-randomization confounding, while still having the limitations associated to narrow eligibility criteria and small samples sizes. Furthermore, recruitment problems have led to failed and underpowered trials, as few people can accept that medication strategy is determined by randomization. Studies using observational data have been published. While attempts have been made to adjust for confounding at baseline, these studies have typically failed to adjust for time-varying confounding, such as fluctuations in illness severity over time.

Results: There are several limitations in conducting RCTs to expand the knowledge gaps: 1) Recruitment problems lead to underpowered or failed RCTs, 2) low adherence to assigned treatment arm introduces confounding, 3) narrow eligibility criteria lead to low real-world generalizability, 4)

there are ethical concerns as superiority of maintenance treatment has already been established. Data from electronical health records with rich longitudinal information may be a feasible way forward. When observational data are used to explicitly emulate a hypothetical (target) trial, they can provide clinically useful estimates of the causal contrast of interest while securing sufficient power and real-world validity and allowing for appropriate adjustment for time-varying confounders. **Conclusion:** To develop evidence-based clinical guidelines for treatment maintenance in FEP, emulating a hypothetical (target) trial using rich observational data may be the solution.

PRECISION PSYCHIATRY APPROACH FOR MOOD DISORDERS: ROLE OF BRAIN BIOMARKERS AND DYSFUNCTIONAL IMMUNE RESPONSE

Manish Jha, University of Texas Southwestern Medical Center

Symposium Synopsis: Modest benefits of currently available treatments for mental illnesses have limited our ability to address the ongoing public health emergency of increasing rates of deaths due to suicide. In fact, over the past decade, suicide rates have increased by 178% and 76% respectively in youths aged 10-14 years and 15-19 years. Current syndromic approaches of diagnosing and investigating mental illnesses are a key barrier to developing mechanistically-guided treatments. Therefore, our proposed panel will bring together early- stage investigators and senior researchers who will present on issues relevant to precision psychiatry approach for mood disorders. The first presentation will discuss neuroimaging-predicted brain age as a novel biomarker that is associated with antidepressant response and with all-cause mortality. The second presentation will focus on how persons with depression should be elevated to be the focus of personalized medicine and improve quality of care. The third presentation will present novel data form a large observational natural-history cohort of patients where integration of brain and immune biomarkers can help in identifying distinct trajectories of depression. The final presentation will focus on the on the topic of the aggregation of marginal gains as a philosophy of care; this recognizes that there are no silver bullets, and for most people it aggregating several small-effect sized factors which are selected on the basis of clinical formulation. Together, these presentations will highlight novel approaches to identifying subgroups of individuals with mental illness and discuss issues relevant to precision approaches for mood disorders.

ACCELERATED AGING OF BRAIN: ASSOCIATION WITH ANTIDEPRESSANT TREATMENT RESPONSE AND ALL-CAUSE MORTALITY

Manish Jha*[1], Abu Minhajuddin[1], Cherise Chin Fatt[1], Madhukar Trivedi[1]
University of Texas Southwestern Medical Center

Objective: Recent reports suggest that neuroimaging-predicted brain age is higher than chronological age (or Δ brain age) in adults with major depressive disorder (MDD). In this presentation, we will discuss its reliability as a biomarker, association with antidepressant treatment response and with all-cause mortality.

Methods: Both studies: Accelerated Brain Age was estimated as difference between T1-weighted structural MRI scan-predicted brain age and individual's chronological age.

Study 1: Mixed model analyses evaluated whether accelerated brain aging at baseline (N=290) in the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study was associated with treatment-related changes in depression severity.

Study 2: Kaplan Meier survival curves and Cox proportional hazards regression were used to estimate the association between accelerated brain aging and all-cause mortality in the second-wave of Dallas Heart Study (DHS-2; N=1948).

Results: In EMBARC, greater accelerated brain aging at baseline was associated with smaller reductions in depression severity with sertraline with sertraline (p=0.019) but not with placebo (p=0.64) after controlling for age, gender, race, ethnicity, and site. In DHS-2, each additional year of accelerated brain aging was associated with 6% higher likelihood of all-cause mortality even after controlling for Framingham 10-year risk score, race, ethnicity, income, education, waist-to-hip ratio, diabetes, hypertension, and history of myocardial infarction. **Conclusion:** Accelerated brain aging was independently associated with poorer outcome to antidepressants in MDD and to higher likelihood of all-cause mortality in an epidemiological sample. Future prospective studies are needed to replicate these associations and elucidate the mechanisms that link accelerated brain aging to poor outcomes.

THE PERSON AND ITS RELATION TO PERSONALIZED MEDICINE AND DEPRESSION TREATMENT

Koen Demyttenaere*[1], *Madhukar Trivedi[2], Michael Berk[3], Manish Jha[2]*

[1]KU Leuven, University Psychiatric Center, [2]The University of Texas Southwestern Medical Center, [3]Deakin University

Objective: Psychiatry has been adopting terminology used in cancer clinics and cancer research: the concepts of remission and of quality of life have been widely adopted and more recently, the concepts of personalized medicine or of precision medicine have also getmore and more attention.
Methods: Given the limitations of currently available biomarkers, we still believe personalized medicine within the scope of depression treatment first of all has to take the 'person' into account.
Results: The poorly defined concept of major depression results in a highly heterogeneous patient population and the very non-specific scales used to assess severity and change during treatment obscure the more subtle clinical effects observed in clinical practice. Moreover, patient sociodemographic characteristics as well as patient beliefs and patient preferences play an important role in predicting outcome. One could even speculate that the currently available biomarkers are more relevant than usually believed if the 'person' would be better taken into account in the prediction models.
Conclusion: Patient preferences, illness beliefs, treatment beliefs and adherence are crucial in what we can expect from treatment modalities.

BRAIN AND IMMUNE BIOMARKER BASED TRAJECTORIES OF DEPRESSION: FINDINGS FROM THE TEXAS RESILIENCE AGAINST DEPRESSION (T-RAD) STUDY

Madhukar Trivedi*[1]

[1] *The University of Texas Southwestern Medical Center*

Objective: Major depressive disorder (MDD) is a heterogenous syndrome which affects 1 in 5 adults during their lifetime and is associated with marked impairments in social, occupational, and interpersonal functioning and reductions in quality of life. Clinical markers have proven to be of minimal benefit in predicting long-term trajectories of symptoms and functioning. Studies using biomarkers, including blood-based and brain neuroimaging, have typically focused on distinct age groups, such as those on youths, young adults, or elderly individuals, and may miss out on age-related differences in these mechanisms. Furthermore, these studies have often not included individuals who are at risk for developing depression and characterize those who are resilient in face of the risk factors and stressors.
Methods: This report is based on findings from the ongoing Texas Resilience Against Depression (T-RAD) study which has enrolled. The individuals undergo comprehensive clinical phenotyping and biomarker assessments using electroencephalogram (EEG), magnetic resonance imaging (MRI) and multiplex immune marker assays.

Results: Between September 2016 to Sep 2022, 1313 individuals aged 10-95 years who either have a diagnosis of unipolar or bipolar depression or have risk factors that predispose them to depression (such as diagnosis of depression in first degree family members) were enrolled. Three-fourths of the sample attended at least two in-person visits, and 57% had at least four in-person visits. Data for less than 6 months, 6-12 months and > 12 months was available for 519 (37.61%), 132 (9.56%), and 729 (52.83%) participants, respectively. Connectomic analyses using EEG data from 1083 individuals revealed distinct patterns of dysfunction within the executive control network. Immunometabolic analyses revealed distinct subgroups of individuals with dysregulation within innate and adaptive immune responses. Ongoing analyses are evaluating how these dysfunctions relate long-term symptom and quality of life trajectories.

Conclusion: This study of individuals with depression or at-risk for depression demonstrates the utility of comprehensively phenotyping and implementing multimodal biomarker assessment.

THE AGGREGATION OF MARGINAL GAINS AS A PHILOSOPHY OF CARE

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to discuss the construct of the aggregation of marginal gains informed by clinical formulation as a philosophy of care and a pragmatic pathway to personalised medicine.

Methods: There are no magic bullets in psychiatry and very few people respond dramatically to any one therapy. For most individuals, one needs a combination of different modalities that are tailored to individual needs. The philosophy of aggregation of marginal gains capitalises on the idea that even small improvements in multiple domains can lead to very large changes because they compound over time. Clinically, each small change can increase capacity to take on subsequent steps, leading to a virtuous cycle which with persistence and time can result in major changes.

Results: At present despite promising developmental work there are no biomarkers capable of stratifying participants to predict response to therapy that are ready for the clinic. However clinical formulation allows one to understand the individual biological psychological and social predisposing, precipitating, perpetuating and resilience factors that allows one to select from the large number of psychological, lifestyle and biological therapies that are available.

Conclusion: In conclusion the philosophies of the aggregation of marginal gains, informed by clinical formulation, supported by a solid therapeutic alliance and consistency of care have the capacity to lead to substantial improvements in clinical outcomes.

Wednesday, June 5, 2024

12:00 p.m. - 4:00 p.m.

Pre-Conference Workshops

ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA - A PRACTICAL COURSE FOR EARLY CAREER PSYCHIATRISTS *Istvan Bitter, Semmelweis University*

Overall Abstract: Antipsychotic treatment of schizophrenia - a practical course for early career psychiatrists. Course director: Prof. Istvan Bitter, Semmelweis University, Budapest, Hungary. This interactive course will summarize evidence-based knowledge based on randomized clinical trials and real-world data about the efficacy and safety of antipsychotic drugs in the acute and maintenance treatment of schizophrenia. The course will address how to individually use different antipsychotic drugs with the help of such information as their pharmacological effects on the neurotransmitter systems (e.g. dopamine D2 occupancy; D2 partial agonists), pharmacokinetic parameters (e.g. the potential roll of metabolites; elimination half-life; long acting injectable antipsychotics) and their clinical effects (use of rating scales or real world data such as time to discontinuation of taking a drug, risk of re/hospitalization and mortality). The importance of regular evaluation of extrapyramidal and metabolic side effects will be highlighted. Such specific topics as the differential diagnosis and treatment of negative symptoms and the management of treatment resistance in schizophrenia will also be discussed. The participants - who request - will receive a short list of selected literature linked to the topic of the course, that could provide help in their daily practice.

USING AI IN SYSTEMATIC REVIEW SCREENING WITH ASREVIEW

Jelle Teijema, Utrecht University

Pre-Conference Workshop Synopsis: This workshop will delve into ASReview, an innovative AI based software designed to transform the process of systematic literature review, making it faster, more accurate, and less labor-intensive. Systematic reviews are foundational to evidence-based practices across disciplines, yet they are time-consuming and prone to bias. ASReview leverages machine learning algorithms to significantly reduce the amount of time researchers spend screening titles and abstracts by prioritizing relevant studies for inclusion. The session will commence with an introduction to the challenges of traditional literature review processes, setting the stage for a detailed exploration of ASReview. Participants will gain insights into the underlying technology, including the machine learning models that power ASReview, and how these models adapt and improve through user interaction. We will address critical questions around the efficacy of ASReview, its impact on reducing researcher workload, and the quality and reliability of the results it produces. A portion of the workshop will be dedicated to hands-on activities, where attendees will have the opportunity to interact with ASReview directly, requiring a laptop. This practical experience aims to equip participants with the knowledge to set up and begin using the software for their own systematic reviews. Additionally, there will be ample time for discussion, allowing participants to raise questions, share experiences, and discuss the implications of integrating such technologies into their research practices. The workshop promises to be an engaging and informative session, offering a blend of theoretical knowledge and practical skills. By the end, participants will be well-prepared to adopt ASReview, enhancing their research efficiency and contributing to the advancement of evidence-based findings.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL *Joan Marsh, The Lancet Psychiatry* **Pre-Conference Workshop Synopsis:** The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry. The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines. The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions. The workshop will include questions and answers throughout and group discussions.

SUCCESSFUL PUBLISHING IN A QUALITY PSYCHIATRY JOURNAL

*RajivTandon*1*
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University of Michigan Medical Center

Objective: This interactive workshop is designed to learn essential steps and augment skills that will enable attendees to successfully publish their scholarship in writing for peer-reviewed journals. Information about what happens to a manuscript after submission will be summarized, with the focus on the editorial and review process.
Methods: This workshop is organized in three parts:
a)40-minute didactic introduction;
b)30-minute interactive process with participants, reviewing vignettes (or personal publishing experiences) that illustrate successful negotiation of challenges across the many steps in the publishing process; and
c)20-minute summation with 7 KEYS to SUCCESSFUL PUBLISHING IN PSYCHIATRY
Results: Participants will discover rich information and techniques for:
(i)Successfully navigating the manuscript publication process after submission;
(ii)Recognize the expectations and priorities of the multiple audiences (editor, reviewer, reader) of the manuscript;
(iii)Producing effective scientific writing that meets expectations of these audiences (specifically editor and reviewers);
(iv) Learn how to respond to reviewers
(v)Being attentive to ethical issues during publication
Conclusion: Attendees will learn specific techniques and receive a checklist that will facilitate acceptance of their manuscripts for publication in high quality scientific journals.

WRITING FOR A HIGH-QUALITY PSYCHIATRY JOURNAL

*Joan Marsh1, Yasin Hasan Balcioglu*2*
[1]The Lancet Psychiatry, 2Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery

Objective: The workshop will address various aspects of writing research papers for high quality biomedical journals. It will be suitable for mid-level and more senior researchers who have participated in or led research projects and published papers but who do not regularly publish in the leading journals in their field. It will advise on ways of improving your chances of getting a paper accepted, with a look 'behind the scenes' of Lancet Psychiatry.
Methods: The workshop will outline the key considerations of editors when selecting articles for Lancet Psychiatry. Participants will gain an insight into editors' expectations throughout the journey of an article, from the submission process to the final decision, as well as the valuable role that detailed input from reviewers plays in enhancing the quality of manuscript for publication. Key areas are: choice of research question, planning the publication output from a research project, in terms of main and subsidiary papers, choice of journal, setting the study in the context of previous literature, and complete and accurate reporting in compliance with the appropriate guidelines.
Results: The workshop will use the CONSORT guidelines for reporting clinical trials as the main guide to the structure of the paper. Topics will include reporting of primary and secondary outcomes, including choice of primary outcome; the trial profile; sex and gender specific reporting; negative findings; and reporting lived experience contributions.
Conclusion: The workshop will include questions and answers throughout and group discussions.

4:15 p.m. - 5:45 p.m.
Concurrent Symposia I

REVISING CONSTRUCT OF SCHIZOPHRENIA: RELEVANCE TO BIOLOGICAL RESEARCH

Rajiv Tandon, University of Michigan Medical Center

Symposium Synopsis: An increasing number of researchers are debating about how schizophrenia has devolved into an "inherently flawed construct". Even as we accumulate increasing amounts of new knowledge about schizophrenia, its definition gets fuzzier. It is clearly time to take stock of what is known and what remains to be known about this syndrome, seriously examine the increasingly mosaic construct/s of schizophrenia, more clearly define the contours of the multiple disease entities encompassed by this term, and identify potential future directions for better understanding and treatment of this complex and heterogeneous syndrome.
In this symposium, we will review the nature of and problems with the current construct/s of schizophrenia, discuss challenges in developing reliable and valid biological markers, and consider the implications for future biological research of ongoing efforts to redefine this entity. Wolfgang Gaebel will briefly summarize the history of schizophrenia leading up to the current ICD-11 definition and description. Rajiv Tandon will review the DSM-5 characterization and outline an ongoing international initiative at reconceptualizing this entity (Schizophrenia Research; 2022, Volume 242; and 2023, 252, 345-347). Florence Thibaut will summarize the current status of biological markers for schizophrenia, updating the WFSBP workgroup report on biological markers. Peter Falkai will discuss implications of the evolving concepts of psychosis and schizophrenia for ongoing and future biological research.

SCHIZOPHRENIA OR OTHER PRIMARY PSYCHOTIC DISORDERS: ICD-11 AND THE ROAD AHEAD

Wolfgang Gaebel*[1]
[1]*German Society for Biological Psychiatry*

Objective: ICD-11 was released by WHO in 2018 and approved by the World Health Assembly (WHA) in 2019 as a global medical classification system. Development, Concept and Structure of ICD-11 will be briefly outlined with the focus on Schizophrenia or other primary psychotic disorders, their potential for adaptation and the debated need for reconstruction in the context of neuroscientific and related developments.
Methods: The development of the new chapter 06 Mental, Behavioural or Neurodevelopmental Disorders including psychotic disorders was guided by the principles of global applicability, scientific validity, reliability, and clinical utility. At that time, neither for DSM-5 nor for ICD-11 schizophrenia spectrum or primary psychotic disorders a conceptual 'paradigm shift' by including biomarkers or other valid diagnostic criteria seemed to be justified.
Results: ICD-11 innovations of primary psychotic disorders diagnostic criteria, dimensional symptom specifiers and course indicators according to the new CDDR (Clinical Descriptions and Diagnostic Criteria) and options for complex digital coding with potential impact on diagnostics, treatment and care will be outlined. Challenges for reconceptualizing the current construct and for national implementation will be briefly summarized.
Conclusion: The presentation will inform about innovations in classifying schizophrenia and other psychosis according to ICD-11 and give an outlook on future options for modifying the construct based on innovative scientific approaches in biological psychiatry.
References: Gaebel W, Stricker J, Kerst A. Changes from ICD-10 to ICD-11 and future directions in psychiatric classification. doi:10.31887/DCNS.2020.22.1/wgaebel
Gaebel W, Salveridou-Hof E. Reinventing schizophrenia: Updating the construct – Primary schizophrenia 2021 – The road ahead. doi.org/10.1016/j.schres.2021.12.021

DSM-5 SCHIZOPHRENIA: DEFINITION AND CLINICAL AND RESEARCH IMPLICATIONS

Rajiv Tandon*[1]
[1]
University of Michigan Medical Center

Objective: Schizophrenia, as currently defined in DSM-5-TR and ICD-11, is conceptualized as a multi-dimensional singular disorder. As questions arise about the very construct of schizophrenia, it is useful to review all that we know about this disease entity and examine what these data reveal about its essential nature. Although the DSM-5 description of schizophrenia was published a decade ago, its essence is still incompletely understood.
Methods: The DSM-5 definition of schizophrenia will be summarized. The outlines of a 2-year ongoing international effort to reconceptualize schizophrenia will be presented.
Results: The DSM-5 definition of schizophrenia is categorical with dimensional elaboration- this will be discussed and its clinical and research implications will be summarized. The initial output from a 50-person international collaboration on redefining schizophrenia will be presented (Schizophrenia Research 2022; Volume 242, 1-3).
Conclusion: Collectively, "facts of schizophrenia" argue against a singular disease entity but do not explicitly elucidate the nature and number of composite disease entities. Research implications of the initial international collaboration formulation of schizophrenia and related psychotic disorders will be outlined.

BIOLOGICAL MARKERS IN PSYCHIATRY

Florence Thibaut**1*

[1]*University Paris Cité*

Objective: A biological marker is an indicator of the pathogenic process of a disease, or of the pharmacological response to a therapeutic intervention. Biological markers may be trait markers (persistent abnormalities) or state-dependent markers (episodic markers).

Methods: Some examples of biomarkers which might be used in psychiatry will be described.

Results: Markers may be used as diagnostic tools, markers of the disease progression, to study the pathophysiology of the disease (risk factors), or to monitor treatment efficacy or side effects (pharmacogenetics).

Conclusion: The sensitivity, specificity and ease-of-use of a biomarker (especially for diagnosis) are the most important factors.

References: Thibaut F, Boutros NN, Jarema M, Oranje B, Hasan A, Daskalakis ZJ, Wichniak A, Schmitt A, Riederer P, Falkai P; WFSBP Task Force on Biological Markers. Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. World J Biol Psychiatry. 2015;16(5):280-90

Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, Collier DA, Corrales A, DeLisi LE, Gallo C, Gill M, Kennedy JL, Leboyer M, Maier W, Marquez M, Massat I, Mors O, Muglia P, Nöthen MM, Ospina-Duque J, Owen MJ, Propping P, Shi Y, St Clair D, Thibaut F, Cichon S, Mendlewicz J, O'Donovan MC, Rujescu D. Genetics of schizophrenia: A consensus paper of the WFSBP Task Force on Genetics. World J Biol Psychiatry. 2017 Oct;18(7):492-505

BEYOND SCHIZOPHRENIA IN DSM-5 AND ICD-11: NEW OPTIONS FOR RESEARCH

Peter Falkai**1*

[1] _____

German Society for Biological Psychiatry

Objective: The classification of schizophrenia has a long history starting with the description of Dementia praecox and Manic-depressive insanity by E Kraepelin paving the way for a dichotomy which still influences our thinking and clinical activities today. ICD-11 and DSM-5 have modified a lot of these assumptions but research has shown that the neurobiological underpinnings of these disorders rather form clusters than sticking to the current classification systems. RDoC and HiTOP will be introduced as examples to use a dimensional approach focussing on the neurobiology and on the other hand using psychopathological dimensions organized into increasingly broad, transdiagnostic spectra.

Methods: Advances and shortcomings of DSM-5 and ICD-11 will be based on published studies.

Results: For future studies a mixture of RDoC and HiTOP might be an optimal way to characterize patients and controls from childhood to old age. New scales need to be developed optimally based on self-rating, being short and having a better validity than currently used classification systems.

Conclusion: The presentation will analyse the shortcomings of currently available classification systems for clinical research and will give an outlook what advantages new systems like RDoC and HiTOP might give to characterize healthy and diseased subjects for research.

BIOMARKERS IN INSOMNIA: EVIDENCE DERIVED FROM A WFSBP TASK FORCE CONSENSUS STATEMENT

Constantin Soldatos, National and Kapodistrian University of Athens

Symposium Synopsis: Thus far, the diagnosis of insomnia is based on purely clinical criteria. Although a broad range of altered physiological parameters has been identified in insomniacs, the evidence to establish their diagnostic usefulness is very limited. Purpose of this symposium is to present a

summary of a WFSBP Task Force consensus statement, based on a systematic evaluation of a series of biomarkers as potential diagnostic tools for insomnia. **Methods:** A newly created grading system was used for assessing the validity of various measurements in establishing the diagnosis of insomnia; these measurements originated from relevant studies selected and reviewed by experts. **Results:** The measurements with the highest diagnostic performance were those derived frompsychometric instruments. Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy, and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm, and certain neuroimaging patterns. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPAaxis, and inflammation indices were not shown to be of satisfactory diagnostic value. Most of the above findings regarding biological measurements, however, need replication as well as establishment of commonly accepted methodology and diagnostic cut-off points. **Conclusions:** Apart from psychometric instruments which are confirmed to be the gold standard in diagnosing insomnia, six biomarkers emerge as being potentially useful for this purpose. **Reference:** D.Dikeos et al. "The potential of biomarkers for diagnosing insomnia: Consensus statement of the WFSBP Task Force on Sleep Disorders" World J Biol Psychiatr (In Press) 2023.

SLEEP EEG AND ACTIGRAPHY IN THE DIAGNOSIS OF INSOMNIA

Adam Wichniak**1*

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Institute of Psychiatry and Neurology, Warsaw

Objective: Although objective assessment of sleep parameters is not necessary for the diagnosis of insomnia, polysomnography and actigraphy frequently provide information that is important for the diagnostic process. The aim of the study was to summarize the evidence on the use of polysomnography and actigraphy in the assessment of insomnia.

Methods: The presentation is based on data from a consensus paper on the diagnostic usefulness of polysomnography and actigraphy in insomnia and results of an original study in 126 insomnia patients that was aimed to assess factors contributing to differences in the assessment of sleep parameters between actigraphy and sleep diary in patients with insomnia.

Results: Polysomnography and more advanced sleep EEG evaluation methods like EEG spectral analysis favor the hypothesis of an increased CNS hyperarousal in patients with insomnia. However, polysomnographic data do not correlate very strongly with the subjective assessment of sleep in sleep diaries. The same observation is true for actigraphy. There are large and variable differences in the assessment of sleep parameters between sleep diaries and actigraphy, which are not strongly related to insomnia severity.

Conclusion: While some studies have confirmed satisfactory accuracy, especially of actigraphy for the evaluation of normal sleep quality, the use of PSG and actigraphy in the assessment of insomnia is limited and indicated only in certain cases, for example in patients with chronic therapy refractory insomnia, when sleep-disordered breathing is suspected (polysomnography) or in case of clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders (actigraphy).

LABORATORY BIOMARKERS FOR INSOMNIA OTHER THAN THOSE DERIVED FROM SLEEP EEG AND ACTIGRAPHY

Thorsten Mikoteit*[1], *Anne Eckert[2], Martin Hatzinger[3]*

[1]Swiss Society for Biological Psychiatry, 2University Clinics of Psychiatry Basel, 3Psychiatric Services Solothurn and University of Basel

Objective: Laboratory measurements are easy and mostly non-invasive to assess, and they might allow to link insomnia to more basic pathways of neuropathology like models of neuroendocrinology, neuroinflammation or neuroplasticity. Further, the advances of neuroimaging have provided findings of alterations in brain activity and connectivity in insomnia. The aim of this review was to evaluate the diagnostic possibility to identify laboratory and neuroimaging biomarkers for insomnia.

Methods: Five different laboratory biomarkers were considered: Markers of the hypothalamic-pituitary-adrenal (HPA) axis, melatonin, inflammatory markers such as C-reactive protein (CRP), and serum brain-derived neurotrophic factor (BDNF) as a proxy of neuroplasticity. Moreover, we considered five neuroimaging studies of insomnia.

Results: Findings of HPA activity patterns were inconsistent. Elevated cortisol levels in the first half of the night and in the morning were found rather in insomnia with shortened total sleep time than in insomnia with normal total sleep time. Melatonin levels revealed a more flattened circadian rhythm in individuals with insomnia, but night-time blood sampling was a limitation for itsclinical application. As reported by two independent studies, the best diagnostic accuracy was provided by measurements of low serum BDNF in insomnia. Neuroimaging studies showed that a key feature of insomnia is a corticolimbic overactivity in brain areas involved in activation, emotion regulation, cognition and conscious awareness.

Conclusion: For laboratory measurements, low serum BDNF levels had the highest diagnostic value for insomnia, linking clinical insomnia to a decreased neuroplasticity. The pattern of neuroimaging findings supported the hyperarousal hypothesis of insomnia. More research is needed to replicate findings and enlarge the body of evidence, to establish appropriate methods and diagnostic cut-offs.

PSYCHOMETRICS IN THE DIAGNOSIS OF INSOMNIA

Dimitris Dikeos*[1]

[1] National and Kapodistrian University of Athens

Objective: To evaluate the diagnostic potential for insomnia of psychometric instruments.

Methods: (a) Search for well cited original papers of scales, questionnaires and personality inventories, which reported on suitable measures of diagnostic validity for insomnia, based on a well-defined population of insomniacs versus a sample of non-insomniac controls. (b) Creation of a novel grading system for establishing diagnostic usefulness for insomnia, based on the one hand on the degree of pertinence of each study's methodology to diagnose insomnia and on the other on the level of diagnostic accuracy for insomnia of the instrument utilized in each study.

Results: Three main categories of psychometric instruments were found to be of diagnostic value for insomnia. Scales and questionnaires for diagnosing insomnia or for evaluating beliefs about sleep were proven to be the gold standard for the diagnosis of insomnia, based on established cut-off scores. Among personality inventories the potential of MMPI as a tool for diagnosing insomnia was found to be quite satisfactory.

Conclusion: Psychometric instruments are a well-proven means for the diagnosis of insomnia, reflecting its subjective nature.

OVERVIEW OF THE DIAGNOSTICS FOR INSOMNIA

Constantin Soldatos*[1]
[1]*National and Kapodistrian University of Athens*

Objective: To synthesise the systematic evaluation of biomarkers as potential diagnostic tools for insomnia based on measures of diagnostic accuracy, as well as an identical assessment of the diagnostic accuracy of psychometric instruments in diagnosing insomnia.
Methods: The findings of a large array of various instruments and methods for diagnosing insomnia, which were presented by the previous three symposium panelists will be comprehensively discussed
Results: Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm and certain neuroimaging patterns. These findings need replication, establishment of commonly accepted methodology and diagnostic cut-off points. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPA axis and inflammation indices were not shown to be of satisfactory diagnostic value. Psychometric instruments are confirmed to be the gold standard in diagnosing insomnia.
Conclusion: Various biomarkers emerge as potentially useful for the diagnosis of insomnia, although psychometric instruments remain the strongest means.

PREDICTIVE BIOMARKERS AND NEW METHODOLOGICAL APPROACHES FOR MENTAL DISORDERS

Oliver Pogarell, University Hospital, LMU Munich

Symposium Synopsis: In psychiatry, a wide spectrum of therapeutic interventions are applied to effectively improve signs and symptoms. However, individual response and remission rates are limited and to date, there are no unequivocal personalized clinical or auxiliary measures to identify responders or predict the course of symptoms under treatment.
Regarding predictive biomarkers new developments in neurophysiological research could play an important role. QEEG or fMRI at rest or under activation are tools for the investigation of different brain states under various conditions including monitoring. Novel analyses address temporal dynamics and functional connectivities that may show differences between disorders or disease states.
We will discuss the potential of neurophysiological biomarkers for the prediction of response or outcomes in psychiatric disorders. This includes novel analyses of QEEG, machine learning techniques or the extraction of treatment related neurophysiological repsonses, e.g. under non-invasive brain stimulation or neurofeedback.
Jonas Björklund will present data on brain oscillations in patients with schizophrenia. He demonstrates the viability of a biomarker predicting transition to full psychosis based on EEG connectivity disturbances. Machine learning techniques applied on physiological EEG/EOG data as demonstrated by Sebastian Olbrich, allow the generation of predictive markers from samples of large cohorts. It will be shown how automated analyses can be used for individual assessments in a clinical setting. Tomiki Sumiyoshi will report data indicating the ability of near-infrared spectroscopy to predict resonse to tDCS in schizophrenia. Finally, Max Maywald applied novel treatment interventions such as rt-fMRI neurofeedback showing that neurophysiological modulations under treatment correlate with response characteristics.

PREDICTIVE PROPERTIES OF QEEG AND OSCILLATIONS

Jonas Björklund*[1], *Moritz Haaf2, Sebastian Vauth2, Saskia Steinmann2, Jonas Rauh2, Christoph Mulert2, Gregor Leicht2*

[1]LMU, 2University Medical Center Hamburg-Eppendorf

Objective: Early detection and prediction of transition to full psychosis in high-risk individuals is crucial for early intervention and improved treatment outcomes. EEG and fMRI-based analyses provide opportunities to assess connectivity disturbances before the onset of clinical symptoms. In a previous study, we demonstrated reduced gamma response in an auditory processing network in individuals at high risk of psychosis (HRP) using EEG-informed fMRI analysis. This study aims to investigate the predictive nature of EEG connectivity disturbances in HRP individuals and explore the potential of using specific EEG-based connectivity disturbances to predict progression to psychosis based on disturbed gamma band oscillations.

Methods: We analyzed datasets of 27 HRP individuals and 26 healthy controls, including combined EEG-fMRI data recorded during an auditory reaction task. We employed Granger causality analysis, correlation analysis, and gPPI to calculate a matrix of individual connectivity values between previously identified ROIs in the dACC, DLPFC and the auditory cortices. Connectivity analysis methods were used to calculate individual connectivity values per subject. By comparing connectivity values between healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis, we aimed to predict the likelihood of developing psychosis within 12 months. Follow-up clinical data and combined EEG-fMRI recordings after 12 months were used to assess the degree of connectivity changes over time.

Results: We observed alterations in connectivity across domains when comparing healthy controls, HRP who developed full psychosis, and HRP who did not switch to psychosis during the 12-month follow-up. We used data generated during the 12-month follow-up visit to verify if early changes in single-subject gamma connectivity persist and correlate with clinical disease progression.

Conclusion: By measuring gamma network disturbance using simultaneous EEG and EEG-informed fMRI, we aim to predict individual likelihoods of developing full psychosis within the next 12 months. EEG-based biomarkers are a relatively low-cost and widely available tool to aid in clinical decision making. The identification of specific EEG gamma band disturbances associated with disease progression and treatment response may enable more personalized treatment strategies for individuals with psychosis.

AUTOMATED AND MACHINE LEARNING ANALYSES OF EEG AND ECG DATA FOR TREATMENT PREDICTION IN MENTAL DISORDERS

Sebastian Olbrich*[1]

[1]Psychiatric University Hospital Zurich

Objective: Addressing the profound impact of psychiatric disorders on global health and socioeconomic systems necessitates a paradigm shift in treatment modalities. The reliance on subjective assessments in psychiatric care underlines a critical need for more objective treatment indicators to enhance patient outcomes across various mental health conditions.

Methods: This presentation will delineate the utilization of automated processing pipelines applied to electrophysiological time series data obtained from electroencephalograms (EEG) and electrocardiograms (ECG). The integration of these methodologies into routine clinical practice through comprehensive biomarker reports will be showcased. Additionally, the session will provide an update on the latest advancements in machine learning and deep learning techniques applied to EEG and ECG data, drawing from extensive datasets from the UK-Biobank and the CANBIND study.

Results: Contemporary advancements in automated electrophysiological processing and biomarker computation have reached a level of sophistication that permits their application in clinical settings. Over recent years, a plethora of biomarkers pertinent to treatment prediction—particularly within the context of major depressive disorders—have been identified, rigorously validated, and consistently replicated. **Conclusion:** The implementation of electrophysiological biomarkers in psychiatric care emerges as a compelling strategy to foster a more stratified approach to patient treatment. The clinical applicability of these biomarkers has been substantiated, with accumulating evidence indicating their potential to significantly influence the management of mental health disorders and enhance patient outcomes.

TRANSCRANIAL

AND DIRECT CURRENT STIMULATION FOR ENHANCING SYMPTOMS FUNCTIONALITY IN PATIENTS WITH SCHIZOPHRENIA; PREDICTION WITH NEUROPHYSIOLOGICAL TOOLS

Tomiki Sumiyoshi*[1], *Yuji Yamada2*
[1]National Institute of Mental Health, National Center of Neurology and Psychiatry, 2National Center Hospital, National Center of Neurology and Psychiatry

Objective: Schizophrenia is one of the most prominent causes of disease burdens worldwide. In addition to positive and negative symptoms, patients with the illness show disturbances of several types of cognitive function (e.g., neurocognition and social cognition). Importantly, cognitive impairment leads to a decline in real-world functional outcome for patients.
Methods: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that modulates neural activity by applying electric currents. tDCS (anodal stimulation) delivered to the dorsolateral prefrontal cortex (DLPFC) alleviates hallucinations and negative symptoms, and improves neurocognitive function, particularly working memory in patients with schizophrenia. Specifically, our group in National Center of Neurology and Psychiatry has reported the first data indicating the ability of neural responses, as measured by the near infra-red spectroscopy, to predict efficacy of tDCS for ameliorating psychotic symptoms in these patients.
Results: This talk will also provide the current state of endeavor to alleviate cognitive impairment and higher-level functional outcomes, by means of tDCS, in patients with schizophrenia. These findings may add to efforts to increase the chance of recovery for patients by using feasible and non-invasive brain stimulation methods.
Conclusion: References; Narita et al. J Psychiatr Res 2018; 103:5-9

PREDICTIVE BIOMARKERS IN REAL-TIME FMRI NEUROFEEDBACK

Maximilian Maywald*[1], *Marco Paolini2, Boris Rauchmann2, Christian Gerz2, Jan Heppe2, Annika Wolf2, Linda Lerchenberger2, Igor Tominschek3, Sophia Stöcklein2, Paul Reidler2, Nadja Tschentscher2, Birgit Ertl-Wagner2, Oliver Pogarell2, Daniel Keeser2, Susanne Karch2*
[1]Psychiatric Hospital of the LMU University Munich, 2University Hospital, LMU Munich, [3]Psychosomatic Day Care Unit Westend, Munich

Objective: The aim of this pilot study was to investigate whether individualized rtfMRI NF training as an adjunct to a psychotherapeutic program can increase connectivity between the insula and the dlPFC and thereby improve symptoms in patients with major depressive disorder (MDD, ICD-10). The second aim was to investigate if there are biomarkers of successful real-time fMRI neurofeedback?
Methods: Sixteen patients with MDD and 19 matched healthy controls (HC) participated in a rtfMRI NF training consisting of two sessions with three runs each, within an interval of one week. RtfMRI NF was applied during a sequence of negative emotional pictures to modulate the connectivity

between the dlPFC and the insula. The MDD REAL group was divided into a 'Responder' (N=6) and a 'Non-Responder' group (N=7). **Results:** The comparison of hemodynamic responses during the first compared to during the last NF session demonstrated significantly increased BOLD-activation in the medial orbitofrontal cortex (mOFC) in patients and HC, and additionally in the lateral OFC in patients with MDD. These findings were particularly due to the MDD Responder group, as the MDD Non-Responder group showed no increase in this region during the last NF run. There was a decrease of neural activation in emotional processing brain regions in both groups in the last NF run compared to the first (HC: insula, parahippocampal gyrus, basal ganglia, and cingulate gyrus; MDD: parahippocampal gyrus). There was no significant reduction of BDI scores after NF training in patients. **Conclusion:** The activation of the mOFC seems to be a predictive biomarker of improved control- strategies and association-learning processes. The increased lOFC activation could indicate a stronger sensitivity to failed NF attempts in MDD. Overall, the rtfMRI NF had an impact on neurobiological mechanisms, but not on psychometric measures in patients with MDD.

THE DIFFERENT FACES OF DEPRESSION ACROSS THE LIFE SPAN: FROM SOCIAL ISOLATION TO SUICIDE

Paolo Brambilla, University of Milan

Symposium Synopsis: Suicidal ideation, also known as suicidal thoughts, is a broad term used to describe a range of thoughts about death and self-harming behaviours. Rates of suicide deaths and suicidal thoughts and behaviours have risen by more than 50% among young people in the past decade, making suicide the second leading cause of death among those aged under 20. Most importantly, suicidal ideation represents a trans-diagnostic feature characterizing several psychiatric conditions (e.g., depression, psychosis) that seems to increase the risk of completed suicide. For instance, it has been shown that treatment-resistant depression (TRD) may increase an individual's likelihood of engaging in suicidal behaviours and up to 30% of people with TRD will attempt suicide at some point in their life. Although individual, environmental, and clinical risk factors (such as social isolation, social stress, apathy and elderly depression) for suicidal thoughts and behaviours have been
well established, these factors have demonstrated low predictive validity. In response, the number of studies examining neurobiological underpinnings of suicidal thoughts and behaviours, in and out of psychiatric populations, has grown exponentially. Nevertheless, understanding the neural mechanisms underlying social isolation, suicidal thoughts and behaviours and their clinical utility remains elusive. Therefore, the present symposium aims at summarizing and discussing recent evidence on the morphofunctional brain correlates of social isolation, social stress, apathy, elderly depression, and suicidal ideation, with a particular focus on their clinical implications for the development of trans-diagnostic tailored treatments.

NEUROIMAGING OF SOCIAL BRAIN

*Marcella Bellani1, Maria Gloria Rossetti*1, Paolo Brambilla2*
[1]University of Verona, 2University of Milan

Objective: According to the social brain hypothesis, the human brain includes a network designed for the processing of social information. This network includes several brain regions that elaborate social cues, interactions and contexts, i.e. prefrontal paracingulate and parietal cortices, amygdala, temporal lobes and the posterior superior temporal sulcus. While current literature suggests the importance of this network from both a psychological and evolutionary perspective, little is known about its neurobiological bases. Specifically, only a paucity of studies explored the neural

underpinnings of constructs that are ascribed to the social brain network functioning, i.e. objective social isolation and perceived loneliness. **Methods:** Overview of neuroimaging studies that investigated social isolation in healthy subjects. **Results:** Social isolation correlated with both structural and functional alterations within the social brain network and in other regions that seem to support mentalising and social processes (i.e. hippocampus, insula, ventral striatum and cerebellum). **Conclusion:** However, results are mixed possibly due to the heterogeneity of methods and study design. Future neuroimaging studies with longitudinal designs are needed to measure the effect of social isolation in experimental v. control groups and to explore its relationship with perceived loneliness, ultimately helping to clarify the neural correlates of the social brain.

SOCIAL STRESS AND SUICIDE: MECANISTIC HYPOTHESES

Aiste Lengvenyte**1*, *Emilie Olié2, Emma Sebti2, Adrian Alacreu3, Philippe Courtet2*

[1]CHU Montpellier, 2University of Montpellier, 3University of Zaragosa

Objective: To assess the biological underpinnings of social adversity that lead to suicidal behaviour.
Methods: Depressed patients are submitted to the Trier Social Stress Test (TSST) in order to examine the changes in emotional and biological markers according to their past history of suicidal behaviour.
Results: We will discuss the association of suicidal behaviour with measures of cortisol, of the autonomous nervous system and inflammatory markers during and after the TSST.
Conclusion: Objective markers of response to a social exclusion task using different kinds of parameters may help to define specific groups of patients at risk of suicide in order to foster a personalized suicide prevention.

CEREBRAL NETWORK OF APATHY AND GOAL-ORIENTED BEHAVIOURS

Jean-Charles Roy**1*, *Julie Cologner1, Gabriel Robert1*

[1] EMPENN Unit, Rennes 1 University, ERL U1228 Inserm, INRIA, CNRS

Objective: We aimed to identify the structural and functional brain subnetworks associated with apathy in LLD in the core resting-state networks (RSN) putatively underlying goal-directed behaviors.
Methods: Diffusion-weighted and Resting-state functional MRI data were collected from 39 non-demented depressed elderly and 26 healthy elderly from October 2019 to April 2022. Apathy was evaluated using the diagnostic criteria for apathy, the apathy evaluation scale and the apathy motivation index. Participants' daily activity was recorded via an accelerometer worn at the wrist for three days. Principal components were derived from accelerometer data to provide a qualitative and quantitative interpretation of daily activity. The clinical significance of these principal components in terms of apathy were assessed by regression with the apathy scales. Brain sub-networks associated with the principal components of activity were identified via the threshold-free network-based statistics. This method combines the network-based statistics approach with the threshold-free cluster enhancement algorithm, producing a powerful identification of the significant sub-networks while controlling for multiple comparisons. Structural tracts were identified via deterministic tractography. Association between the apathy and accelerometry on the diffusion metrics - derived from a multicompartment model - were evaluated by mixed-effect modelling.
Results: LLD patients had an altered intranetwork resting-state connectivity in the default-mode, the cingulo-opercular and the frontoparietal networks compared to healthy controls. The first and second principal components of daily activity were associated with apathy measures, corresponding respectively with a reduced mean diurnal activity and with a late-rise/late-bedtime. Apathy and daily activity were associated with modified intranetwork resting state connectivity in the same networks distinguishing LLD from controls. These networks involved reduced activity of the pregenual cingulate

regions, the dorsal anterior cingulate cortex, the middle insula, but increased connectivity in the dorsolateral prefrontal regions. Internetwork resting-state connectivity of cortical regions related to goal-oriented behavior showed a decoupling between pregenual and dorsal anterior cingulate cortices associated with apathy. Principal components associated with apathy were also associated with increased orientation dispersion index, a measure of inflammation, in the anterior commissure. **Conclusion:** This study suggests that accelerometry provides a proxy for an ecological evaluation of apathy in LLD. Apathy and accelerometry are consistently associated with changes in intra and inter- network connectivity of regions implied in goal-oriented behaviors.

THE FUNCTIONAL NETWORKS OF DEPRESSION IN THE ELDERLY

*Eleonora Maggioni*1, Federica Goffi1, Paolo Brambilla2*
1Politecnico di Milano, 2University of Milan

Objective: To disentangle the complex relationships among environmental risk factors, functional brain connectivity, autonomic nervous system regulation, and frailty and adult-onset depression.
Methods: Control subjects and individuals with adult-onset major depressive disorder (MDD) took part in the study. The dataset included sociodemographic, environmental, and psychopathological information, and simultaneous electrocardiographic (ECG) and functional Magnetic Resonance Imaging (fMRI) data. The ECG and fMRI data were processed to extract information on heart rate variability (HRV) and functional brain connectivity. The associations among stressful life events, frailty level, MDD diagnosis, and HRV and functional brain connectivity were extracted using integrated HRV-fMRI analyses and multivariate models.
Results: The MDD diagnosis was associated with alterations in the activity and connectivity of brain regions that are key nodes of the central autonomic network. Traumatic events and perceived stress were correlated with HRV metrics and showed interactions with depressive symptomatology and sex.
Conclusion: Evidence from our study suggests an impact of environmental risk factors on heart-brain interactions and in turn on depressive symptomatology onsetting in adulthood, and further supports the potential of HRV-fMRI analyses in providing novel information on the neurobiological bases of depression.

MANUSCRIPT WRITING WORKSHOP

Florence Thibaut, University Paris Cité

HOW TO WRITE A SCIENTIFIC PAPER

Dan Rujescu-Balcu1
1Medical University of Vienna

Objective: The World Journal of Biological Psychiatry is a major clinically oriented journal on biological psychiatry. The opportunity to educate (through critical review papers, treatment guidelines and consensus reports), publish original work and observations (original papers and brief reports) and to express personal opinions (Letters to the Editor) makes The World Journal of Biological Psychiatry an extremely important medium in the field of biological psychiatry all over the world.
The aim is to meet the Chief Editor and to discuss all steps from formulating hypotheses, study design, data generation, analysis and finally publication.
Methods: A short presentation of the Journal will be followed by a lively discussion.
Results: N/A

Conclusion: It is important to oversee the whole process from asking the scientific question to study design and generation of original data to manuscript writing, submission and finally publication in a scientific journal.

HOW TO WRITE A SCIENTIFIC PAPER

Michael Berk1
[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: Scientific Journals are a key platform for disseminating critical reviews, treatment guidelines, consensus reports, original research, and personal opinions in the field of biological psychiatry. This session aims to guide participants through the publication process, from formulating hypotheses and designing studies to generating data, analyzing results, and ultimately publishing in scientific journals. Attendees will have the opportunity to engage with the Chief Editor and gain insights into each step of the publication journey.
Methods: The session will begin with a brief presentation on the scope and significance of The World Journal of Biological Psychiatry. This will be followed by an interactive discussion, where participants can ask questions and receive practical tips on navigating the publication process.
Results: While this session does not generate experimental results, it will equip participants with valuable knowledge and strategies to enhance their chances of successfully publishing their research in peer-reviewed journals.
Conclusion: Understanding the comprehensive process of scientific publication—from formulating a research question and designing a study to writing and submitting a manuscript—can significantly increase the likelihood of acceptance in a scientific journal. By attending this session, researchers will be better prepared to contribute meaningful findings to the field of biological psychiatry, thereby advancing evidence-based practice and scientific knowledge.

HOW TO WRITE A SCIENTIFIC PAPER

Florence Thibaut1
[1]*University Paris Cité*

Objective: Publication of scientific papers is important to improve evidence-based practice or scientific knowledge. Most importantly, failure to publish important findings significantly diminishes the potential impact that your findings may have.
Methods: This educational session is intended to give you tips to help you publish in scientific journals.
Results: Most clinical studies are published in peer-reviewed journals, where author's peers, or experts in the area, evaluate the manuscript.
Conclusion: Following this review, the manuscript is recommended for publication, revision or rejection. Having an understanding of the process and structure used to produce a peer-reviewed publication will increase the likelihood that a submitted manuscript will result in a successful publication.

6:30 p.m. - 7:30 p.m.
Opening Plenary I - John Krystal

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

Lakshmi Yatham, The University of British Columbia

REFLECTIONS ON THE FUTURE OF PSYCHIATRY DRUG DISCOVERY

John Krystal1

[1]Yale

Objective: To review challenges that have traditionally plagued the development of medications for psychiatry indications and to highlight two areas of exciting recent developments: 1) ketamine and psychedelics and 2) antipsychotics that may work via targets other than the dopamine D2 receptor.

Methods: This presentation will focus on the advances in neuroscience that have laid the groundwork for the development of Esketamine and the recent “non-D2” antipsychotics. It will begin by tracing steps to understand the mechanisms through which ketamine produces its therapeutic effects. It will then highlight ways that this search has led to ways to optimize ketamine efficacy. It will also highlight ways that insights related to ketamine’s effects that point to other potential novel treatment mechanisms, such as psychedelics, that have convergent effects on neuroplasticity.

Results: This presentation will present a model for cortical microcircuit dysfunction that emerged from studies of ketamine effects in healthy humans and schizophrenia patients. This model highlights the potential for cortical network disinhibition, including disinhibition of projections to the striatum, to be a contributor to pathophysiology in some patients. This model sets the stage for developing a mechanistic context for recent clinical trial data suggesting that drugs enhancing muscarinic M4 receptors (KarXT, Emraclidine) and TAAR1 (Ulotorant) might be effective antipsychotic medications without blocking dopamine D2 receptors.

Conclusion: This presentation will conclude by raising remaining challenges as we grapple with the complexity of the neurobiology of psychiatric disorders, particularly the opportunities and challenges that emerge as we try to translate the genetics of psychiatric disorders to novel therapeutics.

Thursday, June 6, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session II - Nora Volkow

SUBSTANCE USE AND ABUSE: ADVANCES IN NEUROBIOLOGY AND TREATMENT OF SUBSTANCE USE DISORDERS

Allan Young, King's College

HOW HAS THE SCIENCE OF ADDICTION ILLUMINATED OUR UNDERSTANDING OF THE HUMAN BRAIN

Nora Volkow1

[1]*NIDA*

Objective: Addiction, a complex disorder linking genes, development and the social environment has, for decades, been illuminating our understanding of the human brain and is leading the way toward promising strategies for its effective treatment.

Methods: Studies employing neuroimaging technology paired with behavioral measurements, and more recently genetics, have led to remarkable progress in elucidating neurochemical and functional changes that occur in the brains of addicted subjects and the neurocircuits that modulate risk for substance use disorders.

Results: Although large and rapid increases in dopamine have been linked with the rewarding properties of drugs, the addicted state, in striking contrast, is marked by significant decreases in brain dopamine D2 receptor mediated signaling and the downstream dysfunction of circuits that it modulates through striato cortical and limbic projections. Among the most prominently affected is the prefrontal cortex (PFC), including ventral PFC implicated in salience attribution and motivation (orbitofrontal cortex, and anteroventral cingulate gyrus), and dorsal PFC including dorsolateral and medial PFC implicated in executive function and internal awareness.

Conclusion: These PFC disruptions underlie the enhanced value given to drugs and drug-related stimuli at the expense of other reinforcers and the impulsive and inflexible behaviors that lead to compulsive drug consumption. In parallel, dysfunction of limbic projections are believed to underlie the enhanced stress reactivity and negative emotional states that emerge during drug withdrawal.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia II

UNDERSTANDING BODY DYSMORPHIC DISORDER (BDD): LATEST INTERNATIONAL RESEARCH

Susan Rossell, Swinburne University

Symposium Synopsis: Body dysmorphic disorder (BDD) affects 1.7-2.4% of the population worldwide. However, until the last 20 years relatively little was known about BDD, and there was a paucity of research. The aim of this symposium is to bring together and present comprehensive data from four internationally respected research sites specialising in BDD.

Methods: The authors will provide the latest updates on epidemiology, clinical characteristics, brain mechanisms as well as novel treatment insights in relation to BDD.

Results: The four presentations will include recent data on: 1) the epidemiology of BDD using a representative, population-based sample of young people in England. 2) An update on clinical and cognitive characteristics of BDD, including some novel findings on hallucinatory experiences in BDD. 3) A discussion of recent brain imaging data in BDD involving white matter microstructure and dynamic effective brain connectivity in visual systems, and their relationships to appearance

appraisals. 4) Finally, we will review the efficacy, predictors and long-term outcomes of an app-based cognitive behavioral therapy for BDD with coach support. **Conclusion:** Given the prevalence of BDD improving clinicians understanding of this disorder is critical. The authors of this symposium hope by presenting advanced and novel data the audience will improve their awareness of BDD and how to treat it.

EPIDEMIOLOGY OF BODY DYSMORPHIC DISORDER IN YOUTH: PREVALENCE, COMORBIDITY AND PSYCHOSOCIAL IMPAIRMENT

Georgina Krebs**1*, *Bruce Clark2, Tamsin Ford3, Argyris Stringaris1*

[1]University College London, 2South London and Maudsley NHS Foundation Trust, 3University of Cambridge

Objective: Little is known about the epidemiology of body dysmorphic disorder in youth. We evaluated the prevalence, comorbidity, and psychosocial impairment associated with BDD and more broadly defined appearance preoccupation among children and adolescents.

Methods: Data were drawn from the 2017 Mental Health of Children and Young People in England survey. BDD and psychiatric comorbidity were assessed in 5-19 year olds (N = 7,654) according to DSM-5 criteria, using a clinician-rated standardised diagnostic assessment. Psychosocial impairment was measured with a quantitative scale, and also indexed by reported self-harm and suicide attempts, and service utilisation, which were assessed using structured interviews.

Results: The point prevalence of BDD was 1.0% (95% CI 0.8 – 1.3%). BDD was significantly more common among adolescents than children (1.9 vs 0.1%; OR = 22.5, $p < 0.001$), and females than males (1.8% vs 0.3%; OR = 7.3, $p < .001$). Similar age and sex effects were observed for appearance preoccupation. Approximately 70% of young people with BDD had psychiatric comorbidity, most commonly internalising disorders. BDD was associated with self- and parent-reported psychosocial impairment, self-harm and suicide attempts, and service utilisation. Appearance preoccupation was more common than full syndrome BDD, but showed similar age and sex effects, patterns of comorbidity, and associated impairment.

Conclusion: BDD and appearance preoccupation are relatively common, especially among adolescent girls, and associated with substantial co-occurring psychopathology, risk, and impairment. Improved screening is needed to increase detection and diagnosis of BDD, and to facilitate access to evidence-based treatment. Future research should seek to examine appearance preoccupation as a possible target for early intervention.

UNDERSTANDING PSYCHOTIC EXPERIENCES IN PEOPLE WITH BODY DYSMORPHIC DISORDER (BDD)

Susan Rossell**1*, *Grace Fountas1, Wei Lin Toh1*

[1] Swinburne University

Objective: Body dysmorphic disorder (BDD) is a severe mental illness characterised by a preoccupation with a perceived flaw in appearance, along with repetitive behaviours and/or mental acts that occur in response to the preoccupation. Referential delusions (people take special notice of me owing to how I look) are frequently noted in BDD. In DSM-5, there is an optional specifier “with absent insight/delusional beliefs” for patients who hold high conviction that their BDD beliefs are accurate and aligned with reality. This marks a key departure from past editions of the DSM (that is, from DSM-III-R onwards), where non-delusional and delusional variants of BDD were alleged to exist, with the latter double-coded as a delusional disorder, somatic subtype. However, there are only a handful of empirical studies which have examined the presence of delusions and insight in BDD; and no work to date to have explored the existence of hallucinations. Thus, further work is needed in BDD

to characterise the psychotic symptoms of the disorder, especially to understand the possible differences or similarities that may exist with schizophrenia. **Methods:** Data from three clinical will be presented, examining: a) delusions and insight in BDD using Peters Delusion Inventory (PDI) and the Brown Assessment of Beliefs (BABS), respectively; and b) differences in the presentation of psychotic symptoms between BDD and schizophrenia using the Questionnaire for Psychotic Experiences (QPE). **Results:** The data from the PDI and BABS established that the majority of individuals with BDD hold substantial delusional beliefs, which are a) not restricted to referential delusions in terms of delusional themes, and typically include appearance-based (somatic) delusions, and b) the vast majority (>89%) of BDD patients are classified as having absent insight. Further, an extensive examination of hallucinatory experiences using the QPE in BDD has demonstrated that only somatic hallucinations are endorsed more frequently and qualitatively different from healthy controls (there were no differences for auditory, visual, olfactory, gustatory or multimodal hallucinations). With these somatic experiences akin to those present in schizophrenia. **Conclusion:** This is the first study to have reported on hallucinatory experiences in BDD. In conclusion, this work suggests considerable similarities between BDD and schizophrenia in the somatosensory domain when examining psychotic symptoms.

MICROSTRUCTURE AND FUNCTIONAL CONNECTIVITY OF THE VERTICAL OCCIPITAL FASCICULUS IN BODY DYSMORPHIC DISORDER

Jamie Feusner**1*, *Wan Wa Wong2, Joel Diaz1, Ryan Cabeen3*

[1]Centre for Addiction and Mental Health, University of Toronto, 2Centre for Addiction and Mental Health, 3University of Southern California

Objective: Body dysmorphic disorder (BDD) is marked by preoccupations with misperceived appearance flaws, which may be due to disturbances in visual information processing. Previous studies suggest abnormally reduced global visual processing in BDD. While previous fMRI data are informative about the functional global/local visual processing imbalances, the underlying structural connections have been less explored. The vertical occipital fasciculus (VOF) is the major fibre bundle connecting the dorsal and ventral visual systems. Here, we investigated the white matter (WM) microstructure of the VOF, estimated with neurite orientation dispersion and density imaging (NODDI) and diffusion tensor imaging (DTI) metrics, and tested their associations with psychometric measures and dynamic effective connectivity (DEC) during task fMRI.
Methods: 21 unmedicated adults with BDD with face concerns and 23 healthy controls were included. Tractography was performed to obtain microstructure maps of the right and left VOF. Geometric models of WM connectivity were reconstructed from fibre orientation data estimated from diffusion MRI. Bundle-specific analysis was performed, enabling quantitative estimation of NODDI and DTI metrics of the whole bundle. For fMRI, they viewed photos of their own face naturally. Four regions of interest (ROIs) in the dorsal visual stream (DVS), and 4 ROIs in the ventral visual stream (VVS) were selected. DEC, a measure of directional connectivity, was computed using time-varying Granger causality. Linear regressions were used to test associations between NODDI/DTI metrics, psychometric measures, and DEC from DVS to VVS.
Results: In BDD, neurite density index (NDI) (R=.7, FDR-adjusted P=.0076) and fractional anisotropy (FA) (R=.63, FDR-adjusted P=.036) were positively associated with Body Image State Scale (BISS) scores. Mean diffusivity (MD) was positively associated with DEC during face viewing (R=.61, FDR-adjusted P=.046), and there was a trend for NDI negatively associated with DEC (R=-.61, FDR-adjusted P=.053). In healthy controls, no significant associations were found between the NODDI or DTI metrics and BISS scores. In controls, associations between DEC and WM microstructure were

nonsignificant, with only trends for orientation dispersion index (ODI) negatively associated with DEC (R=-.41, unadjusted P=.068), and FA positively associated with DEC (R=.45, unadjusted P=.043).
Conclusion: Those with BDD with worse evaluative body experiences have a lower proportion of axons or dendrites and a lower degree of anisotropy along the vertical occipital fasciculus, which could reflect lower tract integrity. Further, there were different function/structure relationships among those with BDD than among healthy controls. These results provide early insights into how the structural integrity of WM connections involved in the integration between global and local visual processing systems in BDD relate to subjective appraisals of their appearance.

LATEST ADVANCES IN THE TREATMENT OF BODY DYSMORPHIC DISORDER: APP BASED COGNITIVE BEHAVIORAL THERAPY WITH COACH SUPPORT

Sabine Wilhelm*[1], *Jennifer L. Greenberg[2], Hilary Weingarden[2], Susanne S. Hoeppner[2], Ivar Snorrason[2], Emily E. Bernstein[2], Thomas H. McCoy[2], Oliver Harrison[3]*

[1]Harvard Medical School, [2]Massachusetts General Hospital and Harvard Medical School, [3]Koa Health

Objective: This presentation summarizes the current state of the field of cognitive behavioral therapy (CBT) for Body Dysmorphic Disorder (BDD) and offers a vision for the future.
empirically supported psychotherapy for BDD. While this treatment has a lot of promise, we still have a long way to go. Currently, most individuals in need of treatment for BDD receive no mental health services at all, and even those who do often do not receive optimal care. New technology-enhanced therapies have the potential to expand the reach of our interventions to those for whom traditional treatments are currently unavailable. Dr. Wilhelm will present the result of a smartphone-based treatment with coach support, including predictors of treatment outcome.
Methods: A randomized waitlist-controlled trial was conducted. Adults (N = 80) with primary BDD were randomized to 12 weeks of app based CBT or waitlist. Coaches supported engagement and answered questions via in-app messaging and phone calls. BDD severity was measured at baseline, mid-treatment, and end of treatment by blinded independent evaluators. Secondary outcomes, predictors of treatment outcome and long-term outcomes were also examined.
Results: App-based CBT was associated with significantly lower BDD-YBOCS severity at end of treatment (M [SD]: 16.8 [7.5]) compared to the waitlist (26.7 [6.2]; $p < 0.001$, $d = 1.44$). App-based CBT was associated with greater improvements across all secondary measures, including BDD-related insight, depression, quality of life, and functioning. We also examined several predictors of treatment outcome as well as maintenance of treatment gains.
Conclusion: App-based CBT, supported by a bachelor's-level coach, is an efficacious, scalable treatment for adults with BDD. Our results also highlight the importance of efforts to develop stratified care models to optimize treatment allocation.

FROM DAMAGED DNA TO MORBIDITY: MITOCHONDRIAL DYSFUNCTION IN BIPOLAR DISORDER AS A NOVEL THERAPEUTIC TARGET

Aysegul Ozerdem, Mayo Clinic

Symposium Synopsis: Bipolar disorder (BD) is commonly associated with substantial medical comorbidities, premature aging, and mortality. Mitochondria, inflammation, and oxidative stress are important links in the pathogenesis of mood disorders. A crosstalk between nuclear DNA and mitochondrial DNA is needed for proper cellular functioning and homeostasis. Evidence shows alterations in the base excision repair (BER) mechanism of the oxidatively induced DNA damage in BD. Accumulation of DNA damage or mutations and mitochondrial dysfunction are theorized to contribute to the early ageing and age-related diseases which are frequently seen in BD. Reduced

mitochondrial DNA-copy number has been associated with inducing cancer progression via hypermethylation of nuclear DNA promoters. Dysregulated mitochondrial biogenesis often occurs together with other comorbidities in BD such as non-alcoholic fatty liver disease (NAFLD), diabetes and osteoporosis. Mechanism of action of lithium, the gold standard medication for treatment of BD involves regulation of mitochondrial bioenergetics and PARP, an enzyme involved in DNA repair. This symposium aims to explore the interaction between various comorbidities including breast cancer, NAFLD, osteoporosis and bipolar disorder in the context of illness progression and increased morbidity and identify novel treatment targets via regulation of mitochondrial dysfunction for better illness outcome. Another objective of the symposium is to explore if changes in mitochondrial copy numbers, and mitochondrial DNA methylation levels in response to treatment in BD can be a marker for treatment outcome. Data from large cohorts with and without comorbid BD and data from clinical trials will be presented.

MITOCHONDRIAL DNA MODIFICATIONS IN MOOD DISORDERS

Deniz Ceylan*[1], *Bilge Karaçiçek[2], Kemal Uğur Tüfekci[3], Şevin Hun Şenol[1], Şermin Genç[2]*

[1]*Koç University, 2Izmir Biomedicine and Genome Center, 3Izmir Demokrasi University*

Objective: Mood disorders are significant psychiatric conditions that result from a complex interplay of genetic and environmental factors. One intriguing avenue of research in the realm of mood disorders involves investigating alterations in mitochondrial DNA (mtDNA). In the scope of this study, our primary objective was to explore changes in mtDNA in individuals with depressive disorder (MDD) and bipolar disorder (BD).

Methods: Displacement loop methylation (D-loop-met), mitochondrial DNA copy number (mtDNA-cn), and mitochondrial DNA oxidation (mtDNA-oxi) were scrutinized in DNA samples from individuals with major depressive disorder (MDD; n = 34), bipolar disorder (BD; n = 23), and a control group of healthy individuals (HC; n = 40) using real-time polymerase chain reaction. Blood samples were collected from a subgroup of individuals with MDD (n = 15) both during a depressive episode (baseline) and after achieving remission (at the 8th week).

Results: The study groups displayed notable distinctions in D-loop-methylation (D-loop-met) ($p = 0.020$), while mitochondrial DNA copy number (mtDNA-cn) and mitochondrial DNA oxidation (mtDNA-oxi) yielded similar results. During the remission phase (8th week), there were decreased levels of mtDNA-cn ($Z = -2.783$, $p = 0.005$) and D-loop-methylation ($Z = -3.180$, $p = 0.001$) in comparison to the acute MDD baseline, with no significant alteration observed in mtDNA-oxidation levels.

Conclusion: Our findings suggest that there are distinct modifications in mtDNA associated with these conditions. Furthermore, the observed changes in mitochondrial mtDNA-cn and D-loop methylation during the remission phase suggest a potential involvement of mtDNA alterations in the underlying mechanisms of MDD.

This work was supported by TUSEB (TUSEB 20131-Deniz Ceylan) and a BAGEP award by the Science Academy of Turkey

BIPOLAR DISORDER AND BREAST CANCER: CLINICAL INSIGHTS INTO DNA DAMAGE-RELATED MECHANISMS

Mete Ercis*[1], *Melissa Solares-Bravo1, Kathryn J. Ruddy1, Fergus J. Couch1, Vanessa M. Pazdernik1, Nicole L. Larson1, Jorge A. Sanchez-Ruiz1, Mark A. Frye1, Janet Olson1, Stacey J. Winham1, Aysegul Ozerdem1*

[1]*Mayo Clinic*

Objective: Bipolar disorder (BD) is associated with an increased risk of breast cancer in women. The causality between BD and breast cancer is unclear. BD is associated with increased DNA damage and concomitant alteration in gene expression levels of the enzymes operating on base-excision repair (BER) of both nuclear and mitochondrial DNA. FEN1 and PARP1, the two genes of the BER mechanism that are involved in cancer treatment showed genome-wide significant association with BD and significant association with lithium response respectively. Given the involvement of DNA damage and repair mechanisms in both conditions, we aimed to explore the effect of having BD on clinical features of breast cancer including age at breast cancer diagnosis, presenting cancer stage, and survival.
Methods: Our sample included female patients from the Mayo Clinic Breast Disease Registry (MCBDR) with breast cancer only (BC-Only; n=9390) diagnosis and patients with breast cancer and BD comorbidity (BC+BD; n=59). All available information from electronic health records was used to ascertain the diagnosis of BD. Clinical features of breast cancer and lifestyle characteristics of individuals were obtained from the MCBDR data repository. Fisher exact tests, Wilcoxon rank sum tests, Kaplan-Meier survival curves, and Cox proportional hazards models were used to compare BC+BD and BC-Only groups. A multivariable regression on age at breast cancer diagnosis was conducted to estimate the effect of comorbid BD while adjusting for confounding variables.
Results: Age at breast cancer diagnosis was significantly earlier in the BC+BD group (52.8±10.5 years) compared to BC-Only (57.1±12.5 years, p=0.005). BD diagnosis was consistently associated with earlier age at breast cancer diagnosis after adjusting for potential confounders that differed significantly among groups, such as smoking, exercise, and BMI (β=-5.88, p=0.016). Presenting stage of breast cancer or survival did not differ between groups (both $p > 0.05$). Among BC+BD patients, lifetime lithium users had an older age at breast cancer diagnosis (n=32, 54.3±11.5 years) than non-users (n=27, 51.0±9.0 years) although the difference was not statistically significant (p=0.315). Lithium use was not associated with presenting cancer stage, or survival (both $p > 0.05$).
Conclusion: Our initial findings highlight that BD diagnosis is associated with breast cancer development approximately five years earlier than non-BD individuals even after adjusting for confounders, suggesting a possible shared mechanism between the two diseases beyond lifestyle characteristics. Examining the shared genetic mechanisms between breast cancer and BD including their
those involving mitochondrial DNA repair will provide a deeper understanding of pathophysiology toward identifying novel therapeutic targets.

MITOCHONDRIAL TARGETS FOR NOVEL THERAPY DEVELOPMENT

Michael Berk**1*, *Jee Hyun Kim2, Bruna Panizzutti2, Zoe Liu2, Olivia Dean2, Johnny Park2, Ken Walder2*
[1]Australasian Society for Bipolar and Depressive Disorders Ltd, 2Deakin University

Objective: This presentation will highlight the evidence regarding abnormal mitochondrial energy generation in bipolar disorder as a treatment target. Mitochondria are cellular organelles involved in energy production. Symptomatically, bipolar disorder is a biphasic disorder of energy generation. Mania is characterised by increased energy in mania and in depression, by decreased energy. Bipolar disorder can be seen as a biphasic dysregulation of mitochondrial energy generation, typified in depression by inability to upregulate biogenesis in response to metabolic demands, and in mania to downregulate generation when demand abates. There is preclinical, electron microscopic, and post-mortem evidence of mitochondrial changes, and evidence of altered energy generation in the disorder. Many widely used psychotropic agents have effects on mitochondrial energy generation, implying that this is a viable therapeutic target. Several agents that enhance antioxidant defences or mitochondrial functioning have been studied for the treatment of mood disorders as adjuvant

therapy to pharmacological treatments. This could be especially beneficial for treatment-resistant patients.

Methods: This presentation will summarise the evidence supporting the involvement of mitochondrial dysfunction in mood disorders, the effects of current therapies on mitochondrial functions, and highlight novel targeted therapies acting on mitochondrial pathways that might be useful for the treatment of mood disorders. In addition, this presentation will highlight a novel stem cell derived platform for drug repurposing that highlights a mitochondrial therapeutic as having potential for the treatment of bipolar disorder, trimetazidine.

Results: Trimetazidine was identified with no a-priori hypothesis. We used a gene expression signature to determine the effects of a combination of known drugs used to treat bipolar disorder. We then screened a library of off-patent drugs in cultured human neuronal-like cells, identifying trimetazidine. Trimetazidine has cytoprotective and metabolic effects, leading to improved glucose utilization for energy production. It is used to treat angina pectoris and has an excellent safety profile. The preclinical and clinical literature strongly support trimetazidine's potential to treat bipolar depression, as the agent has anti-inflammatory and antioxidant properties while normalizing compromised mitochondrial function. Preclinical models suggest antidepressant effects.

Conclusion: Trimetazidine's established safety and tolerability provide a robust rationale for clinical trials to trial its efficacy to treat bipolar depression that could progress its repurposing to address arguably the major unmet need in the disorder.

SOCIAL ISOLATION IN YOUTHS: PREVENTION AND TREATMENT STRATEGIES

Paolo Brambilla, University of Milan

Symposium Synopsis: Human nature is thought to be rooted in its social interactions and relationships, which support the development and preservation of physical and mental health. In humans, extreme cases of social isolation can lead to the complete avoidance of social contexts including work, school and those involving significant others. This condition is known as Hikikomori syndrome, a phenomenon that affects roughly 2% of the Japanese general population. The evidence to date shows that this phenomenon is growing in both Eastern and Western countries, possibly influenced by cultural and environmental factors and the recent COVID-19 pandemic, with particular regard to the most fragile subgroups such as juvenile and elderly populations. Notably, social isolation and related loneliness have been associated with increased mortality and depressive symptoms, poorer cognitive functioning, faster cognitive decline and alterations in the neuroendocrine systems in healthy individuals. Furthermore, social isolation often constitutes a prodromal symptom of severe psychiatric conditions such as social anxiety disorder, psychosis and depression. Therefore, early interventions aimed at treating social isolation could lead to a more favourable outcome for young patients and reduce the burden on the national health systems. In this symposium, we will discuss the current challenges of preventing and treating social isolation-related disorders in fragile populations in and out of psychiatric trajectories.

SOLITAIRE - DIGITAL INTERVENTIONS FOR SOCIAL ISOLATION IN YOUTHS AND THEIR FAMILIES

Maria Gloria Rossetti*[1]

[1] *University of Verona*

Objective: Social Isolation (SI) is a condition that can lead to complete withdrawal from society, with particular regard to the most fragile subgroups such as juvenile and elderly populations. It often constitutes a core symptom (often prodromal) of severe psychiatric disorders such as the Hikikomori syndrome, social anxiety disorder, psychosis, depression, mood-dysregulation and others. If not treated, SI can degenerate into a complete withdrawal from society. Therefore, early interventions

aimed at treating SI could result in a more favourable outcome for young patients. However, due to the social interaction barrier intrinsic to the condition, current treatments alone are problematic and only partially effective in treating SI. SOLITAIRE aims at implementing a multi-component digital psychiatric intervention to remotely help youths suffering from Social Isolation (SI), based on cognitive behavioural therapy (CBT), Cognitive Remediation (CR) and Psychoeducation (PE) for family members. SOLITAIRE will overcome most barriers and limitations of standard clinical interventions.
Methods: SOLITAIRE aims to test the feasibility and preliminary efficacy of two digital interventions for treating young adults and adolescents suffering from severe social isolation. Recruited participants will be randomly assigned to two arms i.e., experimental versus control. In the experimental arm, patients will undergo a brief cycle of CBT combined with computerized CR. In the control arm, patients will receive only CBT. Additionally, for all recruited patients, a psychoeducational intervention (PE) is planned for family members to alleviate the psychological burden associated with caring for socially withdrawn relatives. SOLITAIRE started in June 2023, and recruitment is ongoing.
Results: In this talk, I will present the preliminary findings of the SOLITAIRE study, with particular emphasis on the challenges encountered during the study design, the implementation of the digital interventions and the data collection.
Conclusion: Due to its multimodal digital approach, SOLITAIRE is expected to significantly impact patients' quality of life and well-being addressing previously unmet clinical needs, possibly exacerbated by the recent pandemic. Moreover, the synergistic CBT+CR intervention is thought to stimulate cognitive processes implied in social cognition and we expect that clinical improvements will be generalized to more ecological scenarios and daily life contexts.

PREDICTORS OF EARLY PSYCHOSIS AND SOCIAL ISOLATION

Stefan Borgwardt*[1]
[1] *University of Lübeck*

Objective: Social isolation has been associated with increased psychopathological symptomatology, poorer cognitive functioning and constitutes a prodromal symptom of psychosis. In this presentation, we will review predictors for early psychosis in the context of social isolation. Furthermore, current challenges of preventing and treating social isolation in people at high-clinical risk for developing severe mental disorders will be reviewed.
Methods: Review of findings from international longitudinal consortia (Psy-Scan, PRONIA, NAPLS 2) and available evidence from early psychosis studies
Results: Social isolation plays a crucial role in longitudinal clinical trajectories of people presenting with attenuated symptoms of psychosis and at clinical high risk for psychosis (CHR).
Conclusion: Further search for improved treatments for social isolation and a comprehensive prediction and prevention model for early psychosis is needed.

HIKIKOMORI: PSYCHOPATHOLOGICAL AND BIOLOGICAL UNDERSTANDING OF SOCIALLY ISOLATED PERSONS

Takahiro Kato*[1]
[1]*Graduate School of Medical Sciences, Kyushu University*

Objective: Hikikomori, a severe form of social withdrawal for more than six months, is originally observed in Japan and now becoming a global mental health issue. I have established the world-first hikikomori research clinic/system to understand/treat multidimensional aspects of hikikomori based on bio-psycho-social analyses. I introduce our hikikomori research system and also show our updated biological data.

Methods: Drug-free patients with hikikomori (n=42) and healthy controls (n=41) were recruited. The severity of hikikomori was assessed using the HQ-25. Blood biochemical tests and plasma metabolome analysis were performed. Based on the integrated information, machine-learning models were created to discriminate cases of hikikomori from healthy controls, predict hikikomori severity, stratify the cases, and identify metabolic signatures that contribute to each model. **Results:** Long-chain acylcarnitine levels were remarkably higher in patients with hikikomori; bilirubin, arginine, ornithine, and serum arginase were significantly different in male patients with hikikomori. The discriminative random forest model was highly performant, exhibiting an area under the ROC curve of 0.854. To predict hikikomori severity, a partial least squares PLS-regression model was successfully created with high linearity and practical accuracy. Additionally, blood serum uric acid and plasma cholesterol esters contributed to the stratification of cases. **Conclusion:** Our findings reveal the blood metabolic signatures of hikikomori, which are key to elucidating the pathophysiology of hikikomori. Our data have suggested the importance of biological understandings of hikikomori in addition to sociocultural aspects.

LONELINESS IN PEOPLE WITH SEVERE MENTAL ILLNESS: A DATA SCIENCE INVESTIGATION

Dulce Alarcón Yaquetto**1*, *Robert Stewart1, Mariana Pinto da Costa1*

1 Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: Loneliness is prevalent and has been linked with different health outcomes.

Objective: To investigate if loneliness is associated with clinical phenotypes of psychosis in people with severe mental illness (SMI).

Methods: We used the Clinical Record Interactive Search (CRIS) platform which provides anonymised copies of the South London and Maudsley NHS Foundation Trust (SLaM) electronic health records. A previously validated natural language processing (NLP) algorithm that identifies instances of loneliness was used to assess exposure.

Results: We identified people based on their first diagnosis of SMI and assessed if loneliness was a predictor of negative, depressive, and manic symptoms during a 12 month follow-up. We will present the findings obtained, with a focus on age and other individual characteristics. The advantages and challenges of using data science and large real world health electronic records to study loneliness will be discussed.

Conclusion: Loneliness can be studied as a predictor of clinical phenotypes in SMI using electronic health records coupled with NLP. As a potentially modifiable factor, this opens up opportunities for future research and interventions aimed at improving treatment outcomes and recovery in SMI patients.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia III

DIGITAL TECHNOLOGIES AND NEW ADVANCEMENTS IN PSYCHIATRY

Oğuz Karamustafalıoğlu, İstanbul-University Cerrahpaşa

ADVANCES IN DIGITAL PHENOTYPING FOR BRIDGING BIOLOGICAL RESEARCH AND CLINICAL CARE

John Torous

State-of-the-Art Synopsis: Digital phenotyping is an increasingly popular method that takes advantage of the multiple sensors and interactions that people have with their smartphones. It enables clinicians and researchers to capture various data streams, including mobility patterns (from GPS and accelerometer sensors), social patterns (from anonymized call and text message logs), self-

reported symptoms (from on-phone surveys), cognition (assessed through response time to on-screen tasks or more formal cognitive tests), and other real-time data on individual functioning. However, like all data streams, there are limitations including patient engagement, data quality, and replicable derived features. This talk will review the state of the art for digital phenotyping with a focus on validation and verification efforts to highlight the current and future use cases for this data. Biological research targets including current ready-to-analyze digital phenotyping datasets as well as clinical use cases of the data will be reviewed to frame the translational potential. Finally, ethical and equity issues concerning digital phenotyping will be presented with action-oriented steps toward ensuring the method is used appropriately. **Objective:** To define digital phenotyping and review relevant data streams. To highlight digital phenotyping data processing pipelines (machine learning) with the goal of highlighting potential sources of bias. To review recent evidence for the use of the method in both biological research and clinical care. To also explore reasons for currently contradictory results. To discuss the ethics of digital phenotyping and present a solutions oriented approach. **Methods:** This talk will draw evidence from published research, the ongoing AMP-Schizophrenia study, and Dr. Torous personal experiences applying it in research/care. **Conclusion:** Digital phenotyping remains a promising method to advance both biological psychiatry and clinical care. However, it is not a panacea and requires thoughtful applications and careful research to yield breakthroughs. The low barriers to entry and use of digital phenotyping mean that a global consortium to advance digital phenotyping is not only possible but necessary to realize its full potential.

NEW INSIGHT AND DEVELOPMENT OF INTEGRATIVE TREATMENT IN SCHIZOPHRENIA

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: The development of integrative treatment of pharmacological and non-pharmacological treatment for people affected by schizophrenia spectrum disorders has been identified as an important and urgent priority. Due to the adverse events and limited effects of medication treatment for schizophrenia, there is a need to identify effective combined interventions that can improve functioning recovery and can be provided within routine care services. This symposium will bring together the evidence evaluating these novel interventions.

Current antipsychotic treatments do not lead to beneficial effects on primary negative symptoms and
cognitive deficits in schizophrenia. Given that these domains of the disorder contribute substantially to low recovery rates and unfavorable disease course, new treatment approaches are warranted. In recent years, different types of exercise interventions have been proposed as promising add-on treatments. L Roell summarizes all current meta-analyses targeting effects of exercise on negative symptoms and cognitive impairments in schizophrenia. He further compares the observed effects sizes to other additional treatment approaches such as cognitive remediation and provides recent evidence on the underlying neural mechanisms that may drive these improvements on the clinical level.

POTENTIAL NEURAL MECHANISMS EXPLAINING BENEFICIAL EFFECTS OF PHYSICAL EXERCISE IN SCHIZOPHRENIA

Lukas Roell**1*, *Daniel Keeser2, Andrea Schmitt3, Alkomiet Hasan3, Isabel Maurus1, Peter Falkai3*

[1]LMU, 2University Hospital, LMU Munich, 3German Society for Biological Psychiatry

Objective: As demonstrated by multiple large-scale meta-analyses, physical exercise interventions in people with schizophrenia improve negative symptoms, cognition, social and occupational functioning, and general disorder severity. However, the underlying neural mechanisms that drive

these improvements remain to be determined. Therefore, we conducted a global exploratory analysis of structural and functional neural adaptations after exercise and explored their clinical implications. **Methods:** Combining meta-analytic techniques with original data of 91 patients with schizophrenia from a large-scale multicentre randomized-controlled trial, we investigated stuctural and functional neural adaptations induced by different types of exercise based on multimodal neuroimaging acquisitions. We further linked obtained changes in the brain to several relevant clinical outcomes. **Results:** Our results indicated that physical exercise in people with schizophrenia can induce structural and functional adaptations within the hippocampal formation, the default-mode network, the cortico-striato-pallido-thalamo-cortical loop, and the cerebello-thalamo-cortical pathway. We further observed that volume increases in the right posterior cingulate gyrus as a central node of the default-mode network were linked to improvements in general disorder severity. **Conclusion:** These findings suggest a positive impact of physical exercise on several neural networks involved in the pathophysiology of schizophrenia and thus provide further insights into neural mechanisms underlying clinical improvements after exercise. A more comprehensive understanding of these mechanisms is essential to gain a deeper insight into the pathophysiology of schizophrenia which in turn may facilitate the development of treatments that specifically target respective mechanisms.

WHAT DOES NON-INVASIVE BRAIN STIMULATION CONTRIBUTE TO THE TREATMENT OF PEOPLE LIVING WITH SCHIZOPHRENIA?

Frank Padberg**1*

1

University Hospital, LMU Munich

Objective: Non-invasive brain stimulation (NIBS) approaches comprise an array neurophysiologically distinct methods, e.g. repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES). NIBS methods have been applied for treating clinical conditions within the spectrum schizophrenia syndromes, mainly predominant negative symptoms and persistent auditory hallucinations. The further implementation of NIBS interventions in clinical routines is a matter of debate.

Methods: The array of NIBS methods and their underlying mechanistic principles will be introduced. The current evidence for efficacy and safety of NIBS in schizophrenia will be critically reviewed and discussed based on the available evidence from randomized controlled trials (RCTs) and meta-analyses.

Results: Two main research lines focusing on predominant negative symptoms (target area: prefrontal cortex subregions) and persistent auditory verbal hallucinations (target area: temporoparietal cortex) have been established over the last two decades, and data from RCTs support their efficacy and safety. Across NIBS approaches and target regions, findings are nevertheless heterogeneous probably also due to different mechanisms of neuroplasticity induction. To date, there is very limited evidence how NIBS interventions could be implemented in clinical care and treatment algorithms.

Conclusion: Growing evidence supports the notion that NIBS methods (mainly rTMS and tES) are efficacious for treatment psychopathological syndroms in people with schizophrenia and could be easily implemented in combined treatment protocols due to their good safety profile and application modalities which are easily scalable for various clinical settings. Future studies should focus on gaining a deeper mechanistic understanding of the respective NIBS methods and systematically include NIBS in RCTs as active comparators to other treatment modalities.

A PILOT RANDOMIZED CONTROLLED TRIAL OF AN INTEGRATIVE INTERVENTION OF TDCS AND YOGA FOR COGNITIVE FUNCTION IN CHRONIC SCHIZOPHRENIA

Jingxia Lin*[1]
[1]*The Hong Kong Polytechnic University*

Objective: The pilot randomized controlled trial aimed to examine the feasibility and effectiveness of a 2-week combined intervention of active tDCS and yoga on cognitive function and clinical symptoms in individuals with chronic schizophrenia.

Methods: A total of 18 participants with chronic schizophrenia were recruited and randomized into two arms: (1) 2-week active tDCS + yoga (a-tDCS-Y) (n=9), and (2) 2-week sham tDCS + yoga (s-tDCS-Y) (n=9). Both interventions were conducted five sessions weekly for two weeks, with each session lasting 1 hour. Active tDCS was applied using a wearable stimulator (LifTid) with a constant stimulation intensity of 1.2mA for 20 minutes, and sham tDCS was performed using the same device but without stimulation. During the yoga training, all participants wore the device and a facilitator turned on the stimulation for participants receiving a-tDCS-Y intervention, and pretended to turn on the stimulation for participants receiving s-tDCS-Y intervention after the first 10-minute warm-up. Outcome measures were conducted at baseline and post-intervention including cognitive tests, quality of life, and clinical symptoms.

Results: There were 16 participants completed the pilot trial with an attrition rate of 11%. Mean age was 44.5 years old, and mean duration of illness was 7.5 years. There were no significant differences in the demographic characteristics between two groups at the baseline. We found a-tDCS-Y had a small-to-medium effect size in executive function measured by the Verbal Fluency Test (Cohen's d=0.39) compared with s-tDCS-Y group. We also found a significant time × group interaction effect on physical function assessed by SF-36 (Cohen's d=0.61) with superior improvements in a-tDCS-Y group. Both groups showed a trend of improving working memory and clinical symptoms (Cohen's d ranged from 0.21 to 0.55).

Conclusion: Overall, the pilot study provides preliminary evidence for the feasibility of our approach and showed encouraging findings on executive function after a 10-session active tDCS + yoga intervention in chronic schizophrenia. Further full-scale RCT to evaluate the additive and synergistic effects of tDCS and yoga on neurocognitive function and to examine the underlying neuro-mechanisms using imaging approach is highly recommended.

OPTIMIZING CARE FOR PEOPLE LIVING WITH SCHIZOPHRENIA THROUGH NON-PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS

Christoph Correll*[1]
[1]*Zucker School of Medicine at Hofstra/Northwell, Hempstead*

Objective: This presentation will focus on the effects of nonpharmacologic psychological and psychosocial treatments when added to antipsychotics across a broad range of outcomes. Additionally, data on the combination of antipsychotic treatment with healthy lifestyle education, instruction or management interventions with be presented, either alone or in conjunction with pharmacologic treatments aimed at reducing appetite, food intake and cardiometabolic risk factors or poor outcomes in people with mental illness. Finally, adaptive monitoring and management strategies will be proposed.

Methods: Review of systematic reviews and meta-analyses as well as umbrella reviews on the topics of nonpharmacologic psychological and psychosocial treatments added to antipsychotics across a broad range of outcomes for people with schizophrenia.

Results: Several meta-analyses, network meta-analyses and umbrella reviews exist regarding the effects of adjunctive nonpharmacologic psychological, psychosocial and lifestyle interventions for

mental and physical health outcomes. In patients with early-phase schizophrenia, integrated or "coordinated specialty" care seems to be the most promising approach. Otherwise, among psychological interventions, cognitive behavioral therapy and family interventions had the most data in support of their adjunctive use. For cognitive health, cognitive remediation and exercise were more effective than control groups. Regarding lifestyle interventions, coached and group interventions had the biggest effect, including on physical health and global as well as social cognition. **Conclusion:** Adjunctive nonpharmacologic psychological and psychosocial treatments as well as healthy lifestyle counseling and interventions are viable options for people with schizophrenia to improve a range of relevant mental and physical health outcomes. Ways to increase initiation of, engagement in and retention related to such interventions as well as their effects on longer-term biopsychosocial outcomes requires further study.

THE ART OF PRESCRIBING CLOZAPINE: NOVEL DEVELOPMENTS

Dragana Ignjatovbic Ristic, University of Kragujevac

Symposium Synopsis: Clozapine is a cornerstone of the management of treatment-resistant schizophrenia, presents unique challenges in clinical management and is underprescribed. Our symposium delves into three key facets of clozapine treatment: therapy adherence, blood levels, and neutrophil counts.

The first presentation explores a novel approach to monitor long-term adherence to clozapine. Utilizing data from the Utrecht Patient Oriented Database, it reveals a significant association between clozapine use and enhanced FL3 neutrophil granulocyte fluorescence. This finding opens avenues for using FL3-fluorescence as a potential biomarker for clozapine adherence, a crucial aspect in schizophrenia management.

Our second presentation shifts focus to therapeutic drug monitoring (TDM) of clozapine. The study analyzed clozapine levels in patients with treatment-resistant schizophrenia in a middle income country who were titrated without TDM. This revealed a substantial interindividual variation in clozapine levels, absence of a relationship between levels and side effects, and only a weak relationship between levels and functional outcome. These results challenge strict adherence to the conventional therapeutic range and support a more personalized approach.

The final presentation revisits the history and current practices surrounding clozapine-induced agranulocytosis. Reviewing literature from 1975-2022, it suggests a reevaluation of the mandatory intensive blood monitoring protocols, advocating for a more nuanced approach that balances the risks and benefits of clozapine treatment, especially in the initial weeks of therapy.

Together, these presentations underscore the importance of personalized, evidence-based approaches in optimizing clozapine treatment for schizophrenia. In this way this symposium hopes to contribute to the removal of hurdles to clozapine treatment.

CLOZAPINE LEVELS AND OUTCOMES IN SERBIAN PATIENTS WITH THERAPY RESISTANT SCHIZOPHRENIA PREVIOUSLY TREATED WITHOUT MEASURING CLOZAPINE LEVELS

Hans de Haas*[1], *Dan Cohen[2], Mariken de Koning[3], Geke van Weringh[4], Veroljub Petrovic[5], Lieuwe de Haan[6], Daan Touw[7], Dragana Ignatovic-Ristic[8]*

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Objective: Clozapine remains the only pharmacological treatment option for therapy resistant schizophrenia. Therapeutic drug monitoring (TDM) of clozapine is recommended, although the evidence for the therapeutic range of 350-600 ng/ml is limited. In various countries including Serbia, TDM of clozapine is not routinely performed. This study evaluated the distribution of clozapine levels in Serbian patients who had not undergone prior TDM and investigated the relationship of clozapine levels with clinical outcomes. **Methods:** Clozapine levels were measured by dried blood spot (DBS) analysis

in patients with therapy resistant schizophrenia. DBS samples were taken in Serbia, and shipped to The Netherlands for analysis. Side effects were evaluated by GASS-c, severity of symptoms and functional impairment with WHODAS, CGI-S and GAF.

Results: Clozapine was determined for 129 of 140 enrolled patients. 51.2% had subtherapeutic levels, 24.8% were in the therapeutic window and 24% had supratherapeutic levels. Clozapine levels were not associated with side effects, and showed a weak positive association with symptom severity and functional impairment. No severe side effects were observed in patients with clozapine levels surpassing 1000 ng/ml (n=8).

Conclusion: Current findings revealed substantial interindividual variation. Especially when patients are titrated without TDM, some patients achieve high clozapine levels with apparently good tolerance and others experience side effects with relatively low clozapine levels. We propose that the upper limit of the therapeutic range should not be regarded as an absolute barrier, and guidelines should allow for a personalized approach when prescribing clozapine.

NEUTROPHIL FLUORESCENCE IN CLOZAPINE TREATMENT: THE FIRST BIOLOGICAL MARKER OF LONG-TERM DRUG ADHERENCE

Wai Hong Man**1*, *Maarten ten Berg1, Ingeborg Wilting1, Albert Huisman1, Wiepke Cahn1, Jan Willem Douma2, Hanneke den Breeijen1, Eibert Heerdink1, Toine Egberts1, Wouter van Solinge1*

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Objective: Non-adherence to medication is a major issue in the treatment of schizophrenia in general and in particular for those treated with clozapine. A reliable tool to quantify patients long-term adherence to clozapine is currently unavailable. Enhanced FL3 neutrophil granulocyte fluorescence was serendipitously observed in a small population of schizophrenic patients treated with clozapine. The present study was aimed at assessing the association between clozapine use and FL3-fluorescence.

Methods: A cross-sectional study was performed using data from the Utrecht Patient Oriented Database (UPOD). A total of 38 390 inpatients were included, of which 124 (0.33%) used clozapine.

Results: FL3-fluorescence was significantly higher (U=240 179, P LESS THAN 0.001) in clozapine users (mean (SD)= 90.5 (11.8)) than in non-users (mean (SD)= 69.8 (3.3)). Observed FL3-fluorescence was found to increase with increasing clozapine dose. The area under the receiver operating characteristic curve was 0.95.

Conclusion: Our results confirm the association between use of clozapine and elevated FL3-fluorescence. Further research is needed to unravel the underlying mechanism and to investigate the true potential of FL3-fluorescence as a clozapine-adherence in clinical practice.

MODIFIED LEUKOCYTE MONITORING IN CLOZAPINE: PROPOSAL BY THE DUTCH CLOZAPINE COLLABORATION GROUP

Dan Cohen**1*, *Peter FJ Schulte1, Selene Veerman1, Jan PAM Bogers2*

[1]MHO North-Holland North, 2MHO Rivierduinen

Objective: After the introduction of clozapine in 1975 in Finland, eight Finnish patients died after developing agranulocytosis, whereupon clozapine was withdrawn from the market. Its reintroduction – from 1990 onwards – was accompanied by mandatory white blood cell monitoring if treatment lasts and strict thresholds at which clozapine must be discontinued definitively. The fear of agranulocytosis and the need for intensive blood monitoring is and remains the single most important barrier for prescribers and patients alike and leads to under prescription of the only effective and approved medication for treatment-resistant schizophrenia.
Methods: We review the literature from 1975-2022 on the incidence of clozapine-associated agranulocytosis and the relation between the occurrence of the agranulocytosis with treatment duration
Results: The risk of agranulocytosis is smaller than perceived at the time of reintroduction, b. the risk of agranulocytosis is concentrated in the first 18 weeks of treatment, c. such risk is not greater than with other antipsychotics and d. that frequent blood monitoring has not demonstrably decreased the rate of agranulocytosis.
Conclusion: 1) Restrict mandatory monitoring of the absolute neutrophil count (ANC) to the first 18 weeks of clozapine treatment, 2) the prescriber and the well-informed patient decide together about further monitoring frequency, 3) Clozapine treatment must be stopped if the ANC falls below 1.0×10^9/L. Continuation of clozapine or a rechallenge are possible if prescriber and patient together determine that the benefits outweigh the risks. 4) National registries which control hematologic monitoring are unnecessary and should be abolished.

EXPLORING CURRENT AND FUTURE DIRECTIONS IN THE MICROBIOME – A FOCUS ON NEUROPSYCHIATRIC DISORDERS

Sian Hemmings, Stellenbosch University

Symposium Synopsis: Humans have co-evolved with the trillions of microbiota that occupy every inch of our bodies, creating habitat-specific ecosystems that play a crucial role in bodily functions. Over the past decade, the interest in the role of that microbiota play in neuropsychiatric disorders, including autism spectrum disorder, posttraumatic stress disorder (PTSD), major depressive disorder and Parkinson's Disease has exploded. Recent evidence has indicated that the microbiome plays a key role in the brain and behaviour at critical windows across the lifespan, with numerous studies supporting the role of the gut microbiome in neurodevelopment. This symposium will bring together four leaders in the field of microbiome research, to discuss the current and future directions in microbiome research in neuropsychiatric disorders across the lifespan. Dr Hemmings will provide an overview of the role of the microbiome in neurodevelopmental disorders, with a focus on fetal alcohol spectrum disorders; Dr Malan-Muller will discuss the emerging role of the gut and oral microbiome in common mental disorders, such as PTSD, anxiety and depression, and Dr El-Aidy will discuss gut microbiome adaptations and implications for Parkinson's Disease treatment. Finally, Dr Walter Pirovano will provide insight into standardised and robust approaches for the identification of microbial markers in neuropsychiatric disorders.
This symposium will feature preclinical and clinical microbiome findings, and discuss the gut microbiome as a potential therapeutic target. Future considerations for holistically investigating the gut microbiome and untangling the molecular mechanisms whereby it influences the brain and behaviour, will also be discussed.

FETAL ALCOHOL SPECTRUM DISORDER: INSIGHTS FROM THE MICROBIOME

Sian Hemmings*[1], *Sian Hemmings2, Natasha Kitchin2, Lauren Martin2, Philip May3, Lindsay Hall4, Raymond Kiu5, Matthew Dalby5, Jacqueline Womersley2, Anna-Susan Marais1, Marlene de Vries1, Soraya Seedat2*

[1]Stellenbosch University, 2Stellenbosch University; Stellenbosch University/South African Medical Research Council Extramural Unit on the Genomics of Brain Disorders, 3Gillings School of Global Public Health, Nutrition Research Institute, University of North Carolina, 4Gut Microbes and Health, Quadram Institute Biosciences; Intestinal Microbiome, School of Life Sciences, ZIEL-Institute for Food and Health, Technical University of Munich; Norwich Medical School, University of East Anglia, 5Gut Microbes and Health, Quadram Institute Biosciences

Objective: Fetal alcohol spectrum disorder (FASD) is an overarching term describing four diagnoses along a severity spectrum, that occur consequential to prenatal alcohol exposure (PAE). Arguably the most profound consequences of FASD are the enduring neurodevelopmental abnormalities and cognitive deficits. In South Africa, the prevalence of FASD is reported to be higher than anywhere else in the world, with prevalences of up to 170-233 per 1,000 children reported, compared to the global prevalence of 7.7 per 1,000. Although FASD is a serious public health problem, both locally and internationally, treatment options are limited and further research is required in order to uncover novel therapeutic targets. Microbiome studies are a rapidly growing area of neuropsychiatric and neurodevelopmental research. Vertical and horizontal transfer of microbes from mother to child during and shortly after birth results in the acquisition of intestinal bacteria which, via the microbiome-gut-brain axis, have been found to play a significant role in neurodevelopment. Microbial alterations in the maternal gut and vaginal bacteriome, as well as the infant gut microbiome, may therefore increase the risk of FASD.

Methods: Participants (n=207) provided both stool and vaginal swab samples. Additionally, stool samples were collected from their infants at birth, six weeks, and nine months of age. Maternal alcohol use was assessed using AUDIT questionnaire and physiological markers of alcohol use. FASD diagnoses were made by triangulating data from dysmorphology examinations, neurodevelopmental assessments, and maternal interviews. Microbial DNA was extracted from maternal stool and vaginal samples, and infant samples at birth, 6 weeks and 9 months of age, and the V1-V2 hypervariable region of the 16S rRNA gene was sequenced. Microbial composition and diversity analyses were performed using R packages dada2, vegan, phyloseq, and MaAsLin2.

Results: Relative abundances of maternal gut Subdoligranulum and Bifidobacterium were lower in participants who birthed infants with FASD, compared to participants who birthed infants not diagnosed with FASD ($q = 0.026$; $q = 0.034$, respectively). Between the ages of 6 weeks and 9 months, Streptococcus relative abundance increased in the gut of infants without FASD, but decreased in infants diagnosed with FASD ($p = 0.023$), while the relative abundance of Bacteroides decreased in infants without FASD, but increased in those with FASD ($p = 0.073$).

Conclusion: Our research findings shed light on the nature and persistence of PAE-induced changes in the gut microbiome, and how alcohol-induced alterations in the microbiome may correlate with the development of FASD symptomology. These studies provide the first step in facilitating the identification of robust maternal and infant biomarkers of FASD, which may enable early identification of individuals most at risk for FASD, offer an early window for intervention, and contribute towards mitigating FASD-related disabilities in later life.

EXPLORING THE ORAL-GUT-MICROBIOME-BRAIN AXIS: ADVANCING FROM ASSOCIATION STUDIES TO MECHANISTIC INSIGHTS AND BEYOND

Stefanie Malan-Muller*[1], *Thomaz Bastiaanssen2, Rebeca Vidal1, Juan Carlos Leza3*
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Objective: Investigate the intricate interplay between the microbiomes of the oral cavity and the gut and explore the underlying molecular mechanisms that link these microbial ecosystems and their influence on anxiety, depression, and trauma-related symptoms.

Methods: In a Spanish cohort, we studied the connection between mental health and fecal and oral microbial characteristics, covering self-reported symptoms and clinical diagnoses of anxiety, depression, and PTSD.

We collected stool, saliva, and blood samples from 290 participants who completed questionnaires. Microbial communities in the gut and mouth were analyzed via 16S rRNA sequencing, examining diversity, structure, and taxonomic abundance. Linear models were used to assess associations between taxonomic abundance and variables while adjusting for covariates.

We used PICRUSt2 to identify Gut-Brain Modules (GBMs) and Gut Metabolic Modules (GMMs) and employed linear models to uncover modules significantly linked to mental health. Analysis of the oral microbiome is ongoing.

We measured plasma LPS levels with ELISA and are currently assessing levels of kynurenine, tryptophan, serotonin, and various inflammatory markers.

Results: A substantial proportion of individuals exhibited anxiety (72.41%), depression (41.38%), and PTSD symptoms (20%), often overlapping. Lower Simpson's diversity was found in those with anxiety disorders and psychiatric medication use. Microbial composition was affected by general health, depression/bipolar disorder diagnoses, childhood abuse, and neglect.

Certain microbial abundances correlated with symptoms: Duodenibacillus, Desulfovibrio, and Senegalimassilia positively correlated, while Parasutterella negatively correlated with CTQ scores. Severe/moderate childhood emotional abuse was linked to higher Prevotella and lower Parasutterella abundances. Severe/moderate childhood physical abuse correlated with higher Desulfovibrio and Senegalimassilia levels.

Individuals with depression symptoms had lower Monoglobus abundances. Those with depression symptoms, diagnosed depression, or PTSD symptoms had reduced Monoglobus and Hungatella compared to mentally healthy controls. Comorbid depression+anxiety and PTSD+depression+anxiety individuals exhibited lower Hungatella and Monoglobus levels. Desulfovibrio positively correlated, while Hungatella negatively correlated with PCL scores.

Comorbid PTSD+depression and PTSD+depression+anxiety cases showed increased glycine degradation. Individuals with depressive symptoms and childhood physical neglect had elevated plasma LPS levels.

Conclusion: In a population-based study, we've uncovered vital connections between gut microbes and mental health. Notably, lower Simpson's diversity was found in anxiety disorders, echoing generalized anxiety disorder trends. Parasutterella negatively correlates with childhood trauma and autism spectrum. Prevotella is higher in childhood emotional abuse cases. We identified lower Hungatella levels in those with multiple mental health symptoms, corrected for psychoactive drug effects. Reduced Monoglobus, linked to poorer life quality, is seen in significant depressive symptoms. Higher glycine degradation is tied to PTSD, depression, and anxiety. Elevated LPS levels

indicate increased gut permeability in individuals with childhood neglect and depressive symptoms. These findings suggest potential early-life interventions for improved mental health.

GUT MICROBIOME ADAPTATION AND TREATMENT IMPLICATIONS IN PARKINSON'S DISEASE

Sahar El Aidy*[1]

[1]*University of Groningen*

Objective: The intricate interplay of the microbiome within the human body is integral to determining overall health. Of particular significance is the dynamic nature of the gut microbiome, influenced by multifaceted factors such as nutrient availability, and interactions with the host. Disruptions in these factors have been observed in conditions like Parkinson's disease, often accompanied by discernible alterations in the microbiome profile. However, the field faces challenges in reconciling conflicting findings that assign specific roles to individual microbes in the development and progression of the disease.
Methods: In this context, research from my lab has shown how specific gut bacteria diminish the bioavailability of the primary treatment for Parkinson's disease (1, 2), and how their metabolic activities affect bowel movement and the overall microbiome profile (3, 4).
Results: Our recent investigations have brought to light the presence of distinct bacterial strains in Parkinson's patients, displaying unique genotypic and phenotypic traits (unpublished data).
Conclusion: Ultimately, these discoveries promise to provide a deeper understanding of how certain microbial community members adapt and flourish within the gut environment, thereby facilitating the development of tailored microbiome-targeted interventions.

NEUROPSYCHIATRIC DISORDERS AND THE MICROBIOME: TOWARDS STANDARDIZED AND ROBUST APPROACHES FOR THE IDENTIFICATION OF MICROBIAL MARKERS

Walter Pirovano*[1]

[1]*Vrije Universiteit Amsterdam*

Objective: In recent years, an increasing number of studies has allocated an important role to the microbiome in the proliferation of neuropsychiatric disorders. Many of these studies focus on the characterization of microbiota imbalances (dysbiosis) and the impact this may have on functioning of the central nervous system by means of the direct and indirect gut-brain axis communication pathways. The differences in sample processing and data analysis methods however result in findings which are often inconsistent and difficult to replicate. To overcome this more standardized and robust approaches are warranted, but we argue also larger and/or combined cohorts are essential to increase the statistical power.
Methods: We reviewed microbiome association studies that link microbial shifts to neuropsychiatric disorders, and summarized the findings together with the study design, lab- and data analysis procedures. The statistical power and suitability of the normalization technique used within each study was assessed as well. Next, studies that shared an overlapping setup were combined and analyzed using different analysis approaches to identify dysbiosis, to link taxa with metadata covariates and to quantify taxa-taxa interactions. The results were compared against findings obtained on the individual datasets as well as the findings of the original studies.
Results: We show that the use of different study designs, lab- and analyses methods have a profound impact on the outcomes of microbiome association studies in neuropsychiatric disorders. We show that the choice of the (biostatistical) analysis method is of particular importance to this regard. That said, the impact of the method is considerably lower when using larger and/or combined cohorts.
Conclusion: We conclude the use of different study setups and protocols for sample processing and data analysis lead to a divergent microbial landscape associated with neuropsychiatric illness. In

order to improve the coherence of studies, the use of standardized and statistically robust approaches is essential. Yet significantly larger and/or combined cohorts are needed to increase the statistical power and to gain a more comprehensive insight into the mechanisms that microbes use to trigger the development of psychiatric illnesses.

GRANT WRITING WORKSHOP

Sophia Frangou, The University of British Columbia

STRATEGIES FOR SUCCESS IN OBTAINING RESEARCH FUNDING

Sophia Frangou1
1 The University of British Columbia

Objective: Present strategies for successful grant writing in psychiatry.
Methods: The presentation will cover the following:
(a) Types of research funding available
(b) Writing a research proposal
(c) What the reviewer are looking for
(d) What the funding agencies are looking for
Results: Participants should be better equipped to apply for competitive funding.
Conclusion: Research funding is very competitive, and applicants benefit for using proven strategies.

EUROPEAN JOURNALS AND IMPACT FACTOR

Paolo Brambilla1
1 University of Milan
Paolo Brambilla, University of Milan

Objective: Young researchers often wonder whether the impact factor or the number of citations is more relevant. My very personal view is that citations become increasingly important with increasing maturity of the career of a scientists.
The older scientists get the more they will be judged for the consistency of their output (how many papers per year during the last 5 or 10 years – but also how many 'excellent' papers per year based on the impact factor and/or citations).
Young researchers often have only one or two publications which are pretty new, thus, the number of citations is limited.
Therefore, for pragmatic reasons, funding institutions and universities will use the impact factor of the journal as a proxy of their scientific excellence. To evaluate the output of more mature scientists the h-index or the m-index may be used which are both based exclusively on citations and not on impact factors.
Thus, young researchers are confronted with the problem that their scientific quality will be judged based on the impact factors of their publications – especially in contexts which are highly relevant for their early careers such as in selection committees (to get hired) and grant committees (to get funding).
Methods: How to build a CV and become an independent researcher.
Find facilities and mentor (also you got to be lucky and causality may help sometimes)
Learn a method, balance quantity and quality of publications in a 2-3 years span, start Networking with colleagues, present posters at conferences, try oral presentations, apply for congresses' awards, and start preparing proposal grants.
intramural / local / national / european-international

The following strategies are well known among senior scientists and will primarily help young researchers to look for feasible ways to improve their studies within the limits of their contract and budget.

1. Look for a mechanism not for a phenomenon
2. Address the same question with additional methods
3. Re-analyze your samples with a different or more complex method
4. Add fancy techniques
5. Develop a fancy technology
6. Collaborate with a statistician
7. Fuse smaller studies
8. Collaborate with experts in the field
9. Look for a journal with the perfect scope and check where your competitors publish
10. Submit to a journal with a much higher impact factor to get reviewers comments

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: EARLY DETECTION, INTERVENTION AND PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Symptoms related to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, loss of synaptic plasticity and nucleotide polymorphisms. Activation of the immune response can alter neurotransmission leading to transmitter deficiency, and increased production of neurotoxic substances. Aberrant levels of proinflammatory cytokines can be detected in serum, plasma, and cerebrospinal fluid. A persistent proinflammatory state, gone undetected and untreated, contributes to neuroprogression. Predicting risk and intervening to prevent and reverse a neuroprogressive course remain a challenge. This symposium will focus on assessment of the homeostatic balance of the autonomic nervous system focusing on vagal nerve activity by measuring heart rate variability. The cholinergic anti-inflammatory pathway of the vagus regulates peripheral immune response. Restoring vagal nerve activity by non-pharmacologic interventions restores normal immune response. Baseline systemic immune-inflammation index (SII) is an indicator of immune response and systemic inflammation based on peripheral blood platelet, lymphocyte, and neutrophil counts, and is a simple way to objectively assess the balance between inflammatory and immune responses. The association between elevated neutrophils (along with SII) and treatment resistance may allude to the role of oxidative stress in the pathophysiology of Bipolar Disorder. Selective genomic testing pertaining to the thyroid pathway can provide guidance in determining vulnerability to treatment resistance, and a neuroprogressive course. Mutations in deiodinase enzymes peripherally and in CNS may explain the pathophysiology and progression of the disease up to cerebral atrophy. These mutations, when addressed with high dose thyroid hormones and rTMS, yield long term stable remission.

HEART RATE VARIABILITY IS AN INDEX OF AUTONOMIC DYSFUNCTION AND A TOOL TO ASSESS NEUROPROGRESSION

Angelos Halaris**1*

[1]*Loyola University Chicago Stritch School of Medicine*

Objective: Autonomic nervous system (ANS) dysregulation is associated with various symptoms of depressive disorder. The beat-to-beat pattern of heart rate (Heart Rate Variability) (HRV) provides a noninvasive portal to ANS function through the quantification of periodic heart rate patterns. In this study we quantified two components of HRV: Respiratory Sinus Arrhythmia (RSA), and Low

Frequency HRV (LFHRV). Both of these components have been extensively reported in studies of depression and have been at least partially associated with reduction in vagal nerve tone. We quantified RSA and LF-HRV in patients with Major Depressive Disorder (MDD) and Bipolar Depression as measures of ANS regulation seeking to establish the utility of components of HRV as potential diagnostic and prognostic biomarkers for treatment outcome. Given the regulatory effect of the vagal pathway on cells of the immune system, HRV provides a non-invasive index of the peripheral inflammatory status of the individual. **Methods:** Respiratory sinus arrhythmia (RSA), low-frequency (LF) of HRV, and systolic blood pressure (SBP) were assessed in patients with bipolar depression (31) and major depressive disorder (MDD=32), and in healthy controls (HCs=32). Since bipolar depressed subjects were maintained on specific medications to manage manic/hypomanic symptoms, we explored whether mood stabilizers (atypical antipsychotics and anticonvulsants or their combinations) could independently affect the physiological parameters. **Results:** When the autonomic measures were analyzed by a multivariate analysis of variance (MANCOVA), after controlling for BMI, the combination of variables (RSA, LF, SBP) discriminated patients with bipolar depression and MDD from HC ($F(6, 178)=3.036$, $p=0.007$, $\Lambda=0.823$, partial $\eta 2=0.093$). In any case, we cannot exclude that mood stabilizers might have affected SBP values in the bipolar group. To deconstruct this multivariate effect, pairwise ANOVAs and discriminant analyses contrasted groups and documented that RSA was the primary variable distinguishing the groups. Discriminant function analyses showed that RSA had a significant discriminating weight between bipolar depressed patients and HC subjects (p LESS THAN 0.0005). By contrast, RSA showed a trend towards statistical significance in discriminating between bipolar depression and MDD patients ($p=0.06$). **Conclusion:** In conclusion, physiological parameters (e.g., RSA and SBP) can be easily assessed in outpatient settings, thus facilitating the differential diagnosis of affective disorders. In addition to other clinical tools, such as pharmacogenomic testing, history, and questionnaires, HRV analyses and BP measurement can add relevant physiological parameters to reach the final diagnosis. Components of HRV may be predictive of antidepressant response in MDD patients. Lastly, we highlight the regulatory influence the ANS exerts on the immune system. It has been shown that inflammation can increase symptomatology in affective disorders, and its modulation can reverse resistance to drug treatment.

THE ROLE OF CBC-BASED INDICES OF PERIPHERAL INFLAMMATION IN PREDICTING CLINICAL OUTCOMES AND NEUROPROGRESSION FOR TREATMENT-RESISTANT BIPOLAR DEPRESSION

Stephen Murata*[1], *Nausheen Baig[2], Kyle Decker[2], Sakibur Hasan[3], Angelos Halaris[4]*

[1]Michigan State University, 2Loyola Stritch School of Medicine, 3Western Michigan University Stryker School of Medicine, 4Loyola University Medical Center

Objective: Dysregulation of the immune system has emerged as an important contributor to the pathophysiology neuropsychiatric illness, including bipolar disorder (BD) and its treatment-refractory depressed form (TRBDD). As we develop a wider armamentarium for treating TRBDD, there is a need for objective biomarkers for stratifying patients by their propensity to respond to treatment, including with augmentation by inflammatory modulators (Halaris et. al 2020), The objective of this study is to characterize the relationship of systemic inflammatory burden with categorical and continuous clinical outcomes in TRBDD. To that end, our specific aims are to describe the relationship of baseline systemic inflammatory indices (constructed from markers in the complete blood count, or CBC) to (1) diagnosis of TRBDD compared to healthy controls (2) pre- and post-treatment

depressive severity after adjunctive celecoxib (COX-2 inhibitor) and (3) relationship to immune-metabolic biomarkers. **Methods:** This is a secondary analysis of biomarkers from our primary study (Halaris et. al 2020), which was a randomized, double-blind, placebo-controlled clinical trial of adjunctive celecoxib for TRBDD (total N=79, HC=32, TRBDD=37). Peripheral inflammatory indices were constructed from the CBC including the systemic inflammatory index (SII = neutrophils x platelets / lymphocytes) and the systemic inflammatory response index (SIRI = neutrophils x monocytes / lymphocytes). SIRI and SII were subjected to (1) group comparisons according to diagnosis and treatment arm and (2) univariate associations with pre- and post-treatment depressive severity (HAMD-17) and biomarkers. We modelled post-treatment depression (main outcome) according to baseline SII or SIRI, adjusted by pre-treatment depression and relevant covariates. **Results:** Inflammatory indices (SII or SIRI) were not distinguished by diagnosis or treatment arm. However, SIRI ($p=0.008$) and monocytes ($p=0.04$) were independently associated with pre-treatment HAMD-17. On multivariate modelling, post-treatment HAMD-17 was associated with pre-treatment SII in older patients ($p=0.001$), and SIRI in more depressed patients at baseline ($p < 0.001$), but no interaction with treatment arm. There were several significant associations with inflammatory indices and cytokines, chemokines, neurotrophic factors, and kynurenine pathway (KP) metabolites. **Conclusion:** There is a need for objective and economical biomarkers to assist in clinical assessment/treatment of neuropsychiatric illness, including TRBDD. These preliminary findings support the potential relevance of blood-based indices of peripheral inflammatory burden (monocytes, SII, and SIRI) as candidate pre-treatment indicators of treatment response, specifically for select subsets of TRBDD patients. Further, larger studies are needed to qualify these results. Once the utility of these blood-based biomarkers has been confirmed, it can also be used to stage and treat neuroprogression.

BIPOLAR SPECTRUM DISORDERS: THYROID PATHWAY GENETIC PROGNOSTIC MARKERS: IMPLICATIONS FOR ASSESSMENT, STAGING OF NEUROPROGRESSION AND TREATMENT

Andy Zamar**[1]*

[1] *The London Psychiatry Centre*

Objective: We aim to incorporate the assessment of SNPs and blood tests specific to those SNPs as well as the management using rTMS / HDT as a standard in the management of bipolar disorders particularly subthreshold presentations. Currently there are no confirmed results for the treatment of subthreshold bipolar disorder, which constitutes 60% of bipolar disorder with a prevalence of 2.5% in the United States. Furthermore, many patients with bipolar disorder 1 and 2 also present with subthreshold symptoms in between episodes and may indeed present only with disabling subthreshold symptoms while on treatment, such as mood stabilizers and antipsychotics which as a rule fail to induce full remission. The mortality of bipolar disorders is as high as circa 60% with 4 out of 10 dying of cardiovascular disease 10 years before the general population and 2 out of 10 dying of suicide and accidents. There is a very high disability rate which a WHO global study found to be higher than cancer, depression, heart disease, and epilepsy.

Methods: We present genetic findings in a cohort of 199 patients with SNPs in Deiodinase enzymes 1 and 2 and SLCO1C1 intracerebral thyroid protein transporter, as well as treatment outcomes in 2 cohorts (20 and 55 subjects). We explore the role of thyroid hormones on mitochondrial function, and the impact of the combined induction of neuroplasticity using rTMS and supraphysiological doses of Levothyroxine (HDT) and discuss their proposed mechanism of action. We also discuss the use of genetics and blood tests to predict tolerability and response to treatment.

Results: Patients achieved a long stable remission of depressive, hypomanic and mixed symptoms in Bipolar 1, 2 and BD-NOS with very few effects or disease burden. They were assessed using the Sheehan Disability Scale, a commonly used WHO scale to measure disease burden.

Conclusion: Precision medicine targeting treatments of mitochondrial dysfunction neuroplasticity provide a valid treatment option for bipolar disorders. The combination of HDT and rTMS is promising and well tolerated. Further studies of mitochondrial function before and after treatment and a randomized Controlled trial of the protocol are warranted. This is the first-time subthreshold symptoms / bipolar disorders are treated to full stable remission of an average of 2 years. The combination of inducing neuroplasticity and use of HDT is novel and may be a valuable tool in assessing the course of neuroprogression and possibly arresting if not reversing it. We are not aware of any guidelines to treat subthreshold symptoms and not even case reports, cohort studies or RCTs.

FROM NEUROPROGRESSION TO DISEASE MODIFICATION IN BIPOLAR DISORDER

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to identify the operative elements of the process of neuroprogression in order to identify clinical targets. The other objective is to define disease modification as a potential treatment effect and therapeutic goal.

Methods: Bipolar disorder progresses from an at-risk period, to the prodrome, a first episode, recurrence then chronicity. Along this path, the illness course and response patterns change, with poorer response in later stages where a greater risk of recurrence and more easily triggered recurrence are evident. There is both evidence of both progressive neurostructural change and cognitive decline aligned with a biological process of neuroprogression that appears to mediate this process.

Results: Many psychotropic agents, especially lithium, but also antidepressants and atypical antipsychotics impact the biological elements of the neuroprogressive cascade. Several repurposed and novel agents including N-acetyl cysteine, statins and anti-inflammatory agents such as statins and metformin may have neuroprotective potential. However the agent was the greatest evidence of ability to modify the clinical course the disorder is lithium. It's also likely that a state of remission regardless of how it is achieved is neuroprotective.

Conclusion: In conclusion it is important to identify disease modification as a realistic and important clinical task and to prioritise agents and clinical strategies that facilitate that goal.

3:30 p.m. - 5:00 p.m. Debate Session I -Stephen Lawrie and Deanna Barch

WHAT HAS NEUROIMAGING DONE FOR BIOLOGICAL PSYCHIATRY?

Stephen Lawrie[1]*

[1]*University of Edinburgh*

Objective: To seek out established facts from neuroimaging studies in people with major mental illness.

Methods: A systematic review of systematic reviews, augmented by adequately powered recent studies

Results: There are highly replicated demonstrations of reduced grey and white matter, hypofrontality and increased dopamine turnover in schizophrenia. These are related to key risk factors, pathophysiologies, symptoms and outcome measures - and show potential for early detection and prognostication. Comparatively little progress has been made in other conditions or in applying these findings to benefit patients. **Conclusion:** Neuroimaging studies tend to be small, noisy and underpowered, but have advanced our understanding of schizophrenia. Co-ordinated large international studies are required in other disorders and to make progress in usefully applying neuroimaging in clinical practice.

HOW HAS NEUROIMAGING HELPED US UNDERSTAND CLINICAL PREDICTION AND TREATMENT

Deanna Barch[*1]*

[1]*Washington University in St. Louis*

Objective: The goal of this debate is to discuss the ways in which neuroimaging has or has not helped us understand effective clinical prediction or treatment outcomes or treatment selection. This will include discussion of the relatively utility of neuroimaging in predicting the development of various forms of mental illness, the magnitude of effect sizes, and what type of data are needed to enhance such predictive utility. It will also include evidence that neuroimaging metrics can help us predict who will respond to treatment and who should be offered one treatment versus another.

3:30 p.m. - 5:00 p.m.
Symposia Concurrent IV

DYSREGULATIONS OF ENDOGENOUS AMINO ACIDS AND RELATED NEUROCIRCUITS IN PSYCHIATRIC DISORDERS

Hsien-Yuan Lane, Graduate Institute of Biomedical Sciences, China Medical University

Symposium Synopsis: Antipsychotic/D2 receptor occupancy triggers multiple trans-synaptic effects. Brain connectivity analysis based on key postsynaptic density proteins' expression (i.e., Homer1) is addressed in animal modeling to disentangle antipsychotics response. Patients' brain connectivity is tackled by novel 18FDG- PET approach to explore antipsychotics' response/resistance. The role of D-amino-acids in antipsychotics-resistance is also envisioned. Animal brain connectivity, patients' in vivo connectivity and metabolic marker altogether represent a multimodal strategy to understand antipsychotics resistance and highlight putative targets for novel treatments.

D-aspartate, an atypical amino acid, acts as an NMDAR agonist. Machine learning findings suggest a link between D-aspartate dysmetabolism and schizophrenia. We investigated serum levels of L-glutamate, D-serine, glycine, L- aspartate, and D-aspartate and found that, compared to healthy controls, schizophrenia patients had decreased D-serine and altered D-aspartate levels, thus confirming abnormal NMDA signaling in schizophrenia.

In addition to lower D-serine, higher D-amino acid oxidase (DAAO) expression/activity was observed in schizophrenia patients. Inhibiting DAAO (to slow D-serine degradation and enhance NMDAR) and multi-target drugs are promising for refractory schizophrenia. Sodium benzoate, targeting DAAO activator (G72)-DAAO-NMDA pathway, antioxidants-anti-inflammatory pathway, and sex hormones, improved clozapine-resistant schizophrenia in a placebo-controlled trial.

NMDAR activation plays critical roles in preventing neurodegenerative disorders. Serum DAAO increased with cognitive decline in elderly in cross-section and prospective studies, supporting hypo-NMDAR hypothesis of Alzheimer's disease. NMDAR enhancement via inhibiting DAAO improved cognition of early-phase Alzheimer's patients. Oxidative stress also leads to neurodegeneration. Glutathione, catalase, superoxide dismutase, etc. may also be implicated in neurodegeneration. Sodium benzoate's effects on antioxidants deserves further investigation.

TRANS-SYNAPTIC AND CONNECTIVITY EFFECTS OF ANTIPSYCHOTICS: IMPLICATION FOR TREATMENT RESISTANT SCHIZOPHRENIA AND ROLE OF D-AMINO ACIDS

Andrea de Bartolomeis*[1], *Felice Iasevoli[1]*

[1]*University of Naples Federico II*

Objective: Treatment-resistant schizophrenia is a severe clinical condition affecting cognition and overall patient functioning. Therefore, there is a need to better understand the molecular basis of antipsychotics' action and to unveil new strategies for TRS. Dopamine D2 receptor occupancy, the main mechanism of action shared by all the available antipsychotics, may trigger multiple trans-synaptic effects strongly associated with dopamine-glutamate interaction. Here we address antipsychotics-dependent modulation of brain connectivity in a preclinical and clinical setting by multimodal imaging and its relevance in treatment-resistant schizophrenia.

Methods: 1) Brain connectivity analysis based on change of key glutamatergic postsynaptic density proteins' expression (i.e. Homer1, PSD.95) was analyzed in animal modeling to disentangle antipsychotics response, 2) Patients' brain metabolic pattern and connectivity were addressed by a18FDG- PET approach to explore brain metabolic related response or resistance to antipsychotics. 3)Structural MRI, TDI, and brain amino-acid in vivo quantitation by MRI spectroscopy were applied for multimodal analysis in a sample of adolescents responsive or resistant to antipsychotic treatment.

Results: 1) Brain networks showed differences in global efficiency and clustering coefficient. The" haloperidol network" showed enhanced interactivity between cortical and striatal regions, and within the caudate-putamen subdivision.

2) Restricted areas of significant bilateral relative hypometabolism in the superior frontal gyrus characterized TRS compared to non-TRS patients. Reduced parietal and frontal metabolism was associated with high PANSS disorganization factor scores in TRS ($P < .001$ voxel level uncorrected, $P < .05$ cluster level FWE-corrected).

3) significant increase of glutamate (absolute integral and ratio values) was detected in the cingulate cortex in TRS patients, compared to HCs (glutamate mean value: patients = 0.95, HCs = 0.66; $p < 0,001$; glutamate/creatine ratio: patients = 0.92, HCs = 0.6; $p < 0.001$)

Conclusion: Altogether, animal modeling of brain connectivity, in vivo brain metabolic detection, and connectivity in patients may suggest that 1) antipsychotics impact trans-synaptically the expression of glutamatergic postsynaptic density proteins and brain connectivity based on postsynaptic density immediate-early gene-based network analysis. 2) the response or resistance to antipsychotics is associated with different metabolism and connectivity in discrete brain regions.
3) Brain concentration of amino acids in patients as measured in vivo by MRI spectroscopy separate normal controls from schizophrenia patients and antipsychotic non-responsive to responsive patients. These changes may support a possible role for glutamatergic-based augmentation therapy such as D-amino acids, whose concentration was demonstrated to be altered in schizophrenia patients' post-mortem brains, enhancing the response to antipsychotics in treatment-resistant schizophrenia patients.

INVOLVEMENT OF THE PRENATAL D-ASPARTATE METABOLISM IN NEURODEVELOPMENTAL DISORDERS

Alessandro Usiello*[1], *Francesco Errico2, Tommaso Nuzzo1*

[1]*University of Naples SUN, 2University of Naples Federico II*

Objective: The atypical amino acid D-aspartate (D-Asp) acts as an N-methyl D-aspartate receptor (NMDAR) agonist. D-Asp has a peculiar spatiotemporal pattern of occurrence in the central nervous system (CNS) of mammals. Indeed, it is abundant throughout prenatal stages and decreases dramatically after birth in concomitance with the expression onset of the catabolic enzyme, D-

aspartate oxidase (DDO) Hence, D-Asp metabolism dysfunction might represent a putative candidate involved in glutamatergic-related neurodevelopmental disorders including schizophrenia (SCZ) and autism spectrum disorders (ASD). **Methods:** This symposium reviews the involvement of D-Asp metabolism dysregulation in neurodevelopmental disorders, including SCZ and autism spectrum disorders (ASD). **Results:** In line with a possible modulatory role of this endogenous NMDA agonist in modulating SCZ related phenotypes, we found that greater D-Asp brain levels in mice are able to attenuate PCP- induced PPI deficits and cerebral activity dysfunction, measured by functional magnetic resonance imaging (fMRI). In addition, consistent with its involvement in NMDA related processes, we have also shown that D-Asp modulates CNS metabolome, as assessed by nuclear magnetic resonance (NMR)- based analysis in mice brain during development. Beyond preclinical results, recently we documented the first clinical case of a young patient with severe intellectual disability (ID) and autism spectrum disorders (ASD)-related symptoms harboring a DNA duplication of 127.8 kb on chromosome 6, including the entire DDO gene. Interestingly, we found that constitutive DDO overexpression and the resulting cerebral D-Asp depletion induce cognitive and social recognition abnormalities and smaller cortical grey-matter volume in adult Ddoov mice, associated with reduced number of dorsal pallium neurons during corticogenesis. In agreement with the involvement of D-Asp in modulating cortical phenotypes, we documented that a human DDO gene variant (rs3757351) leading to lower mRNA expression in the cortex of healthy subjects is associated with increased prefrontal grey matter and prefrontal activity during working memory tasks, as measured by fMRI. Further supporting a possible involvement of D-Asp metabolism in the modulation of cortical processes related to NMDAR signaling, we recently evidenced that a machine learning hypothesis-free algorithm included D-Asp/total Asp ratio within a stable molecular cluster discriminating SCZ patients from non-psychiatric controls in the post-mortem dorsolateral PFC. Remarkably, this observation mirrors a significant 30-40% reduction in D-Asp levels found in the PFC of two post-mortem cohorts of SCZ patients, compared with non-psychiatric subjects. **Conclusion:** Altogether, our findings unveil an intriguing influence of early D-Asp metabolism in the regulation of neurodevelopmental processes and, consequently, provide a translational significance to metabolic D-Asp deregulations as a possible signature of neurodevelopmental psychiatric disorders, including SCZ and ASD.

NOVEL TREATMENT WITH MULTI-TARGETS FOR CLOZAPINE-RESISTANT SCHIZOPHRENIA: MODULATION OF NMDA RECEPTOR, D-AMINO ACIDS, AND RELATED PATHWAYS

Hsien-Yuan Lane*[1]

[1]*Graduate Institute of Biomedical Sciences, China Medical University*

Objective: NMDA receptor (NMDAR) hypofunction is implicated in schizophrenia. Compared with healthy controls, schizophrenia patients had lower D-serine levels in CSF and blood, and higher blood levels of D-amino acid oxidase (DAAO) (Lin et al., Front Bioeng Biotechnol 2020) and DAAO activator (DAOA, or named G72) (Lin et al., Mol Psychiatry 2014). For discovering novel NMDAR enhancers to improve schizophrenia treatment, D-serine and other NMDAR co-agonists were examined in randomized, double-bind, placebo-controlled clinical trials (RDCs), albeit with mixed results. The second route, inhibition of glycine transporter-I, showed promising potential in improving clinical symptoms and cognitive function of schizophrenia (Lane et al., Arch Gen Psychiatry 2005; Chang et al., J Psychopharmacol et al., 2020; Fleischhacker et al., Lancet Psychiatry 2021). However, these strategies have failed in the treatment for the most resistant (clozapine [the last-line antipsychotic agent] resistant) schizophrenia patients (Goff et al., CNS Spectr 2001; Lane et al., Biol Psychiatry 2006). For potentially better treatment, the third avenue is inhibition of DAAO for slowing D-serine

degradation and thereby enhancing NMDAR function (Kuo et al., CNS Drug 2022; Cheng et al., Neuropsychopharmacology 2023). Moreover, multi-target drugs are a promising approach against refractory schizophrenia (Lin et al., Curr Drug Targets 2020). **Methods:** This symposium reviews current status of clinical trials and related mechanisms for treatment-resistant, including, clozapine-resistant schizophrenia. We also address future directions in developing better treatments for the hardest-to-treat schizophrenia. **Results:** We are the first group to discover that sodium benzoate, a pivotal DAAO inhibitor, is more efficacious than other NMDAR enhancers (Chang et al., J Psychopharmacol et al., 2019; Lin et al., Int J Neuropsychopharmacol 2022). In initial RDCs, sodium benzoate improved cognitive function of patients with chronic schizophrenia, no matter it improved clinical symptoms or not (Lane et al., JAMA Psychiatry 2013, Lin et al., World J Biol Psychiatry 2017). Later, benzoate also improved both positive and negative symptoms of clozapine (the last-line antipsychotics)-resistant schizophrenia patients in a RDC (Lin et al., Biol Psychiatry 2018). While the underlying mechanisms require more studies (Huang et al., Neurochem Res 2023), sodium benzoate has been found to possess multi- targets on the NMDA pathway, the antioxidants-anti-inflammatory pathway, and sex hormones (Lin et al., Biol Psychiatry 2018; Lin et al., JAMA Netw Open 2021; Lane et al., Psychiatry Clin Neurosci 2023). In addition to sodium benzoate, other DAAO inhibitors are promising; for example, luvadaxistat was found to be able to improve cognitive function of schizophrenia patients (Kuo et al., CNS Drugs 2022). Furthermore, combination of benzoate and brain stimulation deserves more studies too (Lane et al., Psychiatry Res 2023). **Conclusion:** If these findings can be reconfirmed, modulation of NMDAR, D-amino acids, and related pathways may instill hope for the treatment of the most resistant schizophrenia. However, 6-week benzoate treatment (at doses of 1 and 2 gm/day) still didn't improve cognitive function of clozapine- resistant patients (Lin et al., Biol Psychiatry 2018). More novel approaches are needed to develop effective therapies for the cognitive dysfunction in clozapine-resistant patients (Lin and Lane, Schizophr Res 2023 [Invited Commentary]).

THE CHANGES OF D-AMINO ACIDS AND NMDA RECEPTOR MODULATORS IN NEURODEGENERATION

Chieh-Hsin Lin**1*

[1]Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology

Objective: Glutamate NMDA receptor (NMDAR) activation plays a critical role in cognitive function. Dysregulation of NMDAR is the core of neurodegenerative mental disorders (Lin et al., Curr Pharm Des 2014). As the agonist or co-agonists of NMDAR, D-glutamate, D-serine, and D-alanine differ in their roles in cognitive decline in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) (Lin et al., Pharmacol Biochem Behav 2019). The clinical implications of the changes of D-amino acids and modulators of NMDAR in neurodegeneration deserve studies.

Methods: This symposium reviews the roles of D-amino acids in neurodegeneration as well as the effects of NMDAR modulators in neurodegenerative disorders.

Results: Previously, D-serine levels have been found to be altered in the AD patients. We recently found that peripheral blood levels of D-glutamate were associated with cognitive impairment, therefore a potentially suitable peripheral biomarker for MCI and AD (Chang et al., Psychopharmacol 2021). Of note, serum D-amino acid oxidase (DAAO) levels were significantly associated with D-glutamate and D-serine levels (Lin et al., Sci Rep 2017). Further, DAAO levels increased with the severity of the cognitive deficits in elderly individuals in a cross-section study (Lin

et al., Sci Rep 2017) and a prospective study (Lin and Lane, Int J Neuropsychopharmacol 2022), thereby supporting the hypo-NMDAR hypothesis of Alzheimer's disease (AD). DAAO activator (DAOA, or G72) levels also increase in patients with early phase of AD (Lin et al., Sci Rep 2019). Combination of G72 and cystine/glutamate antiporter SLC7A11 in blood can sensitively and specifically diagnose AD (Lane and Lin, Int J Neuropsychopharmacol 2022). Glutathione, catalase, superoxide dismutase and other endogenous antioxidants may also play important roles in the process of neurodegeneration (Chiang et al., Clin Psychopharmacol Neurosci 2021; Lin and Lane, Antioxidants 2021). NMDAR enhancement via inhibiting DAAO activity by sodium benzoate can improve cognitive function of patients with early-phase AD or late-life depression (Lin et al., Biol Psychiatry 2014; Lane et al., Psychiatry Clin Neurosci 2022; Lin et al., Int J Neuropsychopharmacol 2022) and alter brain activity in MCI patients (Lane et al., Int J Neuropsychopharmacol 2021), while raising blood levels of two endogenous antioxidants, glutathione and catalase (Lane et al., Psychiatry Clin Neurosci 2022). Sodium benzoate also improved cognitive function of women with behavioral and psychological symptoms of dementia (BPSD) with increased estradiol to follicle-stimulating hormone ratios in blood (Lin et al., JAMA Netw Open 2021).

Conclusion: If these findings can be reconfirmed, several potential biomarkers can aid in the diagnoses of neurodegenerative disorders and modulation of NMDAR through inhibition of DAAO may be a novel approach for the treatment of these disorders. In addition, the effects of sodium benzoate on endogenous antioxidants and sex hormones and their roles in precision medicine deserve more studies.

IMMUNE-METABOLIC DYSFUNCTION IN MENTAL DISORDERS: AN UPDATE ON CURRENT EVIDENCE

Ishrat Husain, Centre for Addiction and Mental Health, University of Toronto

Symposium Synopsis: There has been increasing interest in the role of immune-metabolic dysfunction in the pathophysiology of mood and psychotic disorders. Replicating evidence suggests that individuals with mental disorders are more prone to chronic inflammatory illnesses, and metabolic syndrome. Even in the absence of physical illness, individuals with mental disorders display altered levels of peripheral inflammatory markers. Given these associations, several clinical trials have evaluated repurposed agents targeting immune-metabolic pathways in depression, bipolar disorders and psychosis, with mixed results. In order to advance the field of immunopsychiatry, it is important to identify specific subtypes of mental disorders that would benefit from these repurposed agents. Further research is needed to determine specific behavioural symptom subsets that are prevalent among patients with mental disorders and concurrent immune-metabolic dysfunction. The aim of the proposed symposium is to provide an update on evidence for immune-metabolic subtypes of mood and psychotic disorders. We will present synthesized data from observational studies that provide insights into potential pragmatic molecular and genetic biomarkers of "inflamed" subtypes of depression and psychosis. In addition we will present results from recent clinical trials of lipid lowering agents and anti-inflammatory drugs as add-on treatments for treatment-resistant depression and schizophrenia-spectrum disorders. Finally, we will make recommendations for innovative trial designs that may enhance clinical translation of transdiagnostic treatments that target immune-metabolic dysfunction across mental disorders.

UNDERSTANDING THE POTENTIAL ROLE OF INFLAMMATORY MARKERS IN NEUROPROGRESSION ACROSS THE CLINICAL STAGES OF BIPOLAR I DISORDER

Preethi Veerappa Reddy**1*, *Nandhini Bojappen1, Thrinath Mullapudi1, Nikitha Srinivas1, Rajakumari Reddy1, Monojit Debnath1, Muralidharan Kesavan1*

1 National Institute of Mental Health and Neurosciences

Objective: In Bipolar Disorder (BD), illness progression has been linked to worse treatment outcomes and cognitive/functional impairment. Multiple instances of the disease may have the ability to cause neuronal systems to change permanently, according to the kindling model. In contrast to the West, the clinical course of BD-I in India is mania-dominant and is linked to increased intellectual loss and poor functionality. Our study was planned to examine and compare the serum levels of immuno- inflammatory, across different clinical stages of BD-I High risk, early BD, and multiple episode BD (stage 1-3) and healthy controls (HC) **Methods:** Our research was cross-sectional and involved the following groups: high-risk participants (BD-I-Stage 1), early BD-I (First episode), established BD-I (Stage 3), and age- and gender-matched healthy controls (HC). The inflammatory markers that we compared across groups were Interleukin (IL)-1β, IL-6, and Tumor necrosis factor (TNF)-α measured on a Bioplex 200 platform utilizing a multiplex suspension array and soluble TNF receptors 1 and 2 (sTNFR-1 and 2) measured using sandwich enzyme-linked immune-sorbent assay technique. SPSS-16/R software was used to do the statistical analysis. Kruskal Wallis was used to compare the inflammatory markers. **Results:** We recruited a total of 172 subjects, with 43 in each group. In the total sample, we had 100 males and 72 females. There was no group difference in gender noted. The age at assessment there was a group difference (p LESS THAN 0.001), the ME group had a higher age than the other three, who did not differ from each other. The two BD groups did not show any difference in the age of illness onset or the onset of the first episode of mania (p=0.56), family history of psychiatric illness (p=0.11), and duration of remission (p=0.10). There was a significant difference in the duration of illness the ME group by definition had a longer duration of illness compared to FEM ($p < 0.001$). In terms of the inflammatory markers, IL-1β (p=0.66) and TNF-α (p=0.44) levels did not show any group difference. IL-6 levels were significantly higher among the ME and FE-BD groups compared to the controls (h=11.26, p=0.01). ME group also had higher levels than the HR group. sTNF- R1 levels were significantly higher among the ME group compared to the FE, HR, and control groups (h=14.35, p=0.002). These three groups did not show any difference. sTNF-R2 levels were significantly higher (h=29.87, $p < 0.001$) in the patient group (ME and FEM) compared to the non-patient group (HR and HC). **Conclusion:** The important findings of the increased levels of sTNFR-1 in ME compared to FE suggest that the higher the no of manic episodes, the higher the levels of inflammatory markers like sTNFR- 1. The high-risk group did not show any difference from the control group which suggested that probably the inflammatory pathway gets involved after the disease onset. We also noted increased levels of sTNFR-2 in the BD patients compared to high-risk and controls, but no difference between the ME and FE groups. These two are important proteins that are activated in the process of apoptosis (cell death). This is one of the mechanisms of how neuroprogressive changes occur in the brain. This study emphasizes the need for longitudinal studies to evaluate these markers across the stages of BD and establish them as biomarkers of neuroprogression and staging.

NEUTROPHIL EXTRACELLULAR TRAPS (NETS): A NOVEL CELLULAR-BASED MECHANISM IN SCHIZOPHRENIA AND THE IMPLICATIONS OF EARLY-LIFE ADVERSITIES

Fabiana Corsi-Zuelli*[1], *Ayda Henriques Schneider1, Thamyris Santos-Silva1, Camila Marcelino Loureiro1, Rosana Shuhama1, Paulo Rossi Menezes1, Francisco Silveira Guimarães1, Felipe Villela Gomes1, Fernando Queiroz Cunha1, Paulo Louzada-Junior1, Cristina Marta Del-Ben1*

[1]*University of São Paulo, Ribeirão Preto Medical School*

Objective: Previous studies using blood cytokines to stratify patients with schizophrenia suggest that only a subset presents a low-grade inflammatory state. However, these studies have not addressed whether environmental factors such as childhood maltreatment contributed to identifying

inflammatory clusters. Moreover, a neutrophil-related mechanism (NETs) has never been investigated in the field. We investigated NETs as a novel biological mechanism in early schizophrenia and their role together with interleukin-(IL-6) and childhood maltreatment in identifying cluster subgroups. **Methods:** Clinical study: We used data available from the STREAM study, a case-sibling-control investigation conducted in the Ribeirão Preto catchment area (São Paulo, Brazil). The sample included individuals with early-stage schizophrenia spectrum (n=78), sex and age-matched controls (n=78), and unaffected siblings of patients (n=25). Childhood maltreatment was evaluated using the Childhood Trauma Questionnaire. NETs and IL-6 in plasma were evaluated using the Quant-iT PicoGreen kit and multiplex, respectively. Fresh neutrophils were isolated from healthy donors to test the effect of antipsychotic drugs (haloperidol or risperidone) on NETs release in vitro. Group differences on NETs and IL-6 were evaluated using general linear models with Bonferroni post-hoc, adjusted for sex, body mass index (BMI), tobacco smoking, and psychoactive substance use. Two-way ANOVA with Bonferroni post-hoc was used to test the effect of antipsychotics on NETs in vitro.To identify clusters, we applied unsupervised two-step clustering analyses with Bayesian Criterion to estimate the maximum number of clusters after integrating values of NETs, IL-6, and childhood maltreatment scores. Rodent model: Juvenile male Sprague-Dawley rats (postnatal day, PND 24) were exposed to an adolescent early stress protocol (a combination of daily inescapable footshock from PD31-40, and three restraint stress sessions, PD31, 32, and 40) or left undisturbed (controls). At PN51, NETs and IL-6 were evaluated in serum. We also measured levels of NETs released from fresh neutrophils isolated from rats' bone marrow. **Results:** We found increased NETs levels in patients with early schizophrenia compared to their unaffected siblings and community controls ($F=50.79, df=2, p < 0.001$). Using an in vitro assay, we showed that haloperidol and risperidone do not induce but inhibited NETs release from stimulated neutrophils. Using unsupervised two-step clustering analysis, we identified two main clusters; childhood maltreatment scores and NETs were the most important variables contributing to cluster separation (high-CL1 and low-CL2). Patients with high-CL1 (61.5%) had significantly higher childhood maltreatment scores ($F=26.23, df=5, p < 0.001$), NETs ($F=25.17,5, p < 0.001$), and IL-6 ($F=3.87, df=5, p < 0.002$) levels than the remaining groups. Using a rat model based on stress exposure, we found that adolescent stressed rats had higher NETs ($t16=5.18, p < 0.001$) and IL-6 ($t10=6.33, p < 0.001$) levels in serum compared to non-stressed rats, with a tendency to produce more NETs from the bone marrow. **Conclusion:** We demonstrate for the first time a novel cellular mechanism in schizophrenia that suggests neutrophils are in an active and functional state. We further suggest that NETs and early stress should be considered in future studies aiming to identify immune biological subgroups for more personalised treatments.

EXPLORING IMMUNE-INFLAMMATORY MARKERS IN RESPONSE TO ADJUNCTIVE MINOCYCLINE TREATMENT FOR DEPRESSION.

Olivia Dean1, Adam Walker1, Bruna Panizzutti**1*

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Deakin University

Objective: These series of studies aimed to explore the underlying biological response reflecting the clinical improvement seen in participants who took part in a clinical trial of adjunctive minocycline. Markers in the kynurenine pathway and associated inflammatory markers were explored.

Methods: A randomised placebo-controlled trial of adjunctive minocycline (200 mg/day) for people with major depressive disorder (n=71) was conducted and blood samples were collected at baseline

and the end of the treatment phase (week 12). Serum samples were analysed by the Karolinska Institutet and Deakin University to determine levels of biological makers. **Results:** Following correction for false discovery rates, changes in complement C3, IL-1Ra, IL-8/CXCL8, and ICAM-1 were found to be associated with changes in depression scores following adjunctive minocycline treatment. We have new data available on RAGE pathways that we expect to also present at the meeting. **Conclusion:** There has been considerable exploration of individual markers of treatment response in depression. This has led to heterogenous outcomes and difficulties in understanding the specificity of markers in predicting response to treatment. This study used a multi-marker approach to explore the kynurenine pathway to provide a more comprehensive understanding of the treatment response to adjunctive minocycline treatment. These studies provide valuable information alone, but moreover are contributing to a larger study encompassing multipole markers, disorders and therapeutic agents.

EFFICACY OF METHOTREXATE POINTS TO IMMUNE DYSFUNCTION IN PSYCHOSIS

Omair Husain**1*, *Imran Chaudhry2, Bill Deakin3, Nusrat Husain4*

[1]Center for Addiction and Mental Health, 2Ziauddin University, 3University of Manchester, 4Mersey Care NHS Foundation Trust

Objective: There is growing evidence implicating inflammatory processes in the pathogenesis of schizophrenia. NMDA receptor encephalitis presenting as schizophrenia suggests the possible role of cell-mediated immune processes. Several inflammatory cytokines including IL-2, IFN-gamma, TNF-alpha and soluble IL-2 receptor may be elevated in schizophrenia relapse and reduced in remission. In this presentation we will summarise evidence for the use of novel anti-inflammatory agents in the treatment of schizophrenia with a focus on methotrexate.
Methods: We tested if low-dose methotrexate as used in the treatment of systemic autoimmune disorders would be tolerable and effective in people with schizophrenia in a feasibility double-blind randomized control trial. Ninety-two participants within 5 years of schizophrenia diagnosis were randomised to receive once weekly 10mg oral methotrexate (n = 45) or matching placebo (n = 47) both with daily 5mg folic acid, in addition to treatment as usual for 12-weeks.
Results: There were eight dropouts per group. Side effects were non-significantly more common in those on methotrexate and were not severe. One person developed leukopenia. Positive symptom scores improved more in those receiving methotrexate than placebo (β = −2.5; [95% CI −4.7 to −0.4]), whereas negative symptoms were unaffected by treatment (β = −0.39; [95% CI −2.01 to 1.23]).
Conclusion: We conclude that further studies are feasible but should be focussed on subgroups identified by advances in neuroimmune profiling. Methotrexate is thought to work in autoimmune disorders by resetting systemic regulatory T- cell control of immune signalling; we show that a similar action in the CNS would account for otherwise puzzling features of the immuno-pathogenesis of schizophrenia.

INNOVATION IN OPIOID AGONIST THERAPY AND WITHDRAWAL MANAGEMENT

Marc Vogel, Psychiatric University Clinics Basel

Symposium Synopsis: The ongoing epidemic of opioid use disorder (OUD) remains one of the biggest public health problems in the world. Recent years have brought rising numbers of opioid overdose deaths particularly in North America but also in European countries and Australia. The increasing role of ultrapotent opioids such as fentanyl challenges conventional treatment practice. Opioid agonist therapy (OAT) constitutes the treatment of choice but has often not been able to reach vulnerable

populations. Furthermore, retention rates in many parts of the world remain insufficient. The implementation of innovative and patient-centered measures is needed. **Methods:** In this symposium, we present promising new and innovative methods aiming to improve withdrawal management, induction and delivery of OAT. **Results:** Opioid agoinists have different side effect profiles which may allow a patient-centered choice of medication. Buprenorphine microdosing is an innovative approach suitable for inpatient and outpatient initiation of buprenorphine OAT without the need for preceding withdrawal symptoms as in conventional induction. Symptoms inhibited fentanyl induction is an intervention to determine opioid tolerance and rotate patients on a dose of full mu-opioid-agonists suitable for OAT in the course of one day. Nasal diacetylmorphine is a new treatment option for patients not responding to oral OAT, or patients in injectable OAT transferring to a less harmful alternative. **Conclusion:** The OUD epidemic requires an expansion and further development of treatment options. There are several promising innovations in OAT suitable to improve withdrawal symptoms, treatment induction and delivery, expanding treatment access for populations not reached with current treatment methods.

NASAL OPIOID AGONIST TREATMENT

Marc Vogel**1*

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Psychiatric University Clinics Basel

Objective: Not all patients with opioid use disorder respond to oral opioid agonist treatment (OAT). Therefore, other routes of administration have been successfully introduced, e.g. injectable or smokable diacetylmorphine. However, these routes are associated with a higher risk of adverse events. Nasal OAT is a new treatment option likely associated with fewer risks and suitable to reach patients primarily sniffing opioids but not stabilizing in oral OAT.

Methods: We present the method of nasal application and data from an ongoing multicenter prospective observational cohort study accompanying the introduction of nasal OAT in Switzerland's heroin assisted treatment (HAT) centers.

Results: As of 2023, 139 patients of 16 centers initiated nasal HAT, the majority of which were male. Main reason for switching to the nasal route were sniffing being the preferred route of administration, and patients on diacetylmorphine (heroin) tablets desiring a more rapid onset of effect. At 4 and 52 weeks, 88% and 53% respectively were still prescribed the nasal route of administration. Additional substance use remained largely unaltered. Adverse events were rare, and treatment satisfaction was high among those remaining in the nasal route.

Conclusion: Nasal OAT seems to be a viable treatment option for a subpopulation of patients in HAT. It is associated with few adverse events. With switching routes of administration being common in Swiss HAT, patients with higher satisfaction remained with the nasal route. Further research is required on optimizing the application method and to determine which subpopulaton is likely to benefit from nasal OAT.

RAPID LOW-DOSE BUPRENORPHINE INDUCTIONS & SYMPTOM-INHIBITED HYDROMORPHONE & FENTANYL INDUCTIONS

Pouya Azar**1*

1Vancouver General Hospital

Objective: The high prevalence of fentanyl and its analogues in the unregulated drug supply has led to tragic levels of mortality and morbidity in North America and Europe, posing challenges in the clinical management of opioid use disorder due to escalating opioid tolerances. We will share our experiences with the development, implementation, and evaluation of innovative opioid withdrawal

management and opioid agonist treatment (OAT) approaches in Vancouver, the epicentre of the overdose crisis in Canada. **Methods:** We will present our low-dose buprenorphine induction protocols, which involve the administration of small, frequent does of buprenorphine, eliminating the need for a prior period of withdrawal and opioid abstinence. We will also present our pharmacokinetically-guided protocols utilizing hydromorphone and fentanyl to manage withdrawal, facilitate rapid methadone and slow- release oral morphine initiation, and promote adherence to medical treatment. **Results:** We will teach our protocols utilizing practical real-life cases and patient testimonial videos. We will share our results from clinical trials and retrospective chart reviews, and our experiences in the implementation of our protocols. **Conclusion:** Participants will gain a comprehensive understanding of the current landscape of opioid use disorder, overdose fatalities, and withdrawal management and OAT approaches to treat patients who use unregulated fentanyl and its analogues.

SIDE EFFECTS OF DIFFERENT AGONISTS IN OPIOID AGONIST TREATMENT - SYSTEMATIC REVIEW AND META-ANALYSIS

Maximilian Meyer**1*

1

Psychiatric University Clinics Basel

Objective: Opioid agonist treatment (OAT) is the treatment of choice for opioid use disorder. Most often, methadone or buprenorphine are used. However, coverage rates are fairly low and conventional OAT does not reach large parts of the target population. In order to expand treatment access and allow a more patient-centered approach, other opioid agonists such as diacetylmorphine or slow-release morphine, and other routes of administration (injectable, depot) have been introduced. With similar retention rates, the choice of opioid agonist in the future will be guided by the side effects profile.

Methods: We present data of a meta-analysis of side effects in randomized controlled trials of different opioid agonists for treatment of opioid use disorder.

Results: We identified 181 studies, 25 of which were included for potential meta-analysis. Reported opioid agonists were methadone, LAAM, methadyl acetate, buprenorphine, buprenorphine/naloxone, slow-release morphine (SROM), diacetylmorphine, hydromorphone, opium tincture. Where groupe meta-analysis was possible, buprenorphine (all formulations combined) was associated with less risk of sedation than methadone (RR 0.68; 95% CI 0.56-0.82), SROM with higher risk (0.63; 0.58-0.69). Methadone had a lower risk of nausea (0.56; 0.37-0.85) and sweating than methadyl acetate (0.73; 0.59-0.90). Some known side effects were not systematically reported although highly relevant for clinical practice, e.g. sexual dysfunction or QTc-prolongation.

Conclusion: Overall, the quality of side effect reporting in many studies was low and insufficient. Our results challenge some traditional clinical teaching about side effects (e.g. in direct comparison, the risk for sweating was not lower for buprenorphine than for methadone). Future research should actively investigate side effects given their importance for a patient-centered treatment decision. This is particularly true for side effects such as sexual dysfunction and QTc-prolongation, which have high clinical relevance but were not systematically reported at all.

APPLYING PERSONALIZED MEDICINE TO BIPOLAR DISORDER

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: Patients with bipolar disorder (BD) urgently need personalized, data-driven treatments guided by empirically validated predictive biomarkers. In this symposium, we will provide an inspiring overview of cutting-edge, biomarker-driven approaches to precision medicine in BD.

These will include biomarkers as predictors of treatment response, and the application of cutting-edge network analysis methods. First, markers of the gut-brain axis (intestinal permeability, intestinal inflammation and microbiome) will be reviewed as potential biomarkers of treatment response to probiotics. Second, gene expression studies to evaluate CHOP, a pro-apoptotic endoplasmic reticulum stress marker, and ELISA assays to assess mesencephalic astrocyte-derived neurotrophic factor (MANF) levels in BD patients and controls will be reviewed as biomarkers of response to intranasally administered MANF. MANF is an ER resident protein that promotes cellular resilience. Third, an overview of Th17 cells as a potential target for precision medicine approaches will be reviewed. Finally, causal discovery modeling (CDM) will be introduced as a method for interrogating mania and depression symptom networks to identify high-value treatment targets and BD subtypes. CDM uses a combination of graph theory and machine learning to identify central symptoms – those with the densest causal relationships to other symptoms in symptom networks. It offers the promise of a data-driven approach to determining the richest treatment targets and identifying subgroups of patients with different network structures. The symposium will conclude with a discussion of the promise and challenges of data driven discovery of treatment biomarkers and potential future directions.

USING CAUSAL DISCOVERY MODELING TO INTERROGATE MANIC AND DEPRESSIVE SYMPTOM NETWORKS IN BIPOLAR DISORDER

David Bond**1*, *Rahul Mehta2, Kathleen Miley3, Erich Kummerfeld4*

[1]Johns Hopkins University School of Medicine, 2University of Minnesota, 3Health Partners Institute, [4]Institute for Health Informatics, University of Minnesota

Objective: Network theory proposes that psychiatric syndromes like depression and mania are networks of causally interacting symptoms. Depression and mania are triggered when the activation of one symptom leads to activation of the network via the web of causal relationships between symptoms. Feedback loops between symptoms lead to persistent network activation, making episodes self-sustaining. Persistent network activation is most likely in dense (highly interconnected) networks and when central symptoms (those with numerous connections to other symptoms) are activated.

Methods: Causal discovery modelling (CDM) combines causal modeling theory, graph theory, statistics, and machine learning to generate inferences about causal relationships between symptoms in symptom networks. We used CDM to identify causal relationships in manic and depressive symptom networks. We searched the National Database of Clinical Trials for studies that used the Young Mania Rating Scale and Montgomery-Asberg Depression Rating Scale to measure manic and depressive symptoms in bipolar disorder. We used the Greedy Fast Causal Inference (GFCI) algorithm, implemented in Tetrad 6.9, to learn a partial ancestral graph (PAG) of causal relationships.

Results: We obtained data from 19 studies (N=7269). The manic and depressive symptom networks were both densely connected, especially the depressive network. Feedback loops were identified in both networks. Irritability was an important bridge symptom with dense causal relationships to both the manic and depressive networks.

Conclusion: These findings suggest hypotheses about how causal relationships in manic and depressive symptom networks lead to the perpetuation of mania and depression; and why mania and depression can co-occur.

INTRANASAL MESENCEPHALIC ASTROCYTE-DERIVED NEUROTROPHIC FACTOR (MANF) AS A NOVEL TREATMENT FOR BIPOLAR DISORDER

Benicio Frey**1*, *Mohammad Ali2, Bianca Wollenhaupt-de-Aguiar2, Todd Hoare2, Ram Mishra2*

[1]*Canadian Network for Mood and Anxiety Treatments, 2McMaster University*

Objective: Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an endoplasmic reticulum (ER) resident protein that promotes cellular resilience through modulation of ER stress response. We have recently found that lithium promotes ER homeostasis by increasing MANF gene expression (Abu-Hijleh et al., 2021). Our objective is to develop a new treatment option for individuals with bipolar disorder (BD) using hydrogel intranasal spray to administer MANF, and to further investigate the ER stress response pathway in the blood and postmortem brain tissue of individuals with BD.

Methods: Intranasal delivery of MANF was developed using functionalized starch nanoparticle carriers integrated into a mucoadhesive nanoparticle network hydrogel spray. Intranasal MANF is being tested in an animal model of mania. Gene expression was used to evaluate CHOP, a pro-apoptotic ER stress marker, and ELISA assays to assess MANF levels in the serum of 40 individuals with BD and 55 healthy controls, as well as in postmortem hippocampus brain tissues from 20 BD and 19 controls.

Results: The intranasal delivery of MANF is currently being evaluated in animal models to determine the efficacy of nose-to-brain delivery. Serum MANF protein levels were reduced in individuals with BD in a current depressive episode when compared to individuals with BD in euthymia (p=0.013) and controls (p=0.031). CHOP expression was increased in postmortem hippocampus brain tissues of individuals with BD (P LESS THAN 0.05).

Conclusion: These findings provide further evidence of the association between ER stress and BD.

INTESTINAL MARKERS TO PREDICT THE TREATMENT OUTCOME OF PROBIOTICS IN BIPOLAR DISORDER AND PSYCHOTIC DISORDERS

Magdalini Ioannou**1*, *Jenny Borkent1, Sergio Andreu-Sánchez1, Jingyuan Fu1, Iris Sommer1, Bartholomeus C.M. Haarman1*

[1]*University Medical Center Groningen*

Objective: Abnormal immune responses have been reported in patients with bipolar disorder (BD) and psychotic disorders (PD). What lies at the root of the immune system aberrations, however, is still unclear. Intestinal permeability aberrations and inflammation, along with alterations in the intestinal microbiota, may be a significant factor driving the immune dysregulation in these disorders. Probiotics are thought to be promising candidates to improve patients' symptomatology and functioning using lifestyle interventions. What makes these interventions especially relevant is that there are rational methods to personalize their application with biomarkers that measure intestinal inflammation, microbiome, and permeability.

In a novel randomized controlled trial (RCT) (GUTS, SMRI 18T-004, ZonMw 636320010), we investigate whether intestinal permeability improving probiotics influence symptom severity and cognition in patients with BD or PD, and whether we can personalize treatment with measurements of intestinal inflammation, permeability, and microbiome.

In this presentation we will present for the first time the baseline measurements of this thought-provoking study.

Methods: For this analysis, the baseline measurements of 130 patients that participate in the GUTS RCT and 130 healthy controls matched for age, sex, BMI and income were investigated. Measurements of intestinal inflammation (fecal calprotectin, alpha-antitrypsin), intestinal permeability (LPS binding protein, soluble CD14, serum zonulin and fecal zonulin) were performed using standard ELISA procedures. Intestinal microbiome analysis was performed using metagenomic shotgun sequencing.

Results: Analysis results will be available in March 2023 and will be presented for the first time during the conference. **Conclusion:** The results will be discussed in reflection to the applicability for future treatment personalization for gut targeting treatments for BD, e.g. probiotics, prebiotics and diet interventions.

TH17 CELLS: A POTENTIAL TARGET FOR PRECISION MEDICINE APPROACHES FOR BIPOLAR DISORDER

Carmen Schiweck*[1], *Magdalini Ioannou[2], Benno Haarman[2], Hemmo Drexhage[3]*

[1]Goethe University Frankfurt, [2]University Medical Center Groningen, [3]Erasmus MC Rotterdam

Objective: Patients with Bipolar Disorder (BD) have increased numbers of the pro-inflammatory, and potentially pathogenic T helper (Th)-17 cells (1,2). Interestingly, interleukin (IL)-17A, the major cytokine produced by Th17 cells, has also been associated with suicidality and inflammation in major depressive disorder, but to our knowledge this association has not yet been explored in BD. In addition, it has been shown that short chain fatty acids such as butyrate can reduce IL-17A production by Th17 cells and thereby reduce their pathogenicity, but to date, the effect on Th17 cells of patients with BD is unknown. The aim of this research was two-fold: first, we aimed to explore the association of Th17 cells with specific symptoms of patients with BD for the first time. Second we aimed to investigate the effect of short chain fatty acids on IL-17 production in Th17 cells of patients with BD and healthy controls to their efficacy as new and innovative, potential immunomodulatory strategy.
Methods: Th17 cell numbers and suicidality were assessed in 201 patients with a diagnosis of BD and 140 controls of the MOODINFLAME and GEPRO cohorts. Th17 cells were measured using fluorescence-activated cell sorting and confirmation of BD diagnosis and suicidality was assessed with the MINI neuropsychiatric Interview. Analysis of covariance was performed on Th17 cells, with suicidality as grouping variable, age, sex and BMI as covariates. For the in-vitro experiment, peripheral blood mononuclear cells (5 patients with BD, 8 controls, data collection ongoing) were harvested using Ficoll density gradient centrifugation. Naïve CD4+ T cells were extracted, cultured and differentiated to Th17 cells. IL-17 production was measured in cells exposed to butyrate or only medium.
Results: Patients with BD had higher Th17 cells compared to controls. High risk of suicide was rare in this predominantly euthymic patient group. Results regarding stratification according to sample characteristics including suicidality are currently being analysed and will be presented at the conference for the first time. Preliminary results of cell culture experiments revealed a strong reductive effect of butyrate on IL-17 production in Th17 cells (p LESS THAN 0.05).
Conclusion: Th17 cells are higher in patients with BD, and possible associations with suicidality will be presented. Results on short chain fatty acid exposure indicate a potential beneficial role on Th17 cell pathogenicity.
References: 1. Becking K, Haarman BCM, Grosse L, Nolen WA, Claes S, Arolt V, et al. (2018): The circulating levels of CD4+ t helper cells are higher in bipolar disorder as compared to major depressive disorder. J Neuroimmunol 319: 28–36.
2. Vogels RJ, Koenders MA, van Rossum EFC, Spijker AT, Drexhage HA (2017): T Cell Deficits and Overexpression of Hepatocyte Growth Factor in Anti-inflammatory Circulating Monocytes of Middle-Aged Patients with Bipolar Disorder Characterized by a High Prevalence of the Metabolic Syndrome. from Frontiers in Psychiatry, vol. 8. Retrieved https://www.frontiersin.org/articles/10.3389/fpsyt.2017.00034

PERSONALIZED TREATMENT OF BIPOLAR DISORDER

Martin Alda, Dalhousie University

Symposium Synopsis: There is a growing recognition that management of psychiatric disorders needs to be tailored to individual patients and their clinical and biological profiles -- in contrast to the common practice of trial-and-error. To optimize treatment decisions, psychiatry needs to identify reliable markers of diagnosis, relapse risk, and treatment response. Bipolar disorder is among the conditions with perhaps the greatest need for improved management: it is relatively prevalent, affects young people and runs a lifelong course. Poorly stabilized illness leads to a high risk of suicide and functional decline. The most recent treatment guidelines by CANMAT and ISBD recommend nine first-line and seven second-line maintenance treatments. However, there are no reliable guidelines as to how to choose among these options. The treatment decisions are not easy due to the highly variable, capricious clinical course of the illness, its heterogeneity, as well as poorly understood iatrogenic effects of certain medications. In this symposium, we will present data from the most promising modalities to guide the selection of long-term treatment. These include clinical and genomic patient profiles (M. Alda), electronic digital clinical monitoring (A. Ortiz), lithium magnetic resonance spectroscopy (D. Cousins), and epigenetic and microbiome measures (C. Pisanu).

CLINICAL AND GENOMIC DATA CAN INFORM TREATMENT DECISIONS IN BIPOLAR DISORDER

Martin Alda**1*, *Abraham Nunes1, William Stone1, Paul Grof2, Mirko Manchia3, Janusz Rybakowski4, Leonardo Tondo5*
[1]Dalhousie University, 2University of Toronto, 3University of Cagliari, 4University of Poznan, 5Centro Lucio Bini

Objective: Historically, the search for predictors of response to long term treatment of bipolar disorder (BD) started with clinical variables. After more than five decades of research, the most promising data are those related to the outcome of lithium maintenance. A number of clinical and family history measures associated with the outcome of lithium treatment emerged, many supported by replication studies and meta-analyses (e.g. Hui et al. Acta Psychiatrica Scand 2020). Yet, none of these variables have been tested for their predictive power. Here, we report the results of studies assessing the predictive power of clinical and genomic features.
Methods: In a large multi-site study of lithium treated patients, we used random forest machine learning algorithm to test of out sample predictive power of more than 150 clinical, demographic and family history variables in 1266 patients with BD. A total of 321 patients had available whole-genome genotypes. Using 47,465 directly genotyped SNPs we were able to differentiate prototypical responders (R) and nonresponders (NR) to lithium. Finally, we tested the model trained on lithium response in patients with data on their response to the anticonvulsants lamotrigine and valproate.
Results: Our results showed satisfactory predictive power of the clinical data (AUC ~ 0.8) to differentiate R and NR to lithium. Completely episodic clinical course was the hallmark of lithium responsiveness; a number of additional clinical features predicted the (non)response to both lithium and anticonvulsants. Whole genome genotypes discriminated poorly the two groups of patients in general (AUC ~ 0.57) but had an excellent power to differentiate clinically prototypical R and NR (AUC ~ 0.88). Gene ontology analyses identified four gene groups contributing most of the differentiation; these include G-protein coupled receptor genes, and genes in the muscarinic, amyloid secretase, and histaminergic gene families.
Conclusion: Our results support the possibility of using a combination of clinical and genomic data for optimizing long term treatment of BD once accounting for the disease heterogeneity.

IDENTIFYING PATIENT-SPECIFIC BEHAVIORS TO UNDERSTAND ILLNESS TRAJECTORIES AND PREDICT INDIVIDUAL TRAJECTORIES IN BIPOLAR DISORDER USING PASSIVE SENSING

Abigail Ortiz*[1], *Clara Park[2], Christina Gonzalez-Torres[2], Martin Alda[3], Daniel Blumberger[1], Rachael Burnett[2], Ishrat Husain[1], Marcos Sanches[2], Benoit Mulsant[1]*

[1]University of Toronto, 2Centre for Addiction and Mental Health, 3Dalhousie University

Objective: Several studies have reported on the feasibility of electronic (e-)monitoring using computers or smartphones in patients with mental disorders, including bipolar disorder (BD). While studies on e-monitoring have examined the role of demographic factors, such as age, gender, or socioeconomic status and use of health apps, to our knowledge, no study has examined clinical characteristics that might impact adherence with e-monitoring in patients with BD. Here, we describe our results on adherence to e-monitoring in patients with BD who are participating in an e-monitoring study and evaluated whether demographic and clinical factors would predict adherence to (i) daily self-rating scales; (ii) weekly self-rating scales or (iii) wearable use.

Methods: Eighty-seven participants with BD in different phases of the illness were included. Patterns of adherence for wearable use, daily and weekly self-rating scales over 15 months were analyzed to identify adherence trajectories using growth mixture models (GMM). Multinomial logistic regression models were fitted to compute the effects of predictors on GMM classes.

Results: Overall adherence rates were 79.5% for the wearable; 78.5% for weekly self-ratings; and 74.6% for daily self-ratings. GMM identified three latent class subgroups: participants with (i) excellent; (ii) good; and (iii) poor adherence. Women, participants with a history of suicide attempt, and those with a history of inpatient admission were more likely to belong to the group with good adherence.

Conclusion: Participants with higher illness burden (e.g., history of admission to hospital, history of suicide attempts) have higher adherence rates to e-monitoring. They might see e-monitoring as a tool for better documenting symptom change and better managing their illness, thus motivating their engagement.

ESTABLISHING MULTICENTRE MULTINUCLEAR BRAIN LITHIUM IMAGING IN BIPOLAR DISORDER

David Cousins*[1], *Pete Thelwall[1], Fiona Smith[1], Karthik Chary[1], Letizia Squarcina[2], Paolo Brambilla[2], Marie Chupin[3], Emmanuelle Gourieux[3], Fawzi Boumezbeur[4], Edouard Duchesney[4], R-LiNK Group[5], Frank Bellivier[6]*

[1]Newcastle University, 2Università degli Studi di Milano, 3CATI (Centre pour l'Acquisition and le Traitement des Images), 4Neurospin, CEA, 5https://rlink.eu.com, 6Université de Paris

Objective: The R-LiNK initiate is conducting a multicentre, multinational longitudinal study seeking to identify biomarkers/biosignatures capable of predicting response to lithium treatment in bipolar disorder. Brain lithium distribution, determined using a novel multinuclear imaging techniques (7Li-MRI), was identified as a potential marker but prior to the study initiation, its use was restricted to a small number of expert centres. Here we describe the steps taken to establish, coordinate and harmonise data acquisition and analysis in multiple sites.

Methods: Centres in the R-LiNK network were identified based on imaging platform capabilities and commonalities. Dual tuned 1H/7Li volume RF coils were procured and installed in each centre, together with bespoke test-objects (lithium phantoms) representative of the human brain. Acquisition sequences were optimised based on those previously published by our group, with harmonisation work conducted using the standardised phantoms. Data collection from enrolled patients proceeded in accordance with study protocol, supported by centralised sanity and quality

control checks. Acquisition processes were collated into standard operating procedures for Siemens and Philips MRI platforms. **Results:** The application of standard operating procedures enabled the collection of 7Li-MRI data (n**>** 45) from six centres as part of a longitudinal treatment study. Implementation of this novel imaging technique presented challenges, but these were surmountable and did not delay the project objectives. Close coordination between the lithium imaging and standard proton MRI work-package teams within R-LiNK, together with clear and responsive communication from participating sites was central to this success. Centralisation of data collection has proved to be advantageous in the development of novel processing pipelines. **Conclusion:** The R-LiNK initiative has established a network of centres capable of implementing 7Li-MRI as a potential marker for response to lithium as well as for future studies investigating the actions of lithium in various neuropsychiatric conditions. The development of standardised procedures and test-objects for harmonisation paves the way for an expansion of this imaging network to better understand this most important of medications.

MULTIOMICS ANALYSIS OF BLOOD METABOLOME, GUT MICROBIOTA AND GENOME-WIDE METHYLATION TO IDENTIFY BIOLOGICAL SIGNATURES OF RESPONSE TO LITHIUM IN BIPOLAR DISORDER

Claudia Pisanu*****[1], *Raffaella Ardau[2], Luigi Atzori[1], Bernardo Carpiniello[1], Donatella Congiu[1], Caterina Chillotti[2], Maria Del Zompo[1], Mirko Manchia[1], Aldo Manzin[1], Anna Meloni[1], Vanessa Palmas[1], Pasquale Paribello[1], Marco Pinna[1], Cristina Piras[1], Giovanni Severino[1], Martina Spada[1], Alessio Squassina[1]*

[1]*University of Cagliari, 2University Hospital Agency of Cagliari*

Objective: Bipolar disorder (BD) is among the major determinants of disability worldwide, with a very high socio-economic burden. The complex underlying neurobiology and the high heterogeneity in clinical response to the first-line treatments for BD, including lithium, severely impact on the management of this disorder, strongly calling for innovative integrated precision approaches. We will present results from two studies aimed at applying integrative analyses of different types of omics profiles (plasma metabolome, gut microbiota and genome-wide methylation) that represent important players in the relationship between genetic and environmental factors predisposing to psychiatric disorders and clinical response to psychotropic drugs.
Methods: In the first study we explored the role of gut microbiota and its possible interactions with the host metabolome in response to lithium in BD. To this end, we selected 50 patients with BD under lithium treatment at the time of recruitment and characterized as responders or non-responders using the “Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder” (Alda scale) and 50 patients treated with other mood stabilizers. The characterization of the blood metabolome (with nuclear magnetic resonance spectroscopy) and the gut microbiota composition (sequencing of the V3 and V4 hypervariable regions of bacterial 16S rRNA) are undergoing. In the second study, whole blood genome-wide methylation is being assessed with Infinium MethylationEPIC arrays in an extended sample of 70 patients with BD under lithium treatment and 30 controls. Data are analyzed to identify differentially methylated regions between diagnostic and lithium response groups. In addition, we will present data on differences in epigenetic age among studied groups and integrate them with other aging hallmarks measured in the same patients (leukocyte telomere length and mitochondrial DNA copy number), to explore the hypothesis of accelerated cellular aging in BD and of a potential protective effect of lithium treatment.
Results: We expect to find distinctive profiles of the gut microbial community, the host metabolome and methylation in patients exposed to lithium compared to patients treated with other mood

stabilizers or controls, as well as to identify specific biosignatures correlated with the clinical response. In addition, by applying integrative approaches to this multi-omics dataset using the Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO) method, we expect to identify multi-omics biomarker panels predictive of lithium response. **Conclusion:** By taking advantage of a multiomic approach applied to a deeply phenotyped sample of longitudinally followed-up patients, our studies aim to identify biological signatures underlying the clinical response to lithium.

5:00 p.m. - 6:30 p.m.
Symposia Concurrent V

UPDATE ON TREATMENT RESISTANT DEPRESSION

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: Treatment-resistant depression (TRD) is common and associated with multiple serious public health implications. A consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist. Instead, a plethora of definitions have been proposed, which vary significantly in their conceptual framework. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted the most used definition of TRD (i.e., inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment). Evidence indicates that a subset of MDD patients presenting with TRD may exhibit a failed antidepressant response as a consequence of a suboptimal bioavailability of the administered antidepressant, due to rapid metabolizer status. Identifying biomarkers and biosignatures associated with TRD as well as treatment response is an important future research vista. Intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) are established as efficacious in the management of TRD. Several second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine XR) are proven effective as antidepressant augmentation treatments in partial responders, but only the olanzapine-fluoxetine combination has been studied in FDA-defined TRD. The next decade can reasonably expect the regulatory approval of innovative pharmacological treatments targeting systems implicated in the pathophysiology of depression. Non-üphasrmacological treatment options are also available including both psychotherapy as well as ECt or TMS. There is as yet no clear distinction in the algorithm when to place these treatment modalities.

TREATMENT RESISTANT DEPRESSION: TREATMENT CONSIDERATIONS

Roger McIntyre**1*

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University of Toronto

Objective: To discuss the definition of treatment-resistant depression, the limitations of current definitions of treatment resistant depression, and to discuss treatment options used in major depressive disorder.

Methods: Methods are through a Delphi method and review of the literature.

Results: The results are treatment resistant depression does not have a consensus definition. Multiple definitions exist. Moreover, not a large number of treatments are available for major depressive disorder that is treatment resistant. In this program we are going to review the treatments for treatment resistant depression. **Conclusion:** A consensus definition of treatment resistant depression is required. Additionally, multiple treatment strategies are being evaluated which will be presented at this conference.

GENETIC BASIS OF TREATMENT RESISTANT DEPRESSION

Alessandro Serretti1, Chiara Fabbri1, Dan Rujescu**2*

[1]University of Bologna, 2German Society for Biological Psychiatry

Objective: Treatment resistant depression is largely modulated by genetic factors.

Methods: Several antidepressants already have a pharmacogenetic precaution/warning in their labeling for risk of side effects or interactions in CYP2D6 poor metabolizers. Conversely, rapid metabolizers may need higher doses. Other pharmacodynamic gene variants have been suggested, and, based on those evidence, over 40 commercially available pharmacogenetic assays have been implemented and their clinical applicability. While CYP polymorphisms are likely to inform about response/tolerability rates and reduce costs, single pharmacodynamic variants have little or no clinically relevant effects.

Results: More recently, the combined effect of polygenic risk scores has shown much more promising results in terms of reliability and possible drug choice and repurposing, but still explaining a relatively low variance of treatment resistant depression.

The integration of genetic information with clinical data and other biomarkers is a possible strategy to develop future more effective predictive algorithms.

Conclusion: Genetic factors are therefore at present already explaining a part of treatment resistant depression, but integrated models including further genetic and clinical predictors are needed.

DEVELOPMENT OF FAST ACTING ANTIDEPRESSANTS FOR TRD

Siegfried Kasper**1*

[1]Center for Brain Research

Objective: The development of fast acting antidepressants, specifically for treatment of so-called "TREatment resistant depression" will be presented, starting from clinical observations via randomised trials and underlying biological mechanisms

Methods: A literature overview will be given including own findings as part of Multicenter trials as well as own neuroimaging findings on esketamine.

Results: Since this is an overview, the available results published in the literature will be given

Conclusion: By the conclusion of the lecture the audience will be able to understand the development of rapid acting antidepressants with a specific focus on TRD.

NON-PHARMACOLOGICAL AND LONG-TERM TREATMENTS FOR TRD

Johan Saelens1, Anna Gramser1, Victoria Watzal1, Rupert Lanzenberger1, Christoph Kraus**1*

[1]Medical University of Vienna

Objective: Treatment strategies for treatment resistant depressions converge in repetitive trials of pharmaceutical substances with unclear maintenance treatments. Despite the successful establishment of novel rapid acting substances, several disadvantages such as adherence, side-effect profiles or long-term efficacy in relapse prevention remain. In addition, efficacious neuromodulatory treatments such as electroconvulsive therapy have their place in acute and maintenance treatment. However, in the treatment pathway for TRD, the position for other brain stimulation treatments such as transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) and vagus nerve stimulation

(VNS) remain unclear. The central aim of this talk is to present existing evidence on efficacy of neuromodulatory treatments in TRD and to compare efficacy to pharmaceutical treatment strategies. **Methods:** To compare efficacy of existing antidepressant treatments for TRD, we conducted a systematic literature research and network meta-analysis on all existing treatment modalities in TRD (as defined by non-response to two antidepressant treatment trials). Analysis was conducted in R with the netmeta package. **Results:** For the comparative network meta-analysis, 6698 abstracts were screened and 64 randomized, sham- or placebo-controlled trials with a total of 9976 patients were included. Six out of 28 antidepressant therapies in TRD had a significant higher response rate compared to placebo (ECT (OR = 13.78), minocycline (OR = 6.5), theta-burst stimulation (OR = 5.02), rTMS (OR = 4.48), ketamine (OR = 3.31) and aripiprazole (OR = 1.9). Treatments are ranked based on their probability of being the treatment with the highest response rate, with ECT ((p = .85) and theta-burst (p = .84) leading the field. **Conclusion:** In this study, we demonstrate comparative and ranked efficacy of currently available and investigational antidepressant treatments in TRD. Neuromodulatory interventions such as ECT and TMS ranked highest as far as treatment response of acute episodes are concerned. The results of this trial together with a second comparative meta-analysis on efficacy of DBS will be presented in the talk. These novel results will be placed into the context of the current treatment pathway in TRD. The audience will learn about acute and maintenance treatment strategies with neuromodulatory techniques and treatment selection in the daily clinical practice.

INTERNATIONAL STUDIES ON BRAIN MATURATION AND DEVELOPMENTAL PSYCHOPATHOLOGY: FROM BIRTH TO ADULTHOOD

Paolo Brambilla, University of Milan

Symposium Synopsis: Adolescence represents a period of increased opportunity and vulnerability, during which a complex confluence of genetic and environmental factors influences brain growth trajectories, cognition, emotion regulation and mental health outcomes.
In this symposium, international studies focusing on the link between environment, genes, disease-related behaviour and the brain, using a multidisciplinary perspective bridging epidemiology, genetic, neuroimaging and psychopathology will be presented.
Specifically, we will discuss how genetic and environmental risks for developmental disorders translate to brain function, structure and connectivity and how this in turn – ultimately- translated to emotion regulation and behavioural development. In addition, we will explore examples of the long-term psychological and behavioural sequelae in individuals with typical and atypical development, particularly focusing on clinical phenotypes associated with emotional dysregulation and major psychiatric disorders such as schizophrenia, bipolar disorders, major depression and anxiety disorders. Ultimately, we will discuss potential origins transdiagnostically characterising these disorders, associating early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
In addition, while most treatment studies focus on recovery within weeks or months, the long-term course of the above-mentioned disorders remains less established. In this symposium it will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.
Finally, the key role of genetic and neurobiological markers to improve the early detection and personalised treatment of developmental disorders will be analysed, mentioning the role of machine learning techniques and AI.

LONGITUDINAL NEONATAL BRAIN DEVELOPMENT AND ENVIRONMENTAL CORRELATES OF INFANT OUTCOMES FOLLOWING PRETERM BIRTH

Lucy Vanes1, Sunniva Fenn-Moltu1, Laila Hadaya1, Sean Fitzgibbon1, Lucilio Cordero- Grande1, Anthony Price1, Andrew Chew1, Shona Falconer1, Tomoki Arichi1, Serena J. Counsell1, Joseph V. Hajnal1, Dafnis Batalle1, A. David Edwards1, Chiara Nosarti**1*

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Objective: To characterise longitudinal development of neonatal regional brain volume and functional connectivity in the first weeks following preterm birth, sociodemographic factors, and their respective relationships to psychomotor outcomes and psychopathology in toddlerhood.

Methods: We studied 121 infants born preterm (i.e., before 37 completed weeks of gestation) who underwent magnetic resonance imaging shortly after birth, at term-equivalent age, or both. Longitudinal regional brain volume and functional connectivity were modelled as a function of psychopathology and psychomotor outcomes at 18 months.

Results: Better psychomotor functioning in toddlerhood was associated with greater relative right cerebellar volume and a more rapid decrease over time of sensorimotor degree centrality in the neonatal period. In contrast, increased 18-month psychopathology was associated with a more rapid decrease in relative regional subcortical volume. Furthermore, while socio-economic deprivation was related to both psychopathology and psychomotor outcomes, cognitively stimulating parenting predicted psychopathology only.

Conclusion: Our study highlights the importance of longitudinal imaging to better predict toddler outcomes following preterm birth, as well as disparate environmental influences on separable facets of behavioural development in this population.

INTERNALIZING AND EXTERNALIZING SYMPTOMS TRAJECTORIES FROM CHILDHOOD TO EARLY ADULTHOOD, THROUGH ADOLESCENCE, IN CLINICAL AND GENERAL POPULATION SAMPLES: RESULTS FROM THE REMIND PROJECT

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Objective: The REMIND project aimed at identifying specific clusters of symptom trajectories in internalizing and externalizing areas and evaluating their different exposure to risk factors in a developmental perspective.

The involved subjects from a general and a help-seeking population were evaluated at pre-adolescence (T0), adolescence (T1) and young adulthood (T2).

Methods: Psychopathological symptoms were measured through ASEBA questionnaires at the 3 time points, also neurobiological markers were collected. A Multivariate Finite Mixture Model (MFMM) was used to estimate specific developmental clusters considering T1 and T2 symptoms. We evaluated whether belonging to a specific developmental cluster was associated with sociodemographic characteristics, environmental risks (i.e., perinatal complications and stressful life events) and psychopathological symptoms measured at T0.

Results: Anxious-Depressed and Somatic scales showed 3 developmental clusters (“stable high”, “stable low”, “low-to-high”), Withdrawn-Depressed scale showed 2 developmental clusters (“stable high”, “stable low”). Individuals belonging to the ‘stable high’ internalizing developmental clusters,

presented higher emotional/behavioral dysregulation during preadolescence, with the co-occurrence of higher internalizing and externalizing problems.
Conclusion: The longitudinal perspective suggested the presence of specific manifestations trajectories from adolescence to adulthood. The presence of clinical level of psychopathology during preadolescence is a strong predictor of its persistence through lifespan, highlighting both homotypic and heterotypic continuities. These data strongly suggest the importance of accounting for both homotypic and heterotypic continuity in psychopathological traits when planning interventions.

TRAJECTORIES OF BRAIN STRUCTURE IN THE MAJOR MENTAL DISORDERS: FINDINGS FROM LONGITUDINAL STUDIES IN MDD, BD AND SZ

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Objective: Major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder (schizophrenia and schizoaffective disorder) overlap in symptomatology, risk factors, genetics, and other biological measures. It remains unclear whether there are shared regional grey matter volume alterations across these disorders, which past and current phenotypic factors and what course of illness moderate these alterations. We wanted to identify shared but also distinct grey matter volume alterations across patients compared to age- and sex-matched healthy controls.
Methods: Age- and sex matched healthy controls (n=110), DSM-IV-TR diagnosed major depressive disorder (n=110), bipolar disorder (n=110), and schizophrenia spectrum disorder patients (n=110), drawn from a sample of N=1927 were included. Grey matter volume (3T magnetic resonance imaging) was compared between HC and patients. We applied a conjunction analysis to identify shared grey matter volume alterations across the disorders. To identify potential origins of transdiagnostic GMV clusters, we associated them with early and current risk and protective factors, psychopathology, neuropsychology and past course of illness.
Results: Common to all diagnoses (vs. healthy controls), we identified grey matter volume reductions in the left hippocampus. This cluster was associated with stressful life events, the neuropsychology factor working memory/executive functioning, and with global assessment of functioning. Differential effects between groups were present in the bilateral frontal operculae and left insula, with volume variances across groups highly overlapping.
Conclusion: There are shared grey matter volume alterations in the left hippocampus across the major mental disorders. The hippocampus is a central network hub, orchestrating a wide range of mental functions. Our findings underscore the need for a novel stratification of mental disorders, besides categorical diagnoses.

COURSE PREDICTION OF DEPRESSION AND ANXIETY DISORDERS IN THE NESDA PROJECT

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Objective: While most treatment studies focus on recovery within weeks or months, the long-term course of depression and anxiety disorders remains less established. We examined the 2-6 year course trajectories of a large cohort of persons with depression and anxiety disorders, and evaluate whether we can predict chronicity by sociodemographic, clinical and biological data
Methods: Using 9-year longitudinal data from the Netherlands Study of Depression and Anxiety (NESDA, n=2981, 66% female, baseline mean age=42 yrs), we examined the naturalistic course of depression and anxiety disorders.

Results: 58% of the persons with a current depressive and/or anxiety disorder at baseline reported chronic episodes (24 months with symptoms without remission) over 6 years of follow-up (Verduijn et al. BMC Med 2018). Also switching between disorders was frequent. This is despite the fact that many persons in the study did receive pharmacotherapy, psychotherapy or a combination of these. For instance, after 6 year, also, when examining 9-year patterns in symptom severity reports, it appears that 63% of the sample belongs to the symptom cluster group that showed only a minimal improvement (Solis et al. J Affect Dis 2021). Machine learning analyses in which we considered basic clinical, psychological, lifestyle and biological predictors of course, yielded a significant prediction but with only moderate prediction value (accuracy 68%, Dinga et al. Transl Psychiatry 2018). Adding epigenetic or proteomic data did further improve predictive value (accuracy 75-75%, Clarck et al. Mol Psychiatry 2019; Habets et al. in progress). **Conclusion:** Unfortunately, chronicity appeared more the rule than the exception. Strongest predictors of chronicity of depressive and anxiety disorders are clinical baseline characteristics (including severity indicators). However, certain biological parameters did add additional predictive value. It will be presented what these findings tell us about the underlying biological mechanisms of chronicity. It will also be discussed what the implications of the overall chronicity findings are for daily mental health practice in terms of chronic disease management opportunities.

NEUROSCIENCE BASED NOMENCLATURE

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Symposium Synopsis: Symposium synopsis: neuroscience based nomenclature: a country experience:
Neuroscience based Nomenclature is a new classification system for psychotropic agents and now it (neuroscience based nomenclature), many years spent for introduction. It is now time for using NbN for clinical purposes. There is not clear information about how NbN is relevant in clinical use and will guide the clinicians, how different dosing and different pharmacology will change our clinical practice and use of NbN in psychosis and giving guidance for the clinicians. The implementation of NbN is an issue and the experience about implementation of NbN in specific country will be shared. The psychiatrists will be separated into two groups: child and adolescent and adult groups. Regarding the use of NbN the groups will differ in awareness, knowledge, use in practice and perspectives on NbN.

NBN IN THE TREATMENT OF PSYCHOSIS

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Objective: For the last seven decades, medications used to treat psychosis with regulatory approval based on randomized controlled efficacy studies have been dopamine receptor blockers. These medications have been called “antipsychotics”. However, this class of medications has also been used for and received regulatory approval for mania, bipolar depression, unipolar depression, tic disorders, indications that have nothing to do with psychosis. This indication-based nomenclature (is confusing for all stakeholders.

Methods: Review of the principles and procedures of neuroscience-based nomenclature (NbN) and how this approach pertains to treatments for psychosis. This presentation will outline the classification of dopamine blockers and partial agonists, as well as of other, emerging medications for psychosis in NbN.

Results: NbN proposes to categorize treatments for psychosis mechanistically based on the proximal effects as either blockers or enhancers with each of these proximal effects being able to lead to either

excitation or inhibition downstream. Examples of existing and emerging mechanisms of action for the treatment of psychosis are given.

Conclusion: Neuroscience-based nomenclature is a neuroscience and mechanism-based classification system of psychotropic drugs that will help with educating clinicians, patients and families about distinct actions of medications that map onto pharmacological mechanisms and thereby expected indications, benefits and adverse effect risks. Given that agents without dopamine receptor blocking effects are close to regulatory approval for schizophrenia, this NbN-based classification system is even more important for drugs for psychosis. This classification system will need to incorporate in a simple and straightforward way the complexities of proximal postsynaptic as well as presynaptic activity that can lead to either similar or opposite downstream effects.

IMPLEMENTATION NEUROSCIENCE BASED NOMENCLATURE IN TURKEY

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Objective: Neuroscience Based Nomenclature has been introduced more than a decade and even a second revision is published. The use of Neuroscience based Nomenclature is still limited both by adult psychiatrists and child and adolescent psychiatrists. The aim of the study is to understand the use of Neuroscience based Nomenclature among both adult psychiatrists and child and adolescent psychiatrists.

Methods: The questionnaire is prepared to give both adult psychiatrists and children and adolescents to understand the familiarity, purpose of use, their evaluations on various aspects are measured. Both groups are also compared.

Results: The knowledge of Neuroscience Based Nomenclature is limited among both groups. Both groups were not clear about the purpose of use of Neuroscience based Nomenclature .There are not enough information about how NbN is relevant in clinical use and will guide the clinicians how different dosing and different pharmacology will change our clinical practice and use of NbN in psychiatric disorders and giving guidance for the clinicians

Conclusion: The Knowledge of Neuroscience Based Nomenclature and Use of Neuroscience Based Nomenclature especially in clinical practice is very limited among both adult psychiatrists and child and adolescent psychiatrists. The barriers in the use of Neuroscience Based Nomenclature needs clear guidelines to overcome them.

NEUROSCIENCE-BASED NOMENCLATURE (NBN) - INTRODUCTION

Joseph Zohar*[1]

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Objective: Psychopharmacology has advanced remarkably since the emergence of the first psychotropics in the 1950s. However, the pharmacological "language" still lags behind the new advances, leaving clinicians and patients with a disease-based terminology ("antipsychotics", "anxiolytics", "antidepressants'', etc) that is noninformative, stigmatizing and at times misleading. Neuroscience-based Nomenclature (NbN) is a pharmacologically-driven nomenclature, aiming to describe psychotropics through their neurobiological profile. Its main goal is to encourage more precise prescribing, help clinicians make rational and informed treatment choices and decrease patient stigma.

Methods: Chairing the symposium, Prof. Zohar will introduce the NbN concept, demonstrating the need for a new nomenclature amongst clinicians, trainees and patients. He will describe NbN's unprecedented development which was led by 5 major neuropsychiatric organizations (ECNP [European College of Neuropsychopharmacology], CINP [International], ACNP [American], AsCNP

[Asian], and IUPHAR [International Union of Basic and Clinical Pharmacology]), and will present its scope and coverage so far.

Results: NbN describes psychotropics through their mechanism, allowing for a broader understanding of treatment rationale, allowing a clearer view of the similarities and differences between medications and helping better planning of the "next pharmacological steps".

Conclusion: Neuroscience-based Nomenclature is an alternative classification system that strives to create a more scientific and precise pharmacological "language". This terminology might encourage a better understanding of psychopharmacology, help maximize the use of the current pharmacological tools available, and finally incorporate the vast knowledge available to day-to-day practice.

DIFFERENT DOSAGE DIFFERENT PHARMACOLOGY (DDDP)

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Objective: Viewing medications through the "lens" of pharmacology, rather than indication, enables us to understand the underlying mechanism of each drug in a deeper level. The NbN way of thinking reveals that some medications act in differently in the pharmacodynamic level, depending on dosage, and therefore might serve different clinical uses at low dose and at full dose.

Methods: The talk will present some examples of using a medication at low dose for a certain purpose (e.g., low dose aripiprazole for the augmentation of depression), and full dose for an entirely different indication (e.g., aripiprazole for psychosis), while illuminating the pharmacological difference between low vs. full dose, and the clinical importance of distinguishing between these differences.

Results: Looking at the DDDP (Different Dose Different Pharmacology) concept illustrates how taking into consideration the dose of the medication has profound relevance, and how this difference might contribute to clinical practice and the research field alike.

Conclusion: Since continuous NbN contributes to a deeper understanding of psychopharmacology. the more precise our "language" is, the better is our ability to use the pharmacological tools available. DDDP is an example to where this understanding might extend.

TRANSLATING PSYCHIATRIC GENETICS TO CLINICAL APPLICATIONS WITH NOVEL STATISTICAL AND MACHINE LEARNING APPROACHES

Ole Andreassen, University of Oslo

Symposium Synopsis: With the advent of large-scale datasets, the field of psychiatric genetics is moving forward to an era of precision medicine to make individualized predictions. This is becoming possible with the development of novel statistical methods and machine learning techniques, leading to rapid new discoveries, and advancing the field towards clinical applications. In this symposium, we will present and discuss novel statistical methods and applications of machine learning principles in the context of precision medicine and psychiatric genetics that pave the way forward to clinical applications. Specifically, we will showcase a series of methods that we have developed for statistical genetics – boosting genetic discovery using an empirical Bayes approach, development of subject-specific trajectories using longitudinal genome-wide association studies, discovery of underlying biologically-relevant gene sets, and multimodal hazard analysis framework for predicting age of onset of different disorders. Using these novel statistical methods, we will not only present the conceptual foundations of these tools, but ground these in a clinically relevant framework and showcase how using these tools can lead to clinically relevant translational science. Speakers from Asia, Europe and North-America will cover new findings in relevant topics, including clozapine metabolism and clozapine-induced agranulocytosis, identification of gene-sets with greater biological specificity

associated with mental illness, providing new insights into the pathobiology of complex polygenic disorders, improvements in prediction performance of polygenic hazard score models, and longitudinal findings highlighting how the effect of SNPs change with time to reveal factors relevant for development of mental illness applying longitudinal cohorts.

SHARED GENETIC ARCHITECTURE BETWEEN CLOZAPINE METABOLISM, WHITE BLOOD CELL COUNTS, AND AGRANULOCYTOSIS

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Objective: Clozapine is the most effective antipsychotic drug, but its use is limited due to hematological side effects, characterized by a reduction of white blood cells (WBC) including potential life-threatening agranulocytosis. Clozapine´s adverse effect on WBC is likely related to its metabolism. Still, it is not possible to predict or prevent the risk of agranulocytosis with current therapeutic clozapine monitoring methods. Genome-wide association studies (GWAS) of clozapine metabolism and clozapine-induced agranulocytosis have identified only a few genetic loci. However, applying novel statistical genetics approaches could reveal more of the shared genetic etiology of clozapine metabolism and clozapine-induced agranulocytosis. We utilized the conditional false discovery rate (condFDR) method to increase power for genetic discovery of clozapine metabolism and clozapine-induced agranulocytosis, by conditioning on WBC counts.

Methods: We used the largest available GWAS summary statistics for clozapine metabolism (clozapine-to-norclozapine ratio), clozapine-induced agranulocytosis, and WBC counts. To boost discovery of genetic variants associated with clozapine metabolism as well as clozapine-induced agranulocytosis, we applied the condFDR method to identify overlapping single nucleotide polymorphism (SNP) associations across traits. The test statistics of separate GWAS is re-ranked in a primary trait (clozapine metabolism or clozapine-induced agranulocytosis) conditional on the associations in a secondary trait (WBC counts), thereby increasing discovery of trait-associated SNPs. For replication analyses in an independent sample, we used summary statistics from a GWAS on WBC counts in an East Asian sample. For SNPs identified to be significantly (condFDR < 0.01) associated with clozapine metabolism or clozapine-induced agranulocytosis, we tested for association with measures of clozapine metabolism and granulocyte levels in a Norwegian sample of 392 clozapine-treated individuals.

Results: After conditioning on WBC counts, we identified three novel loci associated with clozapine metabolism (condFDR), and six novel loci associated with clozapine-associated agranulocytosis. The majority of the identified loci replicated using the independent WBC count GWAS, and they were associated with clozapine-related measures in the sample of clozapine-treated individuals.

Conclusion: Our findings of shared genetic variants influencing clozapine metabolism, WBC counts, and clozapine-induced agranulocytosis may form the basis for developing prediction models for severe adverse effects of clozapine.

THE MIXER TOOLBOX FOR UNRAVELING GENETIC ARCHITECTURE OF COMPLEX TRAITS

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Objective: Genome-wide association studies (GWAS) are increasingly successful in discovering genomic loci associated with complex human traits and disorders, yet biological interpretation of these results and their translation into accurate and actionable polygenic prediction tools remains challenging. Based on GWAS results, the MiXeR framework has previously allowed us to quantify the polygenicity of complex traits, and the degree of polygenic overlap between traits. In this talk I will give an overview of these methods and introduce two new extensions: (1) GSA-MiXeR, allowing the quantification of partitioned heritability and fold enrichment for small gene-sets, and (2) MiXeR-Pred, a tool for calculating polygenic risk scores that leverage polygenic overlap between traits for improved prediction accuracy.

Methods: GSA-MiXeR applies stochastic gradient-based log-likelihood optimization to fit a model of gene-set heritability, evaluating its fold enrichment over a comprehensive baseline model to account for MAF- and LD-dependency of genetic effects, and for differential enrichment of functional categories, thus taking into account the unique genetic architecture of each trait, while also controlling for linkage disequilibrium (LD) between variants. MiXeR-Pred tool computes enhanced polygenic risk scores, building on the cross-trait MiXeR model to compute the posterior effect size for each trait. This approach differentiates between shared and trait-specific genetic variates using the bivariate distribution of GWAS z-scores, and the estimated pattern of genome-wide overlap between the traits.

Results: In both simulated and real data, we show GSA-MiXeR's capability to reorder gene-sets in a way that promotes smaller gene-sets (with 10 genes or less) while yielding an equivalent or higher replication rate compared to current standards in the field. For schizophrenia, we show that calcium channel function gene-sets had greater fold enrichment than larger gene-sets related to post-synaptic functioning; additionally, the top two most fold enriched gene-sets implicated in GSA-MiXeR analysis were related to dopaminergic neurotransmission, the leading theory of schizophrenia pathogenesis. Using MiXeR-Pred, we show how the latest GWAS of schizophrenia can improve the accuracy of predicting the onset of bipolar disorder in an independent sample, while at the same time reducing the number of SNPs used for prediction.

Conclusion: Our findings illustrate that GSA-MiXeR provides the granularity required to map GWAS tested findings to potentially more informative neurobiological processes which can be experimentally, thus facilitating better characterization of the pathobiology of schizophrenia with potential for identifying new druggable targets and clinical sub-groups. Improved prediction accuracy of the MiXeR-Pred tool is an important step in towards incorporating more accurate polygenic prediction into the MiXeR framework.

POLYGENIC HAZARD SCORE MODEL TO PREDICT AGE OF ONSET OF ALZHEIMER'S DISEASE IN EUROPEAN POPULATIONS

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Objective: Polygenic hazard score (PHS) models are being used to estimate age-dependent genetic risk of various diseases including Alzheimer's disease (AD). The original PHS model for predicting the age of AD onset included 31 common variants and APOE ε2/ ε4 alleles [1]. Here, our aim is to the predictive ability of the PHS model and validate the updated model using genotyping data from

the European Alzheimer and Dementia Biobank (EADB) which includes cohorts from several countries across different regions of Europe. **Methods:** EADB samples whose age of onset (for cases) or age of last follow-up (for controls) are lower than 60 years are excluded resulting in N= 14195 cases, 16956 controls. We split this data into 80% for training and 20% for test data. For developing EADB model we applied genome-wide filtering using existing genome-wide association study (GWAS) of EADB data for AD [2]. We have eliminated single-nucleotide polymorphisms (SNPs) with p-value >10-5. The remaining 12631 candidate SNPs were used for the development of the new PHS model. Training for developing the new model was done via stepwise regression framework as proposed in [1]. As a result, 94 candidate SNPs (including APOE 2/4 alleles) were identified and then incorporated into the Cox proportional hazards model. **Results:** We have evaluated the performance of the new model using the test data. We have plotted corresponding Kaplan Meier curves and Cox regression estimates of the risk groups classified using PHS calculated using both models (for both the original model and the new model). We then calculated the Hazard ratio (HR) between risk groups such as HR of the samples who are in the highest 20 percent with respect to PHS to the lowest 20 percent (HR80/20) and similarly, we calculated HR98/50. The new EADB model surpassed the original model in prediction performance: HR80/20 increased to 3.22 from 2.42 in the original model, and HR98/50 increased to 4.59 from 3.41 in the original model. Furthermore, in the new model, the concordance index of PHS scores increased to 0.65, compared to 0.62 for the original model. **Conclusion:** Preliminary results showed increased prediction performance with the new EADB PHS model compared to the original PHS model. The performance may be further improved by using Lasso Regression, and sex-dependent data. Together, the presented findings indicate that the PHS model for predicting AD has the potential for clinical utility. **References:** [1] Desikan, Rahul S., et al. "Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score." PLoS medicine 14.3 (2017): e1002258. [2] Bellenguez, Céline, et al. "New insights into the genetic etiology of Alzheimer's disease and related dementias." Nature genetics 54.4 (2022): 412-436.

FAST AND EFFICIENT MIXED-EFFECTS ALGORITHM (FEMA) FOR GENOME-WIDE ASSOCIATION STUDIES (GWAS) OF LONGITUDINAL PHENOTYPES

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Objective: Longitudinal data are critical for advancing our understanding of causal mechanisms of complex human diseases. Compared to cross-sectional data, longitudinal dataset provides a wealth of information on subject-specific temporal trajectories of different phenotypes and development of diseases, like psychiatric disorders. While large longitudinal population data have recently become available, there are numerous challenges in performing genome wide association studies (GWAS) for trajectories of phenotypes. We have developed the FEMA-GWAS, a novel analytical tool that allows nuanced analyses of longitudinal phenotypes as well as linear and non-linear interaction with age/time and show results from different phenotypes highlighting how we can leverage trajectories of phenotypes to make subject-specific predictions in mental disorders.
Methods: FEMA-GWAS builds upon FEMA, a recently developed computationally efficient solution to performing mixed effects analyses, enabling the analysis of non-independent observations. For

FEMA-GWAS, we extend FEMA to perform linear and non-linear interaction of each single nucleotide polymorphism (SNP) with time and sex, thereby revealing novel associations of different SNPs with longitudinal phenotypes. We have applied FEMA-GWAS to height, weight, and BMI from the Norwegian mother, father and child cohort study (MoBa), and cortical thickness from the Adolescent Brain Cognitive Development (ABCD) and the UK Biobank datasets.
Results: Our results reveal novel loci that are associated with longitudinal trajectories of height, weight, and BMI in children (from birth to adolescence), with change in cortical thickness during adolescence (ABCD), and with change in cortical thickness during mid-life (UK Biobank). Importantly, we discovered novel loci that show significant SNP×age interaction effect, highlighting how the effect of SNPs change in different periods of time. Further, using these discoveries, we present data on constructing subject-specific precision norms, which can help make predictions on susceptibilities to developing psychiatric illnesses.
Conclusion: We have developed a powerful new tool that can be used for the analysis of genetics of non-independent observations. Using FEMA-GWAS, we discovered promising genetic leads that can help identify individuals who deviate from the normative genetically determined developmental trajectories. This method of identifying individuals at risk for various psychiatric disorders can open up possibilities of early intervention targeting modifiable environmental factors. It also opens up the possibilities of clinical translation by leveraging longitudinal clinical information and genetics in making subject-specific genetically adjusted predictions, thereby bringing us closer to precision psychiatry.

PSYCHIATRIC ELECTROPHYSIOLOGY AS ADD-ON TOOL IN THE MANAGEMENT OF ADDICTION DISORDERS

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Symposium Synopsis: Addiction is a worldwide health problem, still presenting large relapse rates despite decades of research and treatment programs including withdrawal, medication and psychosocial support. Neurophysiological tools (such as qEEG, cognitive event-related potentials, the neuroimaging-guided neurofeedback) are tools to offer new perspectives regarding pathophysiological mechanisms triggering diverse forms of addictions, to monitor states of the disorder and to develop new add-on tools for treatment as well as for prevention. In this symposium, we will furnish up-to-date evidence about new and complementary neurophysiological ways to face with addictive disorders. QEEG studies point at altered brain electric states in subjects with addictions. The investigation of differences and similarities across disorders provide insight into differential pathophysiological aspects that may be relevant for the treatment of dual diagnoses. Cognitive potentials are used to monitor patients during addiction treatment programs and may be such as helpful for predicting treatment outcomes. Neurophysiology based treatments neurofeedback are novel options to augment and improve standard care of patients with addiction including related neurophysiological parameters that may serve as biomarkers to predict clinical short and long-term effects. In summary psychiatric electrophysiology is of increasing relevance not only for basic brain research but also as a contribution to diagnostic and treatment decisions, complementing treatment options in psychiatry.

QEEG CORRELATES OF ADDICTION IN BIPOLAR DISORDER

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Objective: High rates of alcohol and substance abuse have been found in patients diagnosed with bipolar disorder. This study aims to explore the electrophysiological differences in addicted bipolar

patients using quantitative electroencephalography as a technique to measure cerebral cortical activity. **Methods:** Retrospective screening was used to obtain data from patients admitted to a private psychiatry clinic. In the initial stage, the prevalence of alcohol and substance abuse was compared among the most common diagnoses. In the second phase, bipolar patients were compared to healthy individuals in terms of electrophysiology. Within this comparison, alcohol dependent and substance dependent bipolars were studied separately in contrast to the healthy group. Alongside the healthy control, bipolar patients deprived of substance or alcohol abuse were examined in both cases. Statistical analysis involved MANOVA and gender and age were taken into account. **Results:** 1) In the initial analysis of common psychiatric diagnoses (depression, anxiety, OCD, schizophrenia, and bipolar disorder), the percentage of alcohol or substance abuse was significantly higher than otherdiagnoses. 2) Electrophysiological comparison revealed distinct electrophysiological profiles between bipolar patients with addiction and those without, as well as the healthy control group. Specifically, individuals with bipolar disorder and without alcohol dependence exhibited higher general theta, beta, and temporal alpha power compared to those with dependence and healthy individuals. Additionally, the former group demonstrated higher occipital alpha power compared to the healthy control group only. 3) Patients with bipolar disorder, both with and without substance abuse, exhibited higher overall beta power than the healthy control group. **Conclusion:** It can be concluded that alcohol dependence led to significant alterations in brain activity in patients with bipolar disorder compared to non-addicted and healthy patients. In contrast, no such differences were observed in substance dependence, possibly due to the stimulant properties of the substance used. Future research could investigate the changes to the electrophysiological profile within this patient group, depending on the substance type with more detail.

COGNITIVE ERPS IN THE MANAGEMENT OF ADDICTIVE DISORDERS

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Objective: Despite withdrawal, psychotherapy, social support and anti-craving medication, the relapse rate remains tremendous among addicted patients. Cognitive ERPs may be considered as an add-on tool in the management of these patients.
Methods: Different ERP studies dealing with the management of addictive disorders will be reviewed.
Results: Different ERP parameters, such as the oddball P300, the Nogo P3d and the ERN, were identified as interesting biomarkers of abstinence vs. relapse in addictive disorders.
Conclusion: It is time to include ERPs in the management of addictions in order to monitor the evolution of different neurocognitive functions that may subtend relapse.

RTFMR-NEUROFEEDBACK IN ADDICTION PSYCHIATRY - SHORT AND LONG TERM EFFECTS

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1 University Hospital, LMU Munich

Objective: Psychosocial therapies are first line treatments in addictions, but long-term abstinence rates are limited to 40 to 60 %, even if extensive inpatient treatment and rehab has been offered. One risk factor of relapse is craving, that can be induced by alcohol related cues. Neuroimaging studies have revealed evidence for the association of craving with ACC and medial frontal areas during cue exposure. The activity in these regions can be modified by neurofeedback techniques.

Aim of the studies is to investigate neurofeedback in patients with substance use disorders in terms of feasibility, short and long-term effects. **Methods:** We implemented a real-time fMRI design in patients with alcohol and tobacco use disorders. Subjects received fMRI with a paradigm presenting substance related cues to elicit individual brain activations and were asked to modulate the cue induced brain responses. **Results:** There were significant modulations of addiction related brain activities along with slight reductions in craving. Due to small samples long-term data did not show increased abstinence rates so far. Differences between abstainers and relapsers point at predictive properties. **Conclusion:** Neurofeedback is a promising tool to augment treatments in substance use disorders. Larger samples in prospective studies are required to further improve the technique and assess long- term clinical effects.

NEUROFEEDBACK FOR ALCOHOL ADDICTION: CHANGES IN RESTING STATE NETWORK ACTIVITY

Bruna Sanader Vukadinovic**[1]*, *Susanne Karch2, Marco Paolini3, Paul Reidler3, Boris Rauchmann3, Gabrielle Koller2, Oliver Pogarell2, Daniel Keeser2*

[1]University College London Hospitals, 2University Hospital, LMU Munich, 3Institute of Clinical Radiology, University Hospital LMU

Objective: The aim of this study was to investigate whether neurofeedback training can alter resting state fMRI activity in brain regions that play a crucial role in addiction disorders in patients with alcohol dependence.

Methods: For this purpose, a total of 52 patients were recruited for the present study, randomized, and divided into an active and a sham group. Patients in the active group received three sessions of neurofeedback training. A random sample (N=16) remained for the data analysis. We compared the resting state data in the active group as part of the NF training on six measurement days.

Results: When comparing the results of the active group from neurofeedback day 3 with baseline 1, a significant reduction in activated voxels in the ventral attention network area was seen. This suggests that reduced activity over the course of therapy in alcohol-dependent subjects may lead to greater independence from external stimuli. Overall, a global decrease in activated voxels within all three analysed networks compared to baseline was observed in the study.

Conclusion: The use of resting-state data as potential biomarkers in further studies may hold promise, as activity changes within these networks, may help restore cognitive processes and alcohol abuse-related craving and emotions.

THE ROLE OF REWARD SYSTEM IN PSYCHIATRIC DISORDERS: A TRANSDIAGNOSTIC APPROACH

Esin Erdogan, University of Health Sciences, Izmir Faculty of Medicine

Symposium Synopsis: The Diagnostic and Statistical Manual of Mental Disorders categorically classifies various neurodevelopmental and psychiatric disorders, despite their sharing common features in terms of symptoms, causes, and abnormal brain processes. In fact, there are numerous instances where different disorders exhibit similar underlying pathological mechanisms. This overlap suggests the potential benefits of investigating shared patterns of disrupted brain function and associated characteristics. The ultimate objective is to more accurately link these pathological processes to well-founded and targeted interventions. One area that has received growing research attention in both nonclinical and clinical settings is the development of reward-processing systems. This approach revolves around the identification of malfunctioning mechanistic processes that are common to disorders with seemingly distinct symptom profiles. This strategy represents a specific implementation of the endophenotypic approach to uncovering the underlying pathophysiological mechanisms of these diseases. In this symposium, we aim to discuss preclinical models and clinical

research addressing reward circuit dysfunction in various neurodevelopmental and psychiatric disorders such as schizophrenia, mood disorders, eating disorders, and ADHD.

REWARD PROCESSING DYSFUNCTION IN SCHIZOPHRENIA

Aslihan Bilge Bektas*[1]

[1]*İzmir Bozyaka Training and Research Hospital*

Objective: Schizophrenia is a heterogeneous clinical disease with symptoms classified as positive, negative, disorganized, neurocognitive. It is thought that dysfunctional cortico-striatal interactions that worsen the prognosis in schizophrenia, reduce the social functionality of patients, play a role in the formation of negative symptoms that are resistant to treatment prevent the decision-making processes to create goal-directed behavior and cause disruption in the reward processing system.
Methods: Various components of reward processing have been shown to be impaired in schizophrenia. These components include reinforcement learning, the calculation of reward value, effort estimation, action selection, and reward expectation. These impairments are associated with changes in the cortico-striatal pathway. Various models have been proposed in the literature to explain motivation deficits in schizophrenia.
Results: A common assumption in most of these models is that the hedonic response is preserved in schizophrenia. Strauss et al. have proposed an approach that suggests impairments in hedonic systems in schizophrenia.
While individuals diagnosed with schizophrenia have hedonic responses similar to those of healthy individuals, they are less engaged in activities aimed at obtaining rewards. According to Barch and Dowd, this is because these individuals have difficulty using internal representations of emotional experiences, previous rewards, and motivational goals. It is believed that these difficulties in individuals with schizophrenia result from impairments in the components of reward processing, such as reward expectation, representation of reward value, calculation of effort required for rewards, and the ability to plan goal-directed activities.
Similarly, Gold and colleagues have argued that the fundamental problem in reward processing in schizophrenia lies in the creation and maintenance of mental representations of reward value. The model proposed by Kring and Elis in 2013 takes a different approach to explaining reductions in reward seeking and goal-directed behavior.
Conclusion: These models are supported by neuroimaging studies. Previous studies have revealed that anhedonia in patients with schizophrenia is attributed to the dysregulation of the frontostriatal circuit and mesocortical and mesolimbic circuit systems. Reduced OFC and putamen/ventral striatum activity during reward anticipation is linked to greater anhedonia and depressive symptoms in patients with schizophrenia. The motivational deficits of schizophrenia are thought to result from a reduced ability to differentiate between signal gains and instances of loss-avoidance, which are associated with the dysfunction of the frontostriatal pathway, including the vmPFC, dorsal ACC, anterior insula, and ventral striatum. Furthermore, patients with schizophrenia exhibit an inverse correlation between anhedonia-associality and posterior cingulate and precuneus activity, a key part of the DMN, during an auditory oddball task. Dysfunction of the striatum, cortex, and limbic regions and impaired integration of the reward networks may also lead to anhedonia in patients with schizophrenia.
In this session, we planned to discuss the differences in the reward processing process in schizophrenia and its relationship with the clinic in the light of current developments.

REWARD DEFICIT AND ANHEDONIA IN MOOD DISORDERS

Merve Babalioglu*[1]

[1]*Health Sciences University İzmir Tepecik Training and Research Hospital*

Objective: To explain the clinical and behavioral presentation of anhedonia and reward deficit in mood disorders, as well as the differences and commonalities in the underlying neurocircuitry.
Methods: A selective literature search including both human and rat studies were conducted using PubMed and PsychINFO to identify anhedonia and reward deficit in mood disorders.
Results: Mood disorders are common and debilitating conditions characterized in part by profound deficits in reward-related behavioural domains. Evidence suggests that depression is characterized by hypofunction of the reward-related brain structures such as the nucleus accumbens, prefrontal cortex, amygdala and hippocampus, while bipolar disorder manifests dysregulation of the behavioral activation system that increases goal-directed reward behavior. Importantly, strong evidence does not exist to suggest significant differences in anhedonia severity between depressed unipolar and bipolar patients, suggesting that there are more nuanced fluctuations in reward processing deficits in bipolar patients depending on their state. Both euthymic unipolar and bipolar patients frequently report residual reward dysfunction, which highlights the potential of reward processing deficits that give rise to the clinical symptom of anhedonia to be trait factors of mood disorders.
Conclusion: Reward processing represents a potential diagnostic and treatment marker for mood disorders. Further research should systematically explore the facets of reward processing in at-risk, affected, and remitted patients.

WHICH COMES FIRST: ALTERED BRAIN REWARD CIRCUITS IN EATING DISORDERS?

Vefa Erbasan**1*

[1]*İzmir Tepecik Training and Research Hospital*

Objective: It was aimed to examine the role of changes in the brain reward system in eating disorders.
Methods: Eating disorders are multifaceted psychopathologies, and the transdiagnostic approach is currently considered a useful framework to understand their complexity. The transdiagnostic model of eating disorders represents a dimensional approach that cuts across traditional categorical diagnoses and goes beyond them by considering the processes that are relevant to both eating pathology and other psychological disorders. With this approach, reward processing systems were thought to be effective in the development of eating disorders.
Results: Recent evidence has proposed neurobiological and behavioral similarities between substance dependence and excessive consumption of highly processed foods. These findings led to the recognition of food addiction as a key trigger in eating disorders. There is now considerable evidence that food and drug addiction share similar pathways in dopaminergic, opioid, and cannabinoid systems. In fact, dopamine has been associated with the reward mechanism in both food and psychoactive substances. The more rewarding the food or drug evaluated, the greater the release of extracellular dopamine into the nucleus accumbens. Also, pharmacological blockage of dopamine receptors may reduce the reward of both high-sugar foods and drugs of abuse. Studies based on positron emission tomographic imaging have also shown that both obese and drug-dependent individuals have significantly lowered the levels of dopamine receptors.
Conclusion: All this information suggests that the changing brain reward system has an important role in the pathophysiology of eating disorders, and more research should be done in this field to better understand eating disorders.

NEURAL MECHANISMS UNDERLYING REWARD PROCESSING IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Esin Erdogan**1*

[1] *University of Health Sciences, Izmir Faculty of Medicine*

Objective: The prevailing view is that ADHD is characterized by deficits in different cognitive domains. In addition to executive functions, deficits are observed in reward processing, temporal processing and timing, speech and language, memory span, processing speed, response time variability, arousal/activation, and motor control tasks. The aim of this presentation is to enhance our understanding of the behavioral and neural factors associated with reward processing in adults with ADHD and to reconcile discrepancies found in the existing literature. **Methods:** Neuroimaging studies of reward processing (structural imaging studies, functional imaging studies, and imaging of the brain at rest) in ADHD have been examined. **Results:** Various imaging techniques have consistently shown that ADHD is linked to alterations in the neural system responsible for reward processing. Structural studies have identified volume reductions in the Ventral Striatum (VS) and Prefrontal Cortex (PFC). While the precise functional implications of these volumetric differences remain unclear, researchers have initiated functional investigations into reward processing. These efforts have consistently revealed functional changes in adults with ADHD, primarily characterized by reduced brain responses during the anticipation of rewards in the VS and anomalous signaling during the receipt of rewards in the Orbitofrontal Cortex (OFC). The signaling in the VS during reward anticipation has been proposed to reflect either the predicted value of an expected reward (Schultz 2010) or the incentive salience (Berridge and Robinson 2003). Responses in the OFC have been associated with signaling the value of stimuli in our environment, indicating that adults with ADHD may exhibit an exaggerated response to rewarded stimuli, potentially leading to imbalanced decision-making. The evidence regarding neural alterations linked to reward processing in young individuals with ADHD is less conclusive when compared to adults. There are several factors contributing to this uncertainty. Firstly, there have been fewer studies conducted in young participants, and the reported findings exhibit a high degree of inconsistency. These discrepancies pertain to the locations within neural structures where changes occur and the direction of these effects, whether they involve increases or decreases. Secondly, studies involving young participants with ADHD have generally worked with smaller sample sizes. In comparison, the largest study in adults included 136 participants (Hoogman et al. 2011), while studies in adolescents typically involved only 68 participants (Paloyelis et al. 2012). Thirdly, the majority of studies focusing on young participants with ADHD have concentrated solely on the aspect of reward anticipation. **Conclusion:** Hence, it is imperative to conduct further research involving young participants with ADHD, encompassing crucial elements of reward processing, including both anticipation and receipt of rewards. Additionally, the reported alterations in functional connectivity among young individuals with ADHD suggest that viewing brain reward processing from a network perspective could offer additional insights into the neural changes associated with this disorder. Given the absence of research on endophenotypic traits in neural measures associated with reward processing, familial studies are crucial for understanding the hereditary contributions to these neural characteristics.

Friday, June 7, 2024

8:00 a.m. - 9:00 a.m.

Plenary Session III - Catherine Mummery

A NEW ERA IN AD DRUG TRIALS: TRANSLATING HOPE INTO IMPACT

Catherine Mummery1

[1]*University College London*

Objective: The search for treatments for Alzheimer's disease has been a long and arduous one with many negative trials and heated debate on what we should be targeting, and how. However, recent results on anti-amyloid immunotherapies have shown for the first time that we can alter the course of the disease and, while modest, have given us a foundation on which to build.

Methods: In this talk, I will summarise the results we have so far, and what they teach us in terms of next steps; I will then explore the novel targets and mechanisms that are developing and how we are using these in patients with earlier and genetic forms of disease to inform us about the future of treatments.

Results: I will outline some initial results from new genetic therapies as well as other novel therapies.

Conclusion: We are now in a position where we can be more than hopeful; we can be optimistic about the future. We are at the beginning of an era where we will build better disease modifying therapies and develop precision based medicines. We are at a real cornerstone - we are moving towards an ability to treat dementias as chronic diseases, not just offer palliative care for a terminal disease.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VI

THE ROLE OF DOPAMINE IN BIPOLAR DISORDER MOOD CYCLING AND DYSREGULATED CIRCADIAN CYCLES: A DOPAMINERGIC RHYTHMOPATHY? *Sameer Jauhar, King's College, London*

Symposium Synopsis: Mood cycling in bipolar disorders is a complex phenomenon driven by multiple
internal and external factors. We will present brain imaging data implicating Dopamine in this phenomenon, particularly, in mania and psychosis. We will also present data showing how a disrupted circadian cycle, especially by light and other factors, impacts sleep/activity and is associated with many mood symptoms from suicidal ideas to disrupted eating patterns. We will describe methods developed for quantitative ambulatory measurement of patterns in sleep and eating rhythms as well as associations between the two rhythms. Finally, we will integrate these phenomena into a coherent model integrating the role of a group of midbrain dopaminergic neurons
working as a non-circadian oscillator interacting with the circadian timer.

TESTING THE DOPAMINE HYPOTHESIS OF BIPOLAR DISORDER USING PET IN HUMANS

Sameer Jauhar*1, *Oliver Howes1*

[1]*King's College, London*

Objective: Delineate the role of the pre-synaptic dopamine system in bipolar disorder.

Methods: Case-control Positron Emission Tomography study in people with bipolar disorder and controls, using 18F-DOPA.

Results: Converging lines of evidence have implicated changes in the dopamine system in people with bipolar disorder, at trait and state levels. In this proposal I will present our data in first episode

mania psychosis, comparing it to schizophrenia psychosis, as well as newly acquired data in psychotic depression, addressing whether there is a transdiagnostic role for dopamine across these disorders. **Conclusion:** There does appear to be elevation in dopamine synthesis capacity in mania, with psychosis, and a probable reduction in dopamine synthesis capacity in the deprewssive pole of the illness, compared to this. Further longitudinal studies will shed further light on this.

DYSREGULATED RHYTHMS AND SYMPTOMATOLOGY IN BIPOLAR AND EATING DISORDERS

Outi Linnaranta**1*, *Serge Beaulieu2, Clement Bourguignon3, Elaine Tian4, Howard Steiger3, Kai-Florian Storch3*

[1]Finnish Institute for Health and Welfare, 2Canadian Network for Mood and Anxiety Treatments, [3]Douglas Mental Health University Institute, 4University of Hong Kong

Objective: To describe associations between sleep and eating rhythms in cohorts with patients with a diagnosis of a bipolar disorder (n=75) or an eating disorder (n=29).
Methods: Patients in both cohorts completed hourly charts of mood and eating occasions for two weeks. Locomotor activity was recorded continuously by wrist actigraphy for a minimum of 10 days, and sleep was calculated based on periods of inactivity. We computed the center of daily inactivity (CenDi) as a measure of sleep phasing and consolidation of the daily inactivity (ConDI) as a measure of daily sleep rhythm strength. We assessed interday irregularities in the temporal structure of food intake using the standard deviation (SD) of frequency (IFRQ), timing (ITIM), and interval (IINT) of food intake.
Results: In bipolar disorders, sleep timing and fragmentation were robustly associated with eating irregularity. In eating disorders, the phasing and rhythmic strength of sleep showed a moderate, positive correlation with the degree of eating irregularity. The similarity of findings despite several potential confounding factors and differences between the samples strengthen the notion of a potential shared rhythmopathy.
Conclusion: Two cohort studies showed shared rhythmopathy of sleep and circadian rhythms and eating rhythms. The presented methods are valid for descriptive studies on circadian rhythms in humans and deserve further development for use in clinical settings and in intervention studies.

A ROLE FOR MIDBRAIN DOPAMINE NEURONS IN BD CYCLICITY

Kai-Florian Storch**1*, *Pratap S. Markam1, Clement Bourguignon1, Lei Zhu2, Martin Darvas3, Bruno Giros1, Serge Beaulieu1, Outi Linnaranta1*
[1]McGill University2Douglas Mental Health University Institute, 3University of Washington

Objective: The mechanistic basis of cycling in bipolar disorder is poorly understood. Here we aimed to identify the neuronal substrate of cyclicity employing the mouse as a model.
Methods: Chronic treatment with methamphetamine in mice results in the emergence of a second rhythmic locomotor component that can reach periods of 48hrs, a frequency also found in bipolar disorder subjects exhibiting ultra-rapid cycling. We used genetic and pharmacological approaches to ablated or manipulate dopamine (DA) neurons in mice and then tested the resulting animals for deficits in second component emergence.
Results: We found that ablation of the DA neurons of the ventral tegmental area (VTA) abolished the ability of methamphetamine to induce the second component. Selective disruption of the tyrosine hydroxylase gene across the VTA equally led to a loss of second component emergence, while disruption of the gene for the vesicular monoamine transporter 2 in the VTA did not impede second component induction.

Conclusion: Our findings indicate that DA neurons of the VTA or their ability to produce DA are necessary for the emergence of a second rhythmic component regulating sleep-wake, likely harboring the oscillator that drives it. As the period of this component often reaches 48hrs, we suggest that DA neurons of the VTA also drive 48hr cycling in BD, where sleep length rhythmically alters alongside with mood.

DECODING MENTAL DISORDERS - DECIPHERING THE GENETIC BASIS AND EXPLORING ANIMAL AND IPSC MODELS

Florian Raabe, Max Planck Institute of Psychiatry

Symposium Synopsis: The goal of this symposium is to highlight the genetic basis of mental illness and advanced modeling with animal models and induced pluripotent stem cells (iPSCs).

Recent breakthroughs in genetic research have identified numerous risk genes associated with mental illness, and cutting-edge techniques have explored the functional implications of these identified risk genes.

By applying animal models that partially mimic the phenotypic characteristics of psychiatric conditions, researchers can investigate environmental factors that contribute to the development of mental illness and study gene-environment interactions.

The emerging field of induced pluripotent stem cells (iPSCs) enables the generation of various personalized neural subtypes, allowing for the dissection of cellular and molecular mechanisms in patient-derived neurobiological test systems.

The speakers of this symposium will discuss advancements in genetics, animal models, and iPSC technology, highlighting their strengths and limitations on the road towards personalized psychiatry.

PSYCHIATRIC GENETIC DISCOVERIES IN BIPOLAR DISORDERS - NEW INSIGHT IN UNDERLYING BIOLOGY

University of Oslo
Ole Andreassen[1]*, *Kevin O'Connell1, Bipolar Disorders PGC Working Group1*

Objective: We aimed to discover more of the the genetic architecture of bipolar disorders by applying a large transancestry sample.

Methods: Genome-wide association study of bipolar disorder with functional follow up of genetic loci. We analysed 158,036 bipolar disorders cases (including clinical, biobank and self-report cohorts) including diverse samples of European, East Asian, African American and Latino ancestries.

Results: We identified 337 independent genome-wide significant variants mapping to 298 loci. Exploratory enrichment analyses using the novel GSA-MiXeR tool highlighted enrichment of dopamine- and calcium-related biological processes and molecular functions, as well as GABAergic interneuron development, suggesting interesting molecular mechanisms and pathways to consider as targets for drug-repurposing. Genes fine-mapped to associated loci were also shown to be enriched for ultra rare damaging missense and protein-truncating variation in sequenced datasets, respectively, highlighting convergence of common and rare variant signals. We mapped genes to the 298 GWS loci using seven complementary approaches and identified a subset of 47 credible genes that were mapped to loci by at least three of these approaches.

Conclusion: Our findings highlight that increasing ancestral diversity in genetic studies of bipolar disorders improves discovery and ensures equitable benefit from genetic discoveries across ancestry groups.

EXCESS GDNF DEFINES SUBSET OF SCHIZOPHRENIA WITH ENHANCED STRIATAL DOPAMINE

JO Andressoo*[1]
[1]*University of Helsinki*

Objective: Recent evidence shows that only those schizophrenia (SCZ) patients who show striatal elevation in dopamine (DA) metabolism respond to DA blocking drugs. We investigated what mechanism can be responsible for the pathologically high DA metabolism in the striatum.
Methods: We analyzed post-mortem striatal gene expression in SCZ followed by analysis of targeted proteins in the CSF of first episode psychosis patients (FEP). We then analyzed the hit in mouse models.
Results: We found that glial cell line-derived neurotrophic factor (GDNF) mRNA levels are increased in post-mortem striata of SCZ patients. GDNF is among the strongest DA function enhancing proteins known. Similar increase in GDNF protein was found in first episode psychosis (FEP) patients CSF. In mice similar increase in brain endogenous GDNF expression starting from mid-pregnancy resulted in avolition, polydipsia, pre-pulse inhibition defect, enhanced striatal and reduced prefrontal DA metabolism thus resembling striatally DA elevated patients (Mätlik et al Andressoo Mol Psych 2022). Further post-mortem analysis of individual patients striata revealed “GDNF response” gene expression pattern in about 20% of patients which aligned with data from GDNF treated human DA neurons and with data from mice where endogenous brain GDNF expression was doubled at mid-pregnancy.
Conclusion: Our data suggest that excessive GDNF signaling may explain a subset of SCZ with elevated striatal DA. Ongoing work by ERANET NEURON Consortia GDNF UpReg focuses on patient stratification based on GDNF levels and explores options for pharmacological intervention.

MITOCHONDRIA PLAY A KEY ROLE IN THE GENESIS OF SCHIZOPHRENIA-LIKE CELLULAR, MOLECULAR AND BEHAVIORAL PATHOLOGIES IN HIPSCS AND RAT MODELS

Dorit Ben-Shachar*[1], *Hila Ene1, Rachel Karry1*
[1]*Technion, Israel Institute of Technology*

Objective: Ample evidence implicate mitochondria in psychiatric disorders in general and in schizophrenia in particular. Here we will show a causative role for mitochondria in neuronal development and in behavior. We will further suggest a molecular potential target to manipulate mitochondrial function.
Methods: Isolated active normal mitochondria (IAN-Mit) were transplanted into SZ and healthy subjects-derived lymphocyte cell lines (hLCLs) and iPSCs as well as into the medial prefrontal cortex (mPFC) of the Poly I:C SZ-model and healthy rats in adolescence. Cellular, structural, molecular, mitochondrial and behavioral alterations were assessed.
Results: IAN-Mit transplantation into SZ-iPSCs ameliorated mitochondrial function, neuronal sprouting and synaptic connectivity. In rats, IAN-MIT transplantation in adolescence significantly improvement mitochondrial function, neuronal sprouting and activity, enriched proteome metabolic in and neuronal development pathways, consequently restoring mPFC-regulated behaviors adulthood. Opposite effects in all parameters were induced by IAN-Mit in healthy rats. A similar disparate phenomenon was observed in schizophrenia and healthy subjects-derived LCLs. The possibility to mimic the effect of transplanted mitochondria in LCLs by molecular means will be discussed.
Conclusion: This study demonstrates the essential role of adolescent mitochondrial homeostasis in the development of a normal functioning adult brain. In addition, in order to ameliorate mitochondrial function in SZ, we suggest an alternative molecular tool to the transplantation of the double edge sword mitochondria.

IPSC TECHNOLOGY REVEALS COMMON MECHANISMS DESPITE DISTINCT INDIVIDUAL POLYGENIC RISK PROFILES

Florian Raabe*[1]

[1]*Max Planck Institute of Psychiatry*

Objective: Genetic studies have provided correlative evidence suggesting that distinct combinations of genetic risk factors in each patient converge onto common molecular mechanisms.

Methods: To validate this notion on a functional level, a cellular model system was employed, differentiating induced pluripotent stem cells (iPSCs) from 104 individuals with high polygenic risk load and controls into cortical glutamatergic neurons (iNs).

Results: Comprehensive multi-omics profiling revealed widespread differences of numerous synaptic transcripts between iNs derived from SCZ patients and healthy donors. Moreover, omics-based analysis highlights molecular mechanisms that regulate the neuronal transcriptomes that highly correlate with SCZ polygenic risk, and the affected genes were significantly enriched for common genetic variations associated with SCZ.

Conclusion: In summary, the results highlight that iPSC technology offers great potential for deciphering molecular mechanisms in SCZ and demonstrates that distinct individual polygenic risk profiles converge in common downstream signaling pathways.

POTENTIAL CLINICAL TOOLS ACROSS PSYCHIATRIC DISORDERS: FROM BIOMARKERS TO CLINICAL MARKERS

Bo Cao, University of Alberta

Symposium Synopsis: A major goal of translational psychiatry is to develop and identify effective clinical tools that can aid in the diagnosis, prognosis, and outcome prediction of mental illnesses. These tools can be developed from a variety of sources, including cross-species biomarker findings obtained through brain imaging, clinical markers obtained through clinical and behavioral assessments, or data obtained from clinical trials about the placebo effect in mental disorders. Additionally, innovative statistical and computational techniques, such as machine learning, can be leveraged to enhance the predictive power of these tools.

In this symposium, we have invited experts from a range of disciplines to present their latest research on the diagnosis and health outcomes of depression, bipolar disorder, schizophrenia, violence, and suicide. These investigations are all aimed at developing translational tools that can improve the delivery of mental health services.

We hope that this symposium will facilitate a lively discussion on the biological and clinical foundations of these tools, as well as the challenges and concerns associated with their translation into clinical practice. We believe that this symposium will provide a unique opportunity for attendees to explore new ideas and approaches in translational psychiatry for improving mental health services. Ultimately, we hope that this symposium will contribute to the ongoing efforts to provide better mental health care for all individuals, from innovation to practice.

CROSS-SPECIES NEUROIMAGING INTERMEDIATE PHENOTYPES DEEPEN OUR UNDERSTANDING OF DEPRESSION

Huiling Guo1, Shuai Dong1, Yao Xiao1, Jingyu Yang1, Pengfei Zhao1, Tongtong Zhao1, Aoling Cai1, Hui Wang2, Ruifang Hua2, Rongxun Liu2, Yange Wei2, Dandan Sun3, Zhongchun Liu4, Mingrui Xia5, Yong He5, Yankun Wu6, Tianmei Si6, Fay Womer7, Fuqiang Xu8, Jie Wang8, Weixiong Zhang9, Xizhe Zhang10, Fei Wang*[1]

[1]*Affiliated Nanjing Brain Hospital, Nanjing Medical University., 2School of Laboratory Medicine, Xinxiang Medical University., 3The People's Hospital of China Medical University and the People's*

Hospital of Liaoning Province, 4Renmin Hospital of Wuhan University, 5Beijing Normal University, 6Peking University Sixth Hospital, Peking University, 7Saint Louis University, 8Chinese Academy of Sciences-Wuhan National Laboratory for Optoelectronics, 9The Hong Kong Polytechnic University, 10School of Biomedical Engineering and Informatics, Nanjing Medical University.

Objective: Multiple genetic variants and their interplay with environmental factors have hindered the progress of mental disease research and the development of effective markers of neuropsychiatric disorders. Intermediate phenotypes like neuroimaging brain patterns offer unique opportunities to understand multifaceted etiologies of neuropsychiatric diseases such as depression. This study identified neuroimaging intermediate phenotypes bridging etiologic differences and disease behavioral features cross species.

Methods: We established rodent genetic (P11 knockout mice, N=11) and chronic unpredictable mild stress (CUMS, N=15) models of depression to illustrate the effects of different etiologies on neuroimaging patterns of the amplitude of low-frequency fluctuations (ALFF). To identify ALFF patterns in depressed individuals that correspond to the two rodent models, we used t-Distributed Stochastic Neighbor Embedding method and an agglomerative clustering algorithm to delineate two ALFF subtypes of depression in two independent datasets (N=438). Linear regression was performed to identify which ALFF alterations predicted core symptoms of depression across species.

Results: Compared to controls, opposite ALFF patterns in subcortical and sensorimotor regions were found between P11 knockout mice and CUMS. Similarly, two ALFF subtypes with opposite patterns in frontal-subcortical, and sensorimotor regions were clustered and validated in two independent depressed cohorts. Importantly, anhedonia was significantly increased across all rodent models and human subtypes when compared to controls, despite differences in ALFF patterns. Further, anhedonia correlated with subcortical-sensorimotor ALFF in rodent models and human cohorts.

Conclusion: Overall, subcortical-sensorimotor ALFF may serve as an intermediate phenotype that bridges etiologic differences and anhedonia in depression. These results deepened our knowledge of disease mechanisms underlying depression which may facilitate translational applications of animal models to humans with depression other psychiatric disorders.

DIFFERENTIAL POWER OF PLACEBO ACROSS MAJOR PSYCHIATRIC DISORDERS

Bo Cao*[1], *Yang Liu[2], Alessandro Selvitella[1], Diego Librenza-Garcia[2], Ives Passos[3], Jeffrey Sawalha[1], Pedro Ballester[4], Jianshan Chen[1], Shimiao Dong[1], Fei Wang[5], Flavio Kapczinski[2], Serdar Dursun[1], Xin-Min Li[1], Russell Greiner[1], Andrew Greenshaw[1]*

[1]University of Alberta 2McMaster University, 3Hospital de Clínicas de Porto Alegre; Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul, 4School of Technology, Pontifícia Universidade Católica do Rio Grande do Sul, 5China Medical University

Objective: The placebo effect across psychiatric disorders is still not well understood. In the present study, we conducted meta-analyses including meta-regression, and machine learning analyses to investigate whether the power of the placebo effect depends on the types of psychiatric disorders.

Methods: We included 108 clinical trials (32,035 participants) investigating pharmacological intervention effects on major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ). We developed measures based on clinical rating scales and Clinical Global Impression scores to compare placebo effects across these disorders. We performed meta-analysis including meta-regression using sample-size weighted bootstrapping techniques, and machine learning analysis to identify the disorder type included in a trial based on the placebo response.

Results: Consistently through multiple measures and analyses, we found differential placebo effects across the three disorders, and found lower placebo effect in SCZ compared to mood disorders. The

differential placebo effects could also distinguish the condition involved in each trial between SCZ and mood disorders with machine learning. **Conclusion:** Our study indicates differential placebo effect across MDD, BD, and SCZ, which is important for future neurobiological studies of placebo effects across psychiatric disorders and may lead to potential therapeutic applications of placebo on disorders more responsive to placebo compared to other conditions.

A CLINICAL RISK PREDICTION TOOL FOR IDENTIFYING THE RISK OF VIOLENT OFFENDING IN SEVERE MENTAL ILLNESS: A RETROSPECTIVE CASE-CONTROL STUDY

Xiaoping Wang**1*

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Chinese Society of Neuroscience and Psychiatry

Objective: Individuals with severe mental illness are at higher risk of violence than the general population. However, there is a lack of available tools to assess the risk of violence in clinical settings. We aimed to develop an easy-to-use tool to identify risk of violent offences to assist decision-making in Chinese clinical settings.

Methods: We identified 1157 patients with severe mental illness who conducted violent offending and 1304 patients who were not suspected of violent offending in the matched living areas. We used stepwise regression and Lasso's method to screen for predictors, built a multivariate logistic regression model, and performed internal validation with the K-fold method to develop the final prediction model.

Results: The risk prediction model for violence in severe mental illness included age (beta coefficient, b=0.05), male sex (b=2.03), education (b=1.14), living in rural areas (b=1.21), history of homeless (b=0.62), history of previous aggression (b=1.56), parental history of mental illness (b=0.69), diagnosis of schizophrenia (b=1.36), episodes (b=-2.23), duration of illness (b=0.01). The area under curve (AUC) for the predictive model for risk of violence in severe mental disorder was 0.93 (95% CI: 0.92-0.94).

Conclusion: A predictive tool of violent offending containing 10 items that can be easily used for individuals with severe mental illness was constructed in this study. The model was internally validated to have good discrimination and high accuracy and have potential for assessing the risk of violence in patients with severe mental illness in routine care.

PROPHYLACTIC BLUE LIGHT THERAPY IMPROVES DEPRESSION: A STUDY OF LIGHT THERAPY WITH DIFFERENT PARAMETERS

Lingli Cheng1, Ying Yan1, Yang Yu1, Ni Fan1, Hongbo He**1*

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Objective: Previous studies have demonstrated the therapeutic value of blue light therapy for treating depression. Yet the ideal light therapy parameters are not consistent. In the present study, blue light was prophylactically used to test the antidepressant effects of different light therapy parameters. This experiment explored the antidepressant effect of different duration（2 weeks or 3 weeks, or 4 weeks）, daily exposure time（2 hours or 3 hours or 4 hours）, and frequencies (0 Hz or 8 Hz or 40 Hz) of blue light therapy on improving depression-like behaviors.

Methods: Adult male C57/BL6 mice at the ages of 7–8 weeks were used in the present study. (Corticosterone was
Corticosterone-chronic restraint stress (Cort-Crs) depression model
administered subcutaneously at a dose of 20 mg/ kg , Restraint of 2 hours/day, over 4 weeks) was performed as a stress model to study depression along with blue light therapy. The light sources in this experiment are blue light sources with three different frequencies, Its details are as follows: LED, wavelength = 462.8 nm, Tc ≥ 25,000 K, flicking frequency = 0 Hz or 8 Hz or 40 Hz, irradiation power

density = 0.3 mW/cm2. Behavioral experiments including sucrose preference, open field, and tail suspension tests were assessed to evaluate the antidepressive effects of blue light therapy. **Results:** Cort-Crs procedure induced depression like behaviors. Prophylactic blue light therapy improves improved behavioral results. The optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters. **Conclusion:** The results showed that 40 Hz light therapies are the most effective. The antidepressant effect of blue light at various durations was examined for the first time in this study. We found that three weeks of blue light therapy had the greatest antidepressant effect. Moreover, we also found that three hours of blue light therapy per day had the best efficacies. Our results reconfirmed blue light is the effective component of light therapy for treatment of depression. And we determined the optimal parameters of three weeks, three hours a day of prophylactic blue light therapy at 40 Hz shows the maximum antidepressant effects on anhedonia and behavioral despair, while a decline was observed from the optimum effects at other parameters.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia VII

OLIGODENDROCYTE PATHOLOGY AND COGNITION IN SEVERE MENTAL DISORDERS

Peter Falkai, German Society for Biological Psychiatry

Symposium Synopsis: Cognitive deficits are a hallmark of severe mental disorders and remain after the acute treatment period. These symptoms respond only limited to treatment with psychotherapy or antipsychotics and cause disability in everyday life, including functional impairments that prevent social and professional reintegration. In this symposium we add to the new view that disturbed myelin plasticity, more precisely “dysmaturation of oligodendrocyte precursor cells (OPCs)”, is a critical pathophysiological substrate of cognitive disturbance in severe mental disorders and represents an unexplored target for treatment. OPCs generate oligodendrocytes that are capable of myelination. Their dysfunction leads to disturbances in myelination, connectivity, metabolic support of neurons and – on the functional level – cognitive deficits. Recent replicated findings of decreased oligodendrocyte number in the hippocampal subregion CA4 and new data from a postmortem study of OPCs in Schizophrenia will be provided. The relation to cognitive deficits and alterations in Major Depression and Bipolar Disorder will be discussed. Insight in molecular changes related to oligodendrocytes, synaptic plasticity and energy metabolism from proteomic studies in postmortem brains, hiPSCs and organoids in Schizophrenia will be given. An overview on cognitive deficits in Schizophrenia with emphasis on different cognitive domains will be provided. Finally, recent genome-wide association studies (GWAS) in in Major Depression, their relation to the neurobiological background of cognition and an introduction on the clinical relevance of cognition in Major Depression will be discussed.

LOSS OF OLIGODENDROCYTES IN SCHIZOPHRENIA AND ITS RELATION TO COGNITIVE DEFICITS

Peter Falkai*[1], *Andrea Schmitt2, Florian Raabe2, Isabel Maurus2, Sergi Papiol2, Anna Kessel3, Konstantin Schlaaff3, Johann Steiner3*

[1]German Society for Biological Psychiatry, 2LMU Munich, 3University of Magdeburg

Objective: In a diffusion tensor imaging (DTI) study, oligodendrocyte (OL)-related gene variants, such as myelin-associated glycoprotein (MAG), were related to white matter tract integrity and cognitive performance in schizophrenia patients. Interestingly, a single nucleotide polymorphism of the OL lineage transcription factor 2 (OLIG2), which is necessary for maturation of OPCs, was also associated

with reduced white matter fractional anisotropy, indicating impaired myelination in schizophrenia. Therefore in our studies we focused on oligodendrocyte numbers in brains of schizophrenia patients and their relation to cognitive deficits. **Methods:** Using unbiased design-based stereology in postmortem brains from schizophrenia patients, we estimated total number of oligodendrozytes, neurons and astrocytes in hippocampal subregions. In an independent postmortem sample in the hippocampus we tried to replicate these findings and extended the area of interest to the white matter of the cingulum. We applied immunohistochemical staining of breast carcinoma amplified sequence 1 (BCAS1) to identify and quantify density of early myelination oligodendrocyte precursor cells in the hippocampus. **Results:** Our stereological post-mortem findings demonstrated that a reduction in the number of OLs in the cornu ammonis 4 (CA4) subregion of the hippocampus was related to cognitive dysfunction in schizophrenia patients and has impact on the neuronal Papez Circuit. In an independent sample we replicated the finding of reduced OLs in CA4 and found a reduced number of OLs in white matter of the Cingulum. Results from immunohistochemical studies will be presented. **Conclusion:** Targeting the DLPFC in schizophrenia a previous stereological study revealed a loss of OLs, pointing to a network problem involving fronto-temporal regions. Taken together, these findings show that dysconnectivity in schizophrenia is likely related to oligodendrocyte deficits. New treatment strategies are needed that target deficits in OL-related pathological processes, for example by improving differentiation of OPCs to myelinating OLs, thereby promoting myelination and optimally abolishing cognitive symptoms.Physical exercise is so far the only existing means to enhance myelin plasticity and consequently improve cognition in schizophrenia. Accumulating evidence suggests that stimulating myelin plasticity (OPC differentiation and unidentified OL-based molecular mechanisms) represents a promising and thus far unexplored mechanism to enhance cognition.

OLIGODENDROCYTES AS TARGETS FOR SCHIZOPHRENIA TREATMENT

Valéria Almeida**1*, *Daniel Martins-de-Souza2*

[1]University of Muenster, 2University of Campinas (Unicamp)

Objective: Several studies have implicated oligodendrocyte dysfunction and myelin abnormalities, including altered expression of myelin-related genes, with schizophrenia. However, the molecular mechanisms subjacent of these alterations could still benefit of more studies.

Methods: Our group aimed at characterizing the biochemical profiles of different in vitro oligodendrocyte models when treated with the classical antipsychotics such as haloperidol and clozapine as well as with novel treatments such as D-serine and different cannabinoids. For that, we mostly employed shotgun proteomics, using 2DLC–HDMSe and label-free quantitation besides cellular validation assays.

Results: Biochemical pathways commonly affected by the classical antipsychotics were mainly associated to ubiquitination, proteasome degradation, lipid metabolism and DNA damage repair. In turn, metabolic processes, especially the metabolism of nitrogenous compounds, were a predominant target of modulation of clozapine + d-serine treatment. The modulation of cannabinoid signaling in cultured oligodencrocytes was found to affect pathways linked to cell proliferation, migration, and differentiation of oligodendrocyte progenitor cells. Additionally, we found that carbohydrate and lipid metabolism, as well as mitochondrial function, were modulated by different endo- and phytocannabinoids.

Conclusion: Our results open new roads of opportunities, suggesting that cannabinoid signaling in oligodendrocytes might be relevant in the context of demyelinating and neurodegenerative diseases.

COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

Siegfried Kasper**1*

[1]*Center for Brain Research*

Objective: Cognitive dysfunction in schizophrenia has been considered as a main component of the disease in numerous publications

Methods: A summary of the literature is given including recently available data

Results: Cognitive dysfunction in schizophrenia has been shown to be a main component of the disease and can be influenced by second generation antipsychotics but not for the older types of medication called typical neuroleptics. Newer psychopharmacological approaches have been taken which will be summarised.

Conclusion: There is considerable literature and data available to address cognition in schizophrenia and the influence of specific antipsychotic medication

CLINICAL IMPORTANCE AND GENETIC UNDERPINNINGS OF COGNITIVE DYSFUNCTION IN DEPRESSION

Bernhard Baune**1*

[1]*University of Münster*

Objective: Major Depressive Disorder (MDD) often is associated with significant cognitive dysfunction, both during a current episode of depression as well as a trait before onset or between episodes of depression. The biological underpinnings of cognitive function have been explored in healthy individuals, but remains elusive in severe mental illness, such as major depressive disorder (MDD) Here investigated the genetic foundations of cognitive function in MDD.

Methods: To this end, we conducted a meta-analysis of genome-wide interaction of MDD and cognitive function using data from four large European cohorts in a total of 3510 MDD cases and 6057 controls. In addition, we conducted analyses using polygenic risk scores (PRS) based on data from the Psychiatric Genomics Consortium (PGC) on the traits of MDD, Bipolar disorder (BD), Schizophrenia (SCZ), and mood instability (MIN). Functional exploration contained gene expression analyses and Ingenuity Pathway Analysis (IPA®).

Results: We identified a set of significantly interacting single nucleotide polymorphisms (SNPs) between MDD and the genome-wide association study (GWAS) of cognitive domains of executive function, processing speed, and global cognition. Several of these SNPs are located in genes expressed in brain, with important roles such as neuronal development (REST), oligodendrocyte maturation (TNFRSF21), and myelination (ARFGEF1). IPA® identified a set of core genes from our dataset that mapped to a wide range of canonical pathways and biological functions (MPO, FOXO1, PDE3A, TSLP, NLRP9, ADAMTS5, ROBO1, REST). Furthermore, IPA® identified upstream regulator molecules and causal networks impacting on the expression of dataset genes, providing a genetic basis for further clinical exploration (vitamin D receptor, beta-estradiol, tadalafil). PRS of MIN and meta-PRS of MDD, MIN and SCZ were significantly associated with all cognitive domains.

Conclusion: Our results suggest several genes involved in physiological processes for the development and maintenance of cognition in MDD, as well as potential novel therapeutic agents that could be explored in patients with MDD associated cognitive dysfunction.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Arun Ravindran, Canadian Network for Mood and Anxiety Treatments

Symposium Synopsis: Background: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing

subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.
Methods: Strength of evidence was rated based on published literature and clinical expertise. The systematic evaluation focused on the domains of CAM therapies: lifestyle interventions, physical therapies, nutraceuticals and herbal remedies.
Results: The first presentation will focus on lifestyle interventions, including diet and smoking cessation etc., and will outline evidence and recommendations. The second presentation will provide an update on the evidence for the benefit of physical therapies, nutraceuticals and herbal remedies for the treatment of MDD, followed by two presentations on the therapeutic benefit and the proposed neurobiological mechanisms of exercise and yoga. Recent publications confirm the benefit of exercise and yoga reported in previous guidelines, which recommended its use as adjunctive treatment in mild to moderate major depression.
Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

CLINICAL GUIDELINES FOR THE USE OF LIFESTYLE-BASED MENTAL HEALTH CARE IN MAJOR DEPRESSIVE DISORDER: WORLD FEDERATION OF SOCIETIES FOR BIOLOGICAL PSYCHIATRY (WFSBP) TASKFORCE

*Wolfgang Marx1, Sam Manger2, Mark Blencowe3, Greg Murray4, Fiona Yan-Yee Ho5, Sharon Lawn6, James Blumenthal7, Felipe Schuch8, Brendon Stubbs9, Anu Ruusunen10, Hanna Demelash Desyibelew11, Timothy G. Dinan12, Felice Jacka*1, Arun Ravindran13, Michael Berk1, Adrienne O'Neil1*
Deakin University, 2James Cook University, 3Australasian Society of Lifestyle Medicine, 4Swinburne University of Technology, 5The Chinese University of Hong Kong, 6Flinders University, 7Duke University Medical Center, 8Federal University of Santa Maria, 9King's College London, 10University of Eastern Finland, 11Bahir Dar University, 12University College Cork, 13University of Toronto

Objective: The primary objectives of these international guidelines were to provide a global audience of clinicians with (a) a series of evidence-based recommendations for the provision of lifestyle-based mental health care in clinical practice for adults with Major Depressive Disorder (MDD) and (b) a series of implementation considerations that may be applicable across a range of settings.
Methods: Recommendations and associated evidence-based gradings were based on a series of systematic literature searches of published research as well as the clinical expertise of taskforce members. The focus of the guidelines was eight lifestyle domains: physical activity and exercise, smoking cessation, work-directed interventions, mindfulness-based and stress management therapies, diet, sleep, loneliness and social support, and green space interaction.
Results: Nine recommendations were formed. The recommendations with the highest ratings to improve MDD were the use of physical activity and exercise, relaxation techniques, work-directed interventions, sleep, and mindfulness-based therapies (Grade 2). Interventions related to diet and green space were recommended, but with a lower strength of evidence (Grade 3). Recommendations regarding smoking cessation and loneliness and social support were based on expert opinion. Key implementation considerations included the need for input from allied health professionals and support networks to implement this type of approach, the importance of partnering such recommendations with behaviour change support, and the need to deliver interventions using a biopsychosocial-cultural framework.

Conclusion: Lifestyle-based interventions are recommended as a foundational component of mental health care in clinical practice for adults with Major Depressive Disorder, where other evidence-based therapies can be added or used in combination. Further work is also needed to develop innovative approaches for delivery and models of care, and to support the training of health professionals regarding lifestyle-based mental health care.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Brendon Stubbs*[1]
[1]*King's College London, Institute of Psychiatry*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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Conclusion: Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

LIFESTYLE AND CAM THERAPIES FOR WELLNESS AND TREATMENT OF DEPRESSIVE DISORDERS

Kaviraja Udupa*[1]
[1]*National Institute of Mental Health and Neurosciences (NIMHANS) Hosur Road, Bangalore*

Objective: The interest in the use of complementary and alternative (CAM) interventions to promote well-being and treatment of mental illness is growing. CAM interventions can enhance the quality of life for those diagnosed with mental illness and those experiencing subthreshold symptoms. The symposium will have four interrelated presentations on CAM therapies with a focus on clinical benefits and neurobiology. The aim is to provide recommendations to practicing clinicians and enhance the utilization of CAM therapies.

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proposed neurobiological mechanisms of exercise and yoga. Recent publications confirm the benefit of exercise and yoga reported in previous guidelines, which recommended its use as adjunctive treatment in mild to moderate major depression. **Conclusion:** Initial research in CAM therapies has deficiencies, including inconsistent quality and sparse long-term data. While psychotherapy and pharmacotherapy remain the standard of care, there is evolving evidence that CAM therapies can be complementary. With high patient preference, CAM therapies can help clinicians provide comprehensive care in a tailored manner to individual patients.

EARLY INTERVENTION FOR BIPOLAR DISORDER: FROM CUTTING EDGE SCIENCE TO TRANSFORMATIVE CLINICAL PRACTICE

David Bond, Johns Hopkins University School of Medicine

Symposium Synopsis: The success of early psychosis programs has shown that early intervention for serious mental illnesses is feasible, effective, and scalable. For example, building on the Recovery After an Initial Schizophrenia Episode (RAISE) study, a nationwide network of first episode psychosis programs called NAVIGATE was created in the United States to provide coordinated specialty care for people with schizophrenia. Early intervention is also important for bipolar disorder (BD) but early intervention efforts for BD are less advanced. This symposium will highlight scientific advances in identifying people with, and even at risk for, early-stage BD and the development of evidence based clinical interventions to treat them. We will show early results from cutting edge work using endophenotypes to identify people in the prodromal or early stages of BD. The endophenotypes of interest include cortical inhibition and mirror neuron system activity during transcranial magnetic stimulation (TMS), functional near infra-red spectroscopy (fNIRS), eye-movement tracking findings, abnormalities in retinal vasculature, and neurocognitive functioning. We will describe novel intervention programs for early-stage BD patients being developed in the United States and Canada. STRIDE, based at the University of Minnesota, adapts the NAVIGATE early psychosis model for early-stage BD. We will also show key aspects of a novel manualized psychological intervention for prodromal and early-stage BD based at the University of British Columbia. The presenters will highlight opportunities and challenges for early intervention in BD, including possibilities for harmonizing clinical research and treatment.

STRIDE: A BLUEPRINT FOR TAILORING COORDINATED SPECIALTY CARE FOR EARLY INTERVENTION IN BIPOLAR DISORDER

David Bond**1*, *Kathleen Miley2, Carissa Coudray3, Piper Meyer-Kalos3*

[1]Johns Hopkins University School of Medicine, 2Health Partners Institute, 3University of Minnesota

Objective: Early intervention for bipolar disorder (BD) has the potential to improve clinical and functional outcomes. Comprehensive clinical programs are needed. Coordinated specialty care (CSC) models such as NAVIGATE are evidence-based interventions for first episode psychosis that were widely implemented in the US and internationally following results from the Recovery After an Initial Schizophrenia Episode (RAISE) trial. We sought to adapt NAVIGATE to meet the unique needs of people with BD.

Methods: Adaptations to the NAVIGATE model for BD were determined through literature review, international expert consultation, and focus groups with stakeholders including patients, family members, and clinicians.

Results: A detailed model for CSC for BD, called STRIDE, was created based on this iterative process. Strengths of NAVIGATE, including shared decision making and a recovery focus, were maintained. Key adaptations for BD included 1) modification of psychotherapy modules to address prevention

and treatment of mood episodes, 2) new modules on circadian and social rhythms, affective regulation, and comorbidities common in BD, 3) creation of an early-stage BD prescribers manual, 4) broadened focus on health and wellbeing, 5) increased attention to co-occurring substance use disorders; 6) tailored family supports, and 7) incorporation of supported education and employment services. **Conclusion:** NAVIGATE has many strengths and can be adapted to meet the needs of people with BD. Next steps include evaluation of the feasibility of the STRIDE model.

CAN ENDOPHENOTYPES HELP IN EARLY IDENTIFICATION AND INTERVENTION PLANNING IN BIPOLAR DISORDER?

Muralidharan Kesavan**1*, *Sanjay Naik1, Ramkumar Segar1, Daniel Ritish Paul Kavati1, Abhishek Ramesh1, Nandhini Bojappen1, Shivani Sivaramkrishnan1, Preethi Reddy1, Rakshathi Basavaraju1, VijayaKumar KG1, Rajakumari P Reddy1, Urvakhsh Mehta1, Naren Rao1, Venkatasubramanian Ganesan1*

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National Institute of Mental Health and Neurosciences

Objective: The role of first-episode mania (FEM) in the progression of bipolar disorder (BD) is well studied, with reported brain structural and neuropsychological deficits soon after FEM, very early in the course of the disorder. This has been linked to poor clinical and functional outcomes. Hence, there is a need to study biological risk markers for BD, which may be present in individuals at risk for BD, even before disease onset.

Methods: about a series of investigations - in individuals very early in the course of the disorder (BD I- FEM in remission) and in individuals who are yet to develop this disorder (matched healthy individuals with family history of BD I) as compared to healthy subjects (no personal or family history of psychiatric disorders). The three groups of subjects were investigated for (1) cortical inhibition, social cognition and mirror neuron system activity using transcranial magnetic stimulation (TMS), (2) functional near infra-red spectroscopy (fNIRS) during facial emotion recognition and cognitive task performance, (3) eye-movement tracking - saccades and smooth pursuit during facial emotion processing tasks (4) abnormalities in retinal vasculature using nonmydriatic fundus camera and (5) neuropsychological functioning. They were also examined using bedside tests of neurological soft-signs, minor physical anomalies.

Results: TMS markers of cortical inhibition, inteleukin-6, executive functions, emotion processing and eye movement tracking had endophenotypic potential while the other investigations were more of a disease marker rather than risk marker. Interestingly, on all investigations, the FEM subjects differed significantly from healthy subjects indicating that these investigations have tremendous potential in differentiating remitted early bipolar disorder from healthy subjects.

Conclusion: The endophenotypic and diagnostic potential of each of these investigations as well as its translational applications in clinical practice will be discussed.

COGNITIVE ENDOPHENOTYPES AND NEUROPSYCHOLOGICAL INTERVENTIONS IN EARLY BIPOLAR DISORDER

Rajakumari Reddy**1*, *Muralidharan Kesavan1, Ivan Torres2, Nandini Bhojappa1, Shyam Sundar1, Preethi Reddy1, Jayasree Basivireddy2, Lakshmi Yatham2*

[1]National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, 2University of British Columbia

Objective: Bipolar disorder (BD) is characterized by recurrent depressive and manic episodes. First episode of mania (FEM) determines bipolarity and is universally recognized as the onset of BD. The staging model of BD proposes early intervention to be more effective, which could mitigate clinical

and neurobiological consequences of the illness. Meta-analyses have shown that euthymic BD exhibit impairment on attention/working memory, verbal memory, speed and executive functions. Unaffected siblings of BD probands tend to show impairment in executive function and verbal learning and memory suggestive of potential endophenotype markers for BD. An understanding of the course of BD from the onset or even prior, may contribute to the development of early interventions. **Methods:** Site: 1 Cross sectional study using convenient sampling method (India) Remitted First episode mania patients (FEM; n=25), first-degree relatives of patients with BD (HR; n=25) and healthy subjects (HC) Site 2: Longitudinal Study, baseline, 1-year, and 3-year time points (Canada) (FEM, n= 91, 61 healthy subjects) Assessment tools: Cognitive domains assessed using neuropsychological battery, mood scales **Results:** Visual Memory and Verbal Fluency (Executive function) have endophenotypic potential thereby emphasising need for early cognitive screening and institution of early interventions. Patients showed deficits in all domains at baseline, and longitudinal trajectories compared to healthy participants with some gains with time. Cross sectional study indicates the impairment prior to onset, longitudinal study indicates impairment but suggests changes in trajectory. Both studies indicate cognitive deficits which could have cascading effects on course and functional outcome of the patients. **Conclusion:** Integrated approach might be beneficial which in turn could have an impact on the course and outcome of the illness. The intervention initiated early may have more benefits. Components of integrated neuropsychological intervention will be discussed in this context.

A NOVEL MANUALIZED PSYCHOEDUCATION AND RESILIENCE ENHANCEMENT PROGRAM FOR INDIVIDUALS AT HIGH RISK FOR BIPOLAR DISORDER: FINDINGS FROM A FEASIBILITY STUDY

Kamyar Karamatian*[1]

[1]

The University of British Columbia

Objective: Bipolar Disorder (BD) typically emerges during adolescence and early adulthood and is associated with significant cognitive impairment and functional disability. Despite the high prevalence and large disability burden, BD often goes unrecognized and untreated for several years leading to serious consequences including greater severity and frequency of mood episodes, higher number of hospitalizations, and elevated risk of suicide. However, no evidence-based intervention program aimed at early identification of BD has yet been developed. We have recently developed a prototype manualized telehealth-based group Psychoeducational and Resilience Enhancement Program for individuals at high risk for BD (PREP-BD). The overarching objective of our study is to determine whether PREP-BD can be feasibly and effectively implemented to increase knowledge of BD, reduce self-stigma, improve help-seeking and enhance resilience in individuals who are at high risk of developing BD.

Methods: Recruitment for this study started in May 2023 and is expected to be completed in March 2024. Participants, aged 15 to 24 years, who meet the Bipolar At-Risk (BAR) criteria (Bechdolf et al., 2010) are recruited into a single-arm before-and-after pilot study to examine the feasibility and acceptability of PREP-BD. The intervention consisted of 8 weekly group sessions, each 60 minutes in duration. Participants complete the following questionnaires before and after the intervention: Help-Seeking Questionnaire, Bipolar Disorders Knowledge Scale, Self-Stigma of Mental Illness Scale-Short Form, and Connor Davidson Resilience Scale. Following the completion of the intervention, a focus group is conducted after the final intervention session to elicit rich, detailed, and first-person accounts of participants' experiences and their suggestions for improving the intervention. In

addition, participants complete a Client Satisfaction Questionnaire (CSQ-8) and the sum of the individual CSQ-8 item scores are calculated as a measure of the intervention's acceptability.
Results: To date, all participants who were deemed eligible (N=14) signed up to participate in PREP-BD. Preliminary findings from this pilot study confirmed the feasibility and acceptability of PREP-BD.
Conclusion: Although preliminary, our results suggest that a telehealth-based psychoeducational intervention can be feasibly implemented to improve help-seeking and enhance resilience in individuals who are at high risk of developing BD. Directions for future research and clinical implications will be discussed.

TRANSLATIONAL ADDICTION STUDIES OF NOVEL PSYCHOACTIVE SUBSTANCES

Aviv Weinstein, Ariel University
Symposium Synopsis: During the last decade, there has been a worldwide increase in the use and consumption of Novel Psychoactive Substances (NPS) worldwide. NPS are becoming a major health issue because of rising consumption and increasing numbers every. The acute effects of NPS and their long-term side effects are not always known, and safety data regarding their toxicity are often unavailable. Given the rapid increase in the use of NPS, their potential for dependence and abuse, and harmful medical and psychiatric effects, there is a need for pre-clinical and clinical research. The aim of this symposium is to provide an overview on pre-clinical and clinical studies of two of the major classes of NPS, synthetic cannabinoids (SCs) and synthetic cathinones. Results from preclinical studies (behavioral and neurochemical) will be presented. Dr. Maria De Luca who will start by presenting novel findings on repeated exposure to JWH-018 (a major synthetic cannabinoid) in adult and adolescent rats and mice. Dr. Matteo Marti will present studies on the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of the SCs JWH-018 and 5F-PB22 in mice. Prof. Magi Farré will present human clinical studies on Pharmacological effects and toxicity of the synthetic cathinones methylone and clephedrone (4-CMC), and after intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP) evaluating acute pharmacological effects and pharmacokinetics in plasma and oral fluid. Finally, Prof. Weinstein will discuss cognitive and brain imaging studies in regular users of synthetic cannabinoids, with a special focus on mental health.

NEUROBIOLOGICAL SEQUELAE OF THE PASSIVE OR VOLUNTARY ADMINISTRATION OF THE SYNTHETIC CANNABINOID RECEPTOR AGONIST JWH-018

Maria De Luca*[1]
[1] *University of Cagliari*

Objective: The use of Synthetic Cannabinoid Receptor Agonist (SCRA) is growing among adults and adolescents, posing major medical and psychiatric risks. JWH-018 represents the reference compound of SCRA-containing products. Our preclinical studies were performed to evaluate the enduring effects of repeated JWH-018 passive or voluntarily exposure.
Methods: Studies were performed by both passive intraperitoneal (0.25 mg/kg ip for 14 days) or vaping administration (0.3 mg/ml vapor by LJARI vapor chambers for 21 consecutive days) in adult and adolescent rats, respectively. Additional studies were performed by intravenous self-administration (lever pressing, Fixed Ratio 1–3; 7.5 µg/kg/inf) in adolescent mice.
Results: Main results, obtained 24 hours and 7 days after drug discontinuation, showed that repeated JWH-018 exposure in adult rats: (i) induced anxious/aversive behaviors; (ii) decreased spontaneous activity and number of dopamine neurons in the VTA; and (iii) decreased dopamine sensitivity in the NAc shell and core, but not in the mPFC, to a first chocolate exposure; conversely, after a second exposure, dialysate dopamine fully increased in the NAc shell and core but not in the mPFC.

Moreover, passive JWH-018 induced: (iv) astrogliosis (mPFC, NAc shell/core, VTA), microgliosis (NAc shell/core), and downregulation of CB1 receptors (mPFC, NAc shell/core). In addition, we characterized the pharmacokinetic profile of JWH-018 in adolescent male and female rat plasma after passive JWH-018 inhalation. Other studies showed that adolescent JWH-018 IVSA induced at adulthood: (i) repetitive/compulsive-like behaviors; (ii) microgliosis (CPu, NAc) and astrocytopathy (CPu), as revealed by a decreased GFAP expression; (iii) increased of the chemokines MPC1 (striatum) and RANTES (cortex), and a decrease of the cytokines IL2 and IL13 (cortex). **Conclusion:** Taken together, these data suggest that the long-lasting behavioral and neurochemical effects of JWH-018 exposures may not differ substantially as a function of passive or voluntary administration except for some specific aspects of the brain immune response, that deserve further clarification. Nevertheless, this study provides results with high translational value in the field of psychiatric disorders by examining the interaction among environmental factors that are linked to increased psychiatric risk in humans, but also shedding light on the psychiatric risk associated with SCRA vaping, a habit that is becoming increasingly popular.

SEROTONINERGIC SYSTEM IS INVOLVED IN THE PHARMACO-TOXICOLOGICAL EFFECTS INDUCED BY SYNTHETIC CANNABINOIDS IN MICE: PRECLINICAL STUDIES ON JWH-018, 5F-PB22 AND AKB-48

Matteo Marti*[1], *Giorgia Corli[1], Sabrine Bilel[1], Marta Bassi[1], Fabrizio De Luca[2], Elisa Roda[3], Carlo Alessandro Locatelli[3]*

[1]University of Ferrara, [2]University of Milan, [3]Istituti Clinici Scientifici Maugeri, IRCCS Pavia

Objective: Since their first appearance on the illicit drugs market, Synthetic Cannabinoids (SCs) have been frequently detected in biological samples from patients involved in several intoxication and death cases. Consumption of these drugs has been related with the induction of psychotic symptoms, the underlying mechanisms of which are still to be clarified.

Methods: This study primarily investigated the involvement of 5HT2A receptors in the pharmaco-toxicological effects induced by the acute systemic administration of indole-based SCs JWH-018 and 5F-PB22. Secondly, changes induced by the repeated administration of the indazole-based compound AKB48 in mice and neuroplasticity at CB1 and 5HT2A receptor and SERT adaptation have been evaluated.

Results: The present results pointed out that the tested substances deeply alter sensorimotor responses, nociceptive threshold, core temperature, and motor activity in mice. Pretreatment with the selective 5HT2A receptors antagonist MDL100907 at least partially prevented acute sensorimotor disruption, as well as antinociceptive and hypothermic effects induced by both JWH-018 and 5F-PB22. On the other hand, the effects of AKB48 have been significantly influenced by the repeated treatment, as the impairment induced by the third injection was strongly reduced in respect to that of previous administration. Alongside, repeated AKB48 injection caused a rapid downregulation of CB1 receptors and SERT expression, while 5HT2A were upregulated in cerebellar areas.

Conclusion: This evidence states for the first time the relevance of serotoninergic 5HT2A receptors in mechanisms underlying pharmaco-toxicological effects of SCs that may also significantly vary with recurrent use, thus suggesting the emergence of tolerance. Ultimately, the present findings suggest the high-risk profile of SCs as drugs of abuse with reference to the embedding of a possible increased vulnerability for psychotic-like symptoms, further related to mental disorders such as schizophrenia.

SYNTHETIC CATHINONES: ACUTE EFFECTS IN HUMANS

Magi Farre*[1], *Clara Pérez -Mañá[1], Esther Papaseit[1]*

[1]Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona

Objective: Cathinones are derivatives of phenylethylamine, the basic structure of amphetamines, which include a keto group, with cathinone being the most important active substance of the Catha edulis or khat shrub. In recent years, many cathinones of synthetic origin have appeared on the market, forming a relevant part of the so-called new psychoactive substances. The most important are mephedrone, methylone, methylenedioxypyrovalerone (MDPV) or eutylone, among others. These substances are consumed as alternatives to 3,4-methylenedioxymethamphetamine (ecstasy or MDMA). The information available on these substances in humans came from surveys, online description of effects and cases of intoxications. There are few published experimental studies on the pharmacokinetics and pharmacological effects associated with the administration of synthetic cathinones in humans (mephedrone, methylone).

The objective was to evaluate acute pharmacological effects and pharmacokinetics of three synthetic cathinones in humans.

Methods: This paper presents original results of the acute human pharmacology of three different synthetic cathinones. Studies were observational in a recreational setting. A group of 24 volunteers (men and women) were included. Substances include oral doses of clephedrone (4-CMC), and intranasal administration of ethylhexedrone (HEXEN) and ethylpentedrone (NEP). Vital signs and subjective effects were evaluated repeatedly along time. Samples of oral fluid, sweat and urine were collected.

Results: Results showed prototypical effects of psychostimulants in vitals and subjective effects (euphoria, well-being, empathy). The time course of effects/concentrations in saliva were faster after intranasal administration and delayed after oral administration.

Conclusion: The three new synthetic cathinones showed similar effects of other derivatives as methylone and mephedrone. Time course of effects and pharmacokinetics parameters showed some differences that can explain the preference for some substances.

THE EFFECTS OF SYNTHETIC CANNABINOIDS ON EXECUTIVE FUNCTION AND RELATED BRAIN ACTIVITY IN FMRI

Aviv Weinstein*[1], *Koby Cohen[1]*

[1]

Ariel University

Objective: The aims of our studies were to investigate the effects of chronic use of synthetic cannabinoids on the brain's structure and function, cognitive and emotional function and schizotypal personality disorder and big 5 personality traits.

Methods: Cognitive tasks measuring executive function (N-back, WCST, Go-No-GO, Stroop) Structural and functional brain imaging studies in fMRI measuring gray matter and brain activation. Questionnaires assessing depresion, anxiety, Big 5 Personality traits and schizotypal personality disorder.

Results: Synthetic cannabinoid users have exhibited overall smaller grey matter volume than control participants, and in specific regions: insula, the inferior frontal gyrus, the anterior cingulate cortex and the precuneus. These brain regions are rich with cannabinoid CB1-receptors and are associated with addictive behaviors, cannabis use and abstinence. Secondly, SC users were less accurate and showed longer reaction times on the 2-back and 1-back task than control participants. On the high the working memory load, control participants showed additional activation in both parahippocampal gyrus and the precuneus, areas associated with the default mode network. We have further found impairments in mental flexibility (WCST task), impulsivity (Go No Go task) and

response to emotional words (Stroop) in SC users. Furthermore, SC users were more depressed, had higher scores of schizotypal personality disorder and were more introverted, neurotic and less conscientious on the big five questionnaire compared with regular cannabis users and control participants. **Conclusion:** These findings may have major implications for our understanding of the long-term consequences of synthetic cannabis on cognitive and brain function. We currently run a study using F-DOPA in PET MR to assess dopamine function and neural networks in SC users which we hope to report.

PRESENTATION SKILLS WORKSHOP

Peter Falkai, German Society for Biological Psychiatry

PRESENTATION SKILLS WORKSHOP

David Castle1, Peter Falkai2, Susan Rossell3

[1]University of Tasmania, 2German Society for Biological Psychiatry, 3Swinburne University

Objective: To outline a set of strategies to enhance scientific presentations, with a view specifically to upskill more junior colleagues such that they refine and hone their presentation skills to ensure they are engaging, focussed and effective.

Methods: After a brief introduction to the topic, with basic 'do's and don'ts' of presenting skills, the three presenters will deliver examples of what they think are good and not-so-good elements and techniques, augmented by video footage of effective and not-so-effective communication styles from media, including movies and television. The presenters will then discuss amongst themselves and engage the audience in a discussion about what elements of each presentation were effective, and what was not. Tips and strategies will be provided, as well as role play opportunities provided to the audience (nobody will be forced to do anything they don't wish to do!). A particular component will be dedicated to the fine art of how to pose a 'question from the audience' in a succinct and circumscribed manner, as well as how to answer such questions politely and effectively.

Results: We will seek to deliver an interactive presentation skills workshop which will hopefully be both fun and instructive, and show numerous examples to illustrate strategies and techniques to enhance participants' skill set.

Conclusion: Presenting one's research is a key requirement for all researchers. Learning early in one's career can enhance effective skills and hopefully make the experience of future audiences better.

WHAT ARE THE SECRETS TO A GREAT CONFERENCE PRESENTATION?

Susan Rossell1
[1]Swinburne University

Objective: Presenting at conferences is a critical part of science communication for any researcher or academic. Developing a conference presentation is no different to developing any other presentation: you need to be well prepared, consistent throughout and ensure you're able to resonate with your audience. The aim of this workshop presentation will be to provide some important strategies to help deliver a great conference presentation.

Methods: One of the biggest challenges to giving a great presentation is managing your nerves. The current talk will provide some important dos and don'ts' to help you with your anxieties and deliver a professional talk.

Results: I will work through an important checklist, which will include: be prepared and map out what you are going to talk about; make sure that you work within your time constraints; use visuals appropriately; keep things simple and consistent; know your audience; rehearse, rehearse, rehearse; prepare, prepare, prepare; back up your backup; and breathe.

Conclusion: Once you have mastered these tips you will be all set to give a great presentation at any conference big or small.

HOW TO GIVE A TALK AND PRESENT MY SCIENCE AND MYSELF

Peter Falkai1, Florian Raabe2
[1]German Society for Biological Psychiatry, 2Max Planck Institute of Psychiatry
Objective: To show evidence to improve your presentation skills to give a presentation.
Methods: Narrative review of the literature and presenting own experience.
Results: Five tips are given to present yourself and your science successfully.
Conclusion: Taking some time to prepare a talk is a good investment into your career and future.

3:30 p.m. - 5:00 p.m.
Concurrent Workshop I

SEXUAL VIOLENCE AND WOMEN

Florence Thibaut, University Paris Cité

SEXUAL VIOLENCE IN ECUADOR, LATIN AMERICA

Victoria Valdez1
[1]Catholic University of Guayaquil Ecuador, Ecuadorian Society of Biological Psychiatry
Objective: Latin America has the highest rates of gender-based violence in the world, according to the Wilson Center.
Methods: This lecture will focus on gender-based violence, sexual violence concepts, societal factors, drug trafficking industry and present statistical research on this issue.
Results: Sexual violence reveals many areas that need to be explored such as migratory transit violence, migratory consequences, wars and gender-based violence.
INEC (Ecuadorian Statistics) established a total amount of gender-based violence 64.9%, sexual violence 32.7% CEPAM (ONG) complaints 8.682 (2006).
Conclusion: It is important to understand gender violence from a women's rights perspective and not merely as a criminal problem. This way, public policies on gender violence can be designed to include a more comprehensive and effective approach to prevention and treatment.

BEHAVIORAL AND NEURAL FACTORS IN GENDER-RELATED ASPECTS OF VIOLENCE AND ADDICTIONS

Marc Potenza
Objective: Males and females differ with respect to tendencies to engage in and experience violence and aggression as well as in substance and behavioral addictions that may often co-occur with violence and aggression. Understanding better such relationships and the etiological factors could help reduce the effects of aggression, violence and addictions.
Methods: Multiple methods including surveys and neuroimaging involving adolescents and adults have been used to assess and understand gender-related considerations relating to violence, aggression, and addictive behaviors. Factors related to these constructs (e.g., stress and trauma) have also been investigated using these methods, and findings from such studies will be presented.
Results: Gender-related differences exist in relationships between addictive behaviors and violence and aggression. Tendencies such as impulsivity/sensation-seeking appear particularly relevant in males, including at relatively early developmental stages. Women as compared to men tend to experience more stress and trauma in multiple domains (e.g., social, sexual) but not all (e.g., occupational), with stronger links between stress and addictive behaviors seen in women versus men. Sexual trauma is more frequently reported in females versus males, with associated adverse

effects. Gender-related differences in brain responses to stress in women versus implicate multiple cortical brain regions, resonating with gender-related responses to stress and drug cues in people with substance addictions. These findings also resonate with those from studies of youth with higher versus lower levels of childhood trauma, suggesting potential mechanisms for transgenerational cycles of risk for addictions and other poor outcomes. **Conclusion:** Understanding gender-related factors linked to violence, aggression, and addictive behaviors is important for improving the health and well-being of females and males across developmental stages. Neuroimaging approaches are being used to investigate relevant brain- behavior relationships in this regard. Translating an improved biological understanding into improved prevention, treatment and public health interventions is an important next step.

CHEMICAL SUBMISSION AND SEXUAL VIOLENCE

Florence Thibaut1

[1] *University Paris Cité*

Objective: The term chemical submission refers to a substance administration to a person without his/her knowledge to cause him/her a change in the state of consciousness and judgment. This state might be used to perpetrate sexual violence against the victim.

Methods: We will review the main characteristics of the chemical substances consumed and the profiles of victims and aggressors.

Results: It was estimated that up to 17% of sexual assaults could be classified as chemical submission due to the involuntary exposure of the victim to a psychoactive substance. Women under 20 are particularly vulnerable to this form of sexual offence.

Conclusion: Specific prevention programs and training of health personnel is crucial to make the diagnosis (Folgar et al. 2017).

In a changing world (social interactions, dating methods, new technologies) and with the increasing use of new synthetic drugs (designer benzodiazepines, GHB...), the modus operandi of the perpetrators themselves is changing and require increased vigilance at all levels (Chaouachi 2023).

WFSBP TASK FORCE TREATMENT GUIDELINES UNIPOLAR DEPRESSIVE DISORDERS

Michael Bauer, Technische Universität Dresden

RAPID-ACTING ANTIDEPRESSANT TREATMENTS: WHERE IS THEIR PLACE IN THE TREATMENT PATHWAY

Allan Young, King's College London

Background: Mood disorders impose the largest disease related burden related to mental ill-health in adults. Although effective treatments exist, many patients are treatment resistant. New rapidly acting antidepressant treatments (RAATS) are becoming available but their place in the treatment pathway remains to be fully determined.

Objectives: To review the evidence base and science related to RAATS (psychedelics, (s)ketamine).

Methods: Evidence and literature-based workshop.

Findings: Discussion about RAATS in the treatment pathway for mood disorders.

Conclusion: Conclusions: RAATS will play a part in our future treatment pathways.

TREATMENT-RESISTANT DEPRESSION (TRD)

Anthony Cleare1

[1] *Institute of Psychiatry, King's College London*

Objective: To discuss the definitions and epidemiology of TRD

To discuss latest evidence regarding pharmacological and other augmentation strategies in TRD

Methods: Synthesis of literature.
Results: Key findings in TRD include: (1) The need for continued refining of how we diagnose, stage and stratify patients with TRD; (2) Extensive treatment gaps, where few patients are getting optimal treatment (3) accumulating evidence that augmentation strategies are an effective option in TRD and (4) evidence that the poor naturalistic prognosis for many with TRD can be improved using optimised treatment. Data on comparative efficacy of augmentation strategies will be discussed.
Conclusion: TRD remains a key clinical problem. Synthesis of the latest evidence helps us understand the important, pharmacological, role that augmenting antidepressant therapy (with psychotherapeutic and/or neurostimulatory add-on treatments) can play in improving long term outcomes in TRD.

MODERN TREATMENT GUIDELINES: METHODOLOGICAL AND TECHNICAL ASPECTS

*Andrea Pfennig*1, Michael Bauer2, Bettina Soltmann1*

[1]University of Technology Dresden, 2German Society for Biological Psychiatry; University of Technology Dresden

Objective: Methodological and technical aspects of the development of modern treatment guidelines will be presented and discussed. Propositions for the future WFSBP guideline development will be deduced.
Methods: International standards for guideline development will be briefly summarized. The methods applied in the current version of the WFSBP treatment guidelines will be presented.
Results: Challenges in the developmental process of the current version of the WFSBP treatment guidelines will be discussed.
Conclusion: Strategies for the further development of WFSBP treatment guidelines will be presented and discussed including propositions to implement processes of living guideline concepts.

ESTABLISHED AND NOVEL ANTIDEPRESSANT APPROACHES IN THE TREATMENT OF MOOD DISORDERS

Philipp Ritter1

[1]Technische Universität Dresden

Objective: Pharmacological compounds targeting neural components of the monoaminergic signalling system remain the mainstay of treatment for mood disorders. Comparative efficacy, differing side effects profiles and special indications will be reviewed. These classical approaches have more recently been augmented by novel neurostimulatory techniques such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS). The heterogenous landscape of implementation protocols and current evidence base for antidepressant efficacy will be reviewed.
Methods: Evidence and literature-based workshop.
Results: Discussion on the pharmacological and neurostimulatory treatment of mood disorders.
Conclusion: Traditional pharmacological approaches in the treatment of depressive episodes may in future be augmented or in some cases superseded by neurostimulatory approaches to accelerate response and reduce side effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Peter Fried, Beth Israel Deaconess Med. Ctr. and Harvard Medical School

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Mouhsin Shafi1

[1]Beth Israel Deaconess Medical Center

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.

Methods: Review of NIBS Technologies: We will start by examining the fundamental principles underlying the two most common NIBS technologies: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Participants will gain insights into the mechanisms of action, safety considerations, historical and cutting-edge approaches, and ongoing challenges.

Applications Across Neuroscience and Clinical Practice: The workshop will explore the diverse applications of NIBS techniques, including cognitive enhancement, neurophysiologic assessments, treatment of neuropsychiatric disorders, and neurorehabilitation. In-depth discussions will revolve around case studies and ongoing research projects.

Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).

Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions.

Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.

Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF CONCURRENT TRANSCRANIAL ELECTRICAL STIMULATION AND MAGNETIC RESONANCE IMAGING

Shirley Fecteau1

[1]Universite Laval Faculty of Medicine

Objective: We will discuss the use of Transcranial Electrical Stimulation (tES) in patients with neuropsychiatric disorders. We will first describe the main stimulation parameters to consider and the choice of study designs to optimize scientific rigor and clinical responses. We will also address concerns of negative results and the importance of including neuroimaging in tES studies in order to understand its clinical efficacy (or lack of).

When developing neuropsychiatric interventions, it is recommended to measure the hypothesized mechanisms of therapeutic change. Here, the hypothetical mechanism underlying the reduction of a given set of neuropsychiatric symptoms is that tES will modulate brain activity associated with these symptoms. In previous studies, we aimed to reduce symptoms or improve cognition, without identifying the effects of tES on brain activity. A limit of this approach is that when we get null results,

we do not know if they are because tES did not modulate brain activity associated with the targeted symptoms. Also, when the goal is to induce lasting clinical benefits, several tES sessions must be delivered, for example daily sessions for 4 weeks. The effects of a single tDCS session are short-lived. Therefore, before conducting long-term clinical trials, it is important to know whether the proposed tES parameters will likely modulate brain activity relevant to the targeted symptoms.
Methods: We conducted a series of concurrent tES-MRI studies. Specifically, we performed functional and spectroscopic MRI before, during and after tES in groups of healthy adults and adults with substance-related and addictive disorders. Our main questions were: 1) Does tES reach the cortex sufficiently to modulate brain activity? These patients often have cortical abnormalities that may prevent the current from sufficiently reaching the cortex. 2) If tES reaches the cortex, are these effects on brain activity relevant to the targeted symptoms? In this workshop, we will also discuss and demonstrate the technical aspects of how to concurrently use tES and MRI.
Results: Main findings indicate that tES can modulate functional connectivity and neurotransmitters levels. Some of these effects are significant during and/or after stimulation. Some are observed in healthy adults but not in patients, and vice versa. Further, some morphometric properties such as smaller frontal volume in patients correlate with changes induced by tES on functional connectivity and neurotransmitter levels. Functional connectivity of some networks prior to tES can predict tES changes on functional connectivity. Interestingly, none of the published studies from various teams (e.g., delivering tES on both frontal regions found functional connectivity changes inhibitory/excitatory effects) between these frontal regions, despite knowing that the current travels from the anode to the cathode electrodes. The effects are proximal or/and distal to the electrodes (e.g., fronto-parietal network).
Conclusion: Concurrent use of tES and neuroimaging can greatly contribute at understanding the mechanisms of tES and its clinical benefits. Findings from such study designs also contribute at building and developing more specific hypotheses of tES effects, such as potential effects during and after stimulation and how functional connectivity, and priming such connectivity, might influence tES effects.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Paula Davila Pérez1
1
Hospital Universitario Rey Juan Carlos

Objective: This workshop aims to provide a comprehensive overview of the latest developments in non-invasive brain stimulation (NIBS) techniques and their applications. Attendees will come away with a working knowledge of NIBS and how it can be used in both clinical practice and basic research.
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Demonstration: A brief demonstration will be provided covering the fundamental methodology of TMS (the motor hotspot and resting motor threshold) and tES (electrode setup and impedance check).
Results: Recent Breakthroughs in NIBS Research: Workshop participants will be exposed to cutting-edge findings in the field. This includes advancements in personalized NIBS protocols, precision

targeting of brain regions, and the development of closed-loop stimulation systems. These breakthroughs have paved the way for more effective and tailored interventions. Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development. **Conclusion:** Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

NEUROPSYCHIATRIC APPLICATIONS OF NON-INVASIVE BRAIN STIMULATION

Asli Demirtas-Tatlidede1
1

Bahcesehir University, Faculty of Medicine, Istanbul

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Neuroethical Considerations: Ethical and societal implications of NIBS will be examined. Discussions will encompass topics such as informed consent, privacy, and the responsible use of NIBS in various contexts. The workshop will underscore the importance of ethical considerations in the field's development.
Conclusion: Non-invasive brain stimulation continues to be a dynamic and rapidly evolving field with broad potential. This workshop will serve as a platform for experts and novices alike to delve into the approaches, applications, and ethical considerations of NIBS. By promoting cross-disciplinary collaborations and knowledge exchange, we aim to inspire innovation and responsible application in NIBS research. As we look to the future, we anticipate NIBS to further bridge the gap between basic neuroscience, clinical practice, and societal needs, with implications reaching beyond our current understanding of the human brain.

BIG DATA APPROACHES TO DISCOVER DISEASE MECHANISMS OF MENTAL ILLNESS *Ole Andreassen, University of Oslo*

Symposium Synopsis: The last decade has marked a period of growth in psychiatric genetics with new insights into the genetic etiology of psychiatric disorders. As the heritability and the extensive polygenicity of psychiatric disorders are now recognized, gaining a better understanding of the genetic architecture of each disorder is important. Driven by the discoveries of large consortia and big data efforts, large-scale genetic studies have uncovered many common and rare genetic variants associated with psychiatric disorders and related traits. However, there is still much unknown about the underlying disease mechanisms and potential for clinical utility.

As the field progresses and the datasets get larger, there is a need for advanced mathematical approaches. Such big data methodology for translating genetic findings into biological and clinical interpretations are critical to understand the disease mechanisms of psychiatric disorders. We will discuss new big data approaches in psychiatric genetics, to improve discovery, fine-mapping strategies, imaging genetics and clinical utility.

Dr. Nadine Parker (Canada) will present brain imaging genetics results. Dr. Bayram C. Akdeniz (Cypres) will introduce the MiXeR; a causal mixture model tool for estimating the number of causal variants. Naz Karadag (Turkey) will show how the (ConjFDR) tool identifying genetic overlap between neurological disorders and psychiatric disorders. Dr. Shahram Bahrami (Iran) will present the Multivariate Omnibus Statistical Test (MOSTest) and discuss the genetic architecture of hippocampal formation across brain disorders.

These four speakers will highlight the importance of big data approaches in psychiatry, enabling a better understanding of psychiatric disorders and their underlying brain mechanisms.

GENETIC OVERLAP BETWEEN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

*Naz Karadag1, Shahram Bahrami1, Guy F. L. Hindley2, Ole Kristian Drange3, Alexey A. Shadrin1, Srdjan Djurovic4, Anders M. Dale5, Oleksandr Frei1, Ole A. Andreassen6, Olav B. Smeland6, Guy Hindley*7*

1University of Oslo, 2University of Oslo; King's College London, 3Norwegian University of Science and Technology; St. Olavs Hospital, Trondheim University Hospital, 4Oslo University Hospital; University of Bergen, 5University of California, 6University of Oslo; Oslo University Hospital, 7NORMENT, Centre for Mental Disorders ResearchOslo University Hospital, Institute of Clinical Medicine, University of Oslo

Objective: Neurological disorders and psychiatric disorders are heritable brain disorders with overlapping clinical features and high comorbidity. However, the etiological mechanisms underlying the relationships between these disorders are poorly understood. In a series of projects we have aimed to identify overlapping genetic loci between specific neurological and psychiatric disorders to gain a better understanding of their comorbidity and shared clinical features.

Methods: We analyzed non-overlapping genome-wide association study (GWAS) data in over a million participants for neurological disorders epilepsy, migraine, Parkinson's disease and Alzheimer's disease; and for psychiatric disorders schizophrenia, bipolar disorder and depression. We analyzed GWAS summary data using the conjunctional false discovery rate (conjFDR) statistical tool to increase power for locus discovery. Identified genetic loci were then functionally annotated using FUMA.

Results: We find cross-trait genetic enrichment in neurological disorders conditional on associations with psychiatric disorders, and vice-versa, which indicates genetic overlap between these disorders. Several genomic loci have been identified between neurological disorders and psychiatric disorders.

Many of these loci show mixed effect directions, in line with the absent or weak genetic correlations previously reported between these disorders. **Conclusion:** The genetic overlap with mixed effect directions between neurological disorders and psychiatric disorders demonstrates a complex genetic relationship between these disorders and indicates that overlapping genetic risk may contribute to shared pathophysiological and clinical features between brain disorders.

DISTRIBUTED GENETIC ARCHITECTURE ACROSS THE HIPPOCAMPAL FORMATION IMPLIES COMMON NEUROPATHOLOGY ACROSS MAJOR BRAIN DISORDERS

Shahram Bahrami**1*, *Kaja Nordengen1, Alexey A. Shadrin1, Oleksandr Frei1, Dennis Van der Meer2, Anders M. Dale3, Lars T. Westlye1, Ole A. Andreassen1, Tobias Kaufmann4*

[1]University of Oslo, 2University of Oslo; Maastricht University, 3University of California, 4University of Oslo; University of Tübingen

Objective: The hippocampal formation on each side of the medial temporal lobes of the brain plays critical roles in spatial and episodic memory, navigation, emotions, and other complex human behaviours, yet is unexplored about the genetic architecture of the hippocampal formation and its involvement in psychiatric and neurological disorders.

Methods: First, we used multivariate genome-wide association analysis in volumetric data from 35,411 individuals from the UK Biobank (age range: 45–82 years, mean: 64.4 years, s.d.: 7.5 years, 51.7% females) for the main analysis, and of 5262 individuals with non-white ethnicity (age range: 45–81, mean: 62.9, s.d.: 7.6 years, 53.6% females) for the replication in independent data. Second, we used summary statistics from recent large-scale GWAS of total hippocampus volume to identify genetic overlap with eight major developmental and degenerative brain disorders (autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), schizophrenia (SCZ) and bipolar disorder (BIP), migraine (MIG), major depression (MD), Parkinson's disease (PD) and Alzheimer's disease (AD)) by conjunctional FDR statistics (FDR < 0.05).

Results: We revealed 173 unique genetic loci with distributed associations across the hippocampal formation including 153 loci that had not been previously identified. Also, Conjunctional FDR analysis allowed us to test for shared loci between the hippocampus and each of the disorders. We identified 8 loci significantly overlapping with ADHD, 4 loci with ASD, 77 with BIP, 161 with SCZ, 41 with MD, 80 with MIG, 19 with AD and 10 loci significantly overlapping with PD.

Conclusion: Our results suggest a polygenic architecture of the hippocampal formation, distributed across its subregions. The genetic overlap with various brain disorders with typical onset at different stages of life implicated genes, where common genes suggest partly age- and disorder-independent mechanisms underlying hippocampal pathology and it may be relevant targets for future studies.

GENETIC OVERLAP BETWEEN PSYCHIATRIC DISORDERS AND WHITE MATTER MICROSTRUCTURE IMPLICATE DEVELOPMENTAL AND NEURAL CELL BIOLOGY

Nadine Parker**1*, *Weiqiu Cheng1, Pravesh Parekh1, Guy F. L. Hindley2, Alexey A. Shadrin1, Anders M. Dale3, Oleksandr Frei1, Ole A. Andreassen1*

[1]University of Oslo, 2University of Oslo; King's College London, 3University of California San Diego

Objective: Many psychiatric disorders are associated with variations in brain white matter microstructure. A better understanding of the shared genetic basis of psychiatric disorders and white matter microstructure may provide insights into the biological underpinnings of these reported associations. This study aims to characterize the shared genetic architecture between three psychiatric disorders [bipolar disorder (BIP), major depressive disorder (MDD), and schizophrenia (SCZ)] and white matter fractional anisotropy (FA) as well as uncover potential underlying biology.

Methods: Summary statistics were acquired from genome-wide association studies (GWAS) of BIP, MDD, and SCZ from the Psychiatric Genomics Consortium as well as a GWAS of FA performed with UK Biobank participants. Genetic architecture (polygenicity and discoverability) and genetic overlap (genetic correlations and overlapping trait-influencing variants) were estimated along with identification of shared loci. Shared variants were mapped to genes and tested for enrichment among neurodevelopmental, cellular, and molecular gene-sets. The main analyses used average FA across brain white matter while secondary analyses assessed genetic overlap for 21 white matter tracts. **Results:** The polygenicity of BIP, MDD, and SCZ were at least seven-times greater than average FA, although, average FA was more genetically discoverable. Average FA shared an estimated 42.53%, 42.99%, and 90.68% of trait-influencing variants with BIP, MDD, and SCZ, respectively. Additionally, 12, 4, and 28 shared loci were identified for average FA with BIP, MDD, and SCZ, respectively. Enrichment analyses implicated neurodevelopmental gene expression, astrocytes, microglia, myelin, and cell adhesion molecules. The degree of these gene-level associations varied across each psychiatric disorder implicating differing underlying biology. For BIP and SCZ, case vs control tract- level differences in FA correlated with genetic correlations between those same tracts and the respective disorder. Tract-level analyses recapitulated a similar pattern of greater genetic overlap for SCZ followed by BIP and MDD. **Conclusion:** This study shows that BIP, MDD, and SCZ exhibit a polygenic overlap with white matter FA. This supports theories suggesting some psychiatric patients have impaired integration between brain regions while providing potential biological underpinnings.

FINEMAPPING CAUSAL VARIANTS IN HUMAN GENOME USING MIXER MODEL: CURRENT RESULTS AND FUTURE DIRECTIONS

Bayram Akdeniz*[1], *Oleksandr Frei[1], Alexey Shadrin[1], Dmitry Vetrov[2], Dmitry Kropotov[3], Eivind Hovig[4], Ole Andreassen[1], Anders Dale[5]*

[1] NORMENT Centre, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, [2]National Research University Higher School of Economics, Moscow, [3]Lomonosov Moscow State University, [4]Centre for Bioinformatics, University of Oslo, [5]Center for Multimodal Imaging and Genetics, University of California San Diego

Objective: Discoveries from genome-wide association studies can be hard to interpret especially due to the highly correlated genetic variants. Finemapping studies, which aim to identify causal SNPs associated with a trait at a given locus after controlling for correlation among genetic variants, become important in such cases. There are many proposed finemapping methods in the literature that focused on this problem using different approaches [1]. Among these methods, Bayesian methods demonstrated their effectiveness. FINEMAP [2] and SuSiE [3] methods can be considered some of those successful Bayesian methods in terms of accuracy and computational complexity. Our aim in this work is to develop a new finemapping method using a variational Bayesian approach and MiXeR model [4].

Methods: We propose a variational Bayesian approach for finemapping genomic data based on the optimization of Evidence Lower Bound (ELBO) of the likelihood function obtained from MiXeR model. Particularly, we derived the likelihood function of summary statistics using MiXeR model and then ELBO of this likelihood function is determined for optimization. The optimization is done by Adaptive Moment Estimation Algorithm by using the first derivatives of ELBO and corresponding posterior probabilities of being causal are obtained accordingly.

Results: We have tested our method on synthetic data (N=10.000) and UK Biobank (UKB) genome data (N=337.145) with standing height as the phenotype by comparing with FINEMAP and SuSiE. According to the results in both scenarios, our method has given promising results in terms of

accuracy to pinpoint actual causal variants and estimate the phenotype. In the extensive number of experiments both on synthetic data and UKB data, our method gives superior results compared to other methods in the majority of these experiments. **Conclusion:** We have developed a novel finemapping method using the MiXeR model to detect actual causal variants and estimate phenotype. The initial experiments gave promising results compared to the existing methods in the literature. Our next aim is to apply our method to mental disorders to identify underlying causal variants. Furthermore, we are focusing on expanding our mathematical model for cross-trait and trans-ethnic analysis. Another future work is integrating our approach with GSA-MiXeR gene set enrichment analysis to use enriched priors which leads to potential performance improvement [5].

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Saturday, June 8, 2024
8:00 a.m. - 9:00 a.m.
Plenary Session IV- Guy Goodwin

CAN WE RE-MEDICALISE THE PSYCHEDELIC EXPERIENCE?

Guy Goodwin1
[1]University of Oxford

Objective: Despite the widespread availability of multiple antidepressant treatments, depression remains a common and oftentimes debilitating disorder. A proportion of patients with major depressive disorder fail two or more antidepressant treatments and are considered to have treatment-resistant depression (TRD). Recent attention has turned to psilocybin and other psychedelic compounds as potential rapidly acting and durable episodic treatments for psychiatric disorders including depression.

Methods: COMP 001 was the first large, multinational, randomized controlled trial to evaluate the investigational drug COMP360, a proprietary pharmaceutical-grade synthetic psilocybin formulation, optimized for stability and purity, developed by the sponsor COMPASS Pathfinder Ltd in patients with TRD. This was a dose-ranging study that randomized 233 participants equally to 25mg or 10mg, or the 1mg control treatment. Participants down-tapered and washed out any previous antidepressant medications, and received a single administration of COMP360 as monotherapy, after which they were followed for 12 weeks.

Results: On the primary efficacy measure, large dose-dependent reductions from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) scores were evident starting from Day 2. Clinically meaningful differences in MADRS score improvements between the 25mg and 1mg doses were statistically significant through week 6 and remained numerically evident at week 12. Results of secondary and additional efficacy measures were consistent with MADRS results.

Conclusion: COMP360 was generally well-tolerated; in both studies over 90% of adverse events were either mild or moderate in severity. Suicidality remains a concern in TRD studies. These results suggest that COMP360 has potential to become an important contribution to the treatment for TRD and warrant the further clinical development of COMP360 in rigorous, large, randomized controlled studies.

9:30 a.m. - 11:00 a.m.

Concurrent Symposia VIII

PREVENTING AND AMELIORATING TREATMENT-RESISTANT DEPRESSION: BEST PRACTICE AND BEYOND

Allan Young, King's College London

Symposium Synopsis: Depression is the leading cause of disability worldwide, despite the many effective pharmacological and non-pharmacological treatment options available. Treatment-resistant depression (TRD), which is often defined as an insufficient response to two or more adequate treatment trials, affects up to 50% of those with depression. TRD is associated with poorer prognosis, higher mortality, and higher healthcare utilisation costs. With every additional treatment step for depression comes a decreased likelihood of response, and therefore it is critical to optimise care at the earliest possible stage of illness. This symposium will focus on avenues to improving best practice care for depression, with a focus on reducing treatment resistance. Our speakers will cover their work focused around best practice augmentation options for TRD, probiotics as potential novel augmentation options, the potential use of inflammatory markers for treatment stratification and

optimising response through pharmacogenetic-informed treatment selection. All four avenues could provide hope for enhancing the future care of people with depressive illness.

PHARMACOLOGICAL AUGMENTATION STRATEGIES FOR TREATMENT RESISTANT DEPRESSION

Anthony Cleare**1*

[1]*Institute of Psychiatry, King's College London*

Objective: Pharmacological augmentation is one of the most effective interventions for treatment resistant depression (TRD), with accumulating evidence that it may be more effective than antidepressant-switching strategies. However, very few patients with TRD receive augmentation treatment (between 0.2% and 11% depending on setting). The most often recommended first line therapies are lithium, quetiapine and aripiprazole, with other well supported options including thyroid hormone, risperidone, olanzapine, (es)ketamine, mirtazapine, buspirone, lamotrigine and bupropion (British Association for Psychopharmacology/Maudsley Guidelines).

Methods: Despite a relative paucity of RCTs, network metanalyses have helped gain a broad feel for the relative efficacy of the available augmentation strategies, at least in the acute phase. However, relatively few studies directly comparing augmentation treatments head-to-head have been undertaken, and none have looked at longer term outcomes. The LQD Study is a pragmatic RCT that directly compared two of the first line augmentation treatments, lithium and quetiapine, in patients who had failed to respond to at least two adequate antidepressant treatment trials. Clinical and health economic outcomes were collected over 1 year of treatment to address the lack of knowledge regarding longer term effects. Additionally, as TRD response is highly variable with patients often moving between response/remission, partial response and relapse, longitudinal assessment was undertaken using weekly depression ratings.

Results: Detailed results from the LQD study will be presented, including comparative clinical outcomes with lithium versus quetiapine, cost-effectiveness analyses and differential predictors of treatment response.

Conclusion: Pharmacological augmentation strategies for TRD remain underused yet effective treatments. Results from the LQD study add further evidence for their long term efficacy, and will help clinicians in the choice of first line treatment options.

PROBIOTICS AS PUTATIVE AUGMENTATION STRATEGY IN DEPRESSION

Viktoriya Nikolova**1*, *Anthony Cleare2, Allan Young2, James Stone3*

[1]*ADM Protexin, 2King's College London, 3Brighton and Sussex Medical School*

Objective: Research over recent years has outlined a clear role for the microbiota-gut-brain axis in the pathophysiology of depression and has given rise to the development of novel intervention strategies, such as probiotics. However, clinical trials of probiotics are still scarce and further safety and efficacy data are needed to support this treatment approach. Further, their underlying mechanisms of action in clinical populations remain largely unknown.

Methods: Data from meta-analyses identifying the most appropriate mode of administration of probiotics and the gut microbial alterations associated with depression will be presented. Then, this talk will focus on novel findings from a double-blind placebo-controlled pilot trial (RCT) that examined the effects of an 8-week adjunctive multi-strain probiotic intervention in adults with depression taking antidepressants. In addition to psychiatric and safety data, stool and blood samples were collected and a computer-based emotion recognition task was performed.

Results: 49 participants (18-55 years, n=38 female, residing in London, UK) were included in intent-to-treat analyses (n=24 probiotic, n=25 placebo) in the RCT. The intervention was acceptable and well-tolerated with 8% attrition rate (n=3 placebo, n=1 probiotic), 97% adherence rate and no serious

adverse reactions. Standardised effect sizes (SES) from linear mixed models demonstrated that the probiotic group attained greater improvements in depressive (IDS week 8: SES [95%CI]= 0.64 [0.03, 0.87]) and anxiety symptoms (HAMA week 8: SES [95%CI]= 0.79 [0.06, 1.05]), compared to the placebo group. 16SrRNA sequencing of stool samples indicated the probiotic was able to positively modulate the gut microbiota: (i) there was an increase in richness only in the probiotic group ($p < 0.05$); and (ii) post-treatment, only the placebo, but not the probiotic group, had significantly decreased alpha diversity compared to demographically matched healthy controls ($p < 0.05$). The probiotic increased levels of several bacteria, of which Bacilleceae and genus Bacillus remained significant post-FDR correction and correlated with anxiety improvement (rho=-0.43,$p < 0.05$). There was no impact on inflammatory cytokines (CRP, TNFα, IL-1β, IL-6, IL-17) or BDNF; however, probiotics showed a tendency to increase positive affective bias. **Conclusion:** Our research indicated that, compared to placebo, 8-week adjunctive probiotic intake resulted in greater and clinically meaningful improvement in depressive and anxiety scores. The beneficial effects of probiotics were partially mediated by modification of gut microbiota composition. The acceptability, tolerability and estimated effect sizes on key clinical outcomes encourage further investigation of probiotics as augmentation strategy in depression in large-scale clinical trials, with an expanded evaluation of mechanisms.

OPTIMISING RESPONSE THROUGH PHARMACOGENETIC-INFORMED TREATMENT SELECTION

Roos van Westrhenen*[1]

[1] *Parnassia Psychiatric Insitute, Amsterdam*

Objective: Pharmacogenetics is a discipline that investigates genetic factors that affect the absorption, metabolism, and transport of drugs, thereby affecting therapy outcome. These genetic factors can, among other things, lead to differences in the activity of enzymes that metabolize drugs. Studies in depressed patients show that genotyping of drug-metabolizing enzymes can increase the effectiveness of treatment, which could benefit millions of patients worldwide. The audience will be updated on the potential of pharmacogenetics for psychiatry.

Methods: The current status quo of pharmacogenetics in psychiatry will be provided, by presenting an overview of relevant studies, available guidelines and also ongoing projects.

Results: The European guideline on clinical implementation of pharmacogenetics in psychiatry will be shortly discussed, as well as the other available guidelines on pharmacogenetics from the Dutch Pharmacogenetic Working group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). An overview of currently performed clinical studies in psychiatry will be provided, including the recently published Dutch PREPARE trial and the current ongoing Horizon2020-funded PSY-PGx project (www.psy-pgx.org).

Conclusion: Pharmacogenetics can be used to fine-tune medication prescription by assisting in selecting medication type and dosage, for indivdual patients. Guidelines are available for prescribing antidepressants and clinical application will be discussed. The actual implementation of pharmacogenetics in psychiatry is ongoing work and in this lecture potential ways forward will be suggested.

References:

1. Editorial: From Trial and Error to Individualised Pharmacogenomics-Based Pharmacotherapy in Psychiatry R. van Westrhenen and M. Ingelman-Sundberg Frontiers in Pharmacology, 2021 doi: 10.3389/fphar.2021.725565

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CAN WE USE INFLAMMATORY MARKERS TO PERSONALISE TREATMENT FOR TREATMENT-RESISTANT DEPRESSION?

Rebecca Strawbridge**1*, *Estefany Izurieta2, Allan Young2, Anthony Cleare2*

[1]Institute of Psychiatry, King's College, 2King's College London

Objective: It is now established that a subgroup of individuals with depressive illness have immune dysregulations. Treatment-resistant depression is frequently associated with elevated pro-inflammatory biomarkers, and it is likely that some recommended treatments for TRD have downregulatory effects on inflammation. This symposium will consider the effects of TRD treatments on inflammation and inflammatory biomarkers as putative predictors of (differential) treatment responses in TRD.

Methods: The symposium will present findings from naturalistic observational treatment studies in populations with (treatment resistant) depression and systematic review of the effects of recommended TRD treatments on peripheral inflammatory biomarkers across populations of patients.

Results: Ketamine and aripiprazole may reduce pro-inflammatory states. Despite mechanistic and preclinical support for ECT and lithium as anti-inflammatory, evidence of these effects in humans is mixed. Quetiapine may have less anti-inflammatory effects and be more suitable for patients without an apparent inflammatory component to TRD illness. More evidence is required for other therapies with potential anti-inflammatory effects, such as bupropion. Although overall, elevated inflammatory states precede a poor response to treatments in depression, there are some agents which appear to be more beneficial for patients with inflammatory dysregulations.

Conclusion: Inflammatory markers could be used to stratify individuals to optimised treatment. Particular treatments with anti-inflammatory mechanisms may be recommended for those with high inflammation, whereas others may be more suitable for patients without. This avenue of research has the potential to enhance TRD care by directing patients to the 'right' treatment earlier in the course of illness.

NEUROPROGRESSION IN PSYCHIATRIC DISORDERS: BIOMARKERS FOR STAGING AND INTERVENTIONS FOR PREVENTION

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Symposium Synopsis: Neuroprogression subsumes the progressive, recurrent and relapsing course of a specific disorder. In some instances, it is possible to ‘stage’ the course of the disorder based on clinical manifestations, and, to the extent that morphological, biochemical, neurochemical, immunological, physiological and genetic aspects have been established, such parameters as well. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, and loss of synaptic plasticity.

The presenters will discuss the potential utility of specific methods and biomarkers that may assist in identifying vulnerability, determining the stage of the neuroprogressive course, and arrest neuroprogression by utilizing appropriate interventions. Better endophenotypes for affective

disorders are needed to study their neurobiological correlates. Results from a GWAS study on affective temperaments will be presented to demonstrate how polygenic risk scores help understand their association with depressive phenotypes and in interaction with stressors. Development of biomarker profiles to predict mood disorders may also contribute to their staging. Depression with increased inflammation is associated with neurodegenerative changes in corticostriatal and corticolimbic structures and default mode circuitry, affective, and cognitive symptoms – predicting the risk of development of MCI and a neuroprogressive dementia course. Electrical brain activity and the its course in recurrent affective disorders assist in staging and possibly predicting neuroprogressive of course. Lastly, lithium has been associated with neuroprotective or neurotrophic effects. Using neuroimaging and preclinical studies, the model that lithium acts as a synaptic modulator and thus slows neuroprogression in affective disorder will be presented.

POLYGENIC RISK SCORES FOR AFFECTIVE TEMPERAMENTS MAY HELP PREDICT THE ROUTE TOWARDS DEVELOPMENT OF MOOD DISORDERS AND MAY AID STAGING

Xenia Gonda*[1], *Dorka Gyorik1, Zsofia Gal2, Gyorgy Bagdy2, Gabriella Juhasz2*

[1]*Semmelweis University, 2Semmelweis University; NAP-2-SE Neurochemistry Research Group*

Objective: Affective disorders show a moderate-to-high heritability depending on their severity. Furthermore, they are also characterised by remarkable heterogeneity which is paralleled by an equally divergent neurobiological and genetic background. Different subtypes of depression also differ in the relative weight of contributing genetic-internal and environmental-external factors, with the majority of genes playing a role in depression mediating the effects of stress. It is in part due to this large etiological heterogeneity that we still do not fully understand the biological background and genetic determinants of affective disorders. Identifying clinically relevant endophenotypes thus would aid research, and, consequentially, help us find better genetic and other biomarkers for screening, prediction and intervention. Affective temperaments, considered the subclinical manifestation of mood disorders and when present in a dominant form. In the present study we carried out a GWAS of affective temperaments, generated polygenic risk scores (PRS) and investigated their effect on depressive phenotypes in interaction with early traumas and recent life stressors.

Methods: Results of our previous GWAS on affective temperaments as measured by TEMPS-A in a general population was used as a discovery sample. The NewMood database containing 1820 European general population subjects' data on current depression measured by the BSI, as well as data on early childhood traumas and recent severe negative life events occurring in the past 12 months was used as the target sample. We calculated polygenic risk scores for the five affective temperaments (depressive, cyclothymic, irritable, anxious and hyperthymic) using PRSice and adjusting all models for age, gender and the first ten principal components. To calculate the empirical p-value, 10000 permutations were run. In the next step, we analysed the interaction of the five PRS-s with early traumas and recent stress using linear regression models.

Results: Polygenic risk scores calculated for anxious, cyclothymic, depressive and irritable temperaments had a significant effect on severity of current depressive symptoms explaining 0.26-0.71% of variance. In interaction with early childhood traumas, anxious, depressive and hyperthymic temperaments had a significant effect on current depression explaining approximately 10% of variance. Considering a combined effect of early childhood traumas and recent life stress, depressive temperament had a significant effect explaining 13.95% of the variance of current depression severity.

Conclusion: Our findings support the genetic and neurobiological role of affective temperaments in the development of affective disorders and may be useful for prediction and risk screening, as well

as for identifying both psychotherapeutic and pharmacological targets for intervention and possibly for prevention. The next step is to analyse the association of affective temperament PRS-s with different neuroprogressive stages in depression.

INFLAMMATION AND NEURODEGENERATION IN DEPRESSION

Ebrahim Haroon*[1], *Xiangchuan Chen1, Diana Beltran1, Deqiang Qiu1, Felicia Goldstein1, Blaine Roberts1, Jennifer Felger1, Andrew Miller1*

[1]*Emory University School of Medicine*

Objective: Depressed patients experience a 2-5 times higher risk of neurodegenerative disorders, including Alzheimer's dementia. However, predisposing risk factors that enable clinicians to stratify risk and initiate preventive measures are unclear. We propose that chronic inflammatory activation in depression promotes and sustains this risk. Our previous data have demonstrated that increased inflammation in depression increases the risk of glutamate toxicity and leads to toxic disorganization of neural systems linked to emotional and cognitive functions. Herein, we examined if increased inflammation in the brain as measured in cerebrospinal fluid (CSF) was associated with increases in both CSF and neuroimaging makers of neurodegeneration in depressed (with and without cognitive dysfunction) versus controls.

Methods: 54 subjects (35 depressed and 19 non-depressed control subjects) participated in the study and provided CSF samples and clinical and demographic information. Study participants were aged 35-65 and unmedicated with psychotropic medications. Depression was confirmed using SCID-5 for DSMV, and a standardized neurocognitive battery was used to measure psychomotor slowing and executive dysfunction. The immune marker panel included c-reactive protein (CRP), tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1beta, and their circulating receptors [type 2 TNF (TNFR2), IL-6 (IL6sr), and IL-1 receptor antagonist (IL1ra). The neurodegeneration panel included neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), hyperphosphorylated tau-181 (Tau), abeta-(ab)42, and ab40. Diffusion tensor imaging (DTI) and Neurite Orientation Dispersion Density Imaging (NODDI)-based diffusion measures were used to identify regions of interest (ROI) correlated with CSF immune biomarkers after multiple test corrections. The ROIs located in white matter space were identified using an automated probabilistic tractography atlas in the XTRACT toolbox in FSL. Extended instrumental variables regressions were used to compare groups. Linear models were used to examine biomarker/DTI associations.

Results: Of the inflammatory markers, CSF TNFR2 was differentially associated with neurodegeneration markers as a function of depressed group status. Indeed, there was a significant CSF TNFR2 by depressed group interaction that was positively associated with CSF NFL (p-corr=0.002) and CSF GFAP (p-corr < 0.001). CSF TNFR2/NFL association was significant in the DCD+ (pcorr=0.018) but not with DCD- (p=NS) and control (p=NS) groups. Similarly, CSF TNfR2/GFAP association was significant in the DCD+ (pcorr=0.006) and DCD- (p-corr=0.024) but not in the control (p=NS) groups. CSF NFL and GFAP were associated with decreased fractional anisotropy of the right frontal aslant tract (p-corr=0.02 and 0.03, respectively) and increased mean diffusivity of right anterior thalamic radiation (p-corr=0.047 and 0.008, respectively); and CSF NFL was associated with an increased orientation dispersion index (p-corr=0.04) in the left arcuate fasciculus only among depressed groups. No associations between DTI measure with CSF NFL and GFAP were noted in the control group.

Conclusion: Our data indicate that depressed subjects with increased inflammation may have a higher risk of cognitive decline and neurodegeneration. Treatment with immune-modulating or neuroprotective agents and well-known antidepressants may be useful in this group.

ELECTRICAL BRAIN ACTIVITY AND ITS COURSE IN RECCURENT AFFECTIVE DISORDERS

Dimitris Dikeos*[1], *Gerasimos Konstantinou2*
[1]*National and Kapodistrian University of Athens, 2University of Toronto*

Objective: Brain electrical activity is commonly used to assess certain neurofunctional aspects of psychiatric illness. This presentation will focus on relevant findings in mood disorders.
Methods: Search in pubmed and other databases for original papers, reviews and meta-analyses.
Results: In both major depressive disorder (MDD) and bipolar disorder (BD), electroencephalography (EEG) has revealed abnormalities in resting-state EEG and evoked-related potentials (ERPs); the latter are the result of averaging EEG activity time-locked to the onset of the presentation of a stimulus that leads to a stereotyped electrophysiological response consisting of a series of positive and negative voltage deflections.
Conclusion: The validity of the findings as potential biomarkers will be discussed, as well as their contribution to the theory of neuroprogression in affective illness, and the possibility of their use in treatment prediction.

ASSOCIATION OF IMMUNOPSYCHIATRY, TREATMENT RESISTANCE AND NEUROPROGRESSION

Dominique Endres*[1]
[1]*Medical Center - University of Freiburg,*

Objective: Immunopsychiatry is a transdiagnostic, multidisciplinary, and translational field. From a clinical perspective, the discovery of NMDA-R encephalitis has played a vital role in the development of immunopsychiatric research as it was found that neuronal autoantibodies can be associated with both neurological signs and psychotic symptoms. Several other central nervous system autoantibodies have also been described, and international consensus criteria for autoimmune psychosis have been derived from these findings. In addition, other autoimmune-mediated severe mental illnesses, such as autoimmune obsessive–compulsive disorder (OCD) and autoimmune affective syndromes, are also discussed.
Methods: The talk will provide an overview of the controversial field of clinical immunopsychiatry, focusing on autoantibody-associated syndromes.
Results: Case studies, first case series, and retrospectively analyzed groups of patients with psychoses, affective syndromes, and OCD will be presented. The underlying pathophysiological autoantibody mediated processes and relevant biomarkers using electroencephalography, brain imaging, and cerebrospinal fluid analyses will also be addressed.
Conclusion: Red-flag signs will be summarized, and the current immunopsychiatric experience will be discussed in the context of treatment resistance and neuroprogression.

UPDATES IN ECT PRACTICE AND RESEARCH: NEW APPLICATIONS

Georgios Petrides, Robert Wood Johnson Medical School

Symposium Synopsis: In this symposium we will review new data in clinical research of Electroconvulsive therapy (ECT) and discuss new clinical applications.
Dr. Stella Rosson will summarize the meta-analytical evidence and safety of ECT and discuss data from a comprehensive umbrella review of the literature for randomized control trials of non-pharmacologic somatic treatments such as Deep Brain Stimulation, Transcranial magnetic stimulation (TMS), transcranial Direct current stimulation (tDCS) and others.
Dr. Søren Dinesen Østergaard will present unpublished results from a study investigating clinical and sociodemographic characteristics associated with relapse following ECT for bipolar disorder, based on data from more than 1400 Danish patients. He will discuss identified markers indicating high risk for relapse.

Dr. Brent Forester will discuss evidence for the use of ECT for the treatment of agitation in patients with severe dementia, as well as the design and implementation of a multicenter study funded by the National Institute of Mental Health in United States. Dr. Sohag Sanghani will report on the novel use of ECT in patients with autoimmune encephalitis, including ant-NMDA receptor encephalitis, and medication resistant catatonia.

EFFICACY AND SAFETY OF ECT AND OTHER BIOLOGICAL TREATMENTS IN PSYCHIATRIC DISORDERS: RESULTS FROM AN UMBRELLA REVIEW

Stella Rosson*[1]

[1]*East London NHS Foundation Trust*

Objective: To provide a comprehensive overview of the extant evidence of efficacy and safety of electroconvulsive therapy and other biological non-pharmacological treatments in psychiatric disorders.

Methods: We conducted an umbrella review selecting the largest meta-analyses of randomised controlled trials reporting on efficacy and safety of biological non-pharmacological treatments. These were electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and light therapy.

Results: We collected evidence from 102 including meta-analyses. Biological non-pharmacological treatments were found effective in a variety of mental disorders. In depressive disorders, interventions superior to inactive treatment were, in order of magnitude of improvement, ECT (SMD=0.91), TMS (SMD=0.51), tDCS (SMD=0.46), DBS (SMD=0.42) and light therapy (SMD=0.41). In schizophrenia spectrum disorders, effective interventions compared to sham were ECT (SMD=0.88), tDCS (SMD=0.45), and TMS (SMD=0.42-0.58). Other disorders with evidence of efficacy were substance use disorder (TMS, SMD=0.77-1.16), obsessive-compulsive disorder (DBS, SMD=0.89, and TMS, SMD=0.64), post-traumatic stress disorder (TMS, SMD=0.46), generalised anxiety disorder (TMS, SMD=0.68), attention deficit-hyperactivity disorder (tDCS, SMD=0.23), and autism (tDCS, SMD=0.97).
In no case the acceptability of biological treatments was lower than inactive treatment.

Conclusion: There is a large body of evidence in the medical literature regarding efficacy and safety of biological non-pharmacological treatments in a broad array of mental disorders. Among treatments, ECT had the largest effect size in depressive disorders and schizophrenia spectrum disorders. These techniques can be considered as therapeutic tools in an increasing number of psychiatric conditions.

CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH RELAPSE FOLLOWING ELECTROCONVULSIVE THERAPY IN BIPOLAR DISORDER

Soren Dinesen Ostergaard*[1]

[1]*Aarhus University Hospital - Psychiatry*

Objective: Electroconvulsive therapy (ECT) is an effective treatment of severe episodes of bipolar disorder (BD), but relapse in the months following ECT is common. In the present study we aimed to identify clinical and sociodemographic characteristics associated with relapse following ECT in BD.

Methods: Using data from the Danish nationwide registers, we identified all patients receiving their first ECT series with an indication diagnosis of BD in the period from 2006 to 2019. These patients were followed for six months after ECT where relapse was defined as either psychiatric hospital admission or reinitiation of an ECT series. The association between clinical and sociodemographic characteristics and relapse was examined via multivariable Cox proportional hazards regression (survival analysis).

Results: A total of 1498 patients with bipolar disorder will be included in the data analyses, which are ongoing. The results will be shown at the 2024 WFSBP Congress.
Conclusion: The identified characteristics associated with relapse may guide targeted monitoring of patients with bipolar disorder following ECT.

THE SAFETY AND EFFICACY OF ECT FOR THE TREATMENT OF AGITATION IN DEMENTIA

Brent Forester*[1]
[1]*Tufts University School of Medicine*

Objective: We aim to determine the effect, tolerability, and safety of up to 9 Electroconvulsive Therapy (ECT) treatments plus usual care (ECT+UC) on severe agitation in participants with moderate to severe dementia including Alzheimer's Disease, Vascular dementia, Frontotemporal dementia, and Dementia with Lewy Bodies.
Methods: Subject enrollment is limited to individuals admitted to inpatient psychiatry or medical care units with a diagnosis of moderate to severe dementia. Cohen-Mansfield Agitation Inventory (CMAI) cut-off scores are used as the agitation and aggression standard for inclusion. ECT treatment consists of up to 9 ECT sessions administered up to 3 times per week.
Results: The primary outcome is agitation as measured by CMAI score. Secondary outcome measures include Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC), Neuropsychiatric Inventory – Clinician (NPI-C), and the Pittsburgh Agitation Scale (PAS). Participant safety is monitored by assessing cognitive function as measured by the 8-item Severe Impairment Battery (SIB-8), delirium as measured by the Confusion Assessment Method (CAM) and the Family-CAM (FAM-CAM), and routine medical monitoring.
Conclusion: Recruitment challenges, protocol modifications, recommendations for future research and clinical implications will be discussed.

ELECTROCONVULSIVE THERAPY FOR CATATONIC SYNDROME ASSOCIATED WITH AUTOIMMUNE ENCEPHALITIS AND NEW-ONSET PSYCHOSIS OF SUSPECTED IMMUNE ORIGIN: A RETROSPECTIVE CASE-SERIES

Sohag Sanghani*[1], *Georgios Petrides[2], Jason Andrus[1], Heela Azizi[1], Amy Mastrangelo[1], Marc Gordon[1], Cristina Fernandez-Carbonell[1], Simona Proteasa[1], Humaira Shoaib[1], Joanna Drucker[1], Samuel Greenstein[1], Xavier Jimenez[1], Robert Dicker[1], Sanjeev Kothare[1], Souhel Najjar[1]*

[1]*Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 2Robert Wood Johnson Medical School*

Objective: To determine efficacy and safety of ECT in management of catatonia associated with autoimmune encephalitis (AIE) and psychosis of suspected immune origin.
Methods: Medical records of all patients with catatonia and suspected autoimmune encephalitis, who were referred for ECT in the period of Jan 2017 to Dec 2022 at our health system were reviewed. Demographic, clinical characteristics, laboratory and outcome data were recorded. Catatonia symptoms were measured using Bush Francis Catatonia Rating Scale (BFCRS).
Results: Twelve cases that met the inclusion criteria were identified. Of them 4 were cases of anti-NMDA receptor encephalitis and 6 were seronegative cases of probable (n=4) and possible (n=2) origin as per the criteria described by Pollak et al. in 2020. Mean age of the patients was 26 years and about 58% were females. Their mean initial BFCRS score was 18.2 (range: 5-25). All patients showed some response within 3 ECT treatments. On average, patients required 11 (range: 3-21) ECT treatments to achieve maximum improvement. All patients (n=12) responded well to the combination of ECT and immunomodulatory treatments. Eleven of twelve patients (92%) had

complete resolution of catatonia. Introduction of ECT earlier in the course was associated with a relatively lower number of days spent with catatonia. **Conclusion:** To the best of our knowledge, this is the largest case series from a single institution, where ECT was used in the treatment of catatonia associated with autoimmune encephalitis and psychosis of suspected immune origin. Autoimmune Encephalitis is a severe condition that can have varying psychiatric presentations. The possibility of AIE should be considered in the event of new- onset catatonia or psychosis, especially in young individuals. ECT is a safe and effective treatment for catatonia and psychosis associated with AIE. It is not a substitute for immunomodulatory treatments. In the event of non-response to first line immunomodulatory treatments, early initiation of ECT may help to prevent a protracted medical course and may have a synergistic effect with concomitant immunomodulator administration.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Niall Boyce, Wellcome

Symposium Synopsis:
In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence helps to reduce waste and improve efficiency in research. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. This symposium provides a concise, comprehensive introduction to the project, presenting highlights of its work to date. The focus is on the innovative aspects of the project, including hypothesis-generating systematic reviews, meta-analyses aiming to measure effects of interventions and the role of risk factors, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

METHODOLOGY FOR LIVING SYSTEMATIC REVIEWS IN GALENOS

Georgia Salanti**1*

[1] *University of Bern*

Objective: The innovative nature of GALENOS requires methodological developments in the field of systematic reviews. The aim of this presentation is to give an overview of the novel methodological aspects underpinning the GALENOS living systematic reviews.

Methods: To answer the research questions asked in GALENOS, we have developed two types of reviews. Hypothesis testing reviews collect evidence from studies examining mechanisms of action of interventions on mental health outcomes. Then, the role of various biological or psychological mechanisms is evaluated in association evaluation reviews.

We have developed template protocols that describe the review and synthesis methodology from human and non-human studies, include instructions about how to evaluate the confidence in the evidence that these two study designs provide, and describe the planning of evidence triangulation. **Results:** The methodology will be exemplified via three systematic reviews: two association evaluation reviews (Trace amine-associated receptor 1 agonists for psychosis and pro-dopaminergic pharmacological interventions for anhedonia in depression) and one hypothesis-generating review (mechanisms through which exercise reduces symptom severity in posttraumatic stress disorder). **Conclusion:** Several sources of evidence from human and non-human studies and novel methods are required to make sense of the rapidly evolving literature.

LIVING EVIDENCE IN PURSUIT OF A STEP-CHANGE IN NOVEL INTERVENTIONS FOR ANXIETY AND TRAUMA-RELATED DISORDERS

Soraya Seedat**1*

[1]*South African Society of Biological Psychiatry*

Objective: This presentation will highlight the unique process adopted by GALENOS to identify and prioritise research questions for living systematic reviews (LSR) through a rigorous process entailing public private involvement, using an exemplar of a living systematic review on mechanisms of exercise as an intervention for posttraumatic stress disorder. The living systematic reviews produced by GALENOS focus on the most promising scientific findings (from basic laboratory and animal research to clinical studies in humans)

Methods: For the LSR on exercise for PTSD, independent searches were conducted in multiple electronic databases to identify non-human and human studies investigating the biopsychosocial mechanisms through which exercise facilitates extinction learning, memory regulation, and emotional regulation in PTSD. Ontologies were developed to facilitate study identification and data extraction. Two reviewers independently conducted the study selection, data extraction using piloted forms, and risk of bias assessment using relevant tools based on the study design. We extracted data on PTSD-related outcomes and variables that can act as mediators of the effect of exercise or as effect modifiers.

To explain the biopsychosocial mechanisms through which exercise affects the outcome of interest, we extracted effects that relate to the impact of exercise on potential mediating variables and the effect of the later outcomes. We will synthesise study results (total effects of exercise, indirect and direct effects) using meta-analyses, where appropriate.

Results: The results are currently being analysed and will be presented. Data from other living systematic reviews on PTSD/anxiety disorders undertaken by GALENOS until mid-2024 will also be presented.

Conclusion: Elucidating the potential mechanisms underlying the beneficial effects of exercise for PTSD is firstly important for fundamental knowledge; secondly, it can shed light on individual-level differences in the effectiveness of exercise for PTSD; and thirdly, it can inform the discovery of other interventions to target these mechanisms.

GALENOS: A NEW LIVING EVIDENCE RESOURCE FOR RESEARCH PRIORITISATION IN MENTAL HEALTH

Tatenda Kambeu**1*, *Soraya Seedat2, Georgia Salanti3, Niall Boyce4, Andrea Cipriani5*

[1]*Global Experiential Advisory Board for The Global Alliance for Living Evidence on Anxiety, Depression and Psychosis, 2Stellenbosch University; Stellenbosch University/South African Medical Research Council Extramural Unit on the Genomics of Brain Disorders, 3Institute of Social and Preventive Medicine (ISPM), University of Bern, 4Wellcome, 5Oxford University*

Objective: In mental health science, there has been frustratingly slow process in understanding and developing new treatments for anxiety, depression and psychosis, as well as in predicting which treatments will work for whom and in what contexts. To intervene early and deliver optimal care to patients, we need to understand the underlying mechanisms of mental health conditions, develop safe and effective interventions that target these mechanisms, and improve our capabilities in timely diagnosis and reliable prediction of symptom trajectories. Better synthesis of existing evidence is one way to reduce waste and improve efficiency in research towards these ends. Living systematic reviews produce rigorous, up-to-date and informative evidence summaries that are particularly important where research is emerging rapidly, current evidence is uncertain, and new findings might change policy or practice. The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) aims to provide openly accessible co-produced living systematic reviews to tackle the abovementioned challenges. **Methods:** The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis (GALENOS) tackles the challenges of mental health science research by cataloguing and evaluating the full spectrum of relevant scientific research including both human and preclinical studies. GALENOS will also allow the mental health community—including patients, carers, clinicians, researchers and funders—to better identify the research questions that most urgently need to be answered. It is important for GALENOS that we coproduce everything we create with people with lived experience of mental illnesses. Hence, we have set up the GLEAB, a Global Experiential Advisory Board, to provide strategic oversight to the project. In practical terms, people with lived experience will be involved with: choosing the topics of the reviews, developing the review protocols and contributing to conducting them, helping with data analysis and the writing up of the findings. People with lived experience will also be involved in developing the mental health ontology as that develops and identifying research questions that should be prioritised in the future. **Results:** This symposium provides a concise but comprehensive introduction to the project and presents highlights of its work to date. **Conclusion:** The focus of the symposium will be on the innovative aspects of the project, including co-production with lived experience experts, hypothesis-testing meta-analyses, triangulation of human and animal data, and priority setting by individuals with lived experience of mental health problems.

HETEROGENEITY IN PSYCHOTIC DISORDERS ACROSS LEVELS OF RESEARCH

Dost Ongur, McLean Hospital/Harvard Medical School

Symposium Synopsis: This symposium will focus on heterogeneity in psychotic disorders across multiple levels of research. The first presenter is Dr. Michael Benros who will present evidence from blood and CSF studies as well as epidemiology for an "inflammatory" subtype of psychosis linked to early life exposures that may trigger molecular mechanisms in the developing brain and lead to persistent neuroinflammation and ultimately emergence of psychosis. The second presenter is Dr. Tao Li who will present the results of her team's neuroimaging studies examining dynamic connectivity over time in psychotic and mood disorders. Next, Dr. Sinan Guloksuz will present data on lifetime exposures, clinical presentation, and treatment response which reveal significant heterogeneity within psychotic disorders. He will discuss concepts of subtyping vs. dimensional variation in the context of empirical data. Finally, Dr. John Hsu will present evidence from large population-based insurance claims databases which demonstrate highly variable pathways to care, treatment histories, and linkage to various outcomes such as hospitalization among patients diagnosed with psychotic disorders. Dr. Dost Ongur is the discussant, and he will summarize approaches to heterogeneity in psychotic disorders and propose next steps for the field.

IMMUNE-RELATED SUBTYPE OF PSYCHOTIC DISORDERS – EVIDENCE FROM LARGE-SCALE STUDIES TO DETAILED CLINICAL STUDIES

Michael Benros*[1]
[1]*Mental Health Centre Copenhagen*

Objective: The underlying causes of psychotic disorders are likely very heterogeneous with multiple biological underpinnings that are still not fully illuminated. Within the recent decades, the immune system has been shown to be implicated in an increasing number of medical diseases and immunemodulating treatments are one of the areas currently moving fastest within medicine. In this presentation the current evidence for an immune-related subtype of psychotic disorders will be summarized and perspectives for immunemodulating treatments in subgroups of patients with psychotic disorders will be discussed.

Methods: The presentation will include data from large-scale studies to detailed clinical studies within the immunopsychiatric field of psychotic disorders, including nationwide Danish registers and biobanks, large-scale genetic studies, preclinical studies, clinical studies with sampling of the cerebrospinal fluid, meta-analyses of clinical studies and RCTs of immunemodulating treatments for psychotic disorders.

Results: Utilizing Danish nationwide registers we have consistently displayed that infections and autoimmune diseases increases the risk of developing psychotic disorders in a dose-response relationship, where the risk of severe mental disorders particularly increases with the number of infections exposed to and in a temporal manner. Utilizing large national biobank data, we have shown a small immunogenetic contribution with moderate correlation between the genetic susceptibility for infections and mental disorders. Moreover, at diagnosis there are elevated levels of inflammatory markers in the blood, and studies on the cerebrospinal fluid surrounding the brain have shown some evidence for elevated immune markers in the CSF and signs of disrupted blood-brain barrier in some of the patients, making them more vulnerable to potential detrimental effects of immune components. Interestingly, our meta-analyses of randomized clinical trials have shown that anti-inflammatory treatment seems to some extent show promise for the treatment of psychotic disorders. However, studies identifying subgroups that would be most likely to respond to immune modulating add-on treatment are still warranted to pave the field forward.

Conclusion: Although there is compelling evidence for at least a smaller subgroup of psychotic disorders having immune-related underpinnings, it will be discussed what is lacking in the current evidence base, how do we best advance the current knowledge and what should be prioritized within future research to make immunopsychiatry even more clinically relevant for psychotic disorders.

DYNAMIC STRUCTURE–FUNCTION COUPLING ACROSS THREE MAJOR PSYCHIATRIC DISORDERS

Zhe Zhang1, Wei Wei2, Yu Sun1, Tao Li*[2]
[1]*, Zhejiang University, 2Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine*

Objective: Major psychiatric disorders have both similar and distinct patterns of manifestations and cognitive impairments, yet the underlying common and/or unique neural substrates are not well understood.

Methods: We perform a comprehensive brain structure–function coupling analysis to characterize the transdiagnostic and illness-specific neuroimaging patterns across major depressive disorder, bipolar disorder, and schizophrenia.

Results: We find similar abnormalities in the general dynamic structure–function coupling of the rich–club organization across the 3 disorders, and shared and specific regional coupling alterations in

the visual, cognitive control, and default mode regions. Additionally, disorder-dependent atypical associations between structure–function coupling and topological properties of functional networks are mainly dominated by two distinct functional configuration states. **Conclusion:** Our findings demonstrate brain abnormalities across 3 major psychiatric disorders from a perspective of dynamic structure–function relationships, thus opening new avenues for investigating the neurobiological mechanisms underlying these disorders.

INVESTIGATING THE UTILITY OF EXPOSOME SCORE FOR SCHIZOPHRENIA TO UNDERSTAND OUTCOME HETEROGENEITY IN PSYCHOSIS SPECTRUM DISORDER

Sinan Guloksuz**1*

[1]*University Hospital of Maastricht*

Objective: By using a predictive modeling approach, we have recently estimated the exposome score for schizophrenia (ES-SCZ), a cumulative environmental exposure score for schizophrenia, consisted of cannabis use, winter-birth, hearing impairment, bullying, and five domains of childhood adversities (emotional and physical neglect, along with emotional, sexual, and physical abuse)., The ES-SCZ successfully differentiated individuals with schizophrenia, explaining 28% of the variance in an independent case-control sample and showed a good discriminative function for schizophrenia (AUC = 0.84) in an epidemiologically representative general population cohort. Here we tested the performance of ES-SCZ for dissecting the functional and symptomatic outcome heterogeneity in psychosis.

Methods: Our analyses used data from three independent cohorts: the “vulnerability and severity” Work Package 6 of the EUGEI study including 1,261 patients with schizophrenia spectrum disorder, 1,282 unaffected siblings of these patients, and 1,525 healthy controls collected in Turkey, Spain, and the patient population of the GROUP study including 1,119 patients with schizophrenia spectrum disorder collected in the Netherlands; and the Athens First Episode Psychosis Research Study collected in Greece including 225 individuals with first episode psychosis. We investigated the cross-sectional and longitudinal associations of ES-SCZ with functioning and symptom severity assessed using the Global Assessment of Functioning (GAF), the Personal and Social Performance Scale (PSP), and the Positive and Negative Syndrome Scale (PANSS).

Results: Our analyses revealed that ES-SCZ was associated with both the GAF symptom and disability domains in the EUGEI across three groups (patients, their siblings and healthy controls), also after adjusting for polygenic risk score for schizophrenia. We were able to replicate these findings in the GROUP dataset. In the Athens FEP cohort, we replicated these findings. ES-SCZ was associated with the overall scores of GAF and PSP at the baseline and 1-month assessments. Even after adjusting for various other relevant explanatory variables such as environmental factors (ethnic minority status, obstetric complications, migration history), clinical features (symptom severity, antipsychotic use history, duration of untreated psychosis), and family history, these results remained significant. The evaluation of the explained variance (R2) of functioning further supported these findings. Specifically, ES-SCZ was found to be the greatest contributor to the explained variance for the total PSP score, as well as for PSP subscales that measure socially useful activities and personal/social relationships. ES-SCZ was also temporally associated with symptomatic improvement from baseline to 1-month assessment, particularly the negative symptom dimension.

Conclusion: Our findings indicate that ES-SCZ might be a marker for poor functioning and symptomatic improvement in patients diagnosed with schizophrenia spectrum disorder. In addition, the results obtained from the models that took into account polygenic risk score for schizophrenia and clinical features indicate that the links between ES-SCZ and functional outcomes cannot be explained solely by genetic and clinical risk indicators.

THE ROLE OF POLYGENIC SCORES IN STUDYING PHENOTYPIC AND ENVIRONMENTAL HETEROGENEITY OF PSYCHOSIS

Evangelos Vassos*[1]
[1]King's College London
Evangelos Vassos, King's College London

Objective: Psychotic disorders show high heritability and genome-wide association studies have been successful in identifying variants associated with the disease. These variants are combined to estimate polygenic scores, which provide a single measure of genetic predisposition to a disorder or trait. Polygenic scores have been used for risk prediction either in contrast to or in combination with environmental risk factors in studies aiming to explain the heterogeneity of psychotic disorders. In this session, I will present our studies using polygenic scores to predict the development of schizophrenia or affective psychosis among individuals with first episode psychosis and I will explore the limitations of the use of polygenic scores alongside environmental factors in risk prediction.
Methods: We studied two samples of First Episode Psychosis (FEP) patients and controls for association between polygenic scores and psychosis outcome (schizophrenia or affective psychosis). The first sample (Genetics and Psychosis; GAP) was collected in South London consisting of 445 cases and 265 controls and the second (Work Package 2 of the EUGEI study) in six different countries including the UK, Italy, France, Spain, Netherlands and Brazil, including 573 cases and 1005 controls of European ancestry. Environmental risk factors were tested alongside polygenic scores in prediction of affective and non-affective psychosis. Finally, to explore whether polygenic scores and environmental risk factors can be used as independent predictors, we performed a study in the UK Biobank, testing the association of polygenic scores for 8 psychiatric disorders with urbanicity, once of the most replicated risk factors for schizophrenia.
Results: In the GAP study we observed that in addition to the expected association between polygenic score for schizophrenia and case-control status in European ancestry individuals, the former also separated FEP patients who developed schizophrenia from those who developed other psychotic disorders (R2=9.2%, p=0.002). This finding was replicated in a second sample of patients with chronic psychosis.
In the EUGEI study, we found that not only schizophrenia but also depression polygenic scores have a role in separating affective from non-affective psychosis. Furthermore, we found that adding polygenic and poly-environmental risk scores further improves the predictive ability of our model.
In the UK Biobank study, we found evidence supporting the hypothesis of genetic selection of the environment we live in, which intersects the traditional gene-environment dichotomy.
Conclusion: When patients present with first episode psychosis, it is difficult to establish a definite diagnosis and predict the course of illness and optimal treatment. To that effect, better understanding and explaining the heterogeneity of psychosis has important clinical implications. In our studies we find that polygenic scores have a significant yet small effect in separating schizophrenia from affective psychoses and that adding non-genetic risk factors improves prediction. Finally, gene by environment correlation needs to be considered when adding both genetic and environmental factors in prediction models.

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDERS

Allan Young, King's College London

Symposium Synopsis: Cognitive impairment in bipolar disorders.

Impairment in processing speed, attention, verbal memory, and executive functions may be present in up to 50% of young and middle-aged euthymic patients with bipolar disorders. However, our

knowledge in elderly people with bipolar disorder is limited although cognitive impairment is likely more prevalent and severe in elderly patients with mood disorders. Furthermore, compared to healthy older adults, those with mood problems have a higher risk of dementia. In contrast to research on younger patients, clinical correlates of cognitive decline in geriatric patients with bipolar disorder have not been studied systematically. Cognitive impairment worsens psychosocial functioning and treatment response in mood disorders. Therefore, it is essential to prevent and treat cognitive impairment in these people. Few treatment options effectively treat persistent cognitive impairment in remitted phases of bipolar disorders. Cognitive remediation therapy (CRT) may improve cognitive and non-cognitive functioning and recent studies have shown CRT's efficacy. However, its long-term effects are still unknown, therefore additional studies are needed. Also, limited understanding of neurocircuitry characteristics in bipolar disorders hinders search for new treatments and improving current treatment methods, leaving it unclear if proposed treatments can effectively correct cognitive impairments. This symposium aims to address the common problem of bipolar disorder-related cognitive impairment, including the cognitive decline of older patients. Additionally, treatment guidelines and options—including CRT—will be discussed considering neuroimaging, which can be used to identify neural targets for the development of new treatments or the improvement of existing ones for bipolar disorders-related cognitive decline.

COGNITIVE IMPAIRMENT IN BD: IS IT TREATABLE?

Lakshmi Yatham*[1]

[1] *The University of British Columbia*

Objective: 1. To review evidence on magnitude of cognitive impairment in BD

2. To review new data on therapeutic strategies for managing cognitive impairment

Methods: This presentation will review new data on cognitive impairment in BD and present the results of new studies that assessed the efficacy of pharmacological and psychological interventions for treating cognitive impairment in BD.

Results: About two thirds of patients with BD have cognitive impairment even during euthymic periods, which impacts functioning. New clinical trial designs allow testing for efficacy of pharmacological and psychological treatments in improving cognition. The results of these new and novel studies will be presented in this session.

Conclusion: Cognitive impairment in BD can be treated with pharmacological and psychological strategies.

COGNITION IN GERIATRIC BIPOLAR DISORDER

Nese Direk*[1]

[1]*Istanbul University*

Objective: Mood disorders are common and complex, accounting for one of the leading causes of disability. Approximately half of adults with mood disorders have cognitive impairment, which has an impact on their occupational and social functioning as well as their life quality. Cognitive impairment is well-known in younger and middle-aged euthymic adults with mood disorders, with the most impairment reported in processing speed, attention, verbal memory, and executive functions. Cognitive impairment is more common and severe in geriatric patients with mood disorders. It is also known that the prevalence of dementia in patients with mood disorders is higher than in healthy geriatric people. The causes of cognitive impairment in elderly patients with mood disorders are still unknown. Some clinical features, such as the prevalence of previous psychotic episodes, the number of manic episodes, and cardiovascular risk factors, are linked to an increased

risk of cognitive impairment, but the results are mixed. This talk is aimed at elucidating the cognitive profiles and clinical correlates of cognition in geriatric bipolar patients. **Methods:** The Bipolar Disorder in Old Age (BipOld) Study is a longitudinal, open cohort study including bipolar patients aged 50 years and over, aiming to explore progress of bipolar disorder in elderly. Several cognitive domains such as attention, memory, executive functions, social cognition, neurological soft signs and retrospective clinical data was collected. In this talk, baseline results of the BipOld Study will be presented, and results will be discussed in the light of current studies in this field. **Results:** In total 70 bipolar patients aged 50 years and over and 70 healthy controls are compared in terms of cognition. Bipolar patients had worse cognition scores in all domains when compared to healthy controls. Number of psychotic episodes, baseline cognitive impairment, family history of bipolar disorder, number of hospitalizations were related with worse cognition. Even though numbers are limited, patients on lithium monotherapy had better cognitive profile. **Conclusion:** Cognition in elderly patients with bipolar disorder is worse than people with no psychiatric disorder. Associations of clinical characteristics with worse cognition may indicate toxic effects of episodes resulting in neurodegeneration in these patients.

THE PURSUIT OF TREATING COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: CAN MRI BE A USEFUL TOOL IN FINDING NEW TREATMENTS?

Nefize Yalin*[1], *Dimos Tsapekos[2], David Lythgoe[3], Peter Hawkins[3], Rebecca Strawbridge[2], Allan Young[2], Steve Williams[3], James Stone[4]*

[1]National Institute of Mental Health, [2]Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, [3]Institute of Psychiatry, Psychology and Neuroscience, King's College London, [4]Brighton and Sussex Medical School

Objective: Cognitive remediation (CR) is one of the treatment modalities that may address cognitive impairment in bipolar disorder (BD). We recently showed that 12-week CR improves working memory and executive functioning in euthymic patients with BD when compared to the treatment as usual (TAU) group. In this study, we aimed to investigate the potential changes in structural magnetic resonance imaging (MRI), task-based functional MRI, and proton-magnetic resonance spectroscopy (1H-MRS) accompanying the cognitive improvement with CR in comparison to TAU.

Methods: We recruited 24 euthymic BD participants (CR: n = 12, TAU: n = 12). Neuroimaging data was collected using a 3T General Electric MRI at baseline and week 13. For T1 structural MRI images, cortical thickness (CT) and surface area (SA) measures were obtained with FreeSurfer version 7.1.1. Caudal and rostral middle frontal cortex and three subparts of inferior frontal cortex (pars opercularis, triangularis, and orbitalis) were chosen as regions of interest. Repeated measures and general linear models were used to compare CT and SA between groups. For 1H-MRS, glutamate and GABA levels were quantified from the dorsomedial prefrontal cortex (DMPFC) using the PRESS and MegaPRESS sequences, respectively. LC Model 6.3-1N was used for the analysis of spectral data, and the metabolite levels were corrected for cerebrospinal fluid, gray, and white matter fractions in the spectroscopy voxel obtained using Gannet 3.1. We assessed changes in glutamate and GABA levels using a general linear model with repeated measures.For functional MRI, the attentional-capture version of the Stop Signal Reaction-Time (SSRT) task was used to evaluate response inhibition. Regions-of-interest (ROIs) data were extracted with the MarsBaR toolbox for SPM-12. ROIs were cortical areas previously linked to response inhibition in BD, including the right inferior frontal gyrus (rIFG). Activation changes in selected ROIS were compared between groups using repeated measures general linear models.

Results: The mean age was 39.3 ± 12.6 for the CR group and 39.8 ± 14.1 for the TAU group (p = 0.93), and 66.7% of both CR and TAU groups were female (p = 1.0). In structural MRI, there was a significant change in left pars triangularis CT (p = 0.048) and a trend toward change in left rostral middle frontal CT (p = 0.069) and right caudal middle frontal SA (p = 0.054) from baseline to follow-up between groups. All changes showed an increase in CT in the CR group and a decrease in the TAU group from baseline to week 13. In 1H-MRS, we found DMPFC glutamate levels to be increased in the CR group following CR, whereas in the TAU group, glutamate levels were reduced (p = 0.037). We did not find any effect of CR on changes in GABA levels (p = 0.269). In functional MRI, CR relative to TAU was not significantly associated with SSRT-related changes in neural activity of pre-defined ROIs (all p > 0.05). For SSRT behavioral measures, there was only a trend for CR vs. TAU in the accuracy of the stop signal condition (p = 0.06). **Conclusion:** Cognitive improvement related to CRT may be mediated by structural changes and increases in DMPFC glutamate neurotransmission. MRI has a potential in identifying brain-based efficacy markers.

1:30 p.m. - 3:00 p.m.
Concurrent Symposia IX

THE PHARMACOLOGICAL TREATMENT OF EATING DISORDERS: NEW GUIDELINES, INSIGHTS, AND PERSPECTIVES

Siegfried Kasper, Center for Brain Research

Symposium Synopsis: This symposium on novel guidelines, insights, and perspectives for the pharmacological treatment of eating disorders is organized by the WFSBP Task Force Eating Disorders and consists of speakers with a broad range of scientific experience from Germany, Israel, the United Kingdom, and the United States of America and a Chair from Austria.
Over the last three years, the task force has worked on an update of the pharmacological treatment guidelines for eating disorders which will be presented first in this symposium. The new guidelines include several innovations such as a recommendation for lisdexamfetamine in the treatment of binge-eating disorder (BED) and an analysis of pharmacological research in avoidant restrictive food intake disorder (ARFID), rumination disorder and pica. The second presentation will display the results of meta-analytic research regarding the effect of second-generation antipsychotics (SGAs) on appetite and eating behavior which is clinically relevant for the use of SGAs in anorexia nervosa (AN), but also with respect to the resulting weight gain as a side effects of SGA treatment in schizophrenia or bipolar disorder. The second half of the symposium is dedicated to innovative and future treatments for AN. Thus, the third speaker will expound on the microbiome-gut-brain axis as a potential target for new treatment options by presenting new data on altered microbiota in patients with AN and the results from stool transplantation studies; and the fourth speaker will present and explain the study design and the results from studies testing psilocybin therapy in people with AN.

OLANZAPINE FOR YOUNG PEOPLE WITH ANOREXIA NERVOSA (OPEN): RESULTS OF A FEASIBILITY STUDY

Ece Sengun Filiz*[1], *Olena Said[2], Dominic Stringer[3], Ulrike Schmidt[4], Dasha Nicholls[1], Hubertus Himmerich[2]*

[1]Imperial College London, , 2Centre for Research in Eating and Weight Disorders (CREW), Institute of Psychiatry, Psychology and Neuroscience, King's College London, 3Institute of Psychiatry, Psychology and Neuroscience, King's College London, 4 King's College London

Objective: Despite evidence-based treatments for anorexia nervosa (AN), the remission rates are low, and the mortality is high. The atypical antipsychotic olanzapine is often used for the treatment of AN even though the evidence is limited to weight gain. The effect of olanzapine on eating disorders (ED) psychopathology, its efficacy and tolerability in children and young people, and its acceptability and adherence rate are unclear. **Methods:** We assessed the feasibility of a future definitive trial on olanzapine in young people with AN in an open-label, one-armed feasibility study, that aimed to include 55 patients with AN or atypical AN) aged 12-24 who gained **<** 2 kg within at least one month of treatment as usual (TAU) during outpatient, inpatient, or day-care treatment. Time points for assessments were at screening, baseline and at 8-, 16 weeks, 6- and 12 months. The primary feasibility parameters were the number of patients who agreed to take olanzapine and who adhered to treatment and complete study assessments. The change in body mass index (BMI) and changes in ED psychopathology were secondary feasibility parameters. **Results:** From June 2022 to May 2023, 20 participants were recruited across 10 study sites in England (of the 55 participants required). Fifty-two people were assessed at pre-screening; 17 people were ineligible (13 at pre-screening, 4 at formal screening), and another 15 declined or didn't take part for other reasons. All 20 recruited participants started olanzapine. Thirteen out of 20 participants (65%) completed a follow up assessment (either 6 or 12 months). Participants in the trial experienced, on average, a decrease over time in their EDE-Q Global scores, an increase in weight and a corresponding increase in BMI during treatment with olanzapine in addition to TAU. There was a mean BMI increase of 0.08 kg/m2 per week in the whole sample of 20 participants. **Conclusion:** Possible reasons for the recruitment difficulties and the low adherence rate are the reluctance of clinicians to prescribe olanzapine and of patients to agree to take olanzapine under the relatively strict conditions of a clinical study. These conditions include the delay of the start of treatment with olanzapine as ample time should be given to consider participation in the study, a pregnancy test before the start of treatment, the commitment to blood collection at assessments and to complete the questionnaires. However, exploratory data evaluation indicates a benefit of olanzapine regarding weight recovery and reduction of ED symptoms.

BEYOND WEIGHT GAIN: EATING COGNITIONS, EMOTIONS AND BEHAVIOUR UNDER TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS

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Objective: Weight gain and metabolic disturbances are frequent in people treated with second generation antipsychotics (SGA). SGAs have also been proposed as treatment option for people with anorexia nervosa (AN). We aimed to investigate the effect of SGAs on eating behaviors, cognitions and emotions.

Methods: A systematic review and a meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Original articles measuring outcomes relating to eating cognitions, behaviours and emotions, during treatment with SGAs were included in this review. A total of 92 papers with 11,274 participants were included from three scientific databases (PubMed, Web of Science and PsycInfo). Results were synthesized descriptively except for the continuous data where meta-analyses were performed and for the binary data where odds ratios were calculated.

Results: Hunger was increased in participants treated with SGAs with an odds ratio for appetite increase of 1.51. Compared to controls, our results showed that craving for fat and carbohydrates are the highest among other craving subscales. There was a small increase in dietary disinhibition and restrained eating in participants treated with SGAs compared to controls and substantial heterogeneity across studies reporting these eating traits.

Conclusion: Understanding of mechanisms associated with appetite and eating-related psychopathology changes in patients treated with SGAs is needed to inform the development of effective preventative strategies for weight gain during treatment with SGAs. Such understanding might also help to use SGAs as a treatment option for patients with AN.

THE MICROBIOME-GUT-BRAIN AXIS IN ANOREXIA NERVOSA – POTENTIAL TARGET FOR NEW TREATMENT OPTIONS?

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Objective: The gut microbiome has been shown to influence both metabolism and weight gain, as well as brain changes and behavior. This is especially interesting in the case of Anorexia nervosa (AN), where all these areas are known to be affected. Observation studies have repeatedly shown altered gut microbiota in patients with AN – even after weight normalization, and transplantation studies of AN-patients' stool into germ-free animals have shown significant effects regarding weight gain and anxiety/compulsivity.

Methods: Longitudinal observational studies using 16S- or metagenomic shotgun analysis allow the study on which factors influence the gut microbiome in AN and which taxa are associated with good or bad outcome. Transplanting stool of patients with AN or supplementing specific taxa in the activity-based anorexia animal model can give crucial information about causal influences of the microbiome and help elucidate underlying mechanisms.

Results: We present an overview over current study results. Longitudinal studies continue to show beta diversity differences between patients with AN and healthy controls before and after weight gain and remaining differences at follow-up. Taxa belonging to the Sutterella genus helped to predict higher body weight at one year. Animal models show differing alpha- and beta diversity as well as specific taxa to be altered in semi-starvation and support a potential causal role of the gut microbiome in AN.

Conclusion: The predictive power of taxa belonging to Sutterella for clinical outcome could complement known predictors at admission, help to inform patients and clinicians and serve as a candidate for interventions such as probiotic or nutritional supplementation. Trying to generate new microbiome-targeted treatment approaches like pro- and prebiotics, nutritional interventions or even stool transplantations might be interesting options to enhance existing AN-treatment.

EFFICACY OF PSILOCYBIN AND OTHER MEDICATIONS IN THE TREATMENT OF ANOREXIA NERVOSA

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[1]
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Objective: Anorexia nervosa (AN) is a deadly behavioral disorder with no proven treatments to reverse core symptoms and no FDA-approved medications. Novel and innovative treatments methods are urgently needed to improve clinical outcomes and reduce mortality. Research suggests that disturbances of serotonin and dopamine function occur in AN and may contribute to anxiety and other symptoms.

Methods: This is the first trial to report on the safety, tolerability, and preliminary efficacy of psilocybin therapy for AN (ClinicalTrials.gov Identifier: NCT04661514). In this open label feasibility study, 10 participants who met DSM 5 criteria for AN received a single 25mg dose of synthetic psilocybin with psychological support. We assessed safety, tolerability, acceptability, and efficacy at pre-treatment, post-treatment, 1-month and 3-month follow-up.
Results: Psilocybin treatment was safe, well tolerated, and had good acceptability. Measured changes in eating disorder psychopathology were highly variable between participants. Four participants (40% of sample) demonstrated decreases in eating disorder scores to within 1 standard deviation of community norms at 3-month follow-up, qualifying for remission from eating disorder psychopathology.
Conclusion: Results from this open-label study suggest that psilocybin therapy is safe and tolerable in participants with AN. Additionally, data suggest that a single-dose trial of psilocybin therapy may be effective at reducing ED psychopathology in a subset of participants. These preliminary results are promising given the complex physiological dangers associated with AN and the lack of effective and acceptable treatments. We will also review the literature regarding other treatment approaches for AN.

Some studies, but not all, also support the efficacy of fluoxetine in reduction of relapse in restrictor-type AN. In addition, there is limited data suggesting that some atypicals may be useful for AN.

GENETIC RISK PREDICTIONS AND BIOLOGICAL MECHANISMS IN ADHD – TOWARDS PRECISION MEDICINE

James Kennedy, Univ of Toronto

Symposium Synopsis: ADHD is one of the most common mental and behavioral disorders in children, often co-occurring with various behavioral problems. ADHD exhibits high heritability of 74% and recent genome-wide association studies (GWAS) (Demontis, 2021) have identified a number of significant hits in several genes that have implications for new drug targets. Interestingly, the heritability of ADHD changes with its comorbid disorders (CDs) where ADHD had higher heritability when comorbid with disruptive behavior disorders. The objectives of the current symposium are to explore the genetics and biomarkers of ADHD with or without CDs such as aggression, eating disorders (Eds) and autism spectrum disorder (ASD), as well as discuss the current evidence-based treatments, and pharmacogenetic guidance of medication choice for ADHD.
Symposium speakers employ research-based clinical assessment of ADHD, aggression, Eds and ASD. The genotyping employs powerful genome-wide microarray technology that interrogates millions of markers. Analyses of the associations between diagnoses, subtypes and CDs are performed using well-developed GWAS statistical methods. Polygenic risk scores (PRSs) are derived from GWAS and can be applied to behavioral phenotypes in other samples exhibiting related disorders. Genetic factors influencing the effectiveness of drugs for ADHD and its common comorbidities will be discussed, including the use of pharmacogenetics for more precise prescribing.
Overall, results show that ADHD has shared genetic architecture with its CDs. Separating ADHD into its clinical subtypes with/without CDs leads to more specific biological predictors and drug targets, that in turn have the potential to lead to better precision medicine for the treatment of ADHD.

ASSESSMENT OF POLYGENIC RISK SCORE OF ADHD AND AGGRESSION IN YOUTH: RESULTS FROM A CLINICAL AND A COMMUNITY SAMPLE

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Objective: More than 50% of youth with ADHD exhibit clinically significant aggression, representing high comorbidity. Although this points to the common genetic risk variants for the etiology of ADHD and aggression in youth, studies understanding the common genetic variation of ADHD and clinical aggression, and their subtypes, in children are limited. The objectives of this study were to assess the genetic relationship between ADHD and aggression in children. The study tested whether 1) ADHD scores were associated with aggression polygenic risk scores (PRS), and whether 2) aggression case status was associated with ADHD PRS. **Methods:** 1) 3594 children of European ancestry were recruited as part of the Adolescent Brain Cognitive Development (ABCD) study. The sample was genotyped with the Smokescreen® Genotyping Array. Continuous measures of ADH were obtained from Child Behaviour Checklist (CBCL). 2) 232 youth of European white ancestry were recruited as a part of an ongoing study of childhood aggression in Toronto, Canada. The sample was genotyped with Illumina PsychArray Beadchip v.1.2 and v.1.3. The case status was based on the participant scoring GREATER THAN 90th %tile on aggression subscales of both the CBCL and the Teacher Report Form, and a minimum two-year history of this disruptive behavior. Two PRSs were calculated using the standard clumping and thresholding methods with the p-value thresholds from 5x10-8 to 1 in PRSice2. Data for both PRSs came from the pediatric population of the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium. The first PRS was calculated from a genome-wide association meta-analysis (GWAMA) of ADHD (n=17666), while the second PRS was calculated from a GWAMA of aggression (n=87485). Linear and logistic regressions were used to analyze the associations between aggression PRS and ADHD scores in the ABCD sample, and between ADHD PRS and aggression case/control status in the Toronto sample, respectively. **Results:** Aggression PRS significantly explained ~ 0.2% of the variance in the ADHD scores of ABCD sample ($p = 0.007$). ADHD PRS significantly explained ~ 6% of the case-control status for the Toronto Child Aggression sample ($p = 0.002$). **Conclusion:** There were significant associations between aggression PRS with ADHD, and ADHD PRS with aggression case status. Our preliminary results indicate evidence that clinical aggression and ADHD share common genetic factors based on both clinical and community youth samples. The large sample size for the ABCD sample provides increased power for the results. The results may lead to generating better prediction strategies, for example aggression acting as a biomarker for ADHD. Personalized treatment strategies based on the genetic risk score may help with early prevention efforts. We will be exploring the genetic risk underlying ADHD by analyzing the aggression PRS in clinically aggressive children with, and those without, ADHD diagnosis.

GENETICS AND CELL BIOLOGY OF READING DISABILITIES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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Objective: Reading disabilities (RD) represent a major health, social, and educational handicap. Comorbid psychiatric disorders are common in children with RD, particularly ADHD (20%) which shares genetic risk. The high rate of ADHD further impacts academic achievement and social

development. Little is currently known of the genetic, molecular and cellular mechanisms contributing to these neurodevelopmental disorders. **Methods:** To address this gap, we performed a genome-wide association study (GWAS) for word reading. Based on the findings from that study, we then performed a Hypothesis-Driven GWAS testing the relationship between autism spectrum disorder (ASD) and genes involved in neuronal migration/axon pathfinding. We also used the results from the genetic studies, linkage disequilibrium score regression (LDSC) and single cell RNA-seq data to identify which neural cell types are enriched for genes for ADHD and RD risk. We then directly tested migration using stem cell derived neural precursor cells (NPCs) from children with RD. To understand the underlying molecular mechanisms, we investigated the transcriptome of the neurons and NPCs derived from the children. We selected one of the differentially expressed genes for further study by overexpressing the gene using CRISPR activation. **Results:** The results indicate overlap of word reading for genes previously identified for educational attainment, neurodevelopmental and psychiatric disorders, particularly ADHD and ASD. We also identified overlap with genes involved in neuronal migration. This supports the a priori hypothesis that alterations in neuronal migration during neurodevelopment contribute to the risk of RD. To test this, we created stem cells from two children with severe RD and their strong reader siblings. Derived NPCs from RD children migrated significantly faster than their siblings supporting migration alterations. Transcriptome analyses of neurons and neural precursor cells identified 44 genes that were differentially expressed between probands and their siblings in both cell types. One of these, OTX2, has been implicated in analyses of externalizing behaviour including ADHD, depression, educational attainment, and smoking initiation from GWAS studies. OTX2 is a transcription factor and our bioinformatic analyses indicates it may regulate 11 of the 44 genes. To test this, we are currently overexpressing OTX2 in NPCs, using CRISPR activation. Using LDSC, we also determined that specific subclasses of glutamatergic and GABAergic neurons are enriched with RD risk genes. Studies of ADHD identified a different glutamatergic neuron subtype. These findings indicate these cell types for stem cell derived neural models and functional studies. **Conclusion:** The results identify overlap for risk genes for ADHD, ASD and word reading. The findings of overlap for ADHD, support previous twin data showing a genetic relationship. Little is known of the overlap between ASD and RD. Our finding likely stems from shared genetic risk for neurodevelopmental disorders, particularly those contributing to language-related difficulties. Our novel, unpublished observation of altered migration in neural derived cells from RD children, supports previous evidence from neuroanatomical studies for altered neural migration and transcriptome analyses are providing information on the underlying molecular mechanisms.

PHARMACOGENETICS FOR PRESCRIBING MEDICATION TYPE AND DOSAGE IN ADHD: TOWARD PRECISION MEDICINE

James Kennedy**1*

1 Univ of Toronto

Objective: There are many promising genetic findings in terms of risk factors for ADHD. Recently a report by Demontis et al. (2021) provided an updated list of Genome Wide Association Study (GWAS) significant findings for genetic sites from across the genome that contribute to risk for ADHD.
In parallel with these hypothesis-free GWAS studies of the etiology of ADHD, we and others have been examining the application of genomic tools to help predict treatment response and side effects in ADHD. Given that current prescribing practice for ADHD consists mostly of trial-and-error approaches, there is a large unmet need to measure selected biological characteristics (biomarkers) of each patient in order to provide more precise prescribing.

Towards this goal of biomarker-guided precision medicine, Myer, Boland and Faraone (2017) have used meta-analytic methods to examine pharmacogenetic predictors of methylphenidate efficacy in childhood ADHD. They analyzed 36 studies with total n = 3647 children, examining response measures of methylphenidate treatment for association with DNA variants. Pooled data revealed significant association with single nucleotide polymorphisms (SNPs) in the alpha adrenergic 2A receptor gene ADR2A (odds ratio (OR) = 1.69); the norepinephrine reuptake transporter SLC6A2 (OR = 2.93) which is the target of atomoxetine, as well as the repeat variant in the dopamine D4 receptor gene (DRD4, OR = 1.66). Other data has shown that the drug metabolism gene cytochrome CYP2D6 plays a significant role in the liver deactivation of atomoxetine, which in turn influences clinical response. We will provide a critical assessment of these findings regarding their potential utility in clinical decision-making in ADHD. From our laboratory we will present work suggesting that a higher dosage of methylphenidate is helpful for individuals with a DRD4 7-repeat variant, due to impairments in D4 receptor trafficking to the synapse **Methods:** N/A **Results:** N/A **Conclusion:** We provide evidence that use of genetic factors to predict response and side effects, as well as separating ADHD into clinical subtypes, can lead to potential for better precision medicine for treatment of ADHD and its subtypes. Current pharmacogenomic knowledge provides a relevant amount of clinical guidance for selection of medication type and dosage. Further research is necessary for the optimization of personalized interventions in ADHD.

LEVERAGING GENETICS IN THE CLINICAL MANAGEMENT OF ADHD AND DISRUPTIVE BEHAVIOR

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University of California, Los Angeles

Objective: Approaches to the clinical management of ADHD, disruptive behavior and other comorbidities span medication classes and psychotherapeutic techniques. Currently, treatment matching is driven by serial trial-and-error. Given the potentially serious consequences of uncontrolled symptoms, pharmacogenomic and other biomarkers of therapeutic response could represent a substantial advance in the precision treatment of these disorders.
Methods: Current evidence-based pharmacotherapy and psychotherapies for ADHD and disruptive behavior disorders (DBDs) in children and adults will be reviewed, including known predictors and moderators of response. The utility and limitations of commercially available decision support tools (DSTs) will be examined. Research questions and future directions will be suggested.
Results: Little is known about genetic factors influencing drug action at brain targets; however, many genetic variants influencing the pharmacokinetics of psychotropics are well understood. While genetic impairments in stimulant metabolism are rare, large genetic effects are seen with alternative ADHD drugs. Non-stimulant ADHD options, atomoxetine and clonidine, are affected by common CYP2D6 variation, and bupropion is a CYP2D6 inhibitor, phenocopying the CYP2D6 poor metabolizer phenotype. Medication classes used to target disruptive behaviors are broad, including ADHD drugs, antidepressants, mood stabilizers and antipsychotics. Many of these agents are also impacted by known genetic variation. Common ADHD and DBD comorbidities, most frequently mood and anxiety disorders, have the strongest evidence base for integrating genetic information. Genetic data is actionable in ADHD and DBD pharmacotherapy in a considerable proportion of patients. For example, one-third of normal metabolizers never achieve therapeutic atomoxetine levels at the FDA maximum dose and require suprathreshold dosing. The Clinical Pharmacogenomics Implementation Consortium (CPIC) recommendations for incorporating genetic results to optimize response will be summarized. Evidence-based applications of DSTs that are commercially available to guide

prescribing will be outlined. Research supporting the implementation of DSTs in adults is mixed at best, with significant concerns regarding bias. A single DST trial was negative in adolescents and trials in children are non-existent. Recent reports highlight that efficacy in pediatric populations cannot routinely be extrapolated from adult studies. **Conclusion:** Numerous therapeutic options have demonstrated benefits in the management of attention-deficit and disruptive behavior disorders and their common comorbidities. While current pharmacogenomic knowledge cannot predict which interventions are best for individual patients, some clinical guidance can be gleaned from pharmacogenomic data. As our knowledge about mechanisms of psychiatric disease and pharmacologic action expands, the use of pharmacogenomic DSTs in the practice of precision medicine will likewise mature.

INNOVATIONS IN PHARMACOGENOMIC RESEARCH: TRANSLATION AND CLINICAL UTILITY

Bernhard Baune, University of Münster

Symposium Synopsis: The role of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacotranscriptomic approaches, focusing on genetic variants and expression levels of relevant genes for pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry, but still lacking. This concept of the multi-omics foundation of response to pharmacological treatments will be presented. Examples of this approach that entails the analyses of individual omics layers as well as an integrated analysis using multiple omics in relation to response to treatment will be presented. Results on the development of a model precision psychiatry framework that integrates clinical data (wide range of symptomatology assessment, treatment side effects, presence of childhood trauma) and -omics features (genomic, transcriptomic and miRNomic) for the prediction of treatment response in MDD patients will be shown. Moreover, an overview of RCTs on pharmacogenetic-based decision support tools for antidepressant drugs will be critically assessed. Moreover, recent findings on rare genetic variation impacting important clozapine-associated adverse drug reactions as well as such variation varies across ethnicities will be discussed. Finally, results of a recent systematic review on what is currently known about common genetic variation impacting clozapine response will be shown.

NEW DEVELOPMENTS IN THE PHARMACOGENOMICS OF TREATMENT RESPONSE PREDICTION IN PSYCHIATRY

University of Münster
Bernhard Baune*[1]
[1]

Objective: As background, the overall aim of pharmacogenomics is to create an effective therapeutic strategy based on the genomic profile of a patient in order to improve response as well as remission and in particular to reduce relapse. To date, in the psychiatric field, although genomic studies on psychotropic medications have provided important insights into the molecular components involved in clinical outcomes, unfortunately findings have not identified biomarkers with a clear clinical utility. Studies using pharmacogenomics and pharmacoepigenomic approaches, focusing on genetic variants and epigenetic modification related to pharmacokinetic and pharmacodynamic effects of psychotropic drugs are relevant for personalized medicine in Psychiatry. These two layers of omics

and their integration provide important and novel information regarding therapeutic response and side effects, contributing to optimizing pharmacological treatment in an individualized approach. The objective of this presentation is to introduce a concept of the multi-omics foundation of response to pharmacological and non-pharmacological treatments, which entails the genomics, transcriptomics and epigenomics layers of response to a pharmacological intervention and demonstrate this concept in in two case studies using randomised controlled trial (RCT) data from the PREDDICT and CERT-D trials.

Methods: The chosen approach requires the analyses of individual omics layers as well as an integrated analysis of multiple omics in relation to response to treatment. Two examples of RCTs will used to illustrate this multi-omics concept of prediction of treatment outcomes: first, the PREDDICT study, which is a randomized controlled trial to test the efficacy of an antidepressant plus augmentation with celecoxib vs antidepressant plus placebo in major depressive disorder (MDD). In a second case study, he will present multi-omics results from the randomized CERT-D study that tests the antidepressant effects of a personalised cognitive training program in MDD. In both examples, multi-omics predictions of treatment response will be presented.

Results: Results from the CERT-D study show that DNA methylation can be suitable to capture early signs of treatment response and remission following a cognitive intervention in depression. Despite not being genome-wide significant, the CpG locations and GO-terms returned by our analysis comparing patients with and without cognitive impairment, are in line with prior knowledge on pathways and genes relevant for depression treatment and cognition. Results from the PREDDICT study will be presented as well. Results on the integration of genetic and epigenetic layers for both the PREDDICT and CERT-D studies will complete this presentation.

Conclusion: The conceptual approach chosen is useful to better understand the complexity of the underlying biology of treatment response in depression treatment. Methodological developments are underway and encouraged by our findings.

THE PROMPT STUDY: REVEALING NEW KEY PLAYERS IN PREDICTING TREATMENT RESISTANCE

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Objective: Dr Júlia Perera-Bel will present results on the development of a model precision psychiatry framework that integrates clinical data and -omics features (transcriptomic and miRNomic) for the prediction of treatment response in major depression disorder (MDD) patients. This is the overall objective of the PROMPT ("Toward PrecisiOn Medicine for the Prediction of Treatment Response in major depressive disorder through Stratification of Combined Clinical and -Omics Signatures") consortium, which is funded by the European ERA PerMed funding scheme.

Methods: The overall methodology of the project is based on a two-phase design. In the first phase (training phase, retrospective design), 300 already recruited MDD patients, including 150 TRD and 150 responders considered as extreme phenotypes of response, will undergo a deep clinical and omics profiling. These data will be exploited to develop an innovative integrative algorithm for the prediction of MDD treatment outcome. Recruited patients undergo a comprehensive clinical assessment and molecular profiling (genomic, transcriptomic and miRNomic). DNA and RNA for genomic, pharmacogenetic extracted from peripheral blood samples are prepared transcriptomic and miRNomic analyses. RNA library preparation is performed following the manufacturer's recommendations. Final samples pooled library preparations are sequenced on a Novaseq 6000 ILLUMINA, at a depth of 2x30Millions of 100bases reads per sample after

demultiplexing. MiRNomic (+ other small RNA) profiling is conducted by small RNA-Seq. Sequencing yields 20-30 million single-end 50 bp reads per sample on a NextSeq2000 (Illumina). Quality assessment is done with FastQC, and reads are trimmed using Cutadapt before mapping. Sequences with length < 16 nucleotides are discarded. The reads count table is generated using featureCounts, filtered for underrepresented genes, and analyzed using linear models (limma) for differential expression analysis. Functional analysis utilizes available annotations in functional genomics resources. Network-based approaches are employed to visualize miRNA-target connections and perform gene ontology (GO) analyses. STRINGdb is used for protein-protein interaction retrieval, igraph for network analysis, and clusterProfiler for GO and pathway enrichment analyses. Differential expression of miRNAs is validated by qPCR.

Results: We have already recruited 192 patients with MDD, including 104 TRD/88 responders. This cohort is composed of 70% of females, equally represented in both groups. BMI and age are associated with TRD, as well as mental comorbidities (e.g. anxiety, personality disorders). We have identified differentially expressed genes between the two groups. We observed a downregulation of immune-related pathways in TRD patients. Importantly, the microRNA regulation explains most of the differentially expressed genes, thus indicating their causal involvement in treatment resistance, and opening new yet unexplored therapeutic avenues in MDD.

Conclusion: The projects revealed the importance of microRNA as regulators of important molecular pathways underlying treatment response in major depression. Importantly, we detected downregulation of immune-related pathways in TRD patients and deregulated gliucemia and neuroinflammatory pathways. This project will provide a new predictive tool for future use in clinical practice, enabling better prevention and management of MDD treatment resistance.

CLINICAL EFFICACY OF ANTIDEPRESSANT PHARMACOGENETIC TESTS IN CLINICAL PRACTICE: STATE OF THE ART, CHALLENGES AND FUTURE PERSPECTIVES

Alessandra Minelli**1*

1 *Brescia University School of Medicine*

Alessandra Minelli, Brescia University School of Medicine

Objective: Several data indicate that the success of pharmacological treatment in major depressive disorder (MDD) is still unsatisfactory, and matching a patient to his/her optimal treatment generally requires multiple trials with different treatments. It is sobering to note that the more unsuccessful therapies tried, the lower the likelihood that a successful outcome will occur, which could lead to a protracted illness, a worse long-term prognosis, more side effects, and significant medical, social, and financial costs.

Methods: Numerous environmental and biological aspects of the disease as well as medication treatments are to blame for the low response and remission rates. Pharmacogenetic (PG) testing has the potential to improve the accuracy of outcome prediction and lower the rate at which antidepressants are stopped due to adverse effects. Commercial PG tests for antidepressants have been more widely available, but there has also been rising skepticism about their usefulness. Several studies have been carried out, with intriguing but conflicting findings.

Results: Few of them currently are randomized controlled trials (RCTs), and the majority of them are observational studies without a control group. Several limitations were found concerning study design, generalization of results, duration of the trails, patients group studied, and cost-effectiveness ratio. We conducted the first study in Italy concerning the validation of a pharmacogenetic test for antidepressants in clinical daily practice with advocacy license independence. In order to provide a comprehensive view of outcomes, including symptom improvements and the emergence of negative effects, we tried to overcome the limitations of prior studies by applying a wide range of rating scales.

This allowed us to identify the true impact of the pharmacogenetic test on the various symptom phenotypes of depression. **Conclusion:** In conclusion, a number of obstacles have been identified for the widespread use of PG testing for antidepressants in clinical care for patients with MDD. The lack of overall efficacy in some prospective trials necessitates further research and indicates that there are variations between the population seen in prospective clinical trials and the real-world populations that should undergo PG testing. Attempts to gain a better understanding of the subset of people who might benefit and the time frame over which such advantages are required.

GENETICS OF CLOZAPINE RESPONSE AND ADVERSE DRUG REACTIONS: FROM RARE TO COMMON GENETIC VARIATION

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Objective: Little is known about how genetic variation impacts clozapine-related side effects and clozapine response, thus making clinicians and patients often reluctant to start clozapine. Moreover, few studies have examined ancestry-diverse populations in psychiatric genetics. We therefore examined associations of common and rare genetic variants with clozapine response and clozapine-related side effects.

Methods: Both targeted (using Taqman and Sanger sequencing) and whole-genome analyses were conducted in a sample of 800 subjects using clozapine with a diverse ancestry. Genome-wide association studies (GWASs) were conducted. Polygenic risk scores (PRS) for schizophrenia were generated. Linear models correcting for covariates were run to examine associations between clozapine response and PRS. Finally, we examined associations between genotype-predicted CYP1A2, CYP2D6, and CYP2C19 enzyme activities and clozapine response.

Results: In targeted analyses we found that rs113332494 (HLA-DQB1) was significantly associated with clozapine-associated neutropenia/agranlycytosis in the all participants (P = 3.5 × 10−8), in Caucasians (P = 9.3 × 10−6) and in Turkis (P = 2.8 × 10−5). Rs41549217 (HLA-B) was nominally significant in the Caucasian group (P = .018).

Our GWAS indicated that rs1923778 within NFIB showed a suggestive association with symptom severity while on clozapine.

PRS-schizophrenia was positively associated with low symptom severity.

Furthermore, higher genotype-predicted CYP2C19 enzyme activity was independently associated with lower symptom severity while on clozapine.

Conclusion: Ethnicity-dependent and clinically relevant effects of genetic polymorphisms on the risk to develop clozapine-induced neutropenia/agranulocytosis exist. Pharmacogenetic testing can complement clinical decision making and thus empower appropriate CLZ prescribing, but ancestry should be taken into account when performing such testing for CLZ. High schizophrenia-PRS and genotype-predicted CYP2C19 enzyme activity are independently associated with lower symptom severity among individuals treated with clozapine Although it is too early to adopt PRSs in clinical decision-making, these findings strengthen the positioning of PRS-SCZ as relevant to treatment response in psychiatry, particularly in patients with difficult-to-treat symptoms.

PARAM: A NEURODEVELOPMENTAL COHORT FROM INDIA

Vivek Benegal, National Institute of Mental Health and Neurosciences, Bangalore

Symposium Synopsis: The PATHWAYS TO RESILIENCE AND MENTAL-HEALTH [PARAM] is a longitudinal study, in India to trace the normal and deviant neurodevelopmental trajectories which underlie resilience and vulnerability to mental illnesses; and understand the impact of Genome x

Exposome interactions on these processes, across the developmental span. The PARAM seeks to extend and enrich an existing neurodevelopmental cohort (the Consortium on Vulnerability to Externalizing Disorders and Addictions) of individuals aged 6-23 years, set up between 2016-2020 to establish a database and biobank of 9000+ subjects across seven sites in India. The symposium will present data from the cohort to discuss our work in establishing normative brain (and cognitive) developmental trajectories and the impact of exposures to environmental (modifiable) risk factors such as socioeconomic status, nutrition and pollution (PM2.5, arsenic) 1. Introduction to the Indian neurodevelopmental cohort 2. Growth trajectories for executive and social cognition abilities and the impact of psychosocial determinants 3. Impact of Developmental Exposure to Air Pollution and a matrix of environmental risk on Cognitive Function in Adolescent and Young Adults 4. A neurocognitive investigation of low-level arsenic exposure with executive functions and brain structure and resting state activity.

IMPACT OF DEVELOPMENTAL EXPOSURE TO AIR POLLUTION AND A MATRIX OF ENVIRONMENTAL RISK ON COGNITIVE FUNCTION IN ADOLESCENT AND YOUNG ADULTS

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Objective: Brain development is influenced by both genetic and environmental factors and is critical for the normal growth and maturation of mental processes such as attention, memory, learning, and executive functions. It is well established that there are critical periods in the development of the brain when the environment can significantly impact neuroplasticity and cognitive development. The impact of developmental exposure to air pollution and a matrix of environmental risks on cognitive function in adolescent and young adults is a growing area of concern. The Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA) is an accelerated longitudinal cohort based in India that aims to study the impact of genes and environment on brain structure, function, and cognitive abilities. This study focuses on the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, body mass index, and psychopathology.

Methods: The participants of the cVEDA study were assessed at baseline and two follow-up times, and measures of socio-demographics, psychopathology, cognitive functions, and high-resolution ambient air PM2.5 exposure were available for n=6307 at baseline and were included for the current analyses. We performed a hierarchical confirmatory factor analysis and generated a single latent factor (g) representing general cognitive abilities. We then studied the impact of exposure to particulate matter on general cognitive abilities, correcting for age, sex, socio-economic status, BMI and psychopathology.

Results: The study found that exposure to particulate matter was significantly associated with poorer general cognitive abilities, after controlling for confounds. Further, we also found that the impact of developmental exposure to PM2.5 on overall cognitive functioning was significantly greater among people from lower socio-economic backgrounds, indicated by lower wealth scores.

Conclusion: In conclusion, the results of this study provide evidence for the impact of exposure to particulate matter on general cognitive abilities in adolescent and young adults and suggest that the presence of multiple environmental risk factors (eg., malnutrition, poverty etc) may have additive effects on cognitive development. The cVEDA cohort represents a unique opportunity to investigate the interplay between environmental exposures, psychopathology, and cognitive development in a developing country context. These findings highlight the need for further research to understand the potential implications of air pollution on cognitive development in populations exposed to high levels of particulate matter. These findings have important implications for policy and public health initiatives aimed at reducing exposure to environmental pollutants and promoting healthy cognitive development.

GROWTH TRAJECTORIES FOR EXECUTIVE AND SOCIAL COGNITION ABILITIES AND THE IMPACT OF PSYCHOSOCIALDETERMINANTS

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Objective: Structural and functional developmental reorganization of the brain manifests as motor, sensory, cognitive, social, emotional and other functional abilities. Timing and pattern of maturation follow a simple to complex order. Basic sensory and motor functions are fairly well established in early childhood; timelines for certain cognitive and socio-emotional abilities might extend into adulthood. Examining functional brain abilities could help track brain development; they also have a putative role in early risk identification for psychopathology. These abilities need to be better characterized over development, in terms of maturational patterns, implications of delay or deficits, factors that influence developmental change, etc.

Methods: The cVEDA study, an Indian developmental cohort, with data on more than 9000 youth, ages 6-23 years, enabled examination of developmental trajectories (for verbal and visuo-spatial working memory, response inhibition, set-shifting, and social cognition), and how these are influenced by gender, socio-economic status and childhood adversity. Working memory enables holding information temporarily for task performance. Response inhibition is self-regulatory, enabling appropriate inhibition of undesirable responses. Set-shifting is cognitive flexibility, enabling consideration of alternatives. Faux pas recognition that detects social blunders and emotion recognition are necessary for socio-emotional functioning. The sample represented sex, urban-rural background, and psychosocial risk (psychopathology, childhood adversity and wealth index, i.e. socio-economic status) adequately. Quantile regression was used to model developmental change. It models conditional percentiles by representing observations along with their distributions. This method allowed for examination of covariate effects on shape and location of the graph. We could examine whether covariates affected everyone similarly or were there differences in, say, high versus low performers.

Results: Development in both executive and social cognitive abilities continued into adulthood. Maturation and stabilization occurred in increasing order of complexity, from working memory to inhibitory control to cognitive flexibility. Social faux pas recognition matured by adolescence, but emotion recognition abilities continued to develop into early adulthood. Age related change was more pronounced for low quantiles in response inhibition, but for higher quantiles in set-shifting. Wealth index had the largest influence on developmental change across cognitive abilities. Sex differences were prominent in response inhibition, set-shifting and emotion recognition. Childhood adversity had a negative influence on cognitive development.

Conclusion: These findings add to the limited literature on patterns and determinants of functional brain development. They have implications for developmental vulnerabilities in youth, and need for providing conducive environments. Socio-economic status, by providing enriched environments, has the most prominent influence on development, whereas adversity negatively impacts development. Childhood performance level plays a role in adult outcomes. Interestingly, more prominent impact of determinants on lower performance levels of response inhibition and emotion recognition suggests that these abilities can be enhanced by adequate learning opportunities. This could have a cascading impact on other skill development.

A NEUROCOGNITIVE INVESTIGATION OF LOW-LEVEL ARSENIC EXPOSURE WITH EXECUTIVE FUNCTIONS AND BRAIN STRUCTURE AND RESTING STATE ACTIVITY

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Objective: Arsenic, a contaminant of groundwater and irrigated crops, is a global public health hazard. While isolated impairments of cognitive function following chronic exposure to high arsenic levels have been described, a comprehensive assessment of the scope of such impairments and their underlying brain mechanisms does not exist, especially not in the case of the much more common low-level arsenic exposure. We applied multivariate statistical modelling to (i) investigate potential arsenic-related syndromic changes across multiple cognitive domains; (ii) identify arsenic-related changes in brain structure and function; (iii) understand the relationship between arsenic-associated brain and cognitive alterations, and (iv) explore the moderating influence of other measures of environmental risk and physical health.

Methods: We analysed cross sectional data of 1014 participants aged 6 to 23 years of the Indian Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA cohort). Participants were characterised using deep phenotyping measures of behaviour, neuropsychology, psychopathology, brain neuroimaging and exposure to developmental adversities and environmental neurotoxins. Arsenic was measured in urine as an index of exposure. Executive function was measured using cVEDA neuropsychological battery, grey matter volumes were extracted from T1 weighted MRI and functional network connectivity measures were extracted from the resting state functional MRI. Our multivariate approach controls for age, gender, site, educational level and total intracranial volume. We used sparse partial least square (sPLS) analysis to determine the relationship between arsenic, cognition, brain structures and functions through the application of L1 penalization, applied under resampling. Subsequently we carried out mediation analysis. Next, we conducted moderated mediation analysis using data on participant's SES and BMI.

Results: 1014 participants aged 6 to 23 years (44.5% females) were included from 5 geographic locations. Using sparse-partial least squared analysis (sPLS) we describe a negative association of arsenic exposure with executive function (r=-0.12, p=5.4x10-4), brain structure (r=-0.2, p=1.8x10-8) and functional connectivity (within-network: r=-0.12, p=7.5x10-4, between-network: r=-0.23, p=1.8x10-10). Alterations in executive function were partially mediated by localised changes in grey-matter volume (b=-0.004, 95%CIs=-0.007 to -0.002) and within-network functional connectivity (b=-0.004, 95%CIs=-0.008 to -0.002). Socio Economic Status (SES) and Body Mass Index (BMI) moderated the link between arsenic and changes in grey-matter volume, such that the effect is strongest in participants from lower SES and with low BMI.

Conclusion: Our results indicate that low exposure to arsenic, among participants residing in areas with reported groundwater arsenic content below WHO thresholds, is correlated with aberrations in structural and functional brain regions and alterations of cognitive processes of executive function. Further, children from lower standard of living and with low BMI might be more vulnerable to environmental insults associated with arsenic and might point towards a "syndemic" relation between arsenic exposure and low SES, BMI resulting in greater health problems.

MACHINE LEARNING APPROACHES TO IDENTIFY FUNCTIONAL BRAIN NETWORKS CORRELATING WITH COGNITIVE PERFORMANCE IN ADOLESCENTS WITH ADHD

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Objective: Psychopathology is increasingly associated with impairments in cognitive, emotional and behavioural functions due to underlying alterations in distributed neural networks. Using rsfMRI, large-scale resting state networks (RSNs) have been identified consistently in healthy subjects. Connectivity within these networks correlates with cognitive and behavioural measures obtained outside the scanning environment.

Statistical machine learning methods have been successfully used to classify ADHD based on fMRI measures in previous studies. Here, we used reliefF- SVM derived methods with FSL derived ICA networks as input, to evaluate the cognitive performance of adolescents with ADHD, to identify brain networks underlying cognitive dysfunction.

Methods: The subjects in this study were from the cVEDA neurodevelopmental cohort in India. 71 subjects with a diagnosis of Attention Deficit Disorder [mean age (SD) :12.7 (±3.2)years] were included along with 71 healthy controls (HC) matched for age [mean age (SD) – 12.9 (±2.8) years], gender, head-motion profile during fMRI and scanner-site from the cVEDA imaging databank (http://cveda.org/dataset/).

Cognitive task scores from the cVEDA neuropsychological battery, included digit span test, corsi block test, trial making test, now or later test, balloon analogue risk task, stop signal task, sort the cards, emotional recognition task and social cognition rating tool in Indian setting. Scores on these tasks were scaled to a mean of 50 and standard deviation of 10 and summated to compose cognitive domains.

Resting-state functional MR imaging (EPI) scans were obtained (164 dynamics; TR/TE/FA – 2200ms, 30ms, 75°; 38 slices; 3.4x3.4x3.4 mm). Folllowing pre-processing, subject-specific network time-series were derived, using the dual regression approach of FSL. The data was decomposed into 79 components using the Fast ICA algorithm in FSL. For the purpose of machine learning classification, all the 79 components were used to regress out subject-specific time courses and spatial maps. Feature-set reconstruction was carried out and a filter based feature selection method - ReliefF was implemented

Results: The reliefF-SVM algorithm predicted 55/71 ADHD subjects and 54/71 HC correctly. 16 ADHD subjects were misclassified as HC and 17 HC were misclassified as ADHD. The ROC analysis revealed consistent performance of the algorithm across thresholds. The performance of the classifier model was evaluated using a 10-fold stratified cross validation resulting in 128 training instances and 14 test instances. The overall accuracy was 76.76% with 76.05 % specificity and 77.46 % sensitivity.

Among the 62 components there were 18 components that revealed significant group differences. These components belonged to task positive, default mode, cingulate, orbito frontal, sensory motor, temporal, and visual networks. **Conclusion:** Our study found that rsFMRI measures can be used to predict subjects with ADHD and can be used as an adjunct to phenotypic classification of ADHD. Further we found that variations in specific functional brain networks, appeared to correlate with different cognitive, emotional functions including attention, working memory, impulse control, processing speed social cognition and emotion recognition reflecting lower connectivity in these networks as an indicator of a poor performance.

TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON ANTIPSYCHOTICS

Xenia Hart, German Society for Biological Psychiatry

Symposium Symposium For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A personalization of drug treatments towards highest possible efficacy with acceptable tolerability involves titrating towards the best individual dose and dosing strategy by the use of tools implemented to support clinical decision making. Two tools have been introduced in these terms that can be used in clinical practice i) Therapeutic Drug Monitoring of antipsychotic drug levels and ii) pharmacogenetic testing. Valuable additional insights derive from in vivo brain imaging studies.

Methods: We provide details on pharmacokinetics and pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Articles were selected for inclusion and discussion by more than 40 international experts in the field of psychiatry and psychopharmacology. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. In vivo occupancy of target structures occupied by antipsychotic drugs was primarily assessed using positron emission tomography.

Results: Study findings strongly support the use of Therapeutic Drug Monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes to guide antipsychotic drug therapies. Molecular brain imaging is a strong tool to support the definition of target windows for optimal antipsychotic drug action, so called therapeutic reference ranges.

Conclusion: Therapeutic drug monitoring and genotyping are valid tools to guide individual drug therapies, far beyond the typical indications i.e. uncertain adherence, and polypharmacy.

INTRODUCING TOOLS FOR OPTIMIZING ANTIPSYCHOTIC PHARMACOTHERAPY IN PSYCHIATRY (THERAPEUTIC DRUG MONITORING, MOLECULAR BRAIN IMAGING AND PHARMACOGENETIC TESTS)

Xenia Hart**1*

[1] *German Society for Biological Psychiatry*

Objective: For psychiatric disorders such as schizophrenia, drug therapy plays an essential role in the control of acute and long-term symptoms. A large spectrum of antipsychotic drugs is now available in most western countries. A personalization of drug treatments aims at achieving the highest possible efficacy and acceptable tolerability at the same time. It involves not only the selection of the optimal drug for a patient but also the titration towards the best individual dose based on patients' specific characteristics.

Methods: In my talk, I will give a short introduction in to-date available tools that can be used to optimize pharmacotherapy in psychiatry. I will give an overview on how these tools can be used in order to support clinical decision making in antipsychotic drug therapies. The presented findings are

based on an international guideline initiated by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" with a contribution of more than 40 international experts. Therapeutic drug monitoring nowadays represents the most commonly used tool for personalizing drug treatments in clinical psychiatry. After determination of a drugs' blood level, this level is compared to predefined reference ranges published in relevant guidelines. Pharmacogenetic testing is predominantly used to detect genetic polymorphisms of enzymes involved in drug metabolism. However, the clinical application potential goes far beyond this. The third tool introduced in this presentation are in vivo brain imaging studies, primarily using positron emission tomography. **Results:** The guideline developed by the WSFBP task force "Tools for Optimizing Antipsychotic Pharmacotherapy in Psychiatry" provides a detailed review on pharmacokinetics, pharmacodynamics and pharmacogenetics for a total of 50 antipsychotic drugs. Selected studies measured drug concentrations in the blood (i.e., therapeutic drug monitoring), genetic polymorphisms of enzymes involved in drug metabolism, or occupancies of relevant transporters or receptors in the brain. The use of therapeutic drug monitoring and cytochrome P450 genotyping and/or phenotyping of drug metabolizing enzymes are strong tools to guide antipsychotic drug therapies for most drugs. Molecular brain imaging has been used to support the definition of valid therapeutic reference ranges. **Conclusion:** Despite the introduction of useful tools to optimize drug treatments in psychiatry, personalized drug treatment has still not become standard of care in psychiatric patients. Guidelines provide strong support for the use of therapeutic drug monitoring and pharmacogenetic testing. For example, they contain practical instruction for the interpretation of drug monitoring results.

WFSBP TASK FORCE - TOOLS FOR OPTIMIZING PHARMACOTHERAPY IN PSYCHIATRY: FOCUS ON THERAPEUTIC DRUG MONITORING OF ANTIPSYCHOTICS

Frederik Vandenberghe**1*, *Xenia Hart2, Nicolas Ansermot1, Severine Crettol1, Chin B. Eap3*

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Objective: Therapeutic drug monitoring (TDM) is an important tool to optimize pharmacotherapy, in particular for drugs with narrow therapeutic range. The clinical value of TDM during antipsychotic therapy is best established for clozapine. However, because of the wide interindividual variation of plasma levels and treatment responses, most other antipsychotics are good candidates for routine TDM.

Methods: The literature was extensively reviewed by the WFSBP task force to assess pharmacokinetics, therapeutic ranges and relations between plasma concentrations, daily doses and therapeutic responses of 43 common antipsychotics.

Results: The main conclusions of this review will be discussed, with a focus on clinically important data for the TDM of specific antipsychotics. In addition, the following important aspects of TDM will be addressed: a) specific indications (e.g., treatment resistance, evaluations of drug–drug interactions, specific comorbidities affecting drug pharmacokinetics), b) pre-analytical issues (e.g., steady-state conditions and time of blood sampling), and c) post-analytical issues (e.g., clinical interpretations of drug levels and therapeutic recommendations such as dose adjustments and antipsychotic switches).

Conclusion: To be clinically relevant, TDM should be used according to the latest available evidence and with a good knowledge of the pharmacokinetics, pharmacodynamics and safety profile of the drugs. Moreover, TDM should be associated when needed with other valid tools, such as cytochrome P450 phenotyping and/or genotyping, to optimize personalized antipsychotic therapy.

ASSOCIATION BETWEEN CYP2D6 SLOW METABOLIZER STATUS AND EXPOSURE TO ANTIPSYCHOTICS

Marin Jukic1, Céline Verstuyft**2*

[1]University of Belgrade, 2University Paris Saclay

Objective: Precise estimation of the drug metabolism capacity for individual patients is crucial for adequate dose personalization. The aim of this meta analysis was to quantify the difference in the antipsychotic exposure among patients with genetically associated CYP2D6 poor (PM), intermediate (IM), and normal (NM) metabolizers.

Methods: PubMed, Clinicaltrialsregister.eu, ClinicalTrials.gov, International Clinical Trials Registry Platform, and CENTRAL databases were screened for studies. Two independent reviewers performed study screening and assessed the following inclusion criteria: (1) appropriate CYP2D6 genotyping was performed, (2) genotype-based classification into CYP2D6 NM, IM, and PM categories was possible, and (3) 3 patients per metabolizer category were available. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for extracting data and quality, validity, and risk of bias assessments. A fixed-effects model was used for pooling the effect sizes of the included studies. Drug exposure was measured as (1) dose-normalized area under the plasma level (time) curve, (2) dose-normalized steady-state plasma level, or (3) reciprocal apparent total drug clearance. The ratio of means (RoM) was calculated by dividing the mean drug exposure for PM, IM, or pooled PM plus IM categories by the mean drug exposure for the NM category.

Results: the most profound differences were observed in the patients treated with aripiprazole (CYP2D6 PM plus IM vs NM RoM, 1.48; 95% CI, 1.41-1.57; 12 studies; 1038 patients), haloperidol lactate (CYP2D6 PM vs NM RoM, 1.68; 95% CI, 1.40-2.02; 9 studies; 423 patients), risperidone (CYP2D6 PM plus IM vs NM RoM, 1.36; 95% CI, 1.28-1.44; 23 studies; 1492 patients). Exposure differences were also observed for clozapine, quetiapine fumarate; however, these differences were marginal, ambiguous, or based on less than 3 independent studies.

Conclusion: In this systematic review and meta-analysis, the association between CYP2D6 genotype and drug levels of several antipsychotics was quantified with sufficient precision as to be useful as a scientific foundation for CYP2D6 genotype-based dosing recommendations.

THERAPEUTIC PLASMA CONCENTRATIONS OF ANTIPSYCHOTICS: LESSONS FROM PET IMAGING

Gerhard Gründer**1*, *Moritz Spangemacher1, Hiroyuki Uchida2, Xenia Hart1*

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Objective: Positron emission tomography (PET) and single photon emission tomography (SPECT) of molecular drug targets (neuroreceptors and transporters) provide essential information for TDM-guided drug therapy with antipsychotic drugs. Optimal therapeutic windows for D2 antagonists and partial agonists as well as proposed target ranges are discussed based on an up-to-date literature search.

Methods: An overview of neuroimaging findings in humans and primates that after the administration of amisulpride, haloperidol, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, cariprazine, and ziprasidone will be provided. A particular focus is set on dopamine D2-like and 5-HT2A receptors. Target concentration ranges are estimated based on receptor occupancy ranges that relate to the onset of clinical effects or side effects (i.e. EPS). Findings for other relevant receptor systems complement the discussion.

Results: Reported reference ranges for aripiprazole and for clozapine are well in line with findings from PET studies. For haloperidol, risperidone and olanzapine, an adjustment of the previously

published upper limit towards lower concentrations would be indicated from PET studies' findings to decrease the risk for EPS.
Conclusion: Neuroimaging studies provide a strong tool to define target ranges for antipsychotic drug treatment and to direct TDM.

WHITE MATTER IN MENTAL ILLNESS, AS A BIOMARKER AND THERAPEUTIC TARGET

Xinmin Li, University of Alberta
Symposium Synopsis: Since the introduction of drugs used in the treatment of major psychiatric disorders in the 1950s, emphasis has been placed on classical pharmacological actions. Putative therapeutic mechanisms of focus have included effects on monoamine neurotransmitter synthesis, catabolism, release, uptake, and receptor activation. We need to identify alternative and additional targets for drug action in this context. The innovative work that we are leading has indicated possible new mechanisms of action of many of these drugs in terms of effects on neuroprotective effects on neurodegenerative processes in the brain.
Our team approaches mental health disorders as neurodegenerative disorders. We examine whether central white matter damage can produce behavioral symptoms and brain pathology in experimental animal models of schizophrenia or depression as well as neuroimaging, genetic, and clinical studies. We examine whether antipsychotic and antidepressant treatment, rTMS, and ultrasound can prevent white matter damage and/or facilitate recovery which suggests a new role for these treatments and also suggests a new target for future drug development.

RESEARCH ON MYELINATION RELATED SUSCEPTIBLE GENES OF SCHIZOPHRENIA

Weihua Yue*[1], *Hao Yan1, Yuyanan Zhang1, Yaoyao Sun1, Dongxue Chen1, Zhe Lu1, Zhewei Kang1, Tianlan Lu1, Dai Zhang1*

[1]*Insitute of Mental Health, Peking University Sixth Hospital*
Objective: The strategy of genetics has been proven to be effective and helpful to explore the mechanism of schizophrenia and the myelination related susceptible genes of antipsychotic medications. We have been committed to finding the myelination related susceptibility genes of schizophrenia in Chinese Han population.
Methods: We used the genome-wide association study (GWAS) and meta- analysis, the multi-omics approaches, and the pharmacogenomics in Chinese Han population (n = 5934).
Results: We found several myelination related susceptibility genes associated with the risk of schizophrenia (MBP, MAG, MOP, etc.). Combined clues of bioinformatics data and functional experiments by using the gene knock-out or knock-in mice models, we further explored the potential function of the novel susceptible genes. There were very important interactive effects on genetic polymorphisms or variants, on transcriptional levels or neuroimaging characters in schizophrenia patients. With a large sample size of pharmacogenomics (3 stages-design, n = 5934), the applicant reported several susceptible genes associated with individual differences in therapeutic or side effects of common antipsychotic medicines. Patients in the pharmacogenomics-guided pharmacotherapy (PGT) group had greater early-response rate (94.0% versus 80.8%), response rate (83.1% versus 60.3%) and symptomatic remission rate (68.7% versus 46.2%) compared to the treatment-as-usual (TAU) group.
Conclusion: These results will be helpful to interpret the pathogenesis of schizophrenia, as well as the pharmacological mechanism of common antipsychotic medications.

Haiyun Xu*[1]
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Objective: Understanding the pathogenesis of schizophrenia involves exploring various hypotheses, including the dopamine (DA) hypothesis, mitochondrion hypothesis, oligodendrocyte (OL) hypothesis, among others. The coexistence of these hypotheses suggests a potential common neurobiological mechanism underlying schizophrenia.
Methods: This study investigates a potential neurobiological mechanism by utilizing two animal models of schizophrenia, cultured OLs, and neuron-OL co-cultures. The research employs animal behavioral tests, as well as cellular and molecular biological techniques.
Results: Adolescent C57BL/6 mice administered tolcapone (TOL) for two weeks exhibited elevated DA levels in the prefrontal cortex (PFC), mitochondrial dysfunction in brain cells, and dose-dependent hypomyelination in the PFC, hippocampus, and caudate putamen (CPu), alongside schizophrenia-related behaviors. Catechol-O-methyltransferase (COMT) gene knockout (COMT-ko) mice displayed dopaminergic dysfunctions in the PFC and CPu, mitochondrial functional deficits, reduced mature OLs, and hypomyelination in similar brain regions to TOL-treated mice. In cultured OLs, DA inhibited cell development and impaired mitochondrial function in a concentration-dependent manner. These effects were mitigated by the antioxidant N-acetyl-L-cysteine (NAC) and trans-2-phenylcyclopropylamine (TCP), a mitochondrial monoamine oxidase (MAO) inhibitor. Additionally, DA inhibited axonal myelination in neuron-OL co-cultures while impairing mitochondrial function.
Conclusion: These findings underscore the critical role of mitochondria in linking DA catabolism to axonal myelination in the brain, offering new insights into schizophrenia pathogenesis and therapeutic strategies.

MODIFICATION OF MYELINATION AS A TARGET FOR REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND FLUOXETINE TREATMENT IN A MOUSE MODEL OF DEPRESSION

Jue He*[1], *Qianfa Yuan2, Lijing Chen1, Linman Wu1, Huai Li1, Mengbei Lou1, Yanlong Liu1, Yang-Huan Bao3*

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Objective: In order to test the neurotrophic hypothesis on myelination of depression, myelin basic protein (MBP), brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (TrkB) signaling were investigated in a mouse model of depression which was applied by a physical treatment of repetitive transcranial magnetic stimulation (rTMS) or (and) by a medical treatment of fluoxetine.
Methods: After 28 days of chronic unpredictable mild stress (CUMS) exposure, mice were chronically treated with rTMS (10 Hz for 5 seconds per train, total 20 trains per day) and (or) fluoxetine (5 mg/kg/day, intraperitoneally) for 28 days targeting on the frontal cortex. After the behavioral tests, the protein expressions of MBP, BDNF and TrkB were measured by immunohistochemistry and (or) Western Blot.
Results: The results showed rTMS and (or) fluoxetine attenuated the locomotion decrease, anxiety and depressive-like behaviors in the CUMS-exposed mice. In the same time, rTMS and (or) fluoxetine attenuated MBP and BDNF-TrkB decrease in the frontal cortex of the CUMS mice. Our results suggest that rTMS and fluoxetine could both benefit the CUMS-induced abnormal behaviors including depressive-like behaviors, and the beneficial effects of rTMS as well as fluoxetine on depression might be partly related to their common effect on modulating myelination through BDNF-TrkB signaling.
Conclusion: These indicate that modulation of myelination could be a potential novel treatment target for major depressive disorder.

MATRIX METALLOPROTEINASE-9 AS A MYELINATION RELATED PROTEIN IN INTRACEREBRAL HEMORRHAGE AND DEPRESSION

Xin Yu1, Mengzhou Xue Xue*2

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Objective: The zinc-dependent proteinases (MMPs) are a endopeptidases which have the capability of cleaving protein constituents of extracellular matrix. They are physiologically expressed in neurons, astrocytes and microglia, and their aberrant elevation contributes to a few central nervous system diseases.

Methods: Among the MMP members, MMP-9 has generated considerable attention because of its involvement in inflammatory responses, blood-brain barrier permeability, the regulation of perineuronal nets, demyelination, and synaptic long-term potentiation. MMP-9 is strongly detected in many cell types including endothelial cells and infiltrated neutrophils after brain injuries. It can be induced by factors such as the c-fos and c-Jun, immediate early genes and the cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).

Results: Primary hematoma expansion occurs shortly after intracerebral hemorrhage onset and appears to correlate with MMP-9 elevation. Perihematomal edema also seems to be linked to MMP-9 levels. Inhibition of MMP-9 could potentially improve clinical outcome through maintenance of BBB integrity and perihematomal edema reduction. Emerging evidence indicates an association between MMP-9 and the syndrome of depression. MMP-9 is considered to be an important factor in depression, not only as a therapeutic target but also as a biomarker in the condition. Clinical studies suggest that MMP-9 gene polymorphisms are related to depressive symptoms, and altered MMP-9 levels are observed in depressed patients and in depressive-like animal models. The serum MMP-9 may be a novel therapeutic target and biomarker for depression, although that blood level of MMP-9 may not directly correlate with brain MMP-9 content.

Conclusion: MMP-9 is likely to be a target for classical antidepressant treatments and MMP-9 inhibitors possess potential therapeutic effects for depression.

3:30 p.m. - 5:00 p.m. Debate Session III - Anthony Pelosi and Steven Hyman

DOES NATURE FAVOUR DIMENSIONAL OR CATEGORICAL DIAGNOSES? BY THEIR (CLINICAL) FRUITS SHALL YE KNOW THEM

*Anthony Pelosi*1*

[1]*University of Glasgow*

Objective: I will consider some pros and cons of categorical versus dimensional diagnoses in clinical practice and in research.

Methods: Results will be presented from epidemiological and health services research over the decades.

Results: I will argue that, on balance, a categorical diagnostic approach in psychiatry has been more useful to more patients than a dimensional approach over recent decades.

However, I will also also outline some recent worrying developments in British psychiatry that lessen the importance of Mother Nature when it comes to clinical diagnosis. These include the following.

1. Categorical and dimensional diagnoses are being used to exclude certain patients from the caseloads of highly specialised multidisciplinary clinical teams.

2. Specialist clinicians are claiming that they have special diagnostic skills and that diagnoses within their narrow area of interest are being missed by other psychiatrists (see, for example, Report by Bipolar UK 2022). 3. Certain psychiatrists and even their multidisciplinary colleagues are increasingly preoccupied with diagnostic classification. This is sometimes to help them exclude patients from their caseloads. At other times, it is to obtain access to additional resources for their patients that can only follow "an official diagnosis". Some nurses, psychologists, occupational therapists and social workers are taking this approach even though one of the strengths of these professions is that they are trained not to make diagnoses. 4. Patients are sometimes being referred to a clinic for confirmation of a particular self-diagnosis rather than for an assessment by a doctor who understands diagnosis and differential diagnosis and who is aware of their importance and their limitations. 4. Clinical and administrative preoccupation with "an official diagnosis" means that certain patients are passed from pillar to post when they present with mental ill health. Some patients, especially those with severe and complicated conditions, can end up receiving no care and treatment from mental health professionals. In the months before the conference I will be making inquiries of colleagues in other parts of the world about whether they have encountered similar situations. This is with a view to starting a good discussion of what can be done to maximise the benefit of both categorical and dimensional diagnoses and differential diagnoses. **Conclusion:** I will suggest that diagnostic categories in psychiatry remain a useful tool but, like all powerful tools, they can be misused.

DEBATE. NATURE STRONGLY FAVOURS DIMENSIONAL DIAGNOSES

*Steven Hyman*1*
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The Broad Institute

Objective: In this debate, I will present evidence that psychiatric disorders are best captured in dimensional terms that cross current diagnostic boundaries; I will also describe how the dominant DSM categorical system has become reified in a manner that thwarts scientific progress and new treatment development.
Methods: I will describe and synthesize results from epidemiology, genetics, neurobiology, and clinical research that can inform concepts and boundaries of psychiatric disorders.
Results: Psychiatric disorders are genetically and phenotypically highly complex and heterogeneous. Genetic contributions to risk involve thousands of DNA sequence variants (‘risk alleles’) segregating within populations. Each human being has a stochastic grab-bag representing some small fraction of the alleles associated with essentially all common quantitative traits. These range from disorders such as risk of schizophrenia to non-disorder traits such as adult height. Risk alleles for psychiatric disorders act additively, with degree of genetic loading (that can be measured by polygenic scores) being associated probabilistically with quantitative likelihood of unaffected, sub-threshold, or affected status. Common risk alleles are continuously distributed in populations; there are no discontinuities in distributions of polygenic risk that would support categorical distinctions between ill and well. There are also no discontinuities that would support categorical distinctions between disorders. Empirically, risk alleles are shared across psychiatric disorders (e.g., schizophrenia and bipolar disorder share approximately 65% of their common risk alleles) and importantly, some alleles that confer risk for certain disorders confer, at the same time, likelihood of beneficial cognitive and behavioral phenotypes (e.g., alleles that increase risk of obsessive-compulsive disorder, autism spectrum conditions, or anorexia nervosa are associated with greater educational attainment.)

Paralleling genetic risk, symptoms that contribute to psychiatric disorders (e.g., anxiety, social communication difficulties, dysphoric mood, inattention) are also continuously distributed in populations, differing quantitatively between unaffected and affected individuals in number and severity. The symptom counts that DSM-5 uses to define disorders (e.g., 5 of 9 listed symptoms for major depression) represent (unfortunately arbitrary) normative designations. Overall, genetic, clinical, and epidemiological findings impugn the imposition of categorical boundaries between ill and well and favor transdiagnostic dimensional measures.

Conclusion: What is the path forward? (1) Continued pursuit of large-scale unbiased psychiatric genetics and follow-on neurobiology; (2) Use of information emerging from genetics and neurobiology to perform transdiagnostic efforts at biomarker discovery; (3) Epidemiology and genetics at the level of symptoms and symptom covariation, not categorical disorders; (4) Development of quantitative scales based on symptoms and symptom clusters, genetics, and biomarkers with the properties needed for diagnostic measures; (5) Integrative efforts to develop dimensional diagnostic criteria with openness to revision.

3:30 p.m. - 5:00 p.m.
Concurrent Symposia X

WHEN RANDOMIZED TRIALS AREN'T AN OPTION: TARGET TRIAL EMULATION IN PSYCHIATRIC RESEARCH *Helene Speyer, Copenhagen Research Center for Mental Health – CORE Mental Health Center*
Copenhagen; Copenhagen University Hospital

Symposium Synopsis: Because randomized trials in psychiatry are difficult to conduct, clinical decisions may need to be guided by analyses of non-randomized (observational) data. These observational analyses need to use a methodology that appropriately emulates a (hypothetical) randomized pragmatic trial—a target trial—. These challenges are not unique to psychiatry research.

Elsewhere in medicine investigators have applied this method to provide the same answers as randomized trials when other approaches to analyze observational data had failed. Here, we will present four different applications:

First, antipsychotic discontinuation in early psychosis. A research question famous for being hard to answer with randomized trials. But as health-care professionals, we are responsible for providing evidence-based counseling to help patients make informed choices.

Second, functional interventions in patients with a recent hospitalization for major depression disorder. Attrition rates and the small sample sizes rendered existent RCT analyses inconclusive. We will apply the target trial emulation framework to Finnish Registry data.

Third, we will apply this methodology to suicide research, where the event is so rare that it is hard to

find adequate sample sizes to study in randomized trials. We will explore the comparative effectiveness of antidepressants in reducing suicide risk.

Finally, we will discuss how we can use existing randomized trials to strengthen this proposed methodology. By benchmarking observational data analyses against the results of existing randomized trials, we can more confidently extend to new questions. We will discuss this approach using as a case study the EUFEST trial and observational analyses on First Episode Psychosis.

BENCHMARKING OBSERVATIONAL ANALYSES AGAINST RANDOMIZED TRIAL RESULTS: AN APPLICATION TO FIRST EPISODE PSYCHOSIS

Alejandro Szmulewicz*[1], *Gonzalo Martínez-Alés1, Maria Ferrara2, Diane Fredrikson3, Juan Gago4, Vinod Srihari2, Lakshmi Yatham3, Sarah Conderino4, Ann Shinn5, Dost Öngür5, Miguel Hernán1*

[1]Harvard University, 2Yale School of Medicine, 3University of British Columbia, 4New York University Grossman School of Medicine, 5McLean Hospital

Objective: To increase confidence in observational analyses in first episode psychosis (FEP), we would benchmark the observational analyses against existing trial results before extending the observational analyses to answer clinical questions not originally considered in that trial.

Methods: The FEP-CAUSAL Collaboration is an international consortium of observational cohorts of individuals with FEP. We analyzed data from four FEP-CAUSAL cohorts in North America (current N=1,081) to emulate a target trial similar to the EUFEST randomized trial. EUFEST found a higher average 1-year hazard ratio (HR) of treatment discontinuation in haloperidol compared with olanzapine and quetiapine, but similar 1-year probabilities of hospitalization and mean Clinical Global Impressions-Severity (CGI-S) scores. We replicated the results from EUFEST and then extended the emulation to include aripiprazole and risperidone.

Results: Compared with haloperidol, the HR (95% confidence interval) of treatment discontinuation was 0.38 (0.24-0.59) for olanzapine and 0.24 (0.13-0.44) for quetiapine. The 1-year mean of CGI-S for haloperidol, olanzapine, and quetiapine were 3.5, 3.4 and 4.2, respectively, and the 1-year risks of hospitalization were 24.2 (16.2-35.0), 25.4 (18.8-34.0), and 28.2 (21.6-34.2), respectively. Compared with haloperidol, the HR of treatment discontinuation was 0.18 (0.12-0.26) and 0.21 (0.13-0.34) for risperidone and aripiprazole. The 1-year hospitalization risk for aripiprazole was 33.0% (24.7-43.6).

Conclusion: Our observational estimates were similar to those from the EUFEST randomized trial. After benchmarking known effect estimates, we estimated a greater 1-year hospitalization risk for aripiprazole compared with all other drugs. Our findings suggest that this observational dataset may be used to estimate treatment effects in FEP research.

COMPARATIVE EFFECTIVENESS OF ANTIDEPRESSANTS TO LOWER SUICIDE RISK AFTER A SUICIDE ATTEMPT: WHY ARE RCTS UNFEASIBLE AND HOW CAN WE LEVERAGE OBSERVATIONAL DATA TO GUIDE CLINICAL DECISIONS?

Gonzalo Martínez-Alés*[1], *Alejandro Szmulewicz2, Miguel Hernán2*

[1]Harvard TH Chan School of Public Health, 2Harvard University

Objective: Lack of evidence regarding use of commonly prescribed antidepressants (e.g., SSRIs, SNRIs, mirtazapine) for patients discharged after an attempt has important implications for clinical practice, because (i) most of such patients are diagnosed with mental health conditions potentially treatable with antidepressants and (ii) there is conflicting evidence as to whether initiation of antidepressants may temporarily increase risk of suicidal ideation and suicidal behaviors. This presentation is aimed at clarifying limitations of RCTs to examine the potential role of antidepressants for suicide prevention following an attempt, introducing the target trial emulation framework as a way forward, and presenting preliminary results of the first target trial emulation of antidepressants for post-discharge suicide prevention.

Methods: We first critically review RCTs examining use of antidepressants to prevent suicide among suicide attempters. We provide a detailed overview of the limitations of such studies. Then, we introduce the notion of target trial emulation using observational data to guide clinical decision-making for clinicians and patients choosing antidepressant agent and treatment strategy following a suicide attempt. Last, we present results from a large target trial emulation including ~67,000 suicide attempters from the US Veteran Health Administration.

Results: The scarce evidence on antidepressants and suicidality comes largely from randomized controlled trials including antidepressant initiators but excluding patients deemed acutely suicidal (or at high suicide risk, such as recent suicide attempters). Traditionally, the potential inclusion of patients discharged following a suicide attempt in antidepressant trials has raised ethical and safety concerns. In addition to potential ethical concerns, randomized trials including patients discharged following a suicide attempt are difficult to implement because of pragmatic reasons: adequately large samples are arduous to gather, and patients may be reluctant to enroll or remain engaged. Observational data can be used to evaluate the benefits and risks of clinical interventions when randomized trials are not available. In fact, many analyses of observational data are attempts to emulate a hypothetical pragmatic randomized trial. This methodological approach rests on a key idea: observational analyses need to emulate a (hypothetical) target trial as closely as possible, because the process of specifying and emulating a target trial forces the investigators to sharpen their research question in terms of actionable interventions and enhances interpretability of results. Results from the first target trial emulation of antidepressants to lower suicide risk following a suicide attempt, examining the comparative effectiveness of initiation of an SSRI, an SNRI, or mirtazapine with doses following recommendations from standard clinical guidelines, suggest this approach is feasible and can guide clinician decision-making. The outcomes of interest are nonfatal suicide re-attempt, suicide death, and death by any external cause, all measured within 1-, 3-, 6-, and 12-months following discharge. **Conclusion:** By adopting and successfully applying target trial emulation, we can use observational data to generate new avenues to guide decision-making in clinical questions such as post-discharge suicide prevention – where randomized trials are unethical, not feasible, or currently under way.

EARLY VS. DELAYED RETURN TO WORK AMONG INDIVIDUALS DIAGNOSED WITH MAJOR DEPRESSIVE DISORDER: A TARGET TRIAL EMULATION

Kaisla Komulainen*[1], *Mai Gutvilig[1], Ripsa Niemi[1], Markus Jokela[1], Marko Elovainio[1], Christian Hakulinen[1]*
[1]*University of Helsinki*

Objective: Prolonged absence from work among patients with first-episode major depression may add to depression-related functional impairment and impede recovery. The effectiveness of early return to work against adverse functional outcomes is not yet well known and conducting a randomized controlled trial to evaluate the effectiveness is not feasible. We emulate a hypothetical target trial to assess the risk of a new sick leave due to depression among persons with first-episode major depression who returned to work early vs. after a prolonged sick leave period.
Methods: Using individual-level data linked across Finnish nationwide registers, we emulate a target trial among persons who went on sick leave following a diagnosis of first-episode major depressive disorder. Persons are eligible if they received their first recorded diagnosis of major depressive disorder (ICD-10 code F32) between Jan 1, 2009 and Dec 31, 2019, were 25–50 years old at the time of the diagnosis, had no sick leave due to any mental disorder during the 4 years preceding the diagnosis and were granted sick leave for 10–84 days since the diagnosis. We compare assignment to two sick leave strategies: 1) early return to work (sick leave duration 10–28 days) and 2) delayed return to work (sick leave duration 29–84 days). We classify individuals into one of two sick leave strategies according to their records obtained from the sickness absence register of the Social Insurance Institution of Finland, which contains diagnosis-specific administrative information on all sick leaves granted by a physician for > 9 days. The assignment is assumed to be random conditional on baseline covariates including sex, age, educational level, geographical area, depression severity, psychiatric comorbidity and comorbid physical conditions. The outcome of interest is the start of a

new depression-related sick leave during the follow-up period. For each person, the follow-up starts on the first day of sick leave (baseline) and ends on the day of the outcome event of interest (a new sick leave), death, emigration, 2 years after baseline or the administrative end of follow-up on Dec 31, 2019, whichever occurs first. The causal contrast of interest is the observational analogue of the per protocol effect. We evaluate the cumulative incidence estimates of the 2-year risk of a new sick leave, risk differences and risk ratios between individuals with early and delayed return to work. **Results:** There were 114 000 eligible individuals (52 000 with early return to work; 62 000 with delayed return to work). The 2-year cumulative incidences of a new sick leave, risk differences and risk ratios will be presented. **Conclusion:** We will evaluate the implications of our findings on the effectiveness of early vs. delayed return to work among individuals with first-episode depression and discuss the application of target trial emulation using population-based register data in a real-world setting.

WHY OBSERVATIONAL DATA MAY BE THE SOLUTION TO CHALLENGES IN ANTIPSYCHOTIC MAINTENANCE TREATMENT RESEARCH

Helene Speyer*[1]

[1] *Copenhagen Research Center for Mental Health – CORE Mental Health Center Copenhagen; Copenhagen University Hospital*

Objective: Current recommendations, largely based on expert consensus or observational evidence, suggest antipsychotic maintenance treatment for 1-2 years following remission after a first episode of psychosis (FEP). The aim of this presentation is to discuss limitations of randomized controlled trials (RCTs) to address gaps in evidence. Current gaps include lack of long-term studies, limited adherence to studied interventions – and of uptake of proper per-protocol analysis methods, absence of examination of clinically important treatment strategies (e.g., different treatment durations), limited real-world generalizability of study results, and lack of power to detect relevant outcomes (e.g., mortality). We examine the potential of observational data (e.g., from electronic health records), analyzed to emulate a hypothetical (target) trial, to address these limitations and inform clinical guidelines.

Methods: The key to inform clinical decision-making (i.e., choice between available interventions) is to explicitly define the most useful causal contrast of interest for clinicians and patients. In traditional relapse prevention RCTs including participants experiencing FEP, maintenance treatment is compared to an abrupt transition to placebo, assessed in blinded design on samples fulfilling a narrow set of eligibility criteria. These have limited real-world validity. More recent trials compare maintenance treatment to open label, personalized tapering strategies. Despite mirroring real world clinical situations, these trials have low levels of adherence to assigned treatment strategies, especially after long-term follow-ups. When analyzed as intention-to-treat, confounding may lead to underestimation of both beneficial and harmful effects. Indeed, data may approximate observational data and therefore need careful adjustment for potential post-randomization confounding, while still having the limitations associated to narrow eligibility criteria and small samples sizes. Furthermore, recruitment problems have led to failed and underpowered trials, as few people can accept that medication strategy is determined by randomization. Studies using observational data have been published. While attempts have been made to adjust for confounding at baseline, these studies have typically failed to adjust for time-varying confounding, such as fluctuations in illness severity over time.

Results: There are several limitations in conducting RCTs to expand the knowledge gaps: 1) Recruitment problems lead to underpowered or failed RCTs, 2) low adherence to assigned treatment arm introduces confounding, 3) narrow eligibility criteria lead to low real-world generalizability, 4)

there are ethical concerns as superiority of maintenance treatment has already been established. Data from electronical health records with rich longitudinal information may be a feasible way forward. When observational data are used to explicitly emulate a hypothetical (target) trial, they can provide clinically useful estimates of the causal contrast of interest while securing sufficient power and real-world validity and allowing for appropriate adjustment for time-varying confounders. **Conclusion:** To develop evidence-based clinical guidelines for treatment maintenance in FEP, emulating a hypothetical (target) trial using rich observational data may be the solution.

PRECISION PSYCHIATRY APPROACH FOR MOOD DISORDERS: ROLE OF BRAIN BIOMARKERS AND DYSFUNCTIONAL IMMUNE RESPONSE

Manish Jha, University of Texas Southwestern Medical Center

Symposium Synopsis: Modest benefits of currently available treatments for mental illnesses have limited our ability to address the ongoing public health emergency of increasing rates of deaths due to suicide. In fact, over the past decade, suicide rates have increased by 178% and 76% respectively in youths aged 10-14 years and 15-19 years. Current syndromic approaches of diagnosing and investigating mental illnesses are a key barrier to developing mechanistically-guided treatments. Therefore, our proposed panel will bring together early- stage investigators and senior researchers who will present on issues relevant to precision psychiatry approach for mood disorders. The first presentation will discuss neuroimaging-predicted brain age as a novel biomarker that is associated with antidepressant response and with all-cause mortality. The second presentation will focus on how persons with depression should be elevated to be the focus of personalized medicine and improve quality of care. The third presentation will present novel data form a large observational natural-history cohort of patients where integration of brain and immune biomarkers can help in identifying distinct trajectories of depression. The final presentation will focus on the on the topic of the aggregation of marginal gains as a philosophy of care; this recognizes that there are no silver bullets, and for most people it aggregating several small-effect sized factors which are selected on the basis of clinical formulation. Together, these presentations will highlight novel approaches to identifying subgroups of individuals with mental illness and discuss issues relevant to precision approaches for mood disorders.

ACCELERATED AGING OF BRAIN: ASSOCIATION WITH ANTIDEPRESSANT TREATMENT RESPONSE AND ALL-CAUSE MORTALITY

Manish Jha*[1], Abu Minhajuddin[1], Cherise Chin Fatt[1], Madhukar Trivedi[1]
University of Texas Southwestern Medical Center

Objective: Recent reports suggest that neuroimaging-predicted brain age is higher than chronological age (or Δ brain age) in adults with major depressive disorder (MDD). In this presentation, we will discuss its reliability as a biomarker, association with antidepressant treatment response and with all-cause mortality.

Methods: Both studies: Accelerated Brain Age was estimated as difference between T1-weighted structural MRI scan-predicted brain age and individual's chronological age.

Study 1: Mixed model analyses evaluated whether accelerated brain aging at baseline (N=290) in the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study was associated with treatment-related changes in depression severity.

Study 2: Kaplan Meier survival curves and Cox proportional hazards regression were used to estimate the association between accelerated brain aging and all-cause mortality in the second-wave of Dallas Heart Study (DHS-2; N=1948).

Results: In EMBARC, greater accelerated brain aging at baseline was associated with smaller reductions in depression severity with sertraline with sertraline (p=0.019) but not with placebo (p=0.64) after controlling for age, gender, race, ethnicity, and site. In DHS-2, each additional year of accelerated brain aging was associated with 6% higher likelihood of all-cause mortality even after controlling for Framingham 10-year risk score, race, ethnicity, income, education, waist-to-hip ratio, diabetes, hypertension, and history of myocardial infarction. **Conclusion:** Accelerated brain aging was independently associated with poorer outcome to antidepressants in MDD and to higher likelihood of all-cause mortality in an epidemiological sample. Future prospective studies are needed to replicate these associations and elucidate the mechanisms that link accelerated brain aging to poor outcomes.

THE PERSON AND ITS RELATION TO PERSONALIZED MEDICINE AND DEPRESSION TREATMENT

Koen Demyttenaere*[1], *Madhukar Trivedi[2], Michael Berk[3], Manish Jha[2]*

[1]KU Leuven, University Psychiatric Center, [2]The University of Texas Southwestern Medical Center, [3]Deakin University

Objective: Psychiatry has been adopting terminology used in cancer clinics and cancer research: the concepts of remission and of quality of life have been widely adopted and more recently, the concepts of personalized medicine or of precision medicine have also getmore and more attention.
Methods: Given the limitations of currently available biomarkers, we still believe personalized medicine within the scope of depression treatment first of all has to take the 'person' into account.
Results: The poorly defined concept of major depression results in a highly heterogeneous patient population and the very non-specific scales used to assess severity and change during treatment obscure the more subtle clinical effects observed in clinical practice. Moreover, patient sociodemographic characteristics as well as patient beliefs and patient preferences play an important role in predicting outcome. One could even speculate that the currently available biomarkers are more relevant than usually believed if the 'person' would be better taken into account in the prediction models.
Conclusion: Patient preferences, illness beliefs, treatment beliefs and adherence are crucial in what we can expect from treatment modalities.

BRAIN AND IMMUNE BIOMARKER BASED TRAJECTORIES OF DEPRESSION: FINDINGS FROM THE TEXAS RESILIENCE AGAINST DEPRESSION (T-RAD) STUDY

Madhukar Trivedi*[1]

[1] *The University of Texas Southwestern Medical Center*

Objective: Major depressive disorder (MDD) is a heterogenous syndrome which affects 1 in 5 adults during their lifetime and is associated with marked impairments in social, occupational, and interpersonal functioning and reductions in quality of life. Clinical markers have proven to be of minimal benefit in predicting long-term trajectories of symptoms and functioning. Studies using biomarkers, including blood-based and brain neuroimaging, have typically focused on distinct age groups, such as those on youths, young adults, or elderly individuals, and may miss out on age-related differences in these mechanisms. Furthermore, these studies have often not included individuals who are at risk for developing depression and characterize those who are resilient in face of the risk factors and stressors.
Methods: This report is based on findings from the ongoing Texas Resilience Against Depression (T-RAD) study which has enrolled. The individuals undergo comprehensive clinical phenotyping and biomarker assessments using electroencephalogram (EEG), magnetic resonance imaging (MRI) and multiplex immune marker assays.

Results: Between September 2016 to Sep 2022, 1313 individuals aged 10-95 years who either have a diagnosis of unipolar or bipolar depression or have risk factors that predispose them to depression (such as diagnosis of depression in first degree family members) were enrolled. Three-fourths of the sample attended at least two in-person visits, and 57% had at least four in-person visits. Data for less than 6 months, 6-12 months and > 12 months was available for 519 (37.61%), 132 (9.56%), and 729 (52.83%) participants, respectively. Connectomic analyses using EEG data from 1083 individuals revealed distinct patterns of dysfunction within the executive control network. Immunometabolic analyses revealed distinct subgroups of individuals with dysregulation within innate and adaptive immune responses. Ongoing analyses are evaluating how these dysfunctions relate long-term symptom and quality of life trajectories.

Conclusion: This study of individuals with depression or at-risk for depression demonstrates the utility of comprehensively phenotyping and implementing multimodal biomarker assessment.

THE AGGREGATION OF MARGINAL GAINS AS A PHILOSOPHY OF CARE

Michael Berk*[1]

[1]*Australasian Society for Bipolar and Depressive Disorders Ltd*

Objective: The objective of this presentation is to discuss the construct of the aggregation of marginal gains informed by clinical formulation as a philosophy of care and a pragmatic pathway to personalised medicine.

Methods: There are no magic bullets in psychiatry and very few people respond dramatically to any one therapy. For most individuals, one needs a combination of different modalities that are tailored to individual needs. The philosophy of aggregation of marginal gains capitalises on the idea that even small improvements in multiple domains can lead to very large changes because they compound over time. Clinically, each small change can increase capacity to take on subsequent steps, leading to a virtuous cycle which with persistence and time can result in major changes.

Results: At present despite promising developmental work there are no biomarkers capable of stratifying participants to predict response to therapy that are ready for the clinic. However clinical formulation allows one to understand the individual biological psychological and social predisposing, precipitating, perpetuating and resilience factors that allows one to select from the large number of psychological, lifestyle and biological therapies that are available.

Conclusion: In conclusion the philosophies of the aggregation of marginal gains, informed by clinical formulation, supported by a solid therapeutic alliance and consistency of care have the capacity to lead to substantial improvements in clinical outcomes.