Biological Psychiatry
AUSTRALIA

2021

Proceedings of the Biological Psychiatry Australia Virtual Scientific Meeting 2021

Queensland Brain Institute
The University of Queensland

Welcome

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Queensland Brain Institute

The 11th Biological Psychiatry Australia Scientific Meeting

25th October – 27th October 2021

Dear Friends and Colleagues,

On behalf of the Local Organising Committee, we warmly welcome you to the 11th Annual Biological Psychiatry Australia 2021 (BPA2021) Scientific Meeting hosted by the Queensland Brain Institute in Brisbane. This year is our 2nd virtual meeting, and we will be using the Whova portal (Whova.com). You can use the app on a computer or mobile interface to see the agenda, view talks and posters, see all the session times, as well as connect with other attendees, either directly via their profiles are in Session Q&As. Please note all times listed in this book are in AEST, Brisbane, QLD, GMT+10.

On behalf of the Local Organising Committee, we wish you an engaging and stimulating meeting.

Co-Chairs: A/Prof. Thomas Burne (BPA President) and Dr James Kesby (BPA Webmaster)

BPA2021: Physically Distant but Scientifically Connected

Stay connected with our Twitter accounts: @biolpsychaust @BPA_ECRN

If you have any question, please do not hesitate to contact us at biolpsychaust@gmail.com

All online material can be found at https://whova.com/portal/webapp/biolo_202110/

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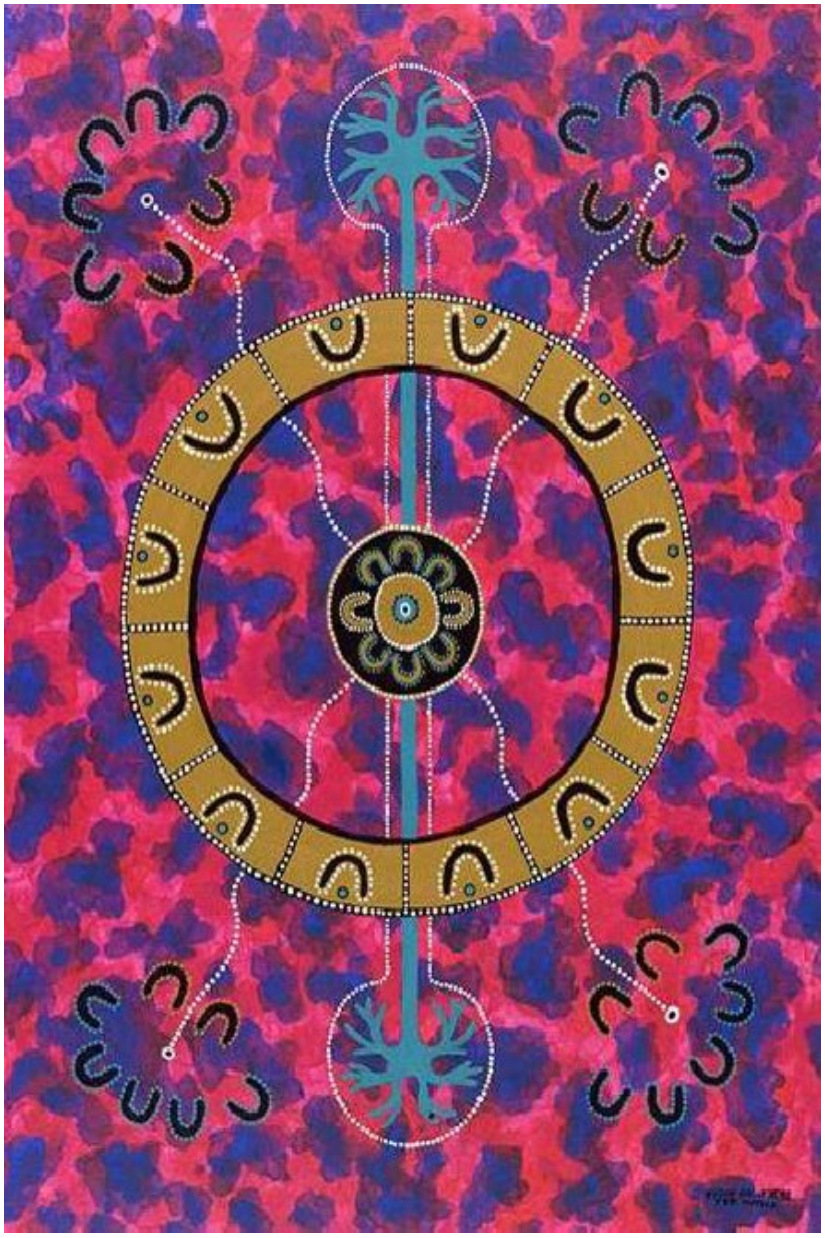
Acknowledgement of Country

We acknowledge the Traditional Owners and Custodians of the lands on which we are hosting this virtual meeting and of the various lands on which you all work. We acknowledge the Aboriginal and Torres Strait Islander people participating in this meeting.

We pay our respects to Elders past and present and celebrate the diversity of Aboriginal peoples and their ongoing cultures and connections to the lands and waters of QLD and Australia. We also extend that respect to all Indigenous people around the world who are attending this meeting.



Psychiatric Research by Ted Watson

This painting, representing collaborative research between people with schizophrenia and mental health professionals, is by an aboriginal mental health service user and was commissioned by the Queensland Centre for Mental Health Research, Australia

Source: Bhugra D (2005) The Global Prevalence of Schizophrenia. PLoS Med 2(5): e151. https://doi.org/10.1371/journal.pmed.0020151

BPA Equality and Diversity Statement

Biological Psychiatry Australia (BPA) has a mission to promote research and innovation in the field of biological psychiatry within Australia.

Diversity drives quality and innovation, and so BPA strives to develop a strong culture of diversity and inclusivity. We aim for all voices to be heard, regardless of gender, race, disability, age, social class, sexuality, or religion.

We recognise our responsibility to our membership to promote equality of opportunity across all our activities, including developing meeting programs, and bestowing prizes and awards.

We will not tolerate actions or language that discriminates against any person or persons based on gender, race, disability, age, social class, sexuality, religion or otherwise at any event held by or sponsored by BPA.

Through fostering a culture of inclusivity, we aim to promote diversity and provide a forum where researchers of all levels and all backgrounds can freely share ideas and inspiration.

Society Profile

Biological Psychiatry Australia is a society established in 2010 for professionals interested in the advancement of biological research in psychiatry.

The research focus of the Society encompasses the application of biological techniques to investigate and better understand the causes of psychiatric disorders and the translation of neuroscience research to the development of more effective clinical treatments.

The society convenes annually at a meeting designed to promote academic exchange and collaboration between researchers and clinicians working in related fields.

Executive Committee

President	Thomas Burne	Queensland Brain Institute
Vice-president	Andrea Gogos	Florey Institute of Neuroscience and Mental Health
Secretary	Tertia Purves-Tyson	Neuroscience Research Australia
Treasurer	Christina Perry	Florey Institute of Neuroscience and Mental Health
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	Sarah Cohen-Woods	Flinders University
	Yann Quidé	University of New South Wales
	Zoltan Sarnyai	James Cook University
	Lauren Harms	The University of Newcastle

Isaac Schweitzer Lecture

2010	*not awarded*
2011	*not awarded*
2012	*not awarded*
2013	Michael Berk
2014	Paul Fitzgerald
2015	John McGrath
2016	Cyndi Shannon Weickert
2017	Patricia Michie
2018	Christos Pantelis
2019	Brian Dean
2020	Susan Rossell
2021	Anthony Hannan

Aubrey Lewis Award

2010	Mark Bellgrove
2011	Melissa Green
2012	Andrea Gogos
2013	Michael Breakspear
2014	Adam Guastella
2015	Irina Voineagu
2016	Andrew Zalesky
2017	Jee Kim
2018	Rachel Hill
2019	Marta Garrido
2020	Bronwyn Graham
2021	Lianne Schmaal

Organisers

Local Organising Committee
Co-Chairs: Thomas Burne and James Kesby
Nathanael Yates, Xiaoying Cui, Jonathan O'Loan, Kyna-Anne Conn, Clarissa Yates, Svetlina Vasileva

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Chair	Elysia Sokolenko	SA Health and Medical Research Institute
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	Luke Ney	University of Tasmania

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Sponsors

We would like to thank all our long-term Sponsors for their continuing support.

Program at a glance

Time			*11th Biological Psychiatry Australia Scientific Meeting, 2021*		
AEST	*ACDT*	*AEDT*	**Monday, October 25**	**Tuesday, October 26**	**Wednesday, October 27**
QLD	*SA*	*NSW/VIC*			
9:00 AM	*9:30*	*10:00*		Oral Session 1	Oral Session 2
			Opening and 9th Isaac Schweitzer Plenary Lecture		
10:00 AM	*10:30*	*11:00*		**ECRN Plenary**	*Morning Tea*
			Symposia Session 1	*Morning Tea*	Symposia Session 4
11:00 AM	*11:30*	*12:00*		Symposia Session 2	
12:00 PM	*12:30*	*1:00*	*Lunch*		*Lunch*
			Data Blitz Session 1	*Lunch*	
1:00 PM	*1:30*	*2:00*	BPA Mentoring Program	Debate	Oral Session 3
2:00 PM	*2:30*	*3:00*	Data Blitz Session 2	Symposia Session 3	**BPA Annual General Meeting / Prizes**
			Poster Viewing - Session 1 (Animals, Molecular, Genetics)		
3:00 PM	*3:30*	*4:00*	Poster Viewing - Session 2 (Animals, Clinical, Imaging)		Conference Discussants
			Poster Viewing - Session 3 (Animals, Molecular, Imaging)	*Afternoon Tea*	*Afternoon Tea*
4:00 PM	*4:30*	*5:00*	Poster Viewing - Session 4 (Animals, Clinical)	**12th Aubrey Lewis Lecture**	**International Plenary**
			Poster Viewing - Late breaking abstracts		
5:00 PM	*5:30*	*6:00*			
6:00 PM	*6:30*	*7:00*	ECRN Social Event	Online Trivia	
7:00 PM	*7:30*	*8:00*			
8:00 PM	*8:30*	*9:00*			

Monday, 25 October 2021

Opening Ceremony

9:25 AM-9:30 AM (AEST, Brisbane QLD , GMT+10)

Thomas Burne

9th Isaac Schweitzer Plenary Lecture

9:30 AM-10:30 AM

Chair: Thomas Burne

Anthony Hannan
Gene-environment interactions informing therapeutic approaches for cognitive and affective disorders

Symposia Session 1

Network mechanisms regulating distinct features of motivated behaviour in psychiatric disorders

10:30 AM-12:00 PM

Chair: Elizabeth Manning Discussant: Susannah Tye

10:35 am **Elizabeth Manning**
OCD and flexible control of motivated behaviour

11:00 am **Roger Varela**
Immunometabolic factors contributing to dopamine dysregulation

11:25 am **Philip Mosley**
Deep brain stimulation for treatment-resistant obsessive-compulsive disorder

Lunch

12:00 PM-12:30 PM

Data Blitz Session 1

12:30 PM-1:00 PM

Chair: Elysia Sokolenko

12:30 pm **Matthew Hudson**
Optogenetic inhibition of parvalbumin interneurons causes an increase in gamma oscillatory power

12:35 pm **Trang Truong**
Long non-coding RNAs as molecular targets of drugs used to treat bipolar disorder

12:40 pm **Sunil Srivastav**
Understanding dopamine release mechanism in an animal model of relevance to Schizophrenia, EDiPs (Enhanced Dopamine in Prodromal schizophrenia)

12:45 pm **Emily Jaehne**
Operant alcohol self-administration in BDNF val68met rats

12:50 pm **Bruna Parry**
Baseline serum amino acid levels predict treatment response to augmentation with N-acetylcysteine (NAC) in a bipolar disorder randomised trial

Monday, 25 October 2021

BPA Mentoring Program 2021

1:00 PM-2:00 PM
Moderator: Ashlea Segal

Data Blitz Session 2

2:00 PM-2:30 PM
Chair: Leigh Walker

2:00 pm **Phoebe Mayne**
Removal of perineuronal nets in the retrosplenial cortex plays a modulatory role in the recall of recent and remote spatial memories

2:05 pm **Lucas Hoffmann**
Elevated paternal glucocorticoids preconception contributes to intergenerational shifts in male attractiveness and major urinary protein expression

2:10 pm **Carolina Gubert**
Faecal matter transplantation promisingly ameliorates cognitive dysfunction in Huntington's disease mice

2:15 pm **Matthew Greaves**
A multiverse analysis of electrodermal activity-estimated fear learning differences between healthy and anxious individuals

2:20 pm **Svetlina Vasileva**
Maternal immune activation and the gut microbiome in offspring

Monday, 25 October 2021

Poster Viewing - Session 1

2:30 PM-3:00 PM

Genetics

David Balfour
Developmental sleep trajectories and adolescent epigenetic age acceleration: A prospective cohort study

Madeliene Turner
Genetic markers and psychological health trajectories of risky drinking behaviour in veterans

Shweta S. Joshi
Identifying novel genes and RNA transcripts in genomic regions implicated in neuropsychiatric diseases

Yann Quidé
Interactive effects of polygenic risk and cognitive subtype on brain morphology in schizophrenia spectrum and bipolar disorders

Elysha Ringin
Exploring the association between type 2 diabetes and cognition in bipolar disorder: A cross-sectional study using the UK Biobank cohort

Animals

Asad Ali
Altered foetal steroidogenesis and dysregulated placental immune response in an animal model of maternal hypoxia

Zilong Du
Stress and dopamine in the dorsal striatum: implications for schizophrenia

Maya Wilde
Spontaneous and auditory evoked neuronal activity in scn1lab-/- zebrafish larvae

Laisa Umpierrez
Cannabidiol and Ethanolic Hemp Extract reduce relapse to methamphetamine and locomotor sensitization

Joel Raymond
Exogenous oxytocin dose-dependently suppresses REM sleep in male and female rats

Molecular

Renata Pertile
Developmental Vitamin D-deficiency affects the expression of miRNAs in dopaminergic neurons

Xiaoying Cui
Enhanced dopamine synthesis altered RNA methylation in dorsal striatum

Brian Dean
Changes in Cortical Gene Expression in the Muscarinic M1 Receptor Knockout Mouse: Potential Relevance to Schizophrenia, Alzheimer's disease and Cognition.

Jessica Chandra
Effect of chronic antipsychotic treatment on neuroinflammation and dopamine neuron health in rats

Jee Hyun Kim
EBRAINS/Human Brain Project open database DOPAMAP: High-resolution microscopic images of dopamine 1 and 2 receptor positive cells in the developing mouse brain

Monday, 25 October 2021

Poster Viewing - Session 2

3:00 PM-3:30 PM

Animals

Claire J Foldi
Investigating the therapeutic efficacy of psilocybin for anorexia nervosa in an animal model
Kyna-Anne Conn
Dopamine D1 and D2 receptor agonism dose-dependently impairs associative learning and goal-directed action in mice.
Max Katz-Barber
Stress reactivity of hypothalamic corticotrophin-releasing hormone (CRH) neurons following cocaine exposure
Adam J. Lawther
Blood Glutamate Scavenging Prevents Inflammation-Induced Depression in Mice
Daniel Bennett
A computational model of rodent behaviour on the trial-unique nonmatching-to-location (TUNL) touchscreen task

Clinical

Robyn da Silva
Reinforcement Learning in Autism: A Systematic Review and Meta-Analysis
Nicola Acevedo
Therapeutic Neurostimulation in Obsessive-Compulsive and Related Disorders: A Systematic Review
Megan Thomas
The neural, stress hormone and inflammatory correlates of childhood deprivation and threat in psychosis: A systematic review
Jessica G. Mills
Cannabidiol as a treatment for early-stage dementia: A double-blind, placebo-controlled clinical trial protocol
Luke Ney
BDNF genotype Val66Met interacts with acute plasma BDNF levels to predict fear extinction and recall
Claire Burley
Disinhibited behaviors in dementia: a scoping review of biopsychosocial mechanisms and systematic review of management approaches

Imaging

Kavinash Loganathan
Valuation system connectivity is correlated with poly-drug use in young adults
Trevor Steward
A thalamo-centric neural signature for restructuring negative self-beliefs
Katherine Bray
Empathy and resting-state functional connectivity in children
Divyangana Rakesh
Similar but distinct – Effects of different socioeconomic indicators on resting state functional connectivity: findings from the Adolescent Brain Cognitive Development (ABCD) Study
Louise Mewton
The relationship between brain structure and general psychopathology in preadolescents
Ashlea Segal
Neural Anatomical Heterogeneity in Psychiatric Disorders using Normative Models

Monday, 25 October 2021

Poster Viewing - Session 3

3:30 PM-4:00PM

Molecular

Carlos M. Opazo
Perturbed Iron Biology of the Prefrontal Cortex in Schizophrenia
Bruna Panizzutti
Transcriptional Modulation of the Hippo Signaling Pathway by Drugs Used to Treat Bipolar Disorder and Schizophrenia
Maria Kuznetsova
Genetic and environmental modulation of small non-coding RNAs in a mouse model of affective disorders
Zoe SJ Liu
The potential role of metabolic profiles in indicating treatment response after adjunctive N-acetylcysteine therapy in bipolar depression
Alice Petty
An imbalance of IgG receptors may contribute to the increased neuroinflammation seen in the midbrain of a sub-group of schizophrenia patients

Animals

Jessica Moretti
Concurrent LI-rTMS induces changes in c-Fos expression but not behavior during a progressive ratio task with adult ephrin-A2A5-/- mice
Benjamin Aliphon
Measuring Cognitive Affective Bias in Rats Over Time
Simone Rehn
Sucrose intake in rats under a binge-type access schedule affected by both intraperitoneal oxytocin administration and time of day
Gabriela Visini
Chronic adolescent cannabidiol increases glutamatergic and GABAergic markers in the hippocampus of male Neuregulin-1 mutant mice
Karly Turner
The behavioural and neural signature of impulsive actions in rodents

Imaging

Kavinash Loganathan
Correlations between value-based decision-making network connectivities and depression symptoms in developing individuals.
Thomas Williamson
Changes in functional activation in PTSD patients following cognitive behavioral therapy
Georgia F. Caruana
Inflammation as a moderator of the relationship between obesity and white matter microstructure in bipolar disorder
Rebecca Cooper
Development of chronotype in adolescence: implications for brain development and psychopathology.
Abdalla Z Mohamed
Self-reported fatigue was associated with increased white-matter alterations in the long-term trauma survivors.
Maria A. Di Biase
Transcriptomic and polygenic manifestations of cortical thickness heterogeneity in schizophrenia

Monday, 25 October 2021

Poster Viewing - Session 4

4:00 PM-4:30 PM

Animals

A. Shaam Al Abed
Modulation of the parvalbumin interneuron activity rescues PTSD-like memory formation in autism spectrum disorder.
Erin McLemon
Sex differences in how metabotropic glutamate 5 receptors modulate morphine reward
Man Kumar Tamang
Developmental vitamin D deficiency is associated with impaired adolescent social behaviour and altered gut microbiota in rats
Rhianne L Scicluna
Cannabidiol alleviates opioid withdrawal but worsens the development of tolerance to the analgesic effects of opioids
Jennifer Collins
Therapeutic potential of cannabidiol during abstinence from cocaine
Isabel Chew
Investigating the Role of Direct and Indirect Spiny Projection Neurons in the Transition to Habits

Clinical

Aron Hill
Modulation of Aperiodic Neural Activity Following Convulsive Therapy in Patients with Major Depressive Disorder
Hannah S. Savage
Temporal and spatial perception of heartbeat sensations in Autism Spectrum Conditions
Alexandre A. Guérin
Comorbid antisocial personality disorder predicts age of onset of methamphetamine use in people with methamphetamine use disorder
Lauren A Hennessy
Improving rTMS protocols: Translation from preclinical models to clinical trials targeting depression
Georgia M. Parkin
Refining a protocol for at-home salivary lithium monitoring

Poster Viewing – Late breaking abstracts

4:30 PM-5:00PM

ECRN Social Event

6:00 PM-8:00 PM
Host: Elysia Sokolenko

Tuesday, 26 October 2021

Oral Session 1

9:00 AM-10:00 AM (AEST, Brisbane QLD , GMT+10)
Chair: James Kesby

9:00 am **Sidhant Chopra**
Longitudinal Illness- and Medication-Related Brain Volume Changes in Psychosis are Shaped by Connectome Architecture

9:15 am **Parsa Ravanfar**
Regional changes of brain iron in individuals with schizophrenia compared with healthy controls, a 7-Tesla neuroimaging study

9:30 am **Michael Notaras**
Schizophrenia is defined by cell-specific neuropathology and multiple neurodevelopmental mechanisms in patient-derived cerebral organoids

9:45 am **Luba Sominsky**
Inflammation mediates the effects of peri-pregnancy diet on the maternal brain

Inaugural Early Career Researcher Network Plenary Award

10:00 AM-10:30 AM
Chair: Elysia Sokolenko

Divyangana Rakesh
Early adversity and the developing brain

Morning Tea
10:30 AM-11:00 AM

Symposia Session 2

Real insights into translational psychiatric research: simultaneously working with cells, rodents, and humans for solutions toward mental health

11:00 AM-12:30 PM
Chair: Jee Kim Discussant: Yann Quidé

11:00 am **Ken Walder**
Gene expression signature screening to repurpose drugs for neuropsychiatric diseases

11:20 am **Katherine Drummond**
Biological plausibility of certain early-life environmental factors impacting brain development

11:40 am **Catherine Toben**
Standardized methodology for biospecimen collection in clinical practice

12:00 pm **Michael Berk**
Pathways to the development of novel therapies focusing on repurposing existing safe and tolerable agents

Lunch
12:30 PM-1:00 PM

Tuesday, 26 October 2021

BPA Debate: The future of artificial intelligence in biological psychiatry

1:00 PM-2:00 PM
Chair: Jonathan Flintoff Panel: Ellen Lee, Nathanael Yates, Dana Bradford, Michael Breakspear

Symposia Session 3

Understanding limitations and strengths of animal models in schizophrenia research

2:00 PM-3:30 PM
Chair: Rachel Hill Discussant: Kelly Newell

2:00 pm **Suresh Sundram**
Deconstructing complex neuropsychiatric disorders enhances face validity in animal models

2:20 pm **James Kesby**
Cross-species reversal learning phenotypes and psychosis: acute amphetamine treatment in mice reflects early psychosis

2:40 pm **Farshad Alizadeh Mansouri**
Dynamic emergence of abstract rules in primate cognition, and of the distributed neural network that supports abstract rule formation, maintenance and task- dependent implementation

3:00 pm **Jaishree Jalewa**
Development of rat models for environmental risk for schizophrenia

Afternoon Tea
3:30 PM-4:00 PM

12th Aubrey Lewis Plenary Award

4:00 PM-5:00 PM
Chairs: Thomas Burne, Penelope Cream

Lianne Schmaal
ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing

Online Trivia

6:00 PM-8:00 PM
Host: Elysia Sokolenko

Wednesday, 27 October 2021

Oral Session 2

9:00 AM-10:00 AM (AEST, Brisbane QLD , GMT+10)
Chair: Tertia Purves-Tyson

9:00 am **Dylan Kiltschewskij**
Examining genetic correlation and causation between blood-based biochemical markers and cortical structure

9:15 am **Cassandra Wannan**
Affinity scores: An individual-centric biopsychosocial fingerprinting framework

9:30 am **Sylvia Harmon-Jones**
It's who you know: Fearfulness of a rat's cagemates influence anxiety-like behaviour and FGF2

9:45 am **Madeleine Wilkop**
Psychiatric polygenic risk and disordered eating in an Australian female twin population

Morning Tea
10:00 AM-10:30 AM

Symposia Session 4

Interaction between BDNF and neuroinflammation in psychiatric disorders and implications for novel treatments

10:30 AM-12:00 PM
Chair: Maarten van den Buuse Discussant: Jessica Chandra

10:30 am **Jessica Chandra**
Interaction between the cytokine and BDNF in chronic schizophrenia

10:50 am **Xu-Feng Huang**
Neuronal survival in neuroinflammatory conditions

11:10 am **Jana Vukovic**
Role of microglial brain-derived neurotrophic factor (BDNF) on neuronal survival and plasticity

11:30 am **Rachel Hill**
Global initiative to monitor the neurodevelopment of children whose mother was exposed to COVID-19 in utero

Lunch
12:00 PM-1:00 PM

Wednesday, 27 October 2021

Oral Session 3

1:00 PM-2:00 PM
Chair: Andrea Gogos

1:00 pm **Alec Jamieson**
Rostral anterior cingulate network effective connectivity in depressed adolescents and associations with treatment response

1:15 pm **Morgan James**
Binge-like eating restores hedonic deficits and becomes 'addictive' in obesity

1:30 pm **William Reay**
Multi-omic prioritisation of drug repurposing opportunities in psychiatry

1:45 pm **Patrick Laing**
Neural signatures of Pavlovian safety learning in humans: an ultra-high field fMRI study

Annual General Meeting, Prizes and Awards

2:00 PM-3:00 PM

Conference Discussants

3:00 PM-3:30 PM
Brian Dean
Melissa Green

Afternoon Tea
3:30 PM-4:00 PM

International Plenary (QBI Seminar)

4:00 PM-5:00 PM
Chair: Svetlina Vasileva
John Cryan
Gut feelings: Microbiome as key regulator of brain and behaviour across the lifespan

Invited Plenary Speakers

9th Isaac Schweitzer Plenary Lecture

Gene-environment interactions informing therapeutic approaches for cognitive and affective disorders

Anthony Hannan - Florey Institute of Neuroscience and Mental Health

Huntington's disease (HD) is one of over 50 tandem repeat disorders and involves neurodegeneration leading to psychiatric, cognitive and motor symptoms. In a transgenic mouse model of HD, expressing an expansion of the CAG tandem repeat encoding a polyglutamine tract in the mutant huntingtin protein, we provided the first evidence that depression, the most common psychiatric disorder associated with HD, could be modelled preclinically. We have demonstrated that environmental enrichment (enhanced cognitive stimulation and physical activity) can delay onset of endophenotypes modelling depression, dementia and movement disorders. These findings have been extended to include exercise and stress models in HD mice, and environmental manipulations in mouse models of other neurological and psychiatric disorders, including schizophrenia, depression and anxiety disorders. Our molecular and cellular investigations have revealed key pathways implicated in HD, including the pathogenesis of depressive-like endophenotypes, and identified novel therapeutic targets. We have also discovered altered brain-body interactions in HD, including the first evidence of gut dysbiosis (dysregulated microbiota) in HD. Most recently, we revealed gut dysbiosis in a genetic mouse model of schizophrenia and have investigated a possible contribution of the microbiota-gut-brain axis to psychiatric endophenotypes. Ongoing studies are exploring the gut microbiome as a therapeutic target and the possibility that specific environmental factors may modulate brain function via microbiota-gut-brain interactions. These findings inform both pathogenic mechanisms and novel therapeutic targets. Our approaches to gene-environment interactions may facilitate the development of 'enviromimetics' for a variety of brain disorders known to be modulated by environmental stimuli. Enviromimetics are a proposed novel class of therapeutics with the potential to mimic or enhance the beneficial effects of cognitive stimulation, physical activity and other environmental stimuli. Subclasses of enviromimetics, including 'exercise mimetics' and 'epimimetics', also have substantial therapeutic potential. In a parallel program of research, we have been exploring epigenetic inheritance via the paternal lineage. We have discovered the transgenerational effects of various paternal environmental exposures. Our findings reveal significant experience-dependent effects on cognitive and affective function of offspring via epigenetic inheritance. We are investigating the impact of specific environmental and pharmacological factors, including exercise and stress hormone elevation, and the relevance of these discoveries in mice to human transgenerational epigenetics and associated 'epigenopathy'. Our ongoing studies are exploring mechanisms whereby experience can modify germ cells and associated sperm epigenetics, and how these epigenetic modifications (of mice and men) may modulate offspring phenotypes and their potential susceptibility to various psychiatric disorders.

Inaugural Early Career Researcher Network Plenary Award

Early adversity and the developing brain

Divyangana Rakesh - Melbourne Neuropsychiatry Centre, The University of Melbourne

The experience of early adversity can shape neurodevelopment during sensitive periods, and is a transdiagnostic risk-factor for most mental disorders. My research has aimed to examine associations between adverse experiences (e.g., childhood maltreatment, socioeconomic disadvantage) and neurodevelopment, and identify neurobiological risk markers that relate to youth psychopathology. Using multivariate and machine learning methods, as well as rich longitudinal data, my work collectively demonstrates the widespread and long-term impacts of early adversity on brain structural and functional development and mental health. This research also revealed psychological and environmental factors that buffer against the detrimental effects of adversity on functional and structural brain development and, in turn, mental health. This talk will aim to summarise some key findings from my doctoral research and provide insight into how early experiences shape neural development.

12th Aubrey Lewis Plenary Award

ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing

Lianne Schmaal - Centre for Youth Mental Health, The University of Melbourne, Orygen

A key objective in the field of translational psychiatry over the past few decades has been to identify the brain correlates of major depressive disorder (MDD). Identifying measurable indicators of brain processes associated with MDD could facilitate the detection of individuals at risk, the development of novel treatments, the monitoring of treatment effects, and predicting who might benefit most from treatments that target specific brain mechanisms. However, despite intensive neuroimaging research towards this effort, underpowered studies and a lack of reproducible findings have hindered progress. Here, I present an overview of the work of the ENIGMA Major Depressive Disorder (MDD) Consortium, which was established to address issues of poor replication, unreliable results, and overestimation of effect sizes in previous studies. The ENIGMA MDD consortium currently includes data from 45 MDD study cohorts from 15 countries across six continents. Findings on structural brain alterations associated with MDD and related phenotypes (including childhood trauma, suicidality and obesity) from the ENIGMA MDD consortium to date will be presented. In addition, some of the current ENIGMA MDD projects that move beyond brain structure and categorical diagnosis will be showcased and future directions of the consortium will be discussed.

International Plenary (QBI Seminar)

Gut feelings: Microbiome as key regulator of brain and behaviour across the lifespan

John Cryan – University College, Cork

We are living in a microbial world and there has never been a time across evolution when the brain existed without signals from the gut microbiota. Thus, the microbiota-gut-brain axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of brain disorders. The routes of communication between the gut and brain include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or via microbial metabolites such as short chain fatty acids. These mechanisms also impinge on neuroendocrine function at multiple levels. Studies in animal models have been key in delineating that neurodevelopment and the programming of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. Recently, the gut microbiota has been implicated in a variety of conditions including obesity, autism, schizophrenia and Parkinson's disease. Moreover, animal models have been key in linking the regulation of fundamental brain processes ranging from adult hippocampal neurogenesis to myelination to microglia activation by the microbiome. Finally, studies examining the translation of these effects from animals to humans are currently ongoing. Further studies will focus on understanding the mechanisms underlying such brain effects and developing nutritional and microbial-based intervention strategies.

Symposia Abstracts

Symposia Session 1

Network mechanisms regulating distinct features of motivated behaviour in psychiatric disorders

Susannah Tye - Queensland Brain Institute

Elizabeth (Lizzie) Manning - University of Newcastle

Disturbances in motivated behaviour are a transdiagnostic feature of psychiatric disorders including addiction, mood disorders and obsessive compulsive disorder. Distinct features of motivated behaviour are regulated by discrete neural circuits in a region and celltype specific manner. External and intrinsic environmental conditions, together with established cue associations, co-regulate these mechanisms to optimise motivated behavioural responses that, from an evolutionary perspective, increase the likelihood of an animal's survival. In psychiatric disorders, however, these otherwise adaptive processes become disrupted to confer maladaptive behavioural states. This symposium will highlight novel cell- and circuit-specific mechanisms regulating distinct features of motivated behaviour and the latest approaches that have been developed to target these mechanisms for the treatment psychiatric disorders. This gender-balanced symposium will include presentations from three rising early career researchers, ranging from preclinical models to translation to clinical populations, from three different institutions across Australia. Presenters will describe complementary lines of research using state-of-the-art imaging tools and behavioural paradgms in translational models and clinical trials, that in turn enable alignment of data across behavioural, systems, cellular and synaptic levels.

OCD and flexible control of motivated behaviour

Elizabeth (Lizzie) Manning - University of Newcastle

Obsessive compulsive disorder (OCD) is a severe neuropsychiatric disorder associated with disturbances in flexible behaviour, including compulsions, flexible learning and bias towards threat related behaviours under motivational conflict. Corticostriatal circuit dysfunction is strongly implicated in the pathophysiology of OCD and flexible control of motivated behaviour, however the neural activity patterns in specific circuits that underly disruption of distinct aspects of flexible behaviour in OCD are poorly understood. I have recently characterized different types of flexible behaviour relevant to OCD in the Sapap3 knockout mouse model, and have used miniature microscopes to characterize single-cell activity patterns in prefrontal cortex and striatum associated with behavioural changes. This has revealed different changes in orbitofrontal cortex activity associated with impairments in flexible behaviour in a reversal learning task compared to compulsive grooming. Downstream in the striatum, specific disturbances in indirect pathway functioning were associated with compulsive behaviour. Delineating the neural patterns associated with distinct behavioural changes in OCD is critical for guiding the development of more effective treatments, including neural stimulation strategies aimed at directly manipulating activity in cortico-striatal circuits. More broadly, these studies highlight the different ways in which corticostriatal circuits contribute to distinct types of flexible motivated behaviour.

Immunometabolic factors contributing to dopamine dysregulation

Roger Varela - Queensland Brain Institute

Mood disorders comprise a heterogeneous pool of neuropsychiatric conditions associated with disturbances in stress coping, reward sensitivity and effort-related decision making. Understanding how distinct neurobiological states underlie discrete behavioural phenotypes has the potential to improve alignment between diagnosis, treatment, and pathophysiology. My research examines how alterations in mesoaccumbens dopamine neurotransmission can be used to define a subgroup of individuals resistant to first-line antidepressant treatments targeting serotonergic and noradrenergic neurotransmitter systems. Dopamine dependent effort-related decision making provides a valuable cross-species tool for quantifying disturbances in nucleus accumbens dopamine neurotransmission, sensitive to pharmacological and neuromodulation treatments targeted to this mechanism. Using the chronic adrenocorticotropic hormone

model of antidepressant resistance and the chronic amphetamine model of mania, I have quantified the impact of bi-directional mesoaccumbens dopamine system neuromodulation on mood-related behaviour. I have further used effort-related decision making to characterise how underlying alternations in mesoaccumbens dopamine signalling contribute to these states and individual capacity for treatment response. In this symposium, I will discuss immunometabolic factors contributing to dopamine dysregulation in these models and the value of utilising behavioural neuroscience as a tool for treatment stratification in psychiatry.

Deep brain stimulation for treatment-resistant obsessive-compulsive disorder

Philip Mosley - QIMR Berghofer Medical Research Institute

Background: Deep brain stimulation (DBS) is a promising treatment for severe, treatment-resistant obsessive-compulsive disorder (OCD). Objectives: To conduct the first Australian randomised, placebo-controlled clinical trial of DBS for a neuropsychiatric indication.
Methods: Nine participants were implanted with DBS electrodes bilaterally in the bed nucleus of the stria terminalis (BNST). Following a one-month postoperative recovery phase, participants entered a three-month randomised, double-blind, shamcontrolled phase before a twelve-month period of open-label stimulation incorporating a course of cognitive behavioural therapy (CBT). The primary outcome measure was OCD symptoms as rated with the Yale-Brown Obsessive-Compulsive Scale (YBOCS).
Findings: In the blinded phase, there was a significant benefit of active stimulation over sham ($p = 0.025$). After the open phase, the mean reduction in YBOCS was 16.6 ± 1.9 points ($p = 3.8 \times 10^{5}$), with seven participants classified as responders. CBT resulted in an additive YBOCS reduction of 4.8 ± 3.9 points ($p = 0.011$). An analysis of the structural connectivity of each participant's individualised stimulation field isolated right-hemispheric fibres associated with YBOCS reduction. These included subcortical tracts incorporating the amygdala, hippocampus and stria terminalis, a brain network implicated in fear conditioning.
Conclusions: This study provides further evidence supporting the efficacy and tolerability of DBS in the region of the BNST for individuals with otherwise treatment-refractory OCD and identifies a connectivity fingerprint associated with clinical benefit. With four positive RCTs now published demonstrating the benefit of this therapy, we suggest that DBS for OCD should be considered an accepted therapy in selected cases.

Symposia Session 2

Real insights into translational psychiatric research: simultaneously working with cells, rodents, and humans for solutions toward mental health

Jee Kim – Deakin University

Yann Quidé - UNSW Sydney

Translation of bench-based research to human psychiatric conditions is critically important, not only to achieve better health for people but also in the context of acquiring Australian funding and the imminent closing of Australia's biggest rodent supplier (Animal Resources Centre). This symposium brings together leaders and EMCRs in translational research across Australia who work with various laboratory models and then apply those discovery-based science to research in humans. We will give firsthand accounts of designing, setting up, and/or conducting translational research to solve problems in mental health. Professor Walder will open the symposium with description of the gene expression signature technology to identify repurposable medications that are currently being clinically trialled in humans. Dr Drummond will describe her latest research in rodents and humans understanding the role of environment in the development of cognition and emotional behaviours. Dr Toben will then describe her ongoing researching collecting empirical data from clinical cohorts as well as animal models of early and later life chronic stress to understand transcriptomic and proteomic signatures associated with alterations in particular symptom domains (such as cognition) of psychiatric disorders. Professor Berk will showcase the current clinical trials focussed on repurposing pharmacotherapy from other disorders, which are novel drugs for psychiatry identified based on discovery science and pharmaco-epidemiology. Dr Quidé will serve as a discussant for the different (or similar) approaches to translational research demonstrated by the speakers. A/Professor Kim will chair the questions to provide further insights, especially on the collaborative effort required to achieve translation.

Gene expression signature screening to repurpose drugs for neuropsychiatric diseases

Ken Walder - Deakin University

Traditional drug discovery approaches for neuropsychiatric disorders take more than a decade, are extremely expensive, and have been shown to have low success rates. Given the urgent need for new treatments, alternative approaches are required. We use gene expression signature screening to repurpose drugs for these diseases. This involves the atheoretical use of genome-wide transcriptomic profiling to identify gene expression profiles that most accurately reflect the overall biological effects of drugs currently used to treat these disorders, known as a gene expression signature. The signature can then be used to screen a library of offpatent drugs to identify those that most closely resemble the overall transcriptomic effects of the currently used drugs. Drugs that act in a manner that is most similar to the currently used drugs are thereby identified as targets for repurposing, and can be further tested in appropriate in vitro and in vivo models. Such confirmation is then translated into Phase 2 clinical trial testing of the compound with immediate clinical implications.

Biological plausibility of certain early-life environmental factors impacting brain development

Katherine Drummond - Florey Institute

Neurodevelopmental conditions (including autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), behavioural problems and learning difficulties) now account for four of the five most common childhood diagnoses by Australian paediatricians. A significant increase in prevalence has occurred over too short a time to reflect genetic factors, and this increase unlikely is attributed to changes in diagnostic criteria alone. To investigate the biological plausibility of certain early-life environmental factors impacting brain development and increasing vulnerability to adverse behavioural development, we have utilised both epidemiological and preclinical developmental neuroscience approaches. Using a genetic epidemiological approach, we first examined how early-life plastic chemical exposure is associated with altered neurodevelopmental outcomes in a birth cohort of 1074 children (Barwon Infant Study, Melbourne,

Australia). Our results suggest that higher pre-natal plastic chemical exposure is associated with deficits in child response inhibition, attention, and an increase in ADHD-related behaviours in parent-reported questionnaires on child behaviour.
Further preliminary analyses have revealed that polymorphisms in key genes in the dopaminergic pathway may modulate these associations. Secondly, utilising a rodent developmental neuroscience approach, we have explored potential mechanisms linking early-life experience with altered neurodevelopment. Our results using Pavlovian fear extinction as a model of fear regulation have revealed that early-life stress can modify the capacity to extinguish fear during development in a sex-specific manner in rats.
Collectively, these results may partly inform our understanding of why some children are more susceptible to acquire neurodevelopmental conditions after certain early-life environmental exposures. We argue for increasing cross-fertilisation between epidemiology and developmental neuroscience research.

Standardized methodology for biospecimen collection in clinical practice

Catherine Toben - University of Adelaide

Heterogeneity and complexity of underlying biological responses within psychiatric disorders remains a challenge in terms of predicting course of disorder as well as treatment response. Therefore, the development of more targeted therapies essentially requires a more in depth understanding of the interactions between the genome, proteome and epigenome and core pathophysiology. One of the remaining challenges in this space is the standardised methodology of biospecimen collection within multicenter studies. This presentation will use two current national and international trials as examples to discuss the current complexities faced by researchers when setting up standardized methodology for biospecimen collection and to show real world examples of how this work contributes to clinical practice. These trials aim to understand efficacy of novel treatment options as well as the reduced need for noninvasive sampling. Confounders include internal factors such as attaining high quality biobanking protocols while external ones such as research funding remain a challenge. Further discussion will be on how to move the field forward in terms of implementing key factors affecting biological integrity as well as extending experimental techniques in cells,
rodents, and humans.

Pathways to the development of novel therapies focusing on repurposing existing safe and tolerable agents

Michael Berk - Deakin University

There is a drought in new treatment development notwithstanding a major unmet need for most psychiatric disorders. This is driven at least in part by the absence of known and singular pathophysiology for most major disorders. This presentation highlights pathways to the development of novel therapies focusing on repurposing existing safe and tolerable agents. There are several potentially productive pathways for treatment development. Firstly, we have developed an innovative treatment discovery model using stem cell cultures by reverse-engineering the effects of combinations of known treatments in terms of their effects on global gene expression that have detected key lead compounds. These are validated via pharmacoepidemiology and preclinical models. Secondly, inflammatory and oxidative and nitrosative processes, altered neurogenesis and apoptosis and mitochondrial dysfunction have been identified to be critical in the aetiology and progression neuropsychiatric disorders. The presence of increased inflammatory activity, oxidative stress, mitochondrial dysfunction as well as altered neurogenesis in disorders such as bipolar disorder has deleterious sequelae that include lipid peroxidation, DNA fragmentation, telomere shortening, protein carbonylation, and vulnerability to apoptosis and hence structural and cognitive changes. Importantly, these pathways are potentially druggable, novel therapeutic opportunities. Novel pharmacotherapeutic avenues such as statins, minocycline, N- acetylcysteine and angiotensin agents that can augment existing approaches and hopefully contribute to better outcomes will be presented. As these repurposable drugs are already approved for use in other indications, the necessity of testing for tolerability, safety, and the regulatory affairs is minimised or eliminated, promoting efficient and competitive bench to bedside translation.

Symposia Session 3

Understanding limitations and strengths of animal models in schizophrenia research

Rachel Hill - Monash University

Kelly Newell - University of Wollongong

Schizophrenia is a complex psychiatric disorder characterized by hallucinations and delusions, social withdrawal and cognitive impairments. These very 'human' behaviours make this disorder impossible to model in a rodent or even a primate. However, there remains significant homology across rodents, primates and humans in several genes associated with schizophrenia. Furthermore, we know that fundamental cellular and neurotransmitter systems that are disturbed in schizophrenia are similar in function in the rodent and primate. Thus, animal models are valuable tools in schizophrenia research in terms of understanding the neurobiology of specific behaviours, understanding how both genetic and environmental risk factors disrupt the brain to impair behaviour, and testing new treatments that may modify the neurobiology of the disorder. However, differences in brain structure and organization as well as behavioural repertoire should be considered in developing and interpreting the results of animal models. This symposium will provide a comprehensive overview of the clinical symptom domains of schizophrenia by national leading psychiatrist Prof. Sundram and will follow with expert speakers in primate and rodent research, Dr's Mansouri, Kesby and Harms to discuss the ability to interrogate pathways associated with each of the clinical domains of schizophrenia. Panel discussants, A/Prof. Rachel Hill, head of the behavioural neuroscience laboratory at Monash University, and A/Prof. Kelly Newell, Head of Unit, Medical and Exercise science, University of Wollongong will guide an interactive 'big picture' discussion on the limitations and strengths of animal models and future directions for studies of animal models in psychiatric research.

Deconstructing complex neuropsychiatric disorders enhances face validity in animal models

Suresh Sundram - Monash University

Conceiving of schizophrenia as a complex neuropsychiatric disorder concurrently implies a commonality of clinical features and a diversity or ignorance of pathogenic processes. The picture is complicated by marked inter-individual variation and an unpredictable progressive intra-individual course. Considerable effort to parse components of the disorder have resulted in RDoC and related systems. The components are then proposed to more closely link to an underlying pathophysiology which may be shared with other disorders with similar features. Thus, insight into causation could be gained by modelling each component. However, this validity is predicated on the identified component representing a singular pathogenic mechanism. Using a robustly verifiable category, response to the atypical antipsychotic drug, clozapine, we identified a putatively implicated molecular target, the EGF system ligand, betacellulin. Modelling this in a rodent knockout model demonstrated pleiotropic effects across a range of diverse features including fear response and hyperlocomotion tractable to clozapine treatment. These data argue against simple linear phenotypic relationships. Instead, the potential for both polygenic and pleiotropic effects need to be considered in identifying mechanisms for apparent component behaviours. Significance: Deconstructing complex neuropsychiatric disorders enhances face validity in animal models but does not obviate the risk of the incorrectly inferred endophenotype.

Cross-species reversal learning phenotypes and psychosis: acute amphetamine treatment in mice reflects early psychosis

James Kesby - Queensland Brain Institute

Flexible decision-making allows us to appropriately adapt behaviours in response to changes in the environment and impairments in these processes are a strong predictor of functional decline in psychosis. To investigate decision-making, we use reversal learning paradigms. These feature two stimuli, where one is rewarded more often than the other, requiring decision making in the presence of misleading positive and negative feedback. The high and low probability reward outcomes are reversed multiple times during the task. In this talk, I will present and compare our reversal learning studies in those with early and persistent psychosis, as well as in mice after amphetamine treatment. We show that those with early psychosis are

less sensitive to recent losses, whereas those with persistent psychosis feature a completely different decision-making phenotype. To model the increased dopamine function associated with psychosis, we treated mice with amphetamine and assessed performance in a novel protocol with high levels of within-session reversal learning (5 reversals/100 trials). Amphetamine-treated mice displayed a decision-making phenotype reflecting that observed in early psychosis. Our work suggests that acute increases in dopamine better reflect decision-making in those with early psychosis than persistent psychosis, and that decision-making processes in those with psychosis change with illness course.

Dynamic emergence of abstract rules in primate cognition, and of the distributed neural network that supports abstract rule formation, maintenance and task- dependent implementation.

Farshad Alizadeh Mansouri - Monash University

Various aspects of human cognition are shaped and enriched by abstract rules, which help to describe, link and classify discrete events and experiences into meaningful concepts. Patients with neuropsychological disorders show deficits in implementing abstract rules. However, where and how these entities emerge in the primate brain and the neuronal mechanisms underlying them remain the subject of extensive research. Evidence from imaging studies in humans and single- neuron recordings in monkeys suggests a pivotal role for the prefrontal cortex in the representation of abstract rules; however, behavioural studies in monkeys and data from neuropsychological examinations of patients with prefrontal damage indicate substantial functional dissociations and task dependency in the contribution of prefrontal cortical regions to rule-guided behaviour. Various lines of studies indicate that the emergence of abstract rules for guiding behaviour encompasses dynamic multistage processes, including rule formation, maintenance and revision as well as goal- directed modulation of other cognitive functions. These processes are linked to a diverse range of executive functions. In this seminar I will describe our current understanding of the dynamic emergence of abstract rules in primate cognition, and of the distributed neural network that supports abstract rule formation, maintenance and task- dependent implementation.

Development of rat models for environmental risk for schizophrenia

Jaishree Jalewa - University of Newcastle

While schizophrenia is diagnosed and characterised by behavioural and psychiatric symptoms, several alterations in neural activity have been observed in those with schizophrenia in electroencephalographic (EEG) studies. Such EEG changes include reduced mismatch negativity, and dysregulated neural oscillations. These present a unique opportunity for animal models for schizophrenia, where we can attempt to model the schizophrenia-like EEG alterations in rodents. Our work has focused on the development of rat models for environmental risk for schizophrenia, such as maternal immune activation and adolescent cannabinoid exposure, and determining the degree to which these rat models emulate schizophrenia-like EEG changes. Using a novel paradigm, we have found that rats exposed to two cumulative risk factors for schizophrenia exhibit a reduction in the size of the mismatch negativity, analogous to what is found in schizophrenia. However, such changes are sex-, latency- and paradigm dependent. These findings suggest that EEG outcome measures can be used to probe the face validity of schizophrenia animal models, with potential to be used in future drug development studies.

Symposia Session 4

Interaction between BDNF and neuroinflammation in psychiatric disorders and implications for novel treatments

Maarten van den Buuse - La Trobe University

Interaction between BDNF and neuroinflammation in psychiatric disorders and implications for novel treatments As heightened neuroinflammation becomes increasingly recognized as a pathological feature of psychiatric illnesses, understanding how these inflammatory processes are regulated and their impact on neuron viability and function becomes imperative. The tissue damaging effects of neuroinflammation may be either exaggerated or attenuated by altered neurotrophic factors. Cytokines and trophic factors need to be studied simultaneously to aid in predicting effects of therapeutically counteracting neuroinflammatoryrelated pathophysiology relative to trophic factor levels and function. BDNF and its receptor (TrkB) are critical in the growth and survival of neurons across multiple brain regions, rendering it a worthy candidate to explore in the context of increased neuroinflammation in the brain and periphery in schizophrenia. First, Dr Huang will explore the relationship between BDNF and cytokines measured in the blood of people with chronic schizophrenia. Next, Jessica will investigate whether BDNF/TrkB levels are altered in people with schizophrenia who also have elevated cytokines and markers of active immune cells in two key brain regions – the midbrain and cortex. Next, Dr Vukovic will explore how the resident immune cells in the brain, microglia, release BDNF to impact neurogenesis. Finally, Dr Hill will discuss how stimulating BDNF signalling could reverse behavioural changes associated with immune system activation early in life, providing proof of principle that novel therapeutic strategies could lie at the interface between inflammation and trophism. The Discussant, Dr van den Buuse, will provide perspective from his extensive experience with animal models and molecular techniques exploring interactions between BDNF and other risk factors of schizophrenia.

Interaction between the cytokine and BDNF in chronic schizophrenia

Xu-Feng Huang - University of Wollongong

Background: Immune-response cytokines are altered in macrophage-derived cytokines in schizophrenia patients. Low levels of brainderived neurotrophic factor (BDNF) are associated with schizophrenia irrespective of antipsychotic drug administration. This project studied the possible relationship or interaction between the cytokine and BDNF and their association with positive and negative scores of schizophrenia patients. Methods: There were 92 schizophrenia patients, and 60 healthy control subjects were involved in this study. All patients met the DSM-IV diagnosis of schizophrenia. The mean antipsychotic dose was ~434 mg/day as per chlorpromazine equivalents. Fasting serum BDNF and cytokines were measured by quantitative ELISA kits. Clinical assessment was performed by the positive and negative syndrome scale (PANSS) in 5-factors as positive, negative, cognitive, depression and excitement. Results: Our study showed that 1) the cytokines were higher and BDNF was lower in the patients than controls; 2) binary regression analysis showed the interactions of BDNF for IL2 and IL8; 3) negative association between IL2 and PANNS positive sub-score as well as BDF and TNF? interaction influencing PANNS cognitive factor. Conclusion: Inflammatory damage and insufficient neurotrophin contribute to the pathophysiology of schizophrenia. Inflammatory injury may interact with BDNF influencing the symptoms of schizophrenia. The major limitation is that this work does not address causal effects.

Neuronal survival in neuroinflammatory conditions

Jessica Chandra - Neuroscience Research Australia

Brain-Derived Neurotrophic Factor (BDNF), signaling via the full-length Tropomyosin kinase B receptor (TrkBTK+) may be upregulated to promote neuronal survival in neuroinflammatory conditions, evident in the midbrain and cortex of ~45% of schizophrenia cases. However, BDNF binding to the truncated receptor (TrkBTK-) on resident immune cells (astrocytes and microglia) diverts trophic support from neurons and further perpetuates pro-inflammatory cytokine release. We investigated whether BDNF and TrkB mRNA is altered in the midbrain and cortex of schizophrenia cases in “low” and “high” inflammatory states. BDNF (exon IV), TrkBTK+ and TrkBTK- mRNA was quantified by qPCR in post-mortem midbrain tissue from the NSW Brain Tissue Resource Centre (28 control/28 schizophrenia) and compared to previous analysis in the

cortex. Gene expression was analysed by diagnosis and low/high inflammatory biotypes (previously defined by 2-step clustering of cytokine mRNAs). BDNF (31%) and TrkBTK+(19%) mRNA was reduced, while TrkBTK-(29%) mRNA was increased in the midbrain of schizophrenia cases compared to controls ($p<0.05$), following a similar pattern of changes as the cortex. In the cortex, high inflammation cases showed a greater reduction in TrkBTK+($p<0.05$) and increase in TrkBTK-($p<0.001$) compared to low inflammation cases. In the cortex, low inflammation cases had increased BDNF but in the midbrain, had reduced BDNF compared to high inflammation cases ($p<0.05$). BDNF and TrkB gene expression is altered in the schizophrenia midbrain. Whilst TrkB changes are similar across cortical and subcortical brain regions, opposing BDNF expression patterns in low inflammatory schizophrenia cases suggests differential BDNF relationship/response to neuroinflammation in the midbrain and cortex.

Role of microglial brain-derived neurotrophic factor (BDNF) on neuronal survival and plasticity

Jana Vukovic - The University of Queensland

Microglia, the resident immune cells of the CNS, have emerged as key regulators of neural precursor cell activity in the adult brain. However, the microglia-derived factors that mediate these effects remain largely unknown. In the present study, we investigated a role for microglial brain-derived neurotrophic factor (BDNF), a neurotrophic factor with well known effects on neuronal survival and plasticity. Surprisingly, we found that selective genetic ablation of BDNF from microglia increased the production of newborn neurons under both physiological and inflammatory conditions (e.g., LPS-induced infection and traumatic brain injury). Genetic ablation of BDNF from microglia otherwise also interfered with self-renewal/proliferation, reducing their overall density. In conclusion, we identify microglial BDNF as an important factor regulating microglia population dynamics and states, which in turn influences neurogenesis under both homeostatic and pathologic conditions.

Global initiative to monitor the neurodevelopment of children whose mother was exposed to COVID-19 in utero

Rachel Hill - Monash University

It is well documented that infections during pregnancy increase the risk for offspring to develop neurodevelopmental disorders, such as autism or schizophrenia. A current disturbing prospect is that in utero exposure to the novel coronavirus could disrupt the neurodevelopment of children. The behavioural neuroscience laboratory at Monash University have established a global initiative to monitor the neurodevelopment of children whose mother was exposed to COVID-19 in utero. This initiative includes obstetricians, neonatal neurologists, paediatricians and child psychiatrists across three Victorian hospital sites as well as partner sites in Londrina Brazil, Tabriz Iran, and New Delhi India. Prospective assessments are underway to understand the risk of COVID-19 exposure to neurodevelopment, with follow up assessments planned up to 15 years of age. In parallel, the team use cell and animal models to understand the mechanism by which exposure to infections such as SARS-CoV2 alters brain development with the goal to identify targets for biomarker discovery and preventative interventions. One promising target is Brain derived neurotrophic factor (BDNF). We found altered BDNF signalling across 3 maternal immune activation (MIA) animal models and a SARS-CoV2 cell model. Interventional studies assessing the preventative effects of BDNF mimetic, 7,8-DHF as a supplement in the drinking water of pregnant dams shows it dampens the inflammatory response in the fetal brain after MIA. In collaboration with Emory University, a structurally modified prodrug of 7,8-DHF, R13 is being investigated for translational potential as a dietary supplement for women who were exposed to infections, such as SARS-Cov2 during pregnancy.

Longitudinal Illness- and Medication-related Brain Volume Changes in Psychosis are Shaped by Connectome Architecture

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Background
Distributed grey matter brain regions are connected by a complex structural network of white matter fibres, which are responsible for the propagation of action potentials and the transport of neurochemicals, proteins, and other molecules. In neurodegenerative disease, these connections constrain the way in which grey matter volume loss progresses. Here, we investigated whether connectome architecture also shapes the spatial patenting of longitudinal grey matter volume changes attributable to illness and/or antipsychotic medication in first episode psychosis (FEP).
Methods
We conducted a triple-blind randomised placebo-control trial where 62 young people with first episode psychosis received either an atypical antipsychotic or placebo over 6 months. A healthy control group was also recruited. Anatomical MRI scans were acquired at baseline, 3-months and 12-months. Deformation-based morphometry was used to estimate gray matter volume changes over time. Structural brain connectivity patterns were derived from the healthy control group using diffusion-weighted imaging. We tested the hypothesis that grey matter volume changes in any given brain region could be predicted by changes in areas to which it is structurally connected.
Results
At baseline, we found that regional illness-related volume differences were strongly correlated with volume differences in structurally connected neighbouring brain regions (r = .608; p < 0.001). We also found a strong correlation between longitudinal regional illness-related change (r = .613; p < 0.001) and medication-related volume change (r = .591; p < 0.001) with volumetric changes in structurally connected areas. No such associations were found for functionally connected regions (all r < 0.391).
Conclusions
Psychosis- and antipsychotic -related grey matter volume changes are strongly shaped by structural brain connections. This result is consistent with findings in other neurological disorders and implies that structural brain connections may act as a conduit for the spread of pathological processes causing brain dysfunction in FEP.

Regional changes of brain iron in individuals with schizophrenia compared with healthy controls, a 7-Tesla neuroimaging study

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Background
Dysregulation of dopaminergic neurotransmission along the cortico basal ganglia pathways is well-documented in schizophrenia. Iron, as the cofactor of the key rate-limiting enzyme in dopamine synthesis pathway, tyrosine hydroxylase, induces production of dopamine. High dopaminergic activity, in turn, leads to increased iron uptake and storage in neural cells. Accumulation of iron and oxidized dopamine metabolites generates reactive oxygen species leading to neural cell death. In this study we investigated brain iron content in the subcortical hubs within the dopaminergic pathways and its correlation with cortical neuro-metabolic profile in schizophrenia.
Methods
In 12 individuals with chronic schizophrenia and 14 healthy age-matched controls, we acquired quantitative susceptibility mapping (QSM) brain MRI at 7-Tesla for detection of brain iron, as well as magnetic resonance spectroscopy (MRS) to evaluate metabolic changes associated with oxidative damage and anaerobic metabolism in the dorsal anterior cingulate gyrus. Iron content in the substantia nigra, nucleus accumbens, putamen, caudate nucleus, globus pallidus, thalamus, and hippocampus, as well as MRS in the dorsal anterior cingulate gyrus were compared between groups. Structural equation modeling was performed between QSM in the subcortical structures and MRS in the dorsal anterior cingulate gyrus.
Results
There was no difference between study groups in terms of age, sex, and serum iron. There was no correlation between QSM in any of the brain regions and antipsychotic medications. In patients with schizophrenia, we found a significantly increased iron content in the putamen bilaterally and the left caudate nucleus. Magnetic resonance spectroscopy showed higher phosphocreatine and lactate in the dorsal anterior cingulate gyrus in patients with schizophrenia. Structural equation modeling showed different patterns of correlation along the cortico basal ganglia pathways between individuals with schizophrenia and healthy controls.
Conclusions
This is the first in vivo human study to investigate regional brain iron changes in chronic schizophrenia. The evidence provided by this study reveals increased iron content in the dorsal striatum. The dorsal striatum is part of the associative functional subdivision of the cortico-striatal circuitry, acting as an integrative hub, moderating information processing between the cortex and midbrain. The finding of higher iron content in the dorsal striatum is consistent with the existing evidence of striatal dopaminergic hyperactivity. Further, the results of the structural equation modeling points to a circuit-wide derangement of iron that correlates with neurometabolic alterations.

Schizophrenia is defined by cell-specific neuropathology and multiple neurodevelopmental mechanisms in patient-derived cerebral organoids

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Background
Due to an inability to ethically access developing human brain tissue as well as identify prospective cases, early-arising neurodevelopmental and cell-specific signatures of Schizophrenia (Scz) have remained unknown and thus undefined. This has correspondingly arrested our understanding of the neurodevelopmental origins of Scz, as well as protracted the development of novel drugs that may yield therapeutic relief by acting upon novel early-arising neuropathology that has not yet been discovered. Therefore, determining novel neurodevelopmental mechanisms of Scz with cell-specific resolution holds tremendous therapeutic potential and would fill a critical void in our understanding of Scz risk and development.
Methods
To overcome the ethical and technical challenges associated with other model systems, here we utilized patient-derived induced pluripotent stem cells (iPSCs) from up to n = 25 donors (8 Ctrl, 17 Scz donors) to generate 3D cerebral organoids. This model system allowed us to generate limitless supply of developing human brain-like tissue from bonafide idiopathic Scz patients that was equivalent to Trimester 1 of in utero cortical development. From this, we subjected hundreds of patient-derived 3D organoids to immunostainings, neurogenesis assays, single-cell DNA content analysis, TMT-LC/MS proteomics, single-cell sequencing, single-unit electrophysiology, and two independent mechanistic assays.
Results
We discovered that Scz organoids exhibited ventricular neuropathology resulting in altered progenitor survival and disrupted neurogenesis. Single-cell sequencing revealed that Scz progenitors were specifically depleted of neuronal programming factors leading to a remodeling of cell-lineages, altered differentiation trajectories, and distorted cell-type diversity. Single-cell sequencing also identified cell-specific alterations as well as a developmental switch in neurotrophin availability. Furthermore, TMT-LC/MS proteomics and single-cell sequencing also replicated the depletion of two novel factors, namely BRN2 and PTN. Subsequently, in two rescue experiments we identified that BRN2 and PTN operate as mechanistic substrates of neurogenesis and cellular survival, respectively, in Scz organoids.
Conclusions
In sum, data from our patient-derived 3D tissue culture system indicates that multiple mechanisms of Scz exist in patient-derived organoids, and that these disparate mechanisms converge upon primordial brain developmental pathways such as neuronal differentiation, survival, and growth factor support. In closing, our identification of multiple mechanisms as well as cell-by-cell encoding of neuropathology represents two major advances in how we conceptualize the developmental ontogeny of Scz, and indicates that disease risk likely begins to unfold decades before onset in early adulthood.

Inflammation mediates the effects of peri-pregnancy diet on the maternal brain

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Background
Maternal mood disorders are serious and specific complications of pregnancy experienced by as many as 1 in 5 mothers worldwide. Maternal obesity doubles the risk of postpartum mood disorders, but the mechanisms are unknown.
Methods
Here we examined the effects of maternal obesity, induced by the consumption of a high-fat-high-sugar (HFSD) diet before and during pregnancy on postpartum brain and behaviour in rats. We also assessed if the effects of HFSD could be reversed by consumption of a healthier diet during pregnancy, specifically by a diet high in omega-3 polyunsaturated fatty acids.
Results
Our data show that consumption of HFSD before and during pregnancy activated magnocellular, but not parvocellular, neurons in the paraventricular region of the hypothalamus, and had a moderate effect on anxiety-like behaviours. However, HFSD-induced pre-conception obesity was associated with increased circulating cytokine levels and reduced microglial complexity; morphology indicative of microglial activation. A shift to a healthier diet during pregnancy alleviated systemic and neuro-inflammation. Surprisingly, both HFSD and omega-3-replete diet increased the numbers of immature neurons in the hippocampus. While outside of pregnancy neurogenesis refines hippocampal activity, the opposite occurs postpartum, where increased neurogenesis may facilitate mood disorders.
Conclusions
These findings highlight the potential role of inflammation in mediating the effects of diet on the maternal brain and support the importance of a balanced dietary intake before and during pregnancy. Our data also indicate the need for future research into key triggers that may influence the neuroimmune balance in the maternal brain.

Examining genetic correlation and causation between blood-based biochemical markers and cortical structure

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Background
Psychiatric disorders such as schizophrenia are frequently associated with alterations to cortical structure, which often vary with clinically relevant features including antipsychotic treatment and duration of illness. While the underlying factors mediating these structural changes are poorly understood, recent genetic evidence suggests circulating metabolites and other blood-based biochemical markers are potentially causal for a number of psychiatric disorders and may contribute to modification of affected cortical areas. However, it is currently unclear whether biochemical traits share genetic architecture and causal relationships with cortical structural properties.
Methods
We leveraged publicly available GWAS summary statistics to examine genetic correlation and causation amongst 50 biochemical traits (UK BioBank release 2) with respect to thickness and surface area measurements from 34 distinct cortical regions (ENIGMA consortium). Genetic correlations were identified using linkage disequilibrium score regression, after which all correlated trait pairings (Benjamini-Hochberg FDR < 0.05) were analysed for causality via a latent causal variable model. Pairings with strong evidence for a causal relationship were further explored and quantified via Mendelian randomisation (MR), utilising the inverse variance weighted estimator with multiplicative random effects (IVWm) as the principal model.
Results
A total of 176 genetically correlated trait pairings were identified, of which six exhibited strong evidence for a causal relationship (|Genetic causality proportion| > 0.6). Analysis of these putative causal relationships via MR revealed evidence for a significant effect of C-reactive protein (CRP) on lingual thickness (Beta = –0.009, P(IVWm) = 0.004, SE = 0.003) and lateral occipital thickness (Beta = –0.0073, P(IVWm) = 0.029, SE = 0.003). Utilising summary statistics covaried for global cortical thickness, we additionally identified a significant causal estimate for vitamin D on temporal pole thickness (Beta = 0.025, P(IVWm) = 0.038, SE = 0.012).
Conclusions
We demonstrate that elevated CRP and vitamin D levels may directly affect the structural properties of specific cortical areas, broadly consistent with the hypothesised role of dysregulated inflammation and altered vitamin D levels in the pathophysiology of psychiatric disorders, particularly schizophrenia. We therefore advocate further investigation of the effects of these circulating biochemical factors in the brain to dissect biological mechanisms contributing to alteration of cortical structure and elucidate their potential contribution to psychiatric illness.

Affinity Scores: An individual-centric biopsychosocial fingerprinting framework

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Background
Symptom overlap across psychiatric disorders, combined with intra-illness heterogeneity and frequent comorbidity, often leads to delay in receiving appropriate treatment, increased disability, parental/familial stress, use of ineffective medications, and accruing socioeconomic burden. Population-centric frameworks of biomarker identification focus primarily on comparing averages between groups and assume that diagnostic groups are (1) mutually-exclusive, and (2) homogeneous. There is a paucity of individual-centric approaches capable of identifying individual-specific fingerprints across cognitive, neuroimaging and clinical domains. To address this gap, we propose a novel framework, combining a range of biopsychosocial markers into higher-level biopsychosocial fingerprints, capable of capturing intra-illness heterogeneity and inter-illness overlap.
Methods
A multivariate framework will be implemented to identify individualised patterns of brain structure, cognition and clinical markers based on affinity to other participants in the database. For each participant and variable-of-interest, affinity scores will be calculated in two steps: 1) A standardized n-dimensional space will be constructed, with participants mapped to a group-specific axis based on their average distance from other participants in their diagnostic group. 2) neighbourhoods will be defined and an n-dimensional affinity-score will be calculated based on group-wise neighbour-count. Resultant affinity scores provide individual-specific multivariate multidimensional 'fingerprints' across domains-of-interest. The framework was applied to the UK-biobank dataset.
Results
Cortical volumes, cognition, symptoms, and biopsychosocial measures were used to calculate affinity fingerprints. Individualised affinity scores provided a 'fingerprint' of brain structure, cognition, and clinical markers, which described the affinity of an individual to the n representative groups in the database (schizophrenia, anxiety, depression, healthy controls). For each variable, the affinity score described a four-dimensional component that quantified affinity of that individual to these four groups. Overall, whilst capturing intra-illness heterogeneity, the Individual's affinity scores tended to map strongly to their diagnostic group and uniquely captured their multidomain multidimensional 'fingerprint'.
Conclusions
Affinity scores demonstrate utility in two keys ways: (1) Early and accurate diagnosis of neuropsychiatric disorders, whereby an individual can be grouped within a diagnostic category (or categories) that best matches their fingerprint, and (2) identification of clinical, cognitive, and psychosocial factors that most strongly characterise a person, and which may be most amenable to intervention. This strategy provides a new method of clinical translation to more judiciously inform biopsychopsychosocial risks and targeted clinical decision

It's Who You Know: Fearfulness of A Rat's Cagemates Influence Anxiety-Like Behaviour and FGF2

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Background
Social interactions and influences are often thought to shape emotional development. Although lab rats are typically group housed, there is relatively little rodent research examining whether a rat's cagemates influence measures of anxiety-like behaviour/emotionality. Emerging research demonstrates that experimentally naïve rats housed with stress-exposed cagemates show physiological and behavioural alterations associated with stress exposure. While these results suggest that being housed with a stressed cagemate can affect behaviour, manipulations used to induce stress in rats are often severe and it is unclear whether natural variations in a rat's emotionality influences the behaviour and physiology of their cagemates.

Methods
Rats were trained to associate a conditioned stimulus (CS) with footshock during infancy (postnatal day 17-18) and tested for CS-elicited freezing 6-7 days later. We have previously shown using the same procedures that fear of the CS predicts anxiety-like behaviour and conditioned fear in adulthood, suggesting that individual differences in infant fear memory are a marker of anxiety-like behaviour. After test, rats were randomly assigned to cage/cagemates. In adulthood, animals were either euthanised and hippocampal fibroblast growth factor-2 (FGF2; a biomarker of fear/anxiety) was measured (Experiments 1 and 2) or tested for anxiety-like behaviour on the light-dark box (Experiment 3).

Results
Mean CS-elicited freezing of a rat's cagemates was calculated as a measure of how fearful/anxious a rat's cagemates were. Mean CS-elicited freezing of a rat's cagemates negatively predicted hippocampal FGF2, but a rat's own CS-elicited freezing in infancy did not predict adulthood FGF2 (Experiments 1 and 2). In addition, both individual and mean CS-elicited freezing of a rat's cagemates in infancy positively predicted anxiety-like behaviour in adulthood (Experiment 3). Furthermore, there was an interaction between individual and mean cagemate CS-elicited freezing such that rats that were less fearful as infants were less affected by having highly fearful cagemates.

Conclusions
These results suggest that natural variations in the fearfulness of a rat's cagemates have an influence on anxiety-like behaviour and related physiology (e.g., FGF2). Rats housed with more fearful cagemates exhibited heightened anxiety-like behaviour and lower FGF2 in adulthood (note that low levels of FGF2 are associated with heightened fear/anxiety). However, the effect on anxiety-like behaviour was more pronounced for rats that were highly fearful as infants. These data suggest that relatively weak social manipulations/interventions can have effects on rodent anxiety-like behaviour and physiology.

Oral 2-4

Psychiatric polygenic risk and disordered eating in an Australian female twin population

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Background
Genetic overlap has been demonstrated across psychiatric disorders, with twin studies showing overlap between different eating disorders. Polygenic risk scores (PRS) can be used to quantify cumulative genetic risk for a trait at an individual level. Recent studies suggest PRS for Anorexia Nervosa (AN) may extend to other disordered eating (DE) behaviours, but studies are few. No study has examined if PRS for AN can predict trajectories of DE through adolescence. This study aimed to investigate whether PRS for AN extends to DE more broadly, and whether PRS for other psychiatric disorders (schizophrenia, OCD, and depression) predict DE.
Methods
Australian adolescent female twins recruited from the Australian Twin Registry (N = 374) were interviewed longitudinally across three timepoints (mean ages 13.96, 15.10, 16.90). Three DE trajectories were identified using growth mixture modelling (low-static, attenuating, escalating), and genomic data was analysed using the Infinium Global Screening Array. GWAS summary statistics for AN, schizophrenia, OCD, and depression were obtained from the Psychiatric Genomics Consortium. PRSs were calculated using PRSice-2 software. Linear mixed models were used to investigate the cross-sectional association between highest DE score and PRS for each disorder, and the relationship between PRS and adolescent DE trajectories, controlling for relatedness.
Results
We will present cross-sectional findings based on the highest DE score for each individual across the three time-points, and longitudinal findings based on trajectories of DE scores across three time-points in adolescence. The cross-sectional findings will demonstrate if individuals with a higher PRS for AN exhibited greater DE symptoms. It will also be reported whether those with higher DE symptoms also have higher PRS for Schizophrenia, OCD, and depression. The longitudinal findings will demonstrate whether PRS for AN predicts different trajectories of disordered eating through adolescence, specifically if associated with an escalating DE trajectory relative to attenuating or low-static trajectories.
Conclusions
This is the first study to undertake such broad DE phenotypic analyses across multiple time-points, and PRSs for multiple psychiatric disorders, as well as in context of DE trajectories. The importance of focusing on the broader disordered eating phenotype, and taking a longitudinal perspective using disordered eating trajectories, will be discussed. Findings may help to establish whether PRSs might be useful in identifying individuals at greater risk of disordered eating, or identifying those with greater likelihood of improving or worsening disordered eating trajectories. In the future, PRSs may have clinical utility in disordered eating classification, intervention, and treatment.

Rostral anterior cingulate network effective connectivity in depressed adolescents and associations with treatment response

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Background
The rostral anterior cingulate cortex (rACC) is consistently implicated in the neurobiology of depression. While associations have been demonstrated between the functional connectivity of the rACC and treatment response, there is a paucity of work investigating the specific directional interactions underpinning these associations.
Methods
We compared the fMRI resting-state effective connectivity of 94 young people with moderate to severe major depressive disorder and 91 healthy controls. Following the fMRI scan, patients were randomized to receive CBT for 12 weeks, plus either fluoxetine or a placebo. We examine the rACC and its connectivity with eight other regions implicated in depression: the left and right anterior insular cortex (AIC), amygdalae, and dorsolateral prefrontal cortex (dlPFC); and in the midline, the subgenual (sgACC) and dorsal anterior cingulate cortex (dACC). Parametric empirical Bayes was used to compare differences between controls and patients and between treatment responders and non-responders.
Results
Depressed patients demonstrated greater inhibitory connectivity of the rACC with the dlPFC, AIC, dACC and left amygdala. Moreover, patients that went on to respond to treatment had greater inhibitory connectivity from the rACC to dACC, greater excitatory connectivity from the dACC to sgACC and less inhibitory connectivity from the sgACC to amygdalae.
Conclusions
The inhibitory hyperconnectivity of the rACC aligns with hypotheses concerning the dominance of the default mode network over other intrinsic brain networks in depressed patients. Interactions between ACC regions implicated in treatment response were particularly predictive of response for those treated with CBT and a placebo.

Oral 3-2

Binge-like eating restores hedonic deficits and becomes 'addictive' in obesity

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Background
Obesity is associated with hedonic deficits. Despite this, obesity is often comorbid with binge eating disorder, which paradoxically is characterized by hypermotivation for food and related stimuli. Here, we tested the hypothesis that binge eating restores the hedonic deficits seen in obesity and thus becomes 'addictive'. We also tested whether binge eating recruits the orexin-dopamine network, a critical circuit for the development of addiction to drugs of abuse.
Methods
We used a behavioral economics paradigm to measure rats' preferred level of sucrose intake (hedonia) vs. their willingness to 'work' to maintain this intake (motivation). Economic demand was measured before and after exposure to a high fat diet, and again following 4w of binge-like eating. We also assessed the expression of several addiction-relevant behaviors, including compulsive (punished) and perseverative responding for palatable food. Using a combination of viral strategies in transgenic animals, along with pharmacological manipulations, we also tested the role of the orexin-dopamine circuit in the expression of these phenotypes.
Results
Diet-induced obesity was associated with a reduction in the hedonic and motivational properties of sucrose, which were partially restored by binge-like eating. Binge-like eating in obese but not lean rats promoted behaviors that were indicative of 'food addiction'. Blocking the activity of orexin neurons or their inputs to midbrain dopamine cells prevented the expression of 'food addiction' phenotypes but did not affect hedonic tone.
Conclusions
Binge-like eating partially restores hedonic and motivational deficits associated with diet-induced obesity in rats. Obese, binge eating rats exhibit compulsive food seeking behaviors, indicating that binge eating might become 'addictive' in obesity due to the negative (rather than positive) reinforcing properties of palatable foods. Reducing activity in the orexin-dopamine network normalized excessive motivation for food without affecting hedonic processing, indicating that targeting this system therapeutically may reduce food overconsumption without affecting hedonic tone in obesity.

Multi-omic prioritisation of drug repurposing opportunities in psychiatry

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Background
Novel interventions are urgently need in psychiatric practice that are effective for patients resistant to conventional pharmacotherapies. Moreover, given the immense heterogeneity of mental health phenotypes, there is an unmet need to target treatments more specifically to individuals. Drug repurposing offers an opportunity to more rapidly alter clinical care relative to the traditional drug development pipeline, however, prioritising suitable candidates remains challenging, as does identifying patients which would likely respond to these compounds. We therefore employed a multi-omic strategy to refine drug repurposing for psychiatric disorders that integrated genetics with transcriptomic, proteomic, and metabolomic data.
Methods
Psychiatric genome-wide association studies (GWAS) were integrated with 50 genetically proxied metabolites and other serum biomarkers from the UK Biobank cohort to identify biochemical traits genetically correlated with at least one psychiatric disorder, with these correlated trait pairs then examined for evidence of a causal effect. Specific genes predicted to be modulated by approved drugs in a risk-decreasing direction were also identified using genetically imputed models of mRNA and protein expression from brain and blood. Genetic risk scores were then constructed amongst the biological networks of those genes to identify individuals for which the repurposing candidate may be particularly effective.
Results
Widespread positive and negative genetic correlations were observed between psychiatric disorders and biochemical traits, with evidence C-reactive protein (CRP), glucose, and urate may exert a causal effect on psychiatric illness. We also found genes for which the genetically predicted direction of disorder associated mRNA or protein expression could be counteracted by an approved compound, and thus, constitute a drug repurposing opportunity. Genetic risk scores using variants annotated to the protein interaction networks anchored by these target genes were significantly associated with psychiatric illness, with distinct biological insights afforded by these partitioned scores relative to a conventional genome wide polygenic score.
Conclusions
Our data suggest that there are shared pathways that influence both biochemical traits and psychiatric illness, some of which could be modulated by existing drugs. Moreover, there were genes for which specific repurposing candidates could be assigned - for instance, decreased cortical expression of the fatty acid desaturase 1 gene (FADS1) was associated with greater odds of bipolar disorder, and thus, FADS1 agonists like omega-3 fatty acids could be efficacious. Given the heterogeneity inherent in psychiatric disorders, we believe that these compounds should be directed to individuals with elevated disorder-associated genetic risk within networks related to target genes like FADS1.

Neural signatures of Pavlovian safety learning in humans: an ultra-high field fMRI study

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Background
Safety learning generates associative links between neutral stimuli and the absence of threat. This process facilitates the regulation of fear and is proposed as a key factor in the aetiology of anxiety-related disorders. Despite its relevance, it is unclear what neural systems are responsible for encoding safety learning in humans. In a 'Pavlovian conditioned inhibition' paradigms, a threat cue is aversively reinforced alone (A+), but not reinforced when paired with a second cue, the conditioned inhibitor (AX-), causing the latter to develop a robust contingency with threat-omission, and thereby become a conditioned safety signal.
Methods
49 healthy adults completed a conditioned inhibition experiment at ultra-high field fMRI to elucidate the neural mechanisms underlying safety learning. Neural activations were compared between a Pavlovian conditioned inhibitor and a more ambiguous 'unpaired' safety signal (, which was unreinforced without proximity to a threat cue.
Results
The Pavlovian inhibitor was associated with the dorsal striatum, insula, thalamic, and midbrain subnuclei, whereas the unpaired signal evoked widespread activations across association cortex regions, including the vmPFC, precuneus, fusiform, and visual cortex. Each stimulus also showed similar subcortical-cortical differences from one another when comparing neural responses during learning versus a subsequent transfer test.
Conclusions
This study provides identification of distinct neural correlates for Pavlovian inhibition which provides a framework for ongoing translational work on dysfunctional safety learning in anxiety.

Optogenetic inhibition of parvalbumin interneurons causes an increase in gamma oscillatory power

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Background
Schizophrenia (SZ) is a complex psychiatric condition and treatment to ameliorate the cognitive symptoms remains as an unmet need. Gamma frequency neural oscillations (30-80Hz) have been tightly associated with numerous higher order cognitive processes and appear to be abnormal in SZ. Of note, a particular cell type, the parvalbumin-positive (PV+) interneuron, has been shown to be functionally impaired in SZ, and these cells are believed to generate gamma oscillations. This study sought to inhibit PV+ interneurons using optogenetic technology, thereby mimicking the functional deficit of these cells in SZ, and assess whether this is sufficient to alter gamma oscillatory activity.
Methods
PV:Cre mice (n = 8) underwent virus injections to allow for expression of st-GtACR2 (an inhibitory opsin) in PV cells of the medial prefrontal cortex. 4 weeks after virus injection, mice underwent anaesthetised electrophysiology recordings using a 16-channel Neuronexus probe coupled with an optic fibre to allow for concurrent electrophysiology recordings and optic modulation of cells. The probe was lowered to the site of virus injection and recordings were obtained during periods of baseline (light OFF) and light stimulation (light ON) and the effects of this modulation on unit activity and gamma oscillations was assessed.
Results
Single unit activity was classified using a semi-automated approach in MATLAB (kilosort2), followed by manual curation of data in python (phy). This analysis revealed an overall significant increase in putative pyramidal cell firing rate during light ON compared to light OFF conditions. In addition, several units, identified as putative fast-spiking interneurons significantly reduced their firing rate in light ON conditions. Gamma oscillatory power was also computed through spectral analysis of the local field potential, and this analysis revealed a significant increase in gamma power during optic stimulation (light ON), compared to light OFF conditions.
Conclusions
These findings demonstrate that inhibition of PV interneurons in the medial prefrontal cortex leads to an increase in putative pyramidal cell firing rate, and elevates gamma oscillatory power. While an abundance of literature indicates the importance of PV interneurons in generating gamma oscillations, these results demonstrate that inhibiting these cells can cause an increase in gamma power, an effect which may be related to the disinhibition and increased firing rate of pyramidal cells. This observation provides insight into how elevated gamma oscillatory activity observed in SZ patients may be directly related to functional impairment in PV+ interneurons.

Long non-coding RNAs as molecular targets of drugs used to treat bipolar disorder

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Background
New drug discovery for bipolar disorder (BD) is limited by lack of understanding of the underlying pathophysiology as well as the mechanism(s) of action of currently prescribed drugs. Long non-coding RNAs (lncRNAs) are a class of RNAs that may play significant roles in co-ordinating transcriptional responses to various stimuli. They are highly expressed in the brain and contribute to the development of psychiatric diseases including BD. Research on mRNA-lncRNA crosstalk and regulatory patterns can unveil insights into the complex mechanisms of action of BD drugs and highlight potential targets for drug development.
Methods
Human neuronal-like cells (NT2-N) were treated with either lamotrigine (50 μM), lithium (2.5 mM), quetiapine (50 μM), valproate (0.5 mM) or vehicle control for 24 hours. Genome wide mRNA expression was quantified by RNA-sequencing, followed by differential expression analysis. Weighted gene co-expression network analysis (WGCNA) was deployed to correlate the expression levels of mRNAs with lncRNAs. Functional enrichment analysis, hub lncRNA identification and confirmation was conducted on key co-expressed modules associated with the drug response.
Results
We constructed lncRNA-mRNA co-expression networks and identified key modules underlying drug treatments, as well as their enriched biological functions. Most enriched pathways were associated with brain function such as synaptic vesicle cycle, axon guidance and neurotrophin signalling pathways. Several lncRNAs such as GAS6-AS1 (FDR adjusted p-value $3.8\times10-6$ in valproate treatment), LINC02381 (FDR adjusted p-value $6.61\times10-11$ in quetiapine treatment), MIR124-2HG (FDR adjusted p-values: $2.37\times10-11$ in quetiapine treatment, 0.032383 in lamotrigine treatment), and MIR100HG (FDR adjusted p-values: 0.001672 in lithium treatment, $3.1\times10-10$ in quetiapine treatment) were highlighted as driver genes of key transcriptional modules.
Conclusions
Our study demonstrates the potentially key role of lncRNAs in the regulatory effect of BD drugs via the associated lncRNA-mRNA co-expression networks. While little has been known regarding the regulation and function of non-coding RNAs in BD, several lncRNAs involved in relevant processes (e.g., neurodevelopment, autophagy, endoplasmic reticulum stress) have been suggested as master regulators of drug response from our results. Therefore, these lncRNAs of interest are worthy of further investigation as potential drug targets for BD.

Understanding dopamine release mechanism in an animal model of relevance to Schizophrenia, EDiPs (Enhanced Dopamine in Prodromal schizophrenia)

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Background
Clinical studies in patients with schizophrenia using PET (Positron Emission Tomography) have shown a progressive increase in dopamine (DA) synthesis capacity in the dorsal striatum (DS) from prodromal stage to first psychotic episode. Based on this important finding, our lab has been successful in developing a novel animal model of relevance to schizophrenia termed as EDiPs (Enhanced Dopamine in Prodromal schizophrenia). Using this model, the major aim of this study is to explore if, increased DA synthesis capacity has any implications on DA release sites and release dynamics.

Methods
Bilateral EDiPs rats were produced as previously reported (Petty et al, 2019). Immunostaining for TH (tyrosine hydroxylase), presynaptic marker Bassoon, and postsynaptic marker PSD95 was done. Bassoon detected within TH axons is defined as high probability release site, and PSD95 located within 90 nm from Bassoon (within TH) is defined as synapse. In another cohort, unilateral EDiPs rats were produced (active EDiPs viral-construct delivered into nigra of one hemisphere and control-construct into contralateral hemisphere). After 8-weeks of viral delivery, FSCV (fast scan cyclic voltammetry) was conducted in dorsal striatum to examine evoked DA release by stimulating median forebrain bundle.

Results
We selected four regions to compare synaptic elements between control and EDiPs. Two regions in DS (medial and lateral) and two regions in nucleus accumbens (shell and core). MANOVA analysis showed no interactions between striatal sub-regions and groups. However, the analysis indicated an overall effect of EDiPs, increasing the number of high probability DA release sites and increased activated dopamine synapses. Our initial FSCV experiments (n=3) indicated EDiPs also leads to increased phasic DA release in the ipsilateral compared to contralateral DS.

Conclusions
EDiPs is a robust model recapitulating the clinical finding of increased DA synthesis and release in the dorsal striatum in schizophrenia. Here we find this model induces an increase in DA release sites and DA-related synapses across the striatum. The absence of selectivity for the synaptic alterations indicates DA changes in the current version of this model are not DS specific. Future studies using a more nigral specific EDiPs construct are warranted. Our initial FSCV data indicate phasic DA may also be elevated in this model, but this requires replication.

Operant alcohol self-administration in BDNF val68met rats

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Background
Reduced brain-derived neurotrophic factor (BDNF) expression has been associated with alcohol use disorders. We previously showed that female BDNF heterozygous (HET) rats display significantly higher reinstatement than female WT controls in an operant self-administration protocol, with no genotype difference in males. Treatment with 7,8-dihydroxyflavone, a BDNF receptor agonist, also increased reinstatement selectively in females. The val66met polymorphism is a common variant of the BDNF gene (rs6265) which reduces activity-dependent BDNF release and which has been suggested as a risk factor for several psychiatric disorders and substance use. Here we report operant alcohol self-administration in a novel val66met rat model.
Methods
We used female and male BDNF val68met rats that were either val/met or met/met and compared them to control littermates without the substitution (val/val). We used an operant self-administration paradigm where the animals were trained in operant chambers to self-administer a 10% ethanol solution. Over several weeks, the animals progressed through acquisition, progressive ratio, extinction, and reinstatement phases.
Results
All rats showed good acquisition for responding to the ethanol lever compared to water with no significant differences between genotypes. There were also no genotype differences in breakpoint responding during a progressive ratio session or in extinction when rewards and cues were removed. When cues were re-introduced in a reinstatement session following extinction however, met/met female rats showed no preference for the lever previously associated with alcohol rewards, while all other groups showed the expected preference.
Conclusions
These results suggest reduced reinstatement behaviour in BDNF met/met females. Because met/met is associated with a functional reduction of BDNF release in the brain, these results fit with our previous findings where enhancing BDNF signalling by treating the animals with a BDNF receptor agonist increased reinstatement. Our seemingly contradictory previous findings in BDNF HET females may be explained by compensatory changes in the circuitry involved in alcohol self-administration in that model of more severe BDNF deficiency.

Baseline serum amino acid levels predict treatment response to augmentation with N-acetylcysteine (NAC) in a bipolar disorder randomised trial

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Background
N-acetylcysteine (NAC) acts on glutamatergic and redox systems, two systems implicated in the pathophysiology of bipolar disorder. This has led to the investigation of NAC as a potential candidate for the treatment of bipolar disorder. The aim of this study was to investigate metabolomic markers to identify predictors of NAC response in a cohort of bipolar disorder participants. This study is a secondary analysis of a 16-week, multi-site, randomized, double-blinded, parallel-group, placebo-controlled trial in bipolar disorder participants with a current acute depressive episode.
Methods
This study included trial participants who received either NAC 2000 mg/day, or placebo. Participants (NAC: n=31, placebo: n=29) were assessed at baseline and week 16 using the Montgomery Åsberg Depression Rating Scale (MADRS) and provided a baseline blood sample. Participants were dichotomised into responders
(MADRS at week 16 50% of MADRS at baseline). Untargeted gas chromatography–mass spectrometry analysis was performed to analyse baseline levels of 68 serum metabolites and differences in levels of metabolites at baseline between the two groups were investigated.
Results
Of the nine metabolites that most clearly differentiated placebo and NAC groups, five were amino acids with lower levels in the NAC responder group compared with the NAC non-responders. Alanine and glycine shared a linear association with change in MADRS scores following treatment. Further analysis generated a predictive model of MADRS improvement including glycine, norleucine, threonine, proline, phenylalanine, tyrosine, glutamic acid, lysine and leucine ($R2 = 0.853$; adjusted $R2 = 0.733$). This prediction model developed using the levels of these nine amino acids predicted 85% of the variance in MADRS outcome after adjunctive treatment with NAC.
Conclusions
Bipolar disorder participants with lower serum levels of free amino acids at baseline may be more likely to respond to adjunctive treatment with NAC. This prediction model using the levels of these nine amino acids can accurately predict the MADRS outcome after adjunctive treatment with NAC.

Removal of perineuronal nets in the retrosplenial cortex plays a modulatory role in the recall of recent and remote spatial memories

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Background
Perineuronal nets (PNNs) are extracellular matrix assemblies that ensheath specific neurons. Once thought to remain stable following the closure of the critical period, research now suggests that PNNs are remarkably dynamic and involved in experience-dependent plasticity. A current postulate is that PNNs undergo remodelling, stabilising new synaptic connections and supporting consolidation of long-term memories. This may be relevant to schizophrenia, where PNN degradation may represent a mechanism of cognitive dysfunction, a hypothesis inferred from post-mortem brain studies. Our aim was to assess whether PNNs in the retrosplenial cortex (RSC), a region interconnected with the hippocampus, would support spatial memory recall.

Methods
Sixty-two adult male BALB/c mice underwent a 5-day Active Place Avoidance (APA) spatial learning task and were randomised into Recent or Remote memory recall groups. The mice received bilateral infusions of the enzyme ChondroitinaseABC (ChABC), to degrade the PNNs, or saline, into the RSC, either 3 days (Recent), or 21 days (Remote) after the completion of the training. All mice then underwent a retention trial 7 days following surgery. Brains were collected and processed for immunohistochemistry. The number of PNN positive (PNN+) cells in the RSC were quantified using a deep learning cell segmentation algorithm and customised Cell Profiler pipeline.

Results
ChABC-treated mice had a significantly shorter latency to enter the shock zone as well as a reduced maximum time to avoid the shock zone on the retention trial, compared to control mice. However, ChABC treatment was not sufficient to completely block memory recall. There were no differences between the Recent and Remote groups. Further analysis revealed a 34% reduction in PNN+ cells in the RSC at 7 days in ChABC-treated mice compared to controls. Intriguingly, PNN regeneration was 24% greater at 7 days following surgery compared to a group of behaviourally naïve mice that also received ChABC treatment.

Conclusions
These data suggest that PNNs in the RSC are experience-dependent and exert a modulatory, but not critical, effect on the recall of spatial memories. Since the RSC functions as an integrative hub for sensory and motor circuits, serving roles in navigation and memory, future experiments should employ a more complex variation of APA whereby mice must segregate irrelevant local and relevant distal cues to avoid the shock zone. This variation may help to ascertain whether PNNs in the RSC are necessary for spatial memory recall. Elucidating the function of PNNs may ultimately provide insight into the pathophysiology of schizophrenia.

Elevated paternal glucocorticoids preconception contributes to intergenerational shifts in male attractiveness and major urinary protein expression

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Background
Previous studies from our lab modelling chronic stress exposure through paternal corticosterone supplementation preconception revealed altered anxiety and depression-relevant behaviours in male progeny. Given the strong presence of sociability deficits in various affective disorders, we sought to characterise social behaviour across generations in our model. Additionally, we had reported significant changes to sperm sncRNA content associated with corticosterone supplementation but DNA methylation, a key epigenetic modification, had yet to be investigated.
Methods
Two generations of adult male progeny derived from C57BL/6J male mice treated with corticosterone for 4 weeks prior to paired-matings were assessed using the Mate-Choice Test. This involved a modified 3-chamber interaction test, where female mice on oestrous explored the apparatus while the males were contained, indicating their relative attractiveness. Protein concentration and gene expression of the male pheromone Major Urinary Protein (MUP) were quantified in urine and liver, respectively. Sperm from corticosterone-treated mice were harvested from the caudal epididymis and DNA was extracted, then processed for Oxford Nanopore long-read sequencing, followed by in-house bioinformatic analyses to detect differential methylation.
Results
Paternal corticosterone exposure was associated with increased female attraction towards male offspring (PatCORT) but conversely decreased for grand offspring (GPatCORT). These observations were not attributable solely to an overall change in urinary MUP protein levels. However, specific MUP subtypes (MUP20 and Major MUP bands) were found to be decreased in PatCORT urine. No differences in these MUP subtypes were found from GPatCORT urine. Interestingly, we found that corticosterone-treatment resulted in reduced sperm DNA methylation in regions proximal to MUP genes. We are currently following-up that finding through qPCR studies of Mup gene expression in the liver.
Conclusions
Paternal stress preconception may influence social behaviour across generations, as we found altered male attractiveness across two generations of progeny. These changes were unexpectedly accompanied by lower urinary MUP levels in the male offspring. Further investigations into the neural responses and brain activation patterns could add to the presently limited understanding of the function of MUP proteins in rodent social interaction.

Faecal matter transplantation promisingly ameliorates cognitive dysfunction in Huntington's disease mice

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Background
Huntington's disease (HD) is a neurodegenerative disorder involving complex symptomatology, including cognitive, psychiatric and motor deficits. The R6/1 HD mouse model expresses a mutant human huntingtin transgene and has been shown to provide an accurate adult-onset disease model. Recently, we discovered that dysregulation of the gut microbial population (gut dysbiosis) occurs in HD mice, and this has been replicated in clinical HD. Therefore, we aimed to verify whether an intervention that returns the HD gut microbiome towards a normal profile will be therapeutic.

Methods
R6/1 (HD) and wild-type littermates (WT) mice were administered a non-absorbable cocktail of antibiotics (ATB) to deplete the host microbiota (7 weeks of age) in preparation for faecal microbiota transplantation (FMT). Mice received FMT by oral gavage (8 weeks of age, 3x - 5g/mL of faeces from age, sex-matched WT donors). We characterized the onset and progression of motor deficits (rotarod, clasping score and digigait) until 20 weeks of age, and also assessed cognitive performance (Y-maze and novel-object recognition). In addition, faeces were collected for microbiome profiling (16S rRNA sequencing) and general health, brain weight and gut function was evaluated.

Results
While the HD phenotype showing a progressive decrease in body weight, motor performance deficits, postural instability and decreased brain weight were established, we didn't see any relevant effect of ATB or FMT in any of these outcomes. Gut microbiome analysis indicated that ATB could deplete the gut microbiome, but the FMT wasn't successful in HD, only in WT mice. Also, gut microbiota instability was identified in HD mice. Nevertheless, promising effects of FMT on cognitive outcomes were observed. Furthermore, at the late stage only, we found an HD-induced increase in gut permeability and a decrease in colon length.

Conclusions
Our study provides further evidence that HD is a whole-body disease, with significant gut dysfunction paralleling, and possibly contributing to, brain dysfunction. The inability of the FMT engraftment to be successful in HD was probably due to the gut microbiome instability observed in these mice. Nevertheless, we identified potential for gut microbiome modulation to improve short-term memory cognitive outcomes in HD. Therefore, other interventions targeting the gut microbiome, that take into account the stability of the gut microbial community, may constitute a promising therapeutic approach for HD.

A multiverse analysis of electrodermal activity-estimated fear learning differences between healthy and anxious individuals

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Background
Although meta-analytic research suggests that anxious and non-anxious individuals differ in their acquisition and extinction of Pavlovian fear responses estimated via electrodermal activity (EDA), recent research has cast doubt on whether these findings are robust to different analytic choices. Accordingly, this study aims to use multiverse analysis to assess potential findings that result from various analytic choices implemented in human fear conditioning research. The analytic choices that appear to impact findings concern: measurement of anxiety, the processing of EDA data, the aggregation of EDA data, and the application of exclusion criteria.
Methods
We utilised data from two previously published two-day extinction recall experiments. Study 1 comprised healthy controls (N = 100); study 2 comprised healthy controls and individuals with specific phobia (equal numbers; N = 60). We compared Pavlovian fear response estimates resulting from more than 1400 EDA pre-processing and analysis pipelines to dimensional and categorical measures of anxiety. EDA pre-processing included trough-to-peak and convolution-based analysis methods, and analyses included calculation of stimulus-specific conditioned responses and extinction retention indices. In addition, we fitted model-free and model-based learning models to response estimates to examine the association between model fit and anxiety.
Results
For study 1, although analytic choices impacted the strength of the association between Pavlovian fear response estimates and measures of anxiety, these choices did not tend to impact the direction of these effects. For study 2, in contrast to trough-to-peak results, convolution-based pre-processing results suggested that non-anxious individuals showed a greater Pavlovian fear response in each phase of the experiment compared to anxious individuals. Furthermore, convolution-based pre-processing produced results suggesting that the fit of model-free learning models improved with increases in anxiety (i.e., the greater the level of anxiety, the better a linear learning rule explained participant's data).
Conclusions
Our findings suggest that the direction of EDA-estimated effects may be consistent across analytic choices when studying healthy controls; however, effects may be unreliable when examining differences between healthy controls and individuals with anxiety-related disorders. This finding challenges the idea that EDA-estimated fear learning deficits confer personalised risk of developing anxiety-related disorders, as ostensible deficits could stem from artifacts of a specific analysis pipeline. The current study, and future empirical work utilising a multiverse approach, can serve as a resource to explain inconsistencies across analytic choices and to help identify an optimal set of analytic choices to study individual differences.

Maternal Immune Activation and the Gut Microbiome in Offspring

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Background
Maternal immune activation (MIA), or the triggering of the maternal immune system during pregnancy, is a well-known risk factor for autism. Pre-clinical studies have suggested that MIA affects the gut microbiome composition of the offspring. Clinical studies of children with autism have also found gut microbiome differences between children with and without a diagnosis, although the evidence is conflicting and the largest published studies report negligible association. The aim of our study was to fill the gap in the literature and assess the gut microbiome of children born to mothers with and without MIA.
Methods
This was a cross-sectional study which included children diagnosed with autism, siblings without a diagnosis and unrelated children without a diagnosis who were recruited into the Australian Autism Biobank. Data was analysed for 174 children, of whom 63 were born to mothers with MIA and 111 were born to mothers without MIA. MIA included asthma/allergies, complications during pregnancy, auto-immune conditions, and acute inflammation. Data was also collected for diet (through the Australian Eating Survey) and maternal stress. Gut microbiome data was collected using shotgun metagenomic sequencing of child faecal samples.
Results
Children born to mothers with MIA were more likely to be diagnosed with autism compared to mothers without MIA. There was no significant difference between bacterial richness, α-diversity or β-diversity between groups. After adjusting for age, sex, diet, maternal stress and autism diagnosis, we still found no microbiome differences between the two groups. A single species, Faecalicatena torques, was found to be significantly increased in the MIA group in differential abundance analyses.
Conclusions
To our knowledge, this is the first study to investigate the effect of MIA on the gut microbiome in children. Consistent with previous findings, we found that children who were born to mothers with MIA were more likely to be diagnosed with autism. Unlike pre-clinical studies, we found negligible microbiome differences between the MIA groups. Given the current interest in the microbiome-gut-brain axis, researchers should exercise caution in translating microbiome findings from pre-clinical models to clinical settings. Microbiome-focused therapies for children with autism should be used with caution and need to be investigated further in relation to autism-related risk factors.

Developmental Sleep Trajectories and Adolescent Epigenetic Age Acceleration: A Prospective Cohort Study

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Background
Research on the molecular consequences of poor sleep in childhood and early adolescence may help improve understanding of the relationship between childhood and adolescent sleep and psychiatric outcomes. Poor sleep has been associated with higher epigenetic age acceleration (EAA), which is a molecular measure of biological age linked to various psychiatric disorders. Sleep problems are common during childhood and adolescence, but it is not yet known if these are associated with EAA. This study investigated if childhood and adolescent sleep problems are associated with EAA by examining caregiver-reported sleep trajectories from age 5 to 17, and EAA at age 17.
Methods
This study investigated a representative sample of 1,134 participants from the Raine Study. Blood-based measures of EAA were calculated at age 17. Sleep trajectories were previously identified using latent class growth analysis on caregiver-reported sleep problem scores from the Child Behaviour Checklist, at ages 5, 8, 10, 14, and 17. To investigate if childhood and early adolescent sleep problems predicted EAA at age 17, sleep trajectories were adjusted for current caregiver-reported sleep problems at age 17. Participant-reported sleep problems at age 17 were also examined in relation to EAA, to investigate the association between current sleep and current EAA.
Results
Participants were assigned to one of three trajectories: persistent, moderate but declining, or consistently minimal sleep problems. The association between trajectory and EAA will be described, after adjusting for caregiver-reported sleep problems at age 17, to represent the relationship between previous sleep and current EAA. The association between participant-reported sleep problems at age 17 and EAA will also be described, to represent the relationship between current sleep and current EAA. Multiple models will be presented, to represent relationships before and after adjusting for demographic and health variables, including the following: ancestry, body mass index, income, sex, smoking.
Conclusions
These findings will inform if and how childhood and adolescent sleep problems accelerate biological ageing, and if this relationship differs from the relationship between EAA and current sleep problems. Biological ageing is characterised by a gradual loss of physiological integrity across the lifespan, resulting in progressive functional decline and increased vulnerability to disease. Biomarkers of ageing, including EAA, have been linked to various psychiatric disorders. Findings will be considered in relation to molecular mechanisms that may underpin the relationship between sleep and psychiatric outcomes. Future studies could explore these mechanisms by investigating EAA as a mediator between sleep and depression.

Genetic Markers and Psychological Health Trajectories of Risky Drinking Behaviour in Veterans

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Background
Problematic alcohol use is an environmental stressor that interacts with genes to influence psychological health outcomes. Veterans have concerning rates of risky drinking behaviour and mood problems such as depression, and have higher incidence of posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) compared to civilians. Risk for psychiatric disorders and alcohol related problems can be genetic and assessed through analysis of SNPs that have been linked to stressors and psychopathology. Candidate genes such as ALDH2, OPRM1, CRHR1, RORA, FKBP5, and NRG1 have top-level epigenome-wide DNA methylated or genome-wide associated alleles with problematic drinking, PTSD or major depression.
Methods
Genome-wide genotypes from the Illumina Psych array (>600k probes) and DNA methylation data from the Illumina EPIC array (>860k probes) was available in a sample of 300 Australian veterans. Statistical analysis was performed using PLINK software, using MAF cut-off of 10% and HWE p-value of 0.0001. Using PLINK, we performed a gene-by-environment (GxE) interaction analysis with alcohol dependence (dependent, not dependent), alcohol misuse (yes, no) and drinking concerns (apparent, absent) to test for association with mental health traits. Mental health traits included depressive symptoms and PTSD symptoms using DASS-21 and CAPS respectively. Multiple testing was performed using Bonferroni corrections.
Results
The GxE was tested for a) known candidate genes associated with alcohol misuse or psychiatric disorders and b) genome-wide SNPs. Among candidate genes, we found significant interaction effects with associations to alcohol traits after gene-wise Bonferroni correction: a SNP within the FKBP5 gene with drinking concerns to PTSD symptom scores, and SNPs within the ALDH2 and CRHR1 genes with alcohol misuse and alcohol dependence respectively to depressive symptoms. At the genome-wide level, we identified 4 SNPs within ABHD18, LMNTD1 and ATAD1 genes that were significantly interacted with alcohol dependence and associated with depressive symptoms after Bonferroni correction (p <5E-8).
Conclusions
FKBP5 and CRHR1 genes are well-known for PTSD and mood disorders, and ALDH2 is an alcohol metaboliser implicated in AUD. Here we show that SNPs within these genes interact with alcohol traits to drive mental health symptoms. Genome-wide results identify 3 novel genes underlying pathogenesis of alcohol dependence and associated depressive symptoms in veterans. Among the novel genes, ATAD1 is a gene highly expressed in the brain, previously associated with Alzheimer's and involved in learning and memory as negative regulation of glutamatergic synaptic transmission. Validation in an independent cohort and assessment of DNA methylation and gene expression is currently underway.

Identifying novel genes and RNA transcripts in genomic regions implicated in neuropsychiatric diseases

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Background
Neuropsychiatric disorders are a spectrum of complex and highly debilitating conditions. Genetic risk plays an important part in who develops neuropsychiatric disorders and recent genome wide association studies (GWAS) have identified hundreds of risk loci, but the underlying mechanisms remain poorly understood. Additionally, many risk loci are in intergenic, unannotated regions of the genome. Therefore, ascertaining their causal significance to disease biology has been a major challenge. Identifying novel, (potentially disease associated) genes and transcripts from these risk loci would be an important step towards understanding disease risk but requires development and use of novel RNA sequencing methodologies.
Methods
CaptureSeq employs oligonucleotide probes to target genomic regions of interest and enriched their sequencing coverage. This study aimed to employ short read (SRcap) and long-read sequencing (LRcap and LRFracCap), coupled with CaptureSeq as complementary methods for the quantification and identification of known and novel risk gene transcripts. Sequencing was performed on three regions (Cerebellum, Superior Temporal Cortex and Striatum) of post-mortem brain obtained from four human samples. The genomic regions of interest included 116 neuropsychiatric risk genes. The targets also overlapped 3130 transcripts (including 1585 lncRNA) and regions containing GWAS significant loci in the unannotated, intergenic spaces.
Results
SRcap, LRcap and LRFracCap achieved an enrichment of 162-fold, 68-fold and 56-fold compared to standard short read sequencing in the genomic regions of interest. The CaptureSeq based methods also identified >85% of the known 116 risk genes and several novel transcriptomic features. 120, 208, and 234 potentially novel, multiexonic transcripts supported by the presence of a known CAGE-peak were quantified by the three CaptureSeq based approaches. LRcap and LRFracCap approaches enabled the identification of several potentially novel transcripts in the unannotated, intergenic regions.
Conclusions
Thus, despite the ~20x greater number of reads sequenced with short-read methods, the two long-read techniques were also extremely effective in identifying novel transcriptomic features missed by the two short-read methods. These results indicate the potential of long-read capture sequencing for effective quantification of the transcriptome and detection of novel isoforms and transcripts.

Interactive effects of polygenic risk and cognitive subtype on brain morphology in schizophrenia spectrum and bipolar disorders

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Background
Cognitive deficits represent a shared intermediate phenotype for schizophrenia spectrum disorders (SSD; referring to schizophrenia and schizoaffective disorder, collectively) and bipolar disorders (BD), to which common genetic vulnerability may contribute. Grey matter volume (GMV) associated with severe cognitive deficits in these disorders may also be associated with polygenic risk for schizophrenia (PRS-SZ). In this study we aimed to test the interactive effects of PRS-SZ and cross-disorder subtypes (of SSD and BD) defined by their cognitive profile on whole-brain grey matter volume. We expected that higher PRS-SZ would be associated with reduced fronto-temporal grey matter volume in cognitive-deficit cases.
Methods
Two-step cluster analysis was performed on 146 clinical cases (69 SSD and 77 BD) assessed on eight cognitive domains (verbal & visual memory, executive function, processing speed, visual processing, language ability, working memory, and planning). Among these participants, 55 BD, 51 SSD, and 58 healthy controls (HC) gave blood for genetic investigation (used to derive PRS-SZ) and underwent magnetic resonance imaging. A series of multiple linear regressions was used to determine the main effects of group, PRS-SZ and their interaction on whole-brain GMV. Significant interactions were followed up by moderation analyses.
Results
Two distinct cognitive subtypes were evident among the combined sample of cases: a ‘cognitive deficit’ (CD) group (N=31; comprising 20 SSD/11 BD) showed severe impairment across all cognitive indices, and a ‘cognitively spared’ (CS) group (N=75; comprising 31 SSD/44 BD) showed intermediate cognitive performance that was significantly worse than the HC group but better than the CD subgroup. A cognitive subgroup-by-PRS-SZ interaction was significantly associated with GMV in the left precentral gyrus. Moderation analyses revealed a significant negative relationship between PRS-SZ and GMV in the CD group only.
Conclusions
This study provides evidence for a relationship between regional changes in brain morphology and polygenic risk for schizophrenia in psychosis spectrum cases with severe cognitive deficits, but not in cases whose cognitive profile is relatively spared. Morphological changes in the precentral gyrus are consistent with dysfunctions of the sensorimotor domain of the Research Domain Criteria (RDoC) framework. Future research could investigate whether the left precentral gyrus offers an effective target for novel therapeutic approaches (e.g., brain stimulation) in SSD and BD cases with severe cognitive deficits.

Exploring the association between type 2 diabetes and cognition in bipolar disorder: A cross-sectional study using the UK Biobank cohort

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Background
Cognitive deficits represent a key component of bipolar disorder (BD), yet factors associated with these deficits remain unknown. Type 2 diabetes (T2D) is associated with declines in cognitive functioning in psychiatrically healthy cohorts. Those with BD experience a high prevalence of T2D, but the effects of T2D on cognition in BD is unclear. We examined whether cognitive performance differed between BD individuals with and without T2D compared to psychiatrically healthy controls.
Methods
Data were obtained from the UK Biobank. Sufficient data was available for 82,501 psychiatrically healthy controls (n = 3,528 with T2D, n = 78,973 without T2D), and 1,530 BD participants (n = 87 with T2D, n = 1,443 without T2D). This included mood disorder, screening, data required for the T2D algorithm, and completion of at least 1 of the cognitive tasks. Associations of T2D status with cognition were tested using analyses of covariance for the continuous cognitive variables (reaction time, visuospatial memory, and fluid intelligence), and logistic regression for the categorical cognitive variable (prospective memory).
Results
A T2D status*diagnostic group interaction was evident for visuospatial memory, with subsequent analyses revealing an effect of T2D on visuospatial memory specific to BD. Significant differences between individuals with and without T2D were also evident in the full sample, with decreased performance in reaction time and prospective memory in those with T2D compared to individuals without T2D. Analyses stratified by diagnostic group revealed significant T2D status*age interactions for both visuospatial memory and reaction time.
Conclusions
Group differences were observed between those with and without T2D for reaction time and prospective memory in this large UK Biobank cohort, suggesting a detrimental effect of T2D on cognitive function. These effects do not appear to be exacerbated by a comorbid diagnosis of BD. An effect of T2D specific to BD was evident for visuospatial memory, suggesting a synergistic effect of T2D and comorbid BD on visuospatial memory. Interaction effects evident between T2D and age suggest a moderating effect of age on the association of T2D with both processing speed and visuospatial memory.

Altered foetal steroidogenesis and dysregulated placental immune response in an animal model of maternal hypoxia

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Background
Emerging evidence suggests that maternal hypoxia during early brain development is a major environmental risk factor for neuropsychiatric disorders including autism spectrum disorder (ASD). Recent studies also showed that important neuro-steroids such as testosterone, androstenedione and cortisol significantly elevated in the amniotic fluid of children who developed ASD. It is also evident that these children are exposed to increased maternal or placental cytokines. Moreover, ex-vivo studies suggest ongoing inflammation in placentas subjected to hypoxia. Using an animal model, here we investigated the effect of maternal hypoxia on foetal steroidogenesis and placental inflammation.
Methods
Pregnant C57BL/6J dams were exposed to 10% oxygen (hypoxia) or atmospheric conditions (control 21% O2) for 48 hours at embryonic day (E)10. Dams had ad lib access to food and water. Dams were euthanised at E12 and placentas were collected to examine the effect of acute hypoxia on placental cytokines. The second cohort of dams was euthanised at E17 and the dam's blood, foetal brain and amniotic fluid samples were collected to examine steroids levels. E17 represents the peak period of steroidogenesis in mice. Placental cytokines were quantified by ELISA and steroids were analysed by liquid chromatography-mass spectrometry.
Results
In the placenta, acute maternal hypoxia had a significant effect on placental cytokines. Both IL-6 ($p=0.0001$) and Tnf-α ($p=0.024$) were significantly elevated in hypoxic placentas compared with controls. Maternal hypoxia also increased corticosterone ($p=0.001$) levels in dam's sera, however, testosterone and androstenedione were not different between the groups. When we investigated the steroid levels in foetal brains, corticosterone was again elevated ($p=0.0001$) in brains exposed to hypoxia during development. This effect was observed in both male and female foetal brains however, the effect was larger in male foetal brains. Amniotic fluid data analysis is ongoing.
Conclusions
These findings support the hypothesis that in-utero exposure to hypoxia is associated with placental inflammation. Prenatal exposure to acute and chronic inflammation is hypothesized to be one of the mechanisms implicated in the pathogenesis of neurodevelopmental disorders. More importantly, we show elevated corticosterone in both dam's circulation and foetal brains. This suggests that maternal hypoxia dysregulates negative feedback mechanism leading to increased maternal corticosterone that may have disrupted foetal HPA-axis. Corticosterone is one of the primary biomarkers of the physiologically stressed state that may program the developing brain.

Stress and dopamine in the dorsal striatum: implications for schizophrenia

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Background
Stress is regarded as one of the major risk exposures for the development of schizophrenia. Increased presynaptic dopamine release within the dorsal striatum is one of the major dopaminergic abnormalities in schizophrenia and is known to be affected by stress. We aimed to understand the precise mechanisms behind this. To achieve this, we treated rats acutely with two well-known stress mediators, corticotropin releasing factor (CRF) and corticosterone. We then measured dopaminergic changes in the dorsal striatum in response to these pharmacological manipulations.
Methods
Adult male Sprague Dawley rats underwent anaesthetized microdialysis to assess changes in dorsal striatal dopamine release following drug administration. The first experiment assessed the effects of systemic CRF administration. The second experiment assessed the effects of systemic stress-level corticosterone administration in combination with systemic corticosterone receptor antagonist, RU486, pretreatment. After this, all groups received systemic amphetamine administration. For the third experiment, CRF and vehicle were locally infused into left and right dorsal striatum within-subject, counterbalanced. All animals then received systemic amphetamine administration.
Results
We show systemic CRF significantly elevated extracellular dopamine levels in the dorsal striatum (N = 7; p = 0.046). In contrast, neither corticosterone, RU486, or their combination, significantly changed extracellular dopamine levels in the dorsal striatum (N = 7-9 per group; p > 0.05). Further, corticosterone did not change dorsal striatal dopamine response to amphetamine (p > 0.05). Finally, locally infused CRF significantly increased extracellular dopamine levels compared to vehicle infusion (N = 8; p = 0.014), but did not alter dopamine response to amphetamine (p > 0.05).
Conclusions
Systemic administration of CRF-like agents, has been used in healthy people to introduce acute stress. These studies indicate an increased dorsal striatal dopamine following drug treatment. We confirm systemic CRF increases dorsal striatal dopamine in the rat. However, systemic stress-level corticosterone does not alter extracellular dopamine suggests previous dopamine increases in people may not be due to hypothalamic-pituitary-adrenal axis-induced glucocorticoid release. The findings from our final experiment provide support for a local CRF-mediated effect in rat dorsal striatum. We now would like to understand the possible mediators of this process by exploring muscarinic/nicotinic receptor mediated mechanisms in the dorsal striatum.

Spontaneous and auditory evoked neuronal activity in scn1lab-/- zebrafish larvae

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Background
Loss of function in the gene Scn1 is associated with autism and epilepsy. While there are neural differences between people with and without autism in both resting activity and activity evoked by auditory stimuli, how these differences are manifested at the cellular level is not well understood. Zebrafish larvae are an attractive model organism for investigating whole brain activity due to their transparency and relatively small brain. These enable non-invasive whole brain imaging at cellular resolution. Zebrafish are also readily genetically modified, and have many homologous genes to humans, including the Scn1 homolog scn1lab.
Methods
We recorded neuronal activity from the brain of larval zebrafish carrying a deletion in the Scn1 homolog scn1lab, both at rest and during auditory stimulation. Larvae expressing neuronal calcium indicator GCaMP6s were mounted in a custom 3D printed chamber and immobilised with agarose. Fluorescent activity throughout the brain was recorded using selective plane illumination microscopy. The auditory stimuli were selected to test auditory sensitivity, pre-pulse inhibition and auditory habituation, and consisted of different volumes of white noise.
Results
We found that the distribution of firing rates in both wild type and scn1lab-/- brains peaked at around 9 spontaneous events per minute, but the scn1lab-/- larvae had more neurons with fewer than 5 spontaneous events per minute than the wild types. We also observe reduced pre-pulse inhibition in the brain of scn1lab-/- larvae.
Conclusions
These findings aid our understanding of how this gene confers differences in the developmental function of the brain. They point towards lower resting activity, but increased excitability in response to auditory stimuli. The results presented here will inform future studies into differences into spontaneous and evoked neuronal activity between wild type and scn1lab-/- larvae.

Cannabidiol and Ethanolic Hemp Extract reduce relapse to methamphetamine and locomotor sensitization

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Background
The psychostimulant methamphetamine (METH) is a highly addictive illicit drug associated with physical and mental health problems. Current pharmacological approaches are plagued by high relapse rates and poor compliance. Hence there is a pressing need for novel therapeutic targets. Cannabis constituents demonstrate therapeutic potential because of their anxiolytic and neuroprotective properties. We have previously shown that cannabidiol (CBD) reduces the relapse to METH seeking behaviour and METH-induced sensitization. Here we aimed to test the ability of an ethanolic hemp extract (Goo), both alone and in combination with CBD, to reduce relapse for METH and hyperactivity caused by METH sensitization.
Methods
Experiment 1:Twenty adult male Sprague-Dawley (SD) rats were trained to self-administer METH during two-hour sessions, then progressed to extinction (responding not reinforced). Rats received CBD (80mg/kg), Goo (43.5mg/kg), CBD+Goo, or vehicle via intraperitoneal (i.p.) injection 30 minutes prior the METH-primed reinstatement sessions. Experiment 2:Twelve adult male SD rats underwent behavioural sensitization, where they were subjected to 7 daily METH injections (1mg/kg - days 1,7/5mg/kg - days 2-6; i.p.). After withdrawal, behavioural changes were examined over 4 challenge days. Treatments were also administered 30 minutes prior to METH challenge (1mg/kg i.p.). Locomotor activity was then measured for 60 minutes.
Results
All the treatments reduced the relapse to METH-seeking and hyperactivity induced by METH sensitization, yet Goo and the combined treatment were more effective than CBD alone in reducing METH relapse.
Conclusions
This is the first study to analyse the effect of an ethanolic hemp extract both alone and supplemented with CBD, and suggests that the constituents of ethanolic hemp extract offer treatment potential for METH use disorder over and above those provided by CBD. Funding acknowledgements: Lambert Initiative for Cannabinoid Therapeutics and Macquarie University.

Exogenous oxytocin dose-dependently suppresses REM sleep in male and female rats

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Background
While dreaming can occur at any stage of sleep, dreams during rapid eye movement (REM) sleep are typically more emotionally-intense, vivid, and detailed. The contents of REM sleep dreams are highly social, social simulation theory proposes that a potential function of dreaming is to simulate social interactions, and social seclusion in humans has been shown to increase the proportion of REM sleep experienced post-isolation. Based on these strong links between REM sleep and the critical role oxytocin plays in social behaviour and neurobiology during wake, the potential influence of oxytocin during REM sleep has been hypothesised but remains relatively under-explored.
Methods
This series of studies investigated the effects of oxytocin on REM sleep outcomes using radiotelemetry-based polysomnography in adult male and female Wistar rats. Oxytocin was administered via the intraperitoneal (IP; 0.1, 0.3 and 1 mg/kg) and intranasal (IN; 0.06, 1, 3 mg/kg) routes. Caffeine (IP and IN; 10 mg/kg) was also administered as a positive control. Additionally, pre-treatment with the oxytocin receptor (OTR) antagonist L-368,899 (IP; 5 mg/kg) and vasopressin 1a receptor (V1aR) antagonist SR49059 (IP; 1 mg/kg) followed by oxytocin (IP; 1 mg/kg) was conducted to determine which receptor(s) mediated sleep-wake effects of oxytocin.
Results
In both male and female rats, IP oxytocin dose-dependently increased REM sleep onset latency and suppressed the proportion of time rats spent in REM sleep, reducing both the frequency and mean duration of REM sleep bouts, for approximately 2.5 hours post-administration. Conversely, IN oxytocin did not significantly alter any REM sleep parameters at any dose tested. Caffeine demonstrated REM sleep suppressant effects under both the IP and IN routes of administration. The involvement of the oxytocin receptor (OXTR) and vasopressin V1a receptor (V1aR) binding in oxytocin-induced effects on REM sleep outcomes will be discussed.
Conclusions
These findings clearly demonstrate that administration of exogenous oxytocin, via the IP but not IN route, dose-dependently delays the onset of REM sleep and suppresses the occurrence of REM sleep in rats. The mechanism underlying this REMS-suppressant effect involves activity at OXTRs and V1aRs, however the brain regions, circuitry, and neuronal populations involved remain unknown. It is possible that endogenous oxytocin still contributes to the social nature of REM sleep and dreaming; future experiments should both observe and manipulate activity within the endogenous oxytocin system during REM sleep to elucidate this potential mechanism.

Developmental Vitamin D-deficiency affects the expression of miRNAs in dopaminergic neurons

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Background
Schizophrenia is a neurodevelopmental disorder and dopamine dysregulation is implicated in its pathogenesis. We have shown in humans that the developmental vitamin D-deficiency (DVD-deficiency) increases the risk of schizophrenia in offspring, and impairs various aspects of brain development in rodents. microRNAS are small non-coding RNAs that regulate gene expression and play a role in normal brain development. While the dysregulation of microRNAs has been found in post-mortem brain of patients with schizophrenia, the biological pathways affected by these alterations are not clear. The aim of this study was to identify the effects of DVD-deficiency on miRNAs expression in dopaminergic neurons.
Methods
We sequenced total and small RNAs in dopaminergic neurons from the well-established developmental vitamin D (DVD)-deficiency rat model at embryonic day 14 - a critical time point in the differentiation of dopaminergic neurons. The results of the sequencing guided us to address the effects of the overexpression of some of the altered miRNAs on dopaminergic neuron neurite growth using immunocytochemistry and the SH-SY5Y human cell model.
Results
Our sequencing results show that DVD-deficiency results in the dysregulation of several genes and miRNAs in dopaminergic neurons. 86 genes were found significantly altered in DVDs versus control (p<0.01); where 40 genes were upregulated and 46 downregulated. 16 miRNAs were found significantly upregulated and 2 downregulated in DVD-deficiency dopamine neurons. Following the correlation results and the most significant interactions, we have chosen to further analyse the involvement of 3 of those miRNAs in the development of dopaminergic neurons: 181c-5p, 124-3p and 17-5p. Our data revealed miRNA 181c-5p decreases TH+ neurite length compared to controls.
Conclusions
These results show that DVD-deficiency increases the expression of several small RNAs in the dopaminergic neurons, likely regulating numerous biological pathways. We have also observed differential expression of genes that are involved in cell cycle and neuronal morphology. Finally, we have shown that one of the altered miRNAs, the 181c-5p, is directly involved in the neurite outgrowth of dopaminergic neurons. This further suggests that vitamin D may play a role in altering the epigenetic landscape in neurons, and it is a potential mechanism by which vitamin D drives the differentiation of dopaminergic neurons.

Enhanced dopamine synthesis altered RNA methylation in dorsal striatum

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Background
The EDiPS model (Enhanced Dopamine in Prodromal Schizophrenia) reiterates the key discovery regarding the development of schizophrenia, that patients experience increased dopamine synthesis and release in the dorsal striatum. Structural alterations exhibited by EDiPS model, include increased dopamine release sites and synapse numbers. Understanding the mechanism underlying these synaptic adaptations is critical to develop effective prophylactic intervention. As one plausible basis for these alterations, we investigated RNA methylation, a post-transcriptional modulation that is essential for brain plasticity and adaption to external challenges. We will determine whether increased dopamine synthesis capacity induces RNA hypermethylation, thereby enhancing dopaminergic transmission in EDiPS model.
Methods
To generate EDiPS animals, we injected a construct coding for tyrosine hydroxylase and GTP cyclohydrolase 1 into the pars compacta of juvenile P35 rats. These enzymes are transported to the dorsal striatum, where they increase dopamine synthesis capacity. Six weeks following construct delivery, we collected the dorsal striatum, extracted RNA and performed methylated RNA(m6A) immunoprecipitation (meRIP) sequencing. Western blot was conducted to assess the expression of RNA modifiers that regulate RNA methylation, RNA splicing and translation. RNA modifiers include m6A methyltransferases Mettl3 and Mettl14, demethylase FTO, m6A readers that facilities m6A-modified RNA translation, and YT521-B homology domain family (YTHDF) proteins.
Results
meRIP-sequencing results showed that 80% of mRNAs in the EDiPS dorsal striatum were significantly hypermethylated (95 out of 119 mRNAs differentially modified). The majority of these m6As were localised in coding regions that are known to promote translation. KEGG pathway analysis revealed that altered m6A RNAs were enriched in synaptic vesicle cycling, glutamate, dopamine synapses and long-term potentiation. These results suggest that enhanced dopamine release induces RNA hypermethylation, which may lead to increased dopamine synaptic number in EDiPS. Consistent with enhanced RNA methylation, there was increased expression of Mettl14 protein and the m6A reader YTHDF1 mRNA in EDiPS dorsal striatum.
Conclusions
Hyper-dopaminergia in the dorsal striatum is a robust marker that provides a highly plausible neurochemical prophylactic target. The EDiPS model provides the opportunity to examine a possible interaction between this clinical finding, and potentially crucial changes to the epitranscriptome. We have provided the first evidence that increased dopamine synthesis capacity in the dorsal striatum enhances RNA methylation, which in turn regulates synaptic structure and plasticity. Further exploration of this finding will not only provide etiological insight, but also help to identify novel treatment targets for schizophrenia.

Poster 1-13

Changes in Cortical Gene Expression in the Muscarinic M1 Receptor Knockout Mouse: Potential Relevance to Schizophrenia, Alzheimer's disease and Cognition.

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Background
Postmortem and neuroimaging studies show low levels of cortical muscarinic M1 receptors (CHRM1) in patients with schizophrenia which is significant because CHRM signalling has been shown to change levels of gene expression and cortical gene expression is altered in schizophrenia.
Methods
We decided to identify CHRM1-mediated changes in cortical gene expression by measuring levels of RNA in the cortex of the Chrm1-/- mouse (n = 10), where there would be no signalling by that receptor, and in wild type mouse (n = 10) using the Affymetrix Mouse Exon 1.0 ST Array.
Results
RNA for 15,501 annotated genes and noncoding RNA were detected; 1,467 RNAs were higher and 229 RNAs lower in the Chrm1-/- mouse. Our overall cortical gene expression data showed 47 genes had altered expression in Chrm1-/- mouse and the frontal pole from patients with schizophrenia; changes in expression of 44 genes being in opposite directions. Some genes with altered expression in the Chrm1-/- mouse have been shown to affect amyloid precursor protein processing which is associated with the pathophysiology of Alzheimer's disease and 69 genes with altered expression in the Chrm1-/- mouse are risk genes for lower human cognitive ability.
Conclusions
Our findings argue CHRM1-mediated changes in gene expression are relevant to the pathophysiologies of schizophrenia and Alzheimer's disease and the maintenance of cognitive ability in humans. Further studies of models of changed CHRM1 signalling, such as the CHRM1-/- mouse, could provide useful information on how CHRM1 signalling could be involved in the genesis of symptoms in schizophrenia and Alzheimer's disease and the modulation of cognitive ability.

Effect of chronic antipsychotic treatment on neuroinflammation and dopamine neuron health in rats

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Background
A large subset of people with schizophrenia (~45%) display elevated cytokine (IL6, IL1B, SERPINA3, TNF) levels in brain regions associated with dopamine dysfunction, particularly in the midbrain. Post-mortem studies have demonstrated elevated gene expression of inflammatory markers is correlated with higher levels of antipsychotic exposure and reductions in cortical grey matter volume, prompting us to question whether antipsychotics may be contributing to neuroinflammation and other pathological features of schizophrenia. Typical antipsychotics have a higher affinity for dopamine D2 receptors compared to atypical antipsychotics and excessive blockade of these receptors is associated with motor impairments.
Methods
At P60, male Sprague Dawley rats were randomly assigned treatment with 0.5 mg/kg haloperidol, risperidone or control (n=16/group) twice daily through supplementation in cookie dough for 6 months, to recapitulate the clinical duration of treatment in our human post-mortem cohort (~19 years). Tail vein bloods were collected at P120 and P180 to measure cytokine levels and drug concentrations using ELISA and HPLC respectively. Vacuous chewy movements (VCM), open-field movement distance and the bar test were conducted fortnightly as indexes of tardive dyskinesia, locomotor activity and catalepsy respectively.
Results
Haloperidol-treated rats displayed cataleptic effects 2-weeks after commencing treatment compared to rats in the risperidone and control group (p8/min at P150 across the treatment group. VCM frequency in the risperidone group (<0.2/min) was less than the haloperidol group and occurred in a smaller subset of animals (n=5/16) (p<0.05), whereas no VCM was apparent in controls. Locomotor activity was also reduced in the haloperidol group compared to risperidone and control groups (p<0.05).
Conclusions
We provide an update on the effects of chronic antipsychotic treatment on behavioural phenotypes and will relate these to peripheral levels of inflammatory markers of rats treated for 6 months. Our study aims to assist in disentangling the effects of antipsychotic treatment from the pathological features of schizophrenia, which poses an ongoing limitation in molecular studies. By understanding the possible detrimental effects of antipsychotics, we can attempt to minimise any potential harm inflicted throughout the long treatment period, often extending from early adolescence until the end of life.

EBRAINS/Human Brain Project open database DOPAMAP: High-resolution microscopic images of dopamine 1 and 2 receptor positive cells in the developing mouse brain

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Background
The dopaminergic system develops and reorganizes to affect mental disorder onset and maintenance across our lifetime. We performed a stereological study to quantify dopamine 1 or 2 receptor (D1R and D2R) positive cells in five regions of the rostral forebrain in mice, which generated >150 immunohistochemically stained brains of male and female mice aged at 5 different cognitive milestones. Partnering with the Human Brain Project (European Union), the aim of this study is to present such comprehensive histological material as a public online collection of atlas-registered microscopic images, which will be interactively showcased (https://search.kg.ebrains.eu/?facet_type[0]=Dataset&q=dopamine) in this presentation.
Methods
Slides from Cullity et al. (2019) were scanned with a Zeiss Axioscan Z1 (20x objective). Pre-processing steps included white balance using ZEN software (RRID:SCR_013672), before images were exported at full resolution (pixel width 0.22 um). All 2D images were spatially registered to 3D reference atlases using QuickNII (RRID:SCR_016854) which allows the user to cut the atlas in any plane of orientation. For the late adolescent (P49) and adult (P70) brains, we used the Allen Mouse Brain Common Coordinate Framework based on P56 mice. For younger brains, developmental 3D brain atlases provided by Newmaster et al. (2020) was used.
Results
The entire 4607 images across 153 brains showing the distribution of D1R and D2R expressing neurons across the mouse forebrain was shared through the EBRAINS Knowledge Graph all hosted under unique DOIs and CC-BY licenses. DOPAMAP collection comprises twenty data sets, each representing one combination of genotype (2 conditions), age (5 conditions), and sex (2 conditions). A brain atlas viewer link is provided for each subject, through which the high-resolution images can be viewed with custom cut atlas plates overlaid. Quality control showed the fit of the brains to the atlas improved with age (p0.05).
Conclusions
DOPAMAP collection is a uniquely rich source of data on D1R and D2R positive cells in developing and adult mouse brains. Until now, our knowledge on these cells has been fragmented across publications focusing on a few brain regions. Researchers can easily confirm presence and/or distribution of these cells in their regions of interest in DOPAMAP. Users interested in age and sex differences can download and utilize the data in novel analyses. Computational researchers can analyse raw images from DOPAMAP without performing new experiments. DOPAMAP represents a new era in open science to understand dopamine-related disorders across maturation.

Poster 2-1

Investigating the therapeutic efficacy of psilocybin for anorexia nervosa in an animal model

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Background
Anorexia nervosa (AN) has the highest mortality rate of any psychiatric disorder and less than 50% of patients ever recover. Despite this, there are currently no effective medicinal treatments for AN. The potential for psilocybin, the psychoactive compound produced by so-called magic mushrooms to improve outcomes in patients with AN is currently being explored in clinical trials and is proposed to act by breaking down the cognitive-behavioural inflexibility that characterises AN, persists after body weight recovery and contributes to the chronic nature of the condition. However, the neurobiological and behavioural processes by which psilocybin could alleviate anorectic symptoms remain unknown.
Methods
We used the activity-based anorexia (ABA) rat model and a home-cage operant reversal learning task to examine the therapeutic effects of psilocybin on pathological weight loss and cognitive-behavioural flexibility. Female Sprague-Dawley rats (n=32; 7 weeks old) were trained to run in wheels and administered psilocybin (1.5mg/kg) or saline 24h prior to the commencement of ABA, consisting of unlimited access to a running wheel paired with time-limited access to food (90min/day). A separate cohort of rats (n=26) were trained at fixed ratio (FR) schedules 1,3 and 5, administered psilocybin (1.5 mg/kg) or saline, and 24h later underwent reversal sessions at FR5.
Results
Psilocybin attenuated the rapid weight loss elicited by exposure to ABA conditions, with a 36% increase in the ability to maintain body weight above 80% of baseline for animals administered psilocybin compared to control animals. This improvement in weight maintenance was driven by both an increase in food intake and a reduction in the compulsive wheel running that typically accompanies food restriction in ABA. Psilocybin also significantly improved cognitive-behavioural flexibility in the reversal learning task, in which rats administered psilocybin were able to more quickly adapt responding to the change in reward contingencies compared to saline treated rats.
Conclusions
The ABA phenotype is proposed to develop via a failure to modify energy output (running wheel activity) when required to adapt to limited food access. Psilocybin improves this adaptive ability in ABA to promote body weight maintenance and similarly improves flexible learning in an operant test paradigm. These findings provide initial support for the therapeutic potential of psilocybin for treating the cognitive inflexibility that allows patients with AN to continue to restrict food intake, even in the face of starvation. Future studies will examine the neurochemical underpinnings of these effects and delineate the neural circuitry involved.

Dopamine D1 and D2 receptor agonism dose-dependently impairs associative learning and goal-directed action in mice.

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Background
Patients with schizophrenia have impaired cognition, and one of the most robust pathophysiological findings is increased dorsal striatal dopamine neurotransmission. Striatal dopamine systems are known to modulate the coordination of motor and action-planning, decision-making and reward learning. Dopamine (D)1 and (D)2 receptors expressing medium spiny neurons (MSNs) respond to striatal dopamine release by activating selected output pathways to direct behaviour. The aim of this study was to examine the effects of stimulating D1 or D2 receptors on learning and the subsequent impact on goal-directed action in mice using the Outcome-specific Devaluation Task (ODT).
Methods
Adult male C57BL6/J mice were treated systemically with either a low 0.05mg/kg or high 0.1mg/kg dose of D1 (SKF-82958), or D2 (Quinpirole) receptor agonist during training on the ODT, in which two separate action-outcome associations are learnt. In a subsequent drug-free choice test, mice then made a choice between the competing actions after one outcome was devalued. Value tests were then conducted, on and off drug, to determine if stimulation of dopamine receptors impacted reward valuation processes. Locomotor activity was also assessed after drug administration pre- and post-operant testing in an open-field test.
Results
D1 and D2 agonism dose-dependently altered motor behaviour and learning. D1 agonism stimulated motor behaviour while D2 agonism had no impact in comparison to controls. In contrast, all treatment groups learnt to lever press at the same rate indicating that stimulation of either receptor subtype did not impact on instrumental learning per se. However, low dose D1 agonism increased magazine approach behaviour. Agonism of either receptor subtype altered associative learning processes with low dose treatment leading to goal-directed action impairments, whereas high doses did not. No impact of agonist treatment was observed on reward valuation processes.
Conclusions
Stimulating either D1 or D2 receptors dose-dependently disrupted the associative learning processes that are required to guide goal-directed action. This suggests that in patients with schizophrenia that have elevated striatal dopamine, too much ‘noise’ may disrupt the ability for D1 and D2 MSNs to respond to reward signals and guide behaviour appropriately. Optimal levels of D1 and D2 MSN activation may therefore be required to ameliorate decision-making dysfunction in schizophrenia. Examining the underlying neurobiology that contributes to these functional impairments will help to identify approaches to improve the quality of life of those living with schizophrenia.

Stress reactivity of hypothalamic corticotrophin-releasing hormone (CRH) neurons following cocaine exposure

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Background
Substance use disorder causes significant societal and social harm. Stress is a common factor commonly linked with drug abuse at all phases of the addiction cycle. Corticotrophin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) are highly responsive to stress and drugs, and control hormonal and behavioural responses to these stimuli. How PVN CRH neurons adapt to drug exposure and contribute to dysregulated stress reactivity is unclear.
Methods
To assess neuronal activity in response to stress, we used two approaches to express the genetically encoded Ca2+ indicator, GCaMP6f, in PVN CRH neurons (termed CRH-Cre::GCaMP6f) and secured a optic fibre probe above the PVN. CRH-Cre::GCaMP6f mice were exposed to 10 days of either saline or cocaine injections (15 mg/kg/i.p.). On day 8 of drug exposure CRH neuron activity was probed by a hand pick up, and again 10 days after exposure, to a novel stimulus (robobug). Corticosterone levels were also measured in response to stress.
Results
On day 8 of drug exposure, PVN CRH neurons in cocaine-exposed animals displayed evidence of altered activity patterns when exposed to the hand grab paradigm compared to saline controls. In response to the presentation of the robobug on day 10, CRH neuron activity was significantly exaggerated in the cocaine exposed group despite animals exhibiting similar defensive behaviours. In addition, corticosterone levels were significantly elevated in cocaine- versus saline-exposed animals.
Conclusions
During abstinence, drug-cues and stress may increase craving and promote relapse. These studies provide the first evidence that PVN CRH neurons are hyper-sensitive to stress following cocaine exposure, providing a potential mechanism by which stress may impact neural activity in downstream targets of PVN CRH neurons to promote craving and relapse. Further work may provide critical insights into the role of PVN in altered stress-reactivity in addiction and lead to new strategies to suppress stress-induced relapse.

Blood Glutamate Scavenging Prevents Inflammation-Induced Depression in Mice

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Background
Inflammation is implicated in the aetiolgoy of depression, at least for a subgroup of people. Inflammation-induced depression can be modeled in rodents and humans by injecting lipopolysaccharide (LPS), which mimics bacterial infection. LPS administration increases inflammatory cytokine expression, inducing a sickness response, followed by increased depression-like behaviour. Disrupted glutamatergic signaling is also implicated in the pathophysiology of depression, and inflammation can increase extracellular glutamate and release of neurotoxic metabolites, such as quinolinic acid. Here, we determine the capacity of reducing blood glutamate, which enhances brain glutamate efflux, to prevent and reverse LPS-induced depression-like behaviour in mice.

Methods
To determine if glutamate scavenging can prevent or reverse inflammation-induced depression, male C57BL6 mice (n=7-9/group) were administered either a low dose of LPS (0.03mg/kg) 1hr after GOT administration and assessed for depression-like behavior 4hr later, or LPS (0.1 mg/kg) 6hr prior to GOT administration and assessed for depression-like behavior 24 h later. To reduce blood glutamate levels, mice received glutamate-oxaloacetate transaminase (GOT; vs. vehicle), followed 1hr later by a 100µl injection of the GOT substrate, oxaloacetate (vs. vehicle). Sickness behaviour was assessed by monitoring bodyweight and locomotor activity. Depression-like behaviour was assessed using the sucrose preference and forced-swim tests.

Results
Low dose LPS increased immobility in the forced swim test, reduced sucrose preference and reduced locomotor activity. Glutamate scavenging prevented increased immobility in the FST, without preventing a decrease in locomotor activity. These findings suggest that glutamate scavenging prevents LPS-induced changes in depression-like behaviour but not LPS-induced sickness behaviour.
GOT administration 6 hours following 0.1 mg/kg LPS did not affect any measure compared to vehicle/LPS treated mice. However, it is possible that depression-like behaviour had already subsided in this cohort, as sucrose preference and immobility in the FST had returned to baseline levels.

Conclusions
These data demonstrate that blood glutamate scavenging can block inflammation-induced depression, further implicating altered glutamatergic neurotransmission in the pathogenesis of depression. More work is needed to determine if glutamate scavenging administered after inflammatory processes are established can block or reverse inflammation-induced depression, which may be particularly useful for severe infection and sepsis. These findings have implications for preventing depression in patients at risk for development of mood-related symptoms undergoing inflammation-inducing treatments , such as chemotherapy, cytokine therapy, or surgery, where glutamate scavenging can be commenced prior to initiation of therapy.

A computational model of rodent behaviour on the trial-unique nonmatching-to-location (TUNL) touchscreen task

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Background
Touchscreen behavioural tasks allow for high-throughput assessment of rodent behaviour and cognition. One popular example is the TUNL task, which is widely used to measure hippocampus-dependent spatial working memory in mice and rats. Standard analysis methods for this task assume that behaviour uniquely measures animals' spatial working memory, and not any other cognitive processes. However, this important assumption—which underpins interpretation of task behaviour—has not previously been empirically tested. In this project we used computational modelling to empirically test whether TUNL behaviour solely measures spatial working memory, or whether it can be deconstructed into additional cognitive subprocesses.
Methods
We analysed a total of 55,331 choices from N = 83 mice performing the TUNL task. We compared a suite of computational models that quantified the degree to which animals' TUNL behaviour reflected four distinct cognitive processes: (i) spatial working memory (i.e., remembering the location of a probe stimulus), (ii) relative-response working memory (i.e., remembering to respond left vs. respond right without remembering the probe stimulus) (iii) conditioned place preference (i.e., responding at frequently rewarded locations, independent of the probe stimulus) and (iv) idiosyncratic side biases (i.e., preferring to respond to the left or right, independent of the choice options).
Results
Formal comparison of computational models revealed that animals' behaviour was best explained by a relatively complex computational model in which all four cognitive subprocesses influenced choices (mean AIC = 790.89; group-level R2 = .94). Notably, this model substantially outperformed a simpler model in which behaviour reflected spatial working memory alone (mean AIC = 841.40; group-level R2 = .59). Inspection of animal-specific parameters of the best-fitting model revealed that spatial working memory accounted for just 42% of explained variance in choices on average, compared to 36% for relative-response memory and 11% each for conditioned place preference and side biases.
Conclusions
Our results demonstrate that, contrary to common assumptions, rodent behaviour on the TUNL task does not reflect spatial working memory alone. Instead, spatial working memory was just one among four distinct cognitive subprocesses that we identified as contributing to animals' choices. Each of the four subprocesses is likely to have distinct neural substrates, and each subprocess might also show differential patterns of impairment by targeted brain lesions or by pharmacological challenge or genetic manipulation. More broadly, these findings illustrate the benefits of using computational modelling to interrogate assumptive models of complex rodent behaviour by identifying underlying cognitive processes.

Poster 2-6

Reinforcement Learning in Autism: A Systematic Review and Meta-Analysis

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Background
Decision-making is based on reward or punishment of previous actions. Reinforcement learning, i.e., learning which actions are rewarded or punished, therefore plays a critical role in decision-making. Therapy using reinforcement learning principles is often administered as an early intervention for autistic children, however there is variability in client responsiveness that could be explained by differences in reward processing and learning. Behavioural studies measuring reinforcement learning in relation to autistic diagnoses and traits have been conducted, but results are conflicting and require integration. This study aimed to systematically review research investigating the relationship between reinforcement learning and autism.
Methods
Electronic databases, PsychINFO, PubMed, and CINAHL were searched in June 2021. Key search terms were variations on autism, decision-making, reinforcement, probabilistic, and feedback learning, and specific tasks such as the Iowa Gambling Task. Inclusion criteria were: human study, peer-reviewed, written in English, used a measure of reinforcement learning, and measured autism or autistic traits. Exclusion criteria were: animal study, abstract only, reviews, theses, studies without a measure of reinforcement or autism. PRISMA criteria were followed. Two independent reviewers screened abstracts, followed by full text screening. Conflicts were resolved upon discussion between reviewers, and if necessary, a third reviewer.
Results
This is the first systematic review and meta-analysis of research that has investigated individual differences in behavioural reinforcement learning ability related to autism. A total of 2543 unique articles were identified and screened. Findings from studies will be integrated, and pair-wise meta-analyses will be presented where appropriate. Quality of each study will be also be presented. Differences between autistic and non-autistic participants, or correlations between tasks and autistic traits will be presented including: overall task performance, win-stay and lose-shift behaviour, learning from rewards compared to punishments, learning speed, learning style, and low probabilistic vs high probabilistic feedback learning.
Conclusions
This systematic review and meta-analysis will lead to a deeper understanding of reinforcement learning ability and autism. Through this review, it may be possible to associate specific decision-making patterns with autistic traits, such as aversive learning and social deficits. Improved understanding has potential to inform behavioural therapy which applies reinforcement learning principles. Reinforcement learning also has neurological importance as it is facilitated by the basal ganglia. Due to the specificity of reinforcement learning tasks and their ability to infer basal ganglia pathway integrity, this review could help guide future research into basal ganglia functioning in autism and decision-making.

Poster 2-7

Therapeutic Neurostimulation in Obsessive-Compulsive and Related Disorders: A Systematic Review

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Background
Obsessive-compulsive and related disorders (OCRDs) are severe conditions, often experienced with anxiety, delusions, guilt, isolation, and impaired well-being. Unfortunately, many remain treatment resistant, and are consumed by distressing ritualistic thoughts and behaviors. Therefore, there is a critical need for alternative therapies that can modulate psychopathology of OCRDs. Neurostimulation therapies can achieve dramatic improvements in psychiatric patients, that are unable to benefit from any other available treatment. Invasive and noninvasive neurostimulation therapies for OCRDs were systematically reviewed. Previous reviews have focused on a narrow scope, statistical rather than clinical significance, grouped together heterogenous protocols, and proposed inconclusive outcomes and directions.
Methods
The PRISMA method was implemented to review all investigations (case reports, pilot studies, clinical care studies, open and closed label trials) of neurostimulation techniques (electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS)) for the treatment of OCRDs. 1756 articles were identified, and 153 were included in the final analysis. The systematic review aimed to assess clinical characteristics, methodologies, neuroanatomical substrates, and varied stimulation parameters. A comprehensive and transdiagnostic evaluation of all clinically relevant determinants is presented with translational clinical recommendations and novel response rates. See link for publication https://www.mdpi.com/2076-3425/11/7/948.
Results
ECT studies were limited in number and quality but demonstrated greater efficacy than previously identified. Targeting the pre-supplementary motor area (SMA)/SMA is recommended for tDCS and TMS. TMS yielded superior outcomes, although polarity findings were conflicting, and refinement of frontal/cognitive control protocols may optimize outcomes. For both techniques, standardization of polarity, more treatment sessions (>20), and targeting multiple structures are encouraged. A DBS 'sweet spot' of the striatum for OCD was proposed, cognitive behavioral therapy is strongly encouraged. Several DBS targets for Tourette's achieved consistent, rapid, and sustained clinical response, these patients exhibited less variance and reliance on treatment optimization.
Conclusions
A novel and comprehensive protocol reviewed all clinically relevant factors of neurostimulation therapies to address their potential role in the continuum of care for OCRD. Across articles, there was greatest evidence for DBS and TMS therapy for the treatment of OCD and Tourette's. Recommendations are proposed to enhance research and clinical protocols. Importantly, analysis of fiber connectivity, as opposed to precise neural regions, should be implemented for target selection. Standardization of stimulation parameters is necessary to achieve translational outcomes.

The neural, stress hormone and inflammatory correlates of childhood deprivation and threat in psychosis: A systematic review.

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Background
Childhood adversity is an established risk factor for the development of psychosis, yet the biological mechanisms underpinning this relationship remain unclear. Research exploring alterations to brain structure, function and connectivity, inflammation and HPA axis function has yielded promising findings, but consideration of the type of adversity may be vital for producing meaningful and consistent results.
Methods
We systematically searched and synthesised the literature to date in these key biological domains to investigate whether a novel conceptual model, the dimensional model of adversity, which disaggregates childhood adversity into dimensions of deprivation and threat, may help to elucidate the mechanisms linking childhood adversity to psychotic illness.
Results
Our search yielded 71 articles examining associations of childhood threat, deprivation, or mixed adversity, with biological characteristics in the neural, inflammatory, and stress-hormone domains, in individuals on the psychosis spectrum. We are currently near the end of the data extraction stage and are synthesising our findings. This will be complete by October when the BPA conference is held.
Conclusions
We plan to present findings relating to deprivation, threat and mixed adversity separately, in order to highlight dimension-specific patterns between the different biological domains and explore the value of the dimensional model for psychosis.

Cannabidiol as a treatment for early-stage dementia: A double-blind, placebo-controlled clinical trial protocol

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Background
As a leading cause of global morbidity and mortality, the prevention or delay of progression of dementia in its early stages is a public health imperative. Accumulating evidence suggests that cannabidiol (CBD) is associated with neuroprotective, regenerative, anti-inflammatory, antidepressant, endocrine and symptom regulating effects, suggesting that it may be of benefit in early-stage dementia treatment, however no human study has examined this. This proposed clinical trial aims to determine whether daily treatment with CBD over a 12-week period is associated with improved neurobiological, physiological, behavioural and psychological outcomes in individuals living with early-stage dementia.
Methods
Sixty individuals diagnosed with early-stage dementia will be recruited for a randomised, double blind, placebo-controlled clinical trial. Community-dwelling participants will be randomised into 99.9% pure CBD or placebo treatment conditions and take two capsules per day. Participants will start the trial on a lower dose of 200mg/day for two weeks before escalating to 300mg/day for the remaining ten weeks. Structural magnetic resonance and diffusion weighted imaging, and blood-based hormone profiles, will be assessed at baseline and post-treatment, and behavioural and psychological symptoms at baseline, mid-trial and post-treatment. Participant health and side effects will be monitored weekly via home visits.
Results
The study has received full ethics approval, and recruitment is anticipated to commence in July 2021. Outcomes include hippocampal and amygdala volume and brain structural connectivity, depressive and anxiety symptoms, cognition and quality of life, examined in relation to plasma biomarkers. Mixed model analyses of variance will test for differences in the dependent variables of interest, with the between-subjects factors of treatment (CBD, placebo), within-subjects factor of time (baseline, mid-point where applicable, post-treatment) and covariates as required. With N=60 and α=.05 we have 90% power to detect a medium effect size (d = 0.50). Final outcomes are anticipated in 2023.
Conclusions
This clinical trial will be the first to investigate the effects of pure oral CBD as a treatment for key characteristics and outcomes in individuals living with early-stage dementia. The intended impact of this trial is to broach new treatment grounds and inform a potential novel and accessible treatment approach to reduce the risk and impacts of early-stage dementia in individuals diagnosed with the condition. If effectiveness of CBD is determined, its widespread implementation has the potential to lead to improved functioning, quality of life and a better prognosis for affected individuals.

BDNF genotype Val66Met interacts with acute plasma BDNF levels to predict fear extinction and recall

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Background
Brain-derived neurotropic factor (BDNF) is a potent regulator of memory processes and is believed to influence the consolidation of fear extinction memories. No previous human study has tested the effect of unstimulated BDNF on fear extinction recall, and no study has tested the association between plasma BDNF levels and psychophysiological responding during an extinction paradigm. Measuring BDNF in relation to these indices could have implications for our understanding of how humans process and retain fear extinction memories, which are central to recovery from disorders such as posttraumatic stress disorder.
Methods
We tested the association between fear responses during a 2-day differential conditioning, extinction and extinction recall paradigm and Val66Met genotype in a group of healthy participants (N=191). The aversive stimulus was an electric shock, which was paired with a coloured circle (the CS+) but not with the safety signal (CS-) during acquisition. The outcome measure was skin conductance response. Blood samples were taken and assayed for plasma BDNF levels in a subset of participants. (n=56).
Results
There were no group differences during habituation or acquisition. Met allele carriers compared to Val homozygotes displayed higher responses to the CS+ compared to the CS- during extinction learning and had higher responding to both the CS+ and CS- during extinction recall. Plasma levels of BDNF protein that were collected in the sub-sample of the group moderated the effect of Met allele presence, such that lower BDNF level was associated with higher skin conductance response in the Met but not Val group to the CS+ during extinction learning and to both the CS+ and CS- during extinction recall.
Conclusions
The current results extend previous observations of a Val66Met effect during fear extinction learning to extinction recall and show for the first time that these effects are moderated by plasma BDNF level. These findings suggest that the Val66Met effects on fear extinction in previous studies are indeed at least partially the result of discrepant BDNF levels. The implications of this finding is that augmentation of BDNF levels may be an effective way to enhance outcomes of exposure therapy treatment for posttraumatic stress and anxiety disorders.

Disinhibited behaviors in dementia: a scoping review of biopsychosocial mechanisms and systematic review of management approaches

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Background
Disinhibited behaviors in dementia, including sexual disinhibition, are associated with multiple negative outcomes, though are under-researched. We aimed to (1) review the literature of biopsychosocial factors (including neurochemical mechanisms) and (2) systematically review approaches that measure disinhibited behaviors in dementia.
Methods
Aim 1: A scoping review identified papers investigating biopsychosocial mechanisms underpinning disinhibited behaviors and impulsivity. A conceptual model of associated factors was developed and case vignettes were described.
Aim 2: Systematic searches of the databases MEDLINE, EMBASE and PsychINFO were conducted for publications published between 2002 and March 2020. We included reviews, original articles, case reports, cohort studies and randomized controlled trials. All studies were rated for research quality. Statistical and clinical significance were considered. Effect sizes were included where provided or calculated where possible. The systematic review only included studies where people living with dementia were recruited.
Results
Aim 1: As with other behavioural and psychological symptoms of dementia (BPSD), biological factors alone do not explain disinhibited behaviors but are integrated with psychological, social, and environmental factors. Our conceptual model incorporates associated factors, and we provide case vignettes to build on understanding of underlying causes of behaviors.
Aim 2: We found a range of pharmacological and nonpharmacological intervention studies that utilized different theoretical/ clinical approaches. These included pain management, antidepressants, models of care, education and/ or training, music-based approaches and physical activity. The Neuropsychiatric Inventory disinhibition subscale was used most often.
Conclusions
Several pharmacological and more so, nonpharmacological approaches were effective in reducing disinhibition. As with other BPSD, emphasis should be on tailoring approaches to the individual person, while considering all underlying factors, and respect the rights of the person living with dementia.

Poster 2-12

Valuation system connectivity is correlated with poly-drug use in young adults

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Background
Poly-substance use involves mixing-and-matching drugs to increase the efficacy or attenuate drawbacks of individual substances. The Valuation (VS) and Executive Control Systems (ECS) are believed to evaluate drug value in the brain, which changes with internal motivations (e.g., euphoria, pain relief) and external factors (e.g., parental use history). We analyzed VS and ECS interactions with poly-substance behaviour by correlating functional connectivity of the VS, ECS and the Valuation-Control Complex (VCC, a hybrid network comprised of VS and ECS regions) with poly-substance use measures in the Human Connectome Project (HCP) Healthy Young Adult dataset using multivariate generalized linear models (GLMs).
Methods
HCP functional MRI data was used (n = 992, 463 males, 529 females; age range = 22-37). VS, ECS and VCC masks were delineated using the Desikan-Killiany and Destrieux parcellations. Drug use measures (alcohol, tobacco cocaine, hallucinogen, opiate, sedative, stimulant, marijuana), parental use history, age, gender and framewise displacement were used as variables. Each participants' VS, ECS and VCC average connectivity was correlated with their substance use history using GLMs. All variables were standardized (mean = 0, standard deviation = 1). Multiple comparisons were controlled using the False Discovery Rate (FDR). p-values < 0.05 post-FDR-correction were deemed significant.
Results
VS connectivity correlated with Sedatives (t=2.3, p=0.03). ECS connectivity correlated with Hallucinogens (t=2.4, p=0.025) and Opiates (t=2.3, p=0.03). Opiates correlated with VS (t=3.3, p=0.002), ECS (t=3.6, p=0.0008) and VCC (t=4.4, p<0.00001) via interaction with Total Tobacco. Sedatives correlated with VS (t=2.6, p=0.017), ECS (t=2.2, p=0.04) and VCC (t=2.3, p=0.03) via interaction with Drink Frequency. Stimulants correlated with VS (t=-2.9 p=0.007), ECS (t=-7.2, p<0.00001) and VCC (t=-4.8 p<0.00001) via interaction with Opiates. Sedatives correlated with ECS (t=7.96 p<0.00001) and VCC (t=8.3, p<0.00001) via interaction with Opiates and with VS (t=3.17 p=0.003) and ECS (t=-2.86, p=0.008) via interaction with Cocaine.
Conclusions
Tobacco and alcohol interactions with VS, ECS and VCC connectivity correlated with Opiates and Sedatives suggests that participants may have started using alcohol and/or tobacco initially but began to incorporate other drugs to enhance their experience. Interactions between Opiates and VS, ECS and VCC connectivity is observed with Stimulants, suggesting attempts to increase euphoria while dampening anxiety and aggression. Finally, interactions between alcohol and VS, ECS and VCC connectivity are observed with Sedatives, suggesting a pain management combination. From these results, we can infer the various motivations behind poly-substance use and their corresponding neural markers.

Poster 2-13

A thalamo-centric neural signature for restructuring negative self-beliefs

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Background
Negative self-beliefs are a core feature of psychopathology. Despite this, we have a limited understanding of the brain mechanisms by which negative self-beliefs are cognitively restructured.
Methods
Using a novel paradigm, we had participants use Socratic questioning techniques to restructure self-beliefs during ultra-high resolution 7-Tesla functional magnetic resonance imaging (UHF fMRI) scanning. Cognitive restructuring elicited prominent activation in a fronto-striato-thalamic circuit, including the mediodorsal thalamus (MD), a group of deep subcortical nuclei believed to synchronize and integrate prefrontal cortex activity, but which has seldom been directly examined with fMRI due to its small size.
Results
Increased activity was also identified in the medial prefrontal cortex (MPFC), a region consistently activated by internally focused mental processing, as well as in lateral prefrontal regions associated with regulating emotional reactivity. Using Dynamic Causal Modelling (DCM), evidence was found to support the MD as having a strong excitatory effect on the activity of regions within the broader network mediating cognitive restructuring. Moreover, the degree to which participants modulated MPFC-to-MD effective connectivity during cognitive restructuring predicted their individual tendency to engage in repetitive negative thinking.
Conclusions
Our findings represent a major shift from a cortico-centric framework of cognition and provide important mechanistic insights into how the MD facilitates key processes in cognitive interventions for common psychiatric disorders. In addition to relaying integrative information across basal ganglia and the cortex, we propose a multifaceted role for the MD whose broad excitatory pathways act to increase synchrony between cortical regions to sustain complex mental representations, including the self.

Empathy and resting-state functional connectivity in children

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Background
Empathy, the ability to understand or share others' thoughts and emotions, is recognized to have both cognitive and affective components. Empathy is important for functioning in the social realm, and alterations in both components have been demonstrated in many developmental and psychiatric disorders. While several studies have demonstrated unique neural underpinnings of empathy components in adults, few have investigated this in young people, particularly children. Investigating associations between empathy and brain function, particularly functional connectivity, during childhood is beneficial to begin to build a comprehensive picture of the neural correlates of empathy across the lifespan.
Methods
112 children (52% female, mean age 10 years) underwent MRI brain scans including a resting-state sequence and completed an empathy self-report measure (the Adolescent Measure of Empathy and Sympathy), and a measure of empathic distress. Pre-processing and first-level analyses were completed using the ENIGMA HALFpipe reproducible pipeline, and group level analyses were run with FSL randomise. Due to the absence of prior work in this age group we considered two complementary approaches; a seed-to-whole-brain connectivity approach using regions identified as important in empathy (identified in prior empathy meta-analyses), and connectivity within key resting state networks (dual regression).
Results
Seed to whole-brain resting-state functional connectivity analyses demonstrated that both affective empathy and empathic distress were associated with decreased connectivity between key hubs of the default mode network (DMN) and other widespread areas in the brain. Analyses of resting-state networks demonstrated that cognitive empathy was associated with both increased and decreased connectivity between dorsal and lateral regions of the DMN and regions outside of the DMN, including the pre and post-central gyrus, and the cerebellum. Affective empathy was associated with increased connectivity between the anterior salience network and the pre and postcentral gyrus.
Conclusions
In conclusion, this study found wide-ranging and diffuse connectivity patterns that related to several components of empathy in a group of 10-year-old children. These wide-ranging findings are not consistent with existing adult task-based literature, and could indicate a more complex picture of brain involvement in empathy processes in childhood, with less specialisation of specific regions or networks and more widespread involvement required to complete the processing. These conclusions are tentative, and will require further replication, and exclusion of potential measurement or analytic specifics.

Poster 2-15

Similar but distinct – Effects of different socioeconomic indicators on resting state functional connectivity: findings from the Adolescent Brain Cognitive Development (ABCD) Study

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Background
Early socioeconomic status (SES) has consistently been associated with child health and cognitive outcomes, in addition to alterations in brain function and connectivity. The goal of the present study was to probe the effects of different facets of SES (parent education, income, and neighborhood disadvantage), that likely represent varying aspects of the environment, on resting state functional connectivity (rsFC).
Methods
We investigated this question in a large sample of 9475 children (aged 9-10 years) from the Adolescent Brain Cognitive Development (ABCD) Study. Specifically, we analyzed the association between household SES (parent education, income-to-needs ratio) and neighborhood disadvantage, and system-level rsFC using within-sample split-half replication. We then tested whether the associations were unique to each SES measure, and whether household SES and neighborhood disadvantage had interactive effects on rsFC.
Results
SES measures had both common and distinct effects on rsFC, with sensory-motor systems (e.g., sensorimotor network) and cognitive networks (e.g., front-parietal network) particularly implicated. The association between neighborhood disadvantage and sensorimotor network connectivity was less pronounced in the presence of high income-to-needs.
Conclusions
Findings demonstrate that different facets of SES have distinct and interacting effects on rsFC, highlighting the importance of considering different indicators when studying the effects of SES on the brain.

Poster 2-16

The relationship between brain structure and general psychopathology in preadolescents

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Background
An emerging body of literature has indicated that broad, transdiagnostic dimensions of psychopathology are associated with alterations in brain structure across the lifespan. The current study aimed to investigate the relationship between brain structure and broad dimensions of psychopathology in the critical preadolescent period when psychopathology is emerging.
Methods
This study included baseline data from the Adolescent Brain and Cognitive Development (ABCD) Study® (n = 11,721; age range = 9-10 years; male = 52.2%). General psychopathology, externalizing, internalizing, and thought disorder dimensions were based on a higher-order model of psychopathology and estimated using Bayesian plausible values. Outcome variables included global and regional cortical volume, thickness, and surface area.
Results
Higher levels of psychopathology across all dimensions were associated with lower volume and surface area globally, as well as widespread and pervasive alterations across the majority of cortical and subcortical regions studied, after adjusting for sex, race/ethnicity, parental education, income and maternal psychopathology. The relationships between general psychopathology and brain structure were attenuated when adjusting for cognitive functioning. There were no statistically significant relationships between psychopathology and cortical thickness in this sample of preadolescents.
Conclusions
The current study identified lower cortical volume and surface area as transdiagnostic biomarkers for general psychopathology in preadolescence. Future research may focus on whether the widespread and pervasive relationships between general psychopathology and brain structure reflect cognitive dysfunction that is a feature across a range of mental illnesses.

Neural Anatomical Heterogeneity in Psychiatric Disorders using Normative Models

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Background
Case-control study designs comparing group mean differences characteristically ignore neuroanatomical heterogeneity in psychiatric disorders. A normative modeling framework has been developed to quantify and map biological heterogeneity at an individual level. Recent work using this approach has found widespread heterogeneity in the brain changes associated with a range of psychiatric disorders. Here we build on this early work to model and statistically characterize the degree of spatial overlap in individual-level anatomical brain changes associated with six different psychiatric disorders (Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, Obsessive-Compulsive Disorder, Depression, and Schizophrenia) collected across multiple sites.
Methods
We collated T1-weighted MRI data from 14 independently acquired datasets (1465 controls, 1294 patients). We modelled age-, sex-, and site-related variation in regional GMV in a training set of controls (n=1196) using the PCNToolkit. Individual-specific deviation maps were then calculated for the patient cohort and the remaining 269 controls. To characterize the degree of spatial overlap in extreme deviations (z-score>|2.6|) for each disorder, we calculated the absolute difference in percentage overlap in the extrema between the held-out neurotypical cohort and each patient group. We then performed permutation testing to assess the statistical significance of the overlap.
Results
We found that individual deviations were common but highly heterogenous in all disorders. There was very little overlap within any brain region for any specific disorder. The maximum overlap in participants for any given region was less than 10% for all disorders. Furthermore, after correcting for multiple comparisons, there were very few regions in which the degree of overlap differed significantly between controls and patients (p<0.05FWE).
Conclusions
Our findings emphasize the considerable individual heterogeneity in structural brain changes observed in patients with the same psychiatric diagnosis and suggest that group-level differences are not representative of individual patients.

Perturbed Iron Biology of the Prefrontal Cortex in Schizophrenia

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Background
Schizophrenia is a debilitating neuropsychiatric disorder that is linked to oxidative stress, cognitive impairment, and cortical atrophy. Iron, the most abundant transition metal in the brain, is critical for key neurobehavioral pathways. Labile iron, when dysregulated can provoke catecholamine production, induce oxidative stress and neurodegeneration. Parvalbuminergic interneurons, implicated in schizophrenia, are particularly sensitive to ferroptosis, an iron-dependent, lipid peroxidation-mediated, regulated cell death. Despite the implication of these features in the cortex in schizophrenia, systematic analysis of labile iron in the cortical tissue from patients has not been reported.
Methods
Specimens from the prefrontal cortex (PFC) of individuals with schizophrenia (n=86) and matched controls (n=85) were obtained from three independent brain tissue resources. Selected transition metals (iron, copper) and proteins (ferritin, amyloid precursor protein [APP] and glutathione peroxidase 4 [GPX4]) were quantified in brain supernatant fractions by inductively-coupled plasma mass spectrometry (ICP-MS) and Western blots, respectively.
Results
With the control group as reference, mean PFC iron in individuals with schizophrenia was elevated (0.62 SDs, p=0.0002). The effect of diagnosis on iron was moderated by age (t161=-3.14, p=0.002), with the largest difference in iron manifesting in individuals who died in their early twenties. This association was unlikely to be driven by demographic and sample variables or by exposure to antipsychotic medications. In contrast, protein levels of ferritin, which stores iron in a redox-inactive form, and of APP, which facilitates export of intraneuronal iron, were decreased in schizophrenia patients (-0.63 SDs, p<0.0001, and -0.49 SDs, p=0.001, respectively).
Conclusions
Our data indicate a conspicuous elevation of labile iron in PFC tissue of individuals with schizophrenia, which is most prominent in young-adulthood and coincides with the age at which negative symptoms and executive dysfunction typically emerge. Coupled with an apparent deficit in mitigating iron-dependent accumulation of toxic lipid peroxides, our findings are consistent with a mechanistic link between iron dyshomeostasis and neuroprogressive changes and highlight the therapeutic potential of targeting ferroptosis susceptibility in schizophrenia.

Transcriptional Modulation of the Hippo Signaling Pathway by Drugs Used to Treat Bipolar Disorder and Schizophrenia

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Background
Recent reports suggest a link between positive regulation of the Hippo pathway with bipolar disorder (BD), and the Hippo pathway is known to interact with multiple other signaling pathways previously associated with BD and other psychiatric disorders.
Methods
In this study, neuronallike NT2 cells were treated with amisulpride (10 μM), aripiprazole (0.1 μM), clozapine (10 μM), lamotrigine (50 μM), lithium (2.5 mM), quetiapine (50 μM), risperidone (0.1 μM), valproate (0.5 mM), or vehicle control for 24 h. Genome-wide mRNA expression was quantified and analysed using gene set enrichment analysis (GSEA), with genes belonging to Hippo, Wnt, Notch, TGF- β, and Hedgehog retrieved from the KEGG database.
Results
Five of the eight drugs downregulated the genes of the Hippo pathway and modulated several genes involved in the interacting pathways.
Conclusions
We speculate that the regulation of these genes, especially by aripiprazole, clozapine, and quetiapine, results in a reduction of MAPK and NFκB pro-inflammatory signaling through modulation of Hippo, Wnt, and TGF-β pathways. We also employed connectivity map analysis to identify compounds that act on these pathways in a similar manner to the known psychiatric drugs. Thirty-six compounds were identified. The presence of antidepressants and antipsychotics validates our approach and reveals possible new targets for drug repurposing.

Genetic and environmental modulation of small non-coding RNAs in a mouse model of affective disorders

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Background
miRNAs are small non-coding RNA molecules with an average length of 19-24 nucleotides. Their main function is regulating post-transcriptional gene expression through mRNA degradation or inhibition of translation. Neuronal miRNAs are involved in regulating neurogenesis and neuroplasticity. They are known to be differentially expressed after exercise, stress, environmental enrichment and in various psychiatric disorders, including depression and anxiety. Polymorphisms in the serotonin transporter gene moderate the influence of stressful life events on depression and are linked to altered anxiety-related measures. Serotonin transporter knockout mice (5-HTT KO) are a strong model of depression and anxiety.
Methods
5-HTT KO and wild-type mice at 8 weeks of age were randomly assigned to either standard housing, exercise, or corticosterone treatment groups for 4 weeks. Hippocampal tissues were collected for miRNA-seq, which was analysed using bioinformatic approaches. Reads were aligned to the GRCm38/mm10 mouse genome using BWA tool. The reads were mapped to miRNA database using subread featureCounts. Normalization and differential gene expression analysis on the miRNA count data was performed using limma-voom software package. To evaluate the biological significance of the differentially expressed miRNAs, the downstream gene targets of miRNAs were determined using miRWalk, GO and KEGG tools.
Results
We analysed small non-coding RNA sequencing data in wild-type and 5-HTT KO mice after exercise and an intervention modelling stress (corticosterone in the drinking water). We determined differentially expressed miRNAs in 5-HTT KO comparing to WT animals in standard-housing conditions. Moreover, stress and exercise led to different expression patterns both in WT and KO mice. Target analysis of DE miRNAs revealed genes associated with neurogenesis, glutamatergic signaling and the hypothalamic–pituitary–adrenal axis. Our sequencing data suggest that exercise and chronic treatment with corticosterone differentially influence miRNA expression in both WT and 5-HTT KO mice.
Conclusions
To follow up these findings, we plan to mimic the effects of these environmental interventions using oligonucleotide administration (antagomirs and mimics) to modulate miRNA levels in the brain and change affective behaviours and cognitive function in WT mice. We hypothesize that modulation of miRNAs will lead to altered levels of miRNAs and expression of their target genes and change relevant behaviours, thus mimicking the effects of exercise and stress. In addition, oligonucleotide therapy will be used to alleviate anxiety- and depression-like behaviours in 5-HTT KO mice.

The potential role of metabolic profiles in indicating treatment response after adjunctive N-acetylcysteine therapy in bipolar depression

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Background
N-acetylcysteine (NAC) has shown direct and indirect effects on neurogenesis, mitochondrial bioenergetics, inflammation and oxidative stress, which have been implicated in the pathophysiology of mood disorders. The prediction of treatment response in individuals with bipolar depression has been a major focus in the field. Previous studies have failed to address a) whether adjunctive NAC therapy could improve participants' social functioning and b) what biomarkers could predict such responses. We hypothesised that NAC could have a positive impact on social functioning and that metabolic profiles could indicate treatment responses.
Methods
60 participants (NAC n=31; placebo n= 29) with bipolar disorder and current depressive symptoms were enrolled in a 16-week, double-blinded, randomised controlled trial where participants were randomised to 2,000mg/day NAC in addition to treatment as usual or placebo. The primary outcome was change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to endpoint (ie. week 16). Social and Occupational Functioning Assessment Scale (SOFAS) and Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) were used to quantify level of social functioning. Metabolites were measured in plasma samples collected at baseline using semi-quantitative gas chromatography.
Results
We found that neither SOFAS nor LIFE-RIFT at baseline was associated with NAC treatment response (ie. MADRS scores) and no difference in both clinical scores was found between NAC responders (ie. difference in MADRS from baseline to endpoint >50%) and non-responders (<50%). Metabolomics analysis detected a total of 82 metabolites in the samples. Higher levels of some metabolites (mostly common protein breakdown products) at baseline were associated with worse social functioning at after the study endpoint, but the associations were non-significant after adjustment for multiple testing.
Conclusions
Our findings suggest that SOFAS and LIFE-RIFT were not affected by adjunctive NAC therapy and that the association between baseline metabolite levels and reduction in social functioning could be investigated further. We are currently exploring whether the level of C-reactive protein is associated with response to adjunctive NAC therapy and social functioning.

An imbalance of IgG receptors may contribute to the increased neuroinflammation seen in the midbrain of a sub-group of schizophrenia patients

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Background
There is growing evidence that neuroinflammation may contribute to schizophrenia pathology. Elevated proinflammatory cytokines are evident in the midbrain from schizophrenia subjects, and these findings are driven by a sub-group of patients, characterised as a
high inflammation
biotype. Cytokines trigger the release of antibodies, of which immunoglobulin G (IgG) is the most common. Testing whether IgG contributes to the neuroinflammatory abnormalities in this sub-group of schizophrenia patients may help direct novel treatment targets. Therefore, we measured IgG protein, IgG receptor transcripts, and IgG transporter levels in midbrain tissue from schizophrenia patients (both high- and low-inflammation biotypes) and healthy control subjects.
Methods
Post-mortem tissue was obtained from the NSW Tissue Resource Centre, and schizophrenia subjects were previously clustered into high- and low-inflammation (HI, LI) biotypes. All healthy controls were LI. Midbrain tissue was dissected from 60µm sections for qPCR and western blot. Immunofluorescence to label IgG and TH (a dopamine marker) was performed on adjacent 14µm sections. Semi-quantitative analysis determined levels of IgG in the nigra using mean fluorescent intensity (ImageJ). Three non-mutually exclusive cohorts were used: mRNA = 28 controls, 15 LI, 13 HI; western blot = 28 controls, 13 LI, 12 HI; immunofluorescence = 10 controls, 10 LI, 10 HI.
Results
Although the abundance of IgG protein in midbrain tissue homogenates was unchanged between groups, immunofluorescence analysis suggests a significant difference between diagnostic/inflammatory groups for levels of parenchymal IgG in the nigra ($p=0.03$). Additionally, mRNA levels of the pro-inflammatory IgG receptor FcGR3A were increased in the high inflammation biotype schizophrenia subjects (p<0.0001) in comparison to low inflammation patients and healthy controls. In contrast, mRNA levels of the anti-inflammatory IgG receptor FcGR2B were unchanged. Finally, gene transcript (but not protein) levels of the IgG transporter were elevated in high inflammation schizophrenia subjects ($p=0.02$), suggesting that there may be changes in transporter turnover.
Conclusions
Future work will quantify whether the anatomical distribution (as well as abundance) of IgG in the midbrain is altered between diagnostic and/or inflammatory groups. However, even if levels of IgG are comparable between groups, the imbalance between the pro-inflammatory FcGR3A and anti-inflammatory FcGR2B receptors suggests that high inflammation biotype schizophrenia patients may have an exaggerated response to IgGs. We will next determine whether this elevation in FcGR3A is specific to a certain cell-type, thereby providing critical information regarding the nature of this neuroinflammatory abnormality in a sub-group of schizophrenia patients.

Concurrent LI-rTMS induces changes in c-Fos expression but not behavior during a progressive ratio task with adult ephrin-A2A5-/- mice

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Background
Changes within the dopaminergic system induced by repetitive transcranial magnetic stimulation (rTMS) may contribute to its therapeutic effects; however, dopamine-related behavioral effects of rTMS have not been widely investigated. We recently showed that ephrin-A2A5-/- mice completed significantly fewer trials in a visual task than wildtype mice, and that concurrent low-intensity (LI-) rTMS during the task could partially rescue the abnormal behavior [Poh et al. 2018, eNeuro, vol. 5]. Here, we investigated whether the behavioral differences in ephrin-A2A5-/- mice are due to abnormal motivation, primarily a dopamine-modulated behavior, and whether LI-rTMS would increase motivation.
Methods
Ephrin-A2A5-/- and wildtype mice underwent 14 daily sessions of progressive ratio (PR) tasks and received either sham or LI-rTMS during the first 10 min. We stained for c-Fos in the prelimbic area (PrL), ventral tegmental area and nucleus accumbens (NAc) core and shell to examine neuronal activity from the final PR session.
Results
Ephrin-A2A5-/- mice responded more than wildtype comparisons, and LI-rTMS did not influence task performance for either strain. Therefore concurrent stimulation does not influence motivation in a PR task. However, ephrin-A2A5−/− mice did have abnormal performance in the PR tasks after a change in the PR schedule which suggests perseverative behavior. C-Fos expression for sham ephrin-A2A5-/- mice was lower in the PrL and NAc vs. wildtype mice. Ephrin-A2A5-/- mice that received LI-rTMS showed c-Fos expression closer to wildtype levels in the NAc.
Conclusions
Low c-Fos expression in the PrL and NAc and high PR performance compared to wildtype comparisons indicate that ephrin-A2A5−/− mice show an abnormal shift to habitual responding and LI-rTMS may attenuate this shift.

Measuring Cognitive Affective Bias in Rats Over Time

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Background
A major challenge in preclinical research into affective disorders such as depression is the validity of the tests used on animal models. Current tests, such as the forced swim test, remain controversial because they measure behaviours that are considered to have little relevance to human conditions. Recently developed cognitive affective bias (CAB) tests are thought to be much more valid measures of affective disorders as they are present in both humans and non-human animals. Although protocols have been developed to measure CABs in rodents, these have not been developed as repeated-measures tests, limiting their use in drug research and development.
Methods
Adult Sprague Dawley rats (4 males, 4 females) were trained to associate large and small rewards with scent, spatial and tactile cues. The CAB of the animal was determined by their choice of either a large (positive bias) or small (negative bias) reward in response to an intermediate (ambiguous) tactile cue. The assay was repeated at weekly intervals for 4 weeks to confirm task retention and stability of the CAB over time.
Results
Results showed that all rats acquired the task within 9 days. Males were quicker to learn the task, taking on average 6.5 days, while females took on average 8.5 days. In contrast to previous publications, all rats showed a positive CAB, by making significantly more positive reward choices than negative reward choices ($\chi 2=18.75$, p<0.001). In addition, performance and CAB remained stable over the 4 weeks of testing ($q=6.361$, $p=0.174$).
Conclusions
These results indicate that the repeated-measures adapted CAB assay is a stable measure of rodent affective states and has the potential to be used in affective disorder and novel drug research that utilises a repeated-measures design.

Sucrose intake in rats under a binge-type access schedule affected by both intraperitoneal oxytocin administration and time of day

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Background
Daily limited access to a palatable food or drink at a fixed time is commonly used in rodent models of bingeing. Under these conditions, entrainment may modulate intake patterns. Oxytocin is involved in circadian patterns of intake and when administered peripherally, reduces sucrose intake. However, oxytocin's effects on intake under limited-access conditions and its potential interaction with entrainment have not been explored. This study examined the role of entrainment on intake patterns, oxytocin's effects on sucrose intakes and locomotor activity and whether oxytocin's effects were mediated by its actions at oxytocin or vasopressin V1a receptors.
Methods
Sated rats received daily 1-h access to 10% sucrose solution either at a fixed or varied time of day. Rats received intraperitoneal oxytocin (0, 0.3, 1, 3 mg/kg) prior to sucrose access and spontaneous locomotor activity was assessed in an open-field test. Rats were then pre-treated with an oxytocin receptor antagonist, L368,899 or a vasopressin V1a receptor antagonist, SR49059 prior to oxytocin before sucrose access.
Results
Intake patterns did not differ between fixed- or varied-time presentations, rats consumed more sucrose solution in the middle as opposed to early dark phase. Oxytocin dose-dependently reduced sucrose intakes, but also reduced locomotor activity. There was some evidence of partial blockade of oxytocin-induced sucrose intake reductions by both L368,899 and SR49059, but results were unclear.
Conclusions
Time of day and oxytocin impact sucrose solution intake under daily limited access in rats, and the sedative-like effects of oxytocin should be considered in future studies on oxytocin and food intake

Chronic adolescent cannabidiol increases glutamatergic and GABAergic markers in the hippocampus of male Neuregulin-1 mutant mice

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Background
Schizophrenia can be caused by gene-environment interactions. Cannabidiol (CBD) is a non-psychoactive cannabinoid and has potential antipsychotic effects, however the molecular basis of CBD's antipsychotic effects are unclear. CBD is a positive allosteric modulator for γ-aminobutyric acid (GABA) A receptors and a negative allosteric modulator for CB1 receptors, and it is possible these neurotransmitter systems are altered by chronic CBD exposure. As adolescence is a potential window for therapeutic intervention in schizophrenia, we investigated long-term effects of adolescent CBD treatment on glutamate, GABA and endocannabinoid markers in the Neuregulin 1 transmembrane domain heterozygous (Nrg1 TM HET) mouse model of schizophrenia.
Methods
Male Nrg1 TM HET and wild type-like (WT) mice were treated daily with 30 mg/kg CBD or vehicle from postnatal day ~35 for 6 weeks. During the last 3 weeks of CBD treatment, animals underwent behavioural testing in schizophrenia-relevant behavioural domains (locomotion, exploration, social interaction, prepulse inhibition, fear-associated memory). The hippocampus was dissected out and snap frozen 24 hr after the last CBD injection. Tissue was analysed using western blotting for glutamate N-methyl-D-aspartate (NMDA, NR1 subunit), glutamate A1 receptor subunit (GluA1), glutamate-GABA decarboxylase enzyme GAD67, CB1 receptors, and fatty acid amide hydrolase (FAAH), an enzyme involved in anandamide metabolism.
Results
GluA1 protein levels were lower in Nrg1 mutant mice compared to WT mice when treated with vehicle. Importantly, adolescent CBD selectively increased expression of GluA1 in Nrg1 mutants only. In addition, another interaction showed GAD67 levels were increased in vehicle-treated Nrg1 mutants and CBD treatment reversed this back to WT levels. Nrg1 genotype and CBD did not affect CB1, NR1 or FAAH protein levels. Further markers are currently being analysed.
Conclusions
Nrg1 mutation increased levels of GAD67 in the hippocampus, suggesting there may be more glutamate-GABA conversion in this region. Nrg1 may also modulate the excitatory effects of CBD in this region, as CBD increases binding locations for glutamate and decreases the capacity for GABA synthesis in the hippocampus. As aberrant hippocampal activity is associated with dopaminergic dysregulation and is involved in the pathophysiology of schizophrenia, alterations to these systems by CBD may increase later symptom severity where Nrg1 mutation is present.

Poster 3-10

The behavioural and neural signature of impulsive actions in rodents

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Background
Impulsive actions are premature responses that do not achieve our goals and often lead to negative consequences. This should prevent them from being repeated, so why do impulsive actions persist? These experiments aimed to determine the behavioural and neural mechanisms that support impulsive actions.
Methods
To understand the associative learning processes supporting impulsivity, I combined a test of goal-directed control with a translationally relevant measure of impulsive action in Long Evans rats. I then used real-time in vivo calcium imaging in the nucleus accumbens core (NAcC) to compare activity during premature and correct responses on this task.
Results
Individuals with high levels of impulsivity had impaired goal-directed control and persisted in approach behaviour despite the omission of reward. Activity in the NAcC differs during responses preceded by sustained waiting compared to premature responses. Specifically, there was inhibition of the activity during waiting and a sharp response when the rat made a lever press and collected a reward. Premature presses did not show any of these features, despite requiring very similar patterns of movement.
Conclusions
These novel results suggest that impulsive actions occur when instrumental goal-directed control fails to suppress approach behaviour and that this is reflected in the inhibition of activity during waiting within the NAcC. Understanding the psychological and neural processes that support impulse control may help to unlock more effective treatment strategies that can reduce symptoms associated with impaired impulse control.

Correlations between value-based decision-making network connectivities and depression symptoms in developing individuals.

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Background
Impaired value-based decision-making, avolition and amotivation is characteristic of depression, possibly mediated via three brain-wide networks: the valuation (VS), executive control (ECS) and prospection (PS) systems. Understanding the correlation between network connectivity and depression symptoms can give insight into dysfunctional value-setting (VS), cognitive control (ECS) and future thinking (PS) that destabilizes the goal-directed, motivated pursuit of aims and rewards. We investigated VS, ECS and PS connectivity correlations with depression symptoms in developing individuals using the Philadelphia Neurodevelopment Cohort (PNC). Additionally, the valuation-control-prospection (VCP) complex (comprising the VS, ECS and PS as a single construct) was used to analyze inter-network connectivity.
Methods
VS, ECS, PS and VCP brain masks were delineated using Desikan-Killiany and Destrieux parcellations. The PNC was sourced for resting-state functional MRI scans from participants (n = 770, ages 10-18) with lifetime endorsement (present: 1; absent: 0) of four depression symptoms (DEP001, DEP002, DEP004, DEP006). VS, ECS, PS and VCP connectivity matrices were extracted from each participant and separately correlated with each of the four depression symptoms using the network-based statistic (NBS). Participant age, gender and framewise displacement were the other covariates used in this analysis. Multiple comparisons were controlled using the false discovery rate.
Results
DEP001 (Feelings of sadness or depression): ECS ($p = 0.001$, $r2 = 0.09$), PS ($p = 0.008$, $r2 = 0.57$) and VCP ($p = 0.01$, $r2 = 0.0378$) connectivity negatively correlated with DEP001. VS connectivity only correlated with DEP001 when ECS and PS networks present as a part of the VCP.
DEP002 (Excessive crying): PS connectivity ($p = 0.025$, $r2 = 0.727$) negatively correlated with DEP002.
DEP004 (Easily irritable, angry): VS connectivity ($p = 0.011$, $r2 = 0.33$) negatively correlated DEP004.
DEP006 (Avolition and amotivation): VS ($p = 0.007$, $r2 = 0.283$) connectivity negatively correlated with DEP006.
Conclusions
VS, ECS, PS and VCP connectivity negatively correlated with depression symptoms (DEP001, DEP002, DEP004 and DEP006). Increased connectivity may represent resilience against depression symptoms, focusing valuation (VS) and decision-making in a goal-directed manner (ECS) towards salient outcomes to achieve long-term goals (PS). The VS was only correlated with DEP001 as a part of the VCP. Connections within the VS and between the VS and other networks were only correlated with DEP001 when the ECS and PS were included, indicating that enhanced value-setting (VS) was intrinsically tied to elevated cognitive control (ECS) and future thinking (PS) in staving of DEP001.

Changes in functional activation in PTSD patients following cognitive behavioral therapy

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Background
Trauma-focused cognitive behavioral therapy (TF-CBT) is a frontline treatment for posttraumatic stress disorder (PTSD). However, 30-50% of patients do not respond to this treatment. Whilst many studies examine how neural biomarkers predict the outcome of TF-CBT in PTSD, fewer studies examine how neural changes occurring across treatment may reflect changes in PTSD symptoms. The current study examined changes in functional activation and connectivity from pre-treatment to post-treatment in three cognitive tasks.
Methods
27 PTSD patients and 21 controls completed a response inhibition task, an emotional face processing task, and a cognitive reappraisal task while neural data was recorded using functional magnetic resonance imaging. The PTSD group then underwent a 9-week course of trauma-focused cognitive behavioural therapy. Both groups repeated the tasks 12 weeks after the initial scans and changes in activation and connectivity across time were evaluated in relation to changes in PTSD symptom severity.
Results
For the emotional face processing task, increased activation in the left insula and decreased activation in the left hippocampus from pre-treatment to post-treatment was associated with a reduction in PTSD symptoms. A generalized psychophysical interaction (gPPI) found decreased connectivity between the right insula and left inferior frontal gyrus was associated with a reduction in PTSD symptoms, and that decreased connectivity between the left hippocampus and left amygdala was also associated with improvements in PTSD symptoms. For the cognitive reappraisal task, decreased activation in the left superior frontal gyrus across the two scans was associated with a reduction in PTSD symptoms.
Conclusions
Changes in fMRI responses reflecting PTSD symptom improvement were found in tasks involving an emotional component, however were not found in the purely cognitive response inhibition task. This may reflect alterations in emotional processing resulting from TF-CBT and could be a useful indication of treatment success in future.

Inflammation as a moderator of the relationship between obesity and white matter microstructure in bipolar disorder

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Background
Obesity is a leading comorbidity in bipolar disorder (BD), known to worsen functional and behavioural outcomes for those living with the disorder. Generally, obesity is characterised as an inflammatory condition, but its correlations with analogous biological substrates of BD, such as peripheral inflammation and altered white matter microstructure remain unknown. This study, therefore, aimed to examine the relationship between obesity and white matter microstructure in BD and determine if these associations were influenced by inflammation.
Methods
With an exploratory approach, 45 people with BD and 18 healthy controls underwent whole-brain diffusion tensor imaging, body mass index (BMI) assessment and plasma cytokine analysis of pro and anti-inflammatory profiles (C-reactive protein, tumor necrosis factor-, interferon-γ, interleukin-6 and interleukin-8, interleukin-4 and interleukin-10 respectively). Correlational analyses were used to study associations, with multivariate regression modelling applied to test interaction effects. In these models, BMI was specified as the primary predictor, the pro-inflammatory/anti-inflammatory profiles as the moderator, and white matter microstructural measures (fractional anisotropy, axial diffusivity, radial diffusivity and mean diffusivity) defined as the outcome.
Results
BMI and whole-brain white matter microstructure were not significantly correlated. No significant interactions between BMI and the proinflammatory profile upon white matter microstructure were detected. Increased BMI did, however, predict decreases in axial diffusivity, in BD participants with lowered concentrations of the anti-inflammatory profile.
Conclusions
The relationship between BMI and white matter microstructure in BD is complex, but the interplay between BMI and the anti-inflammatory cytokines, interleukin-4 and interleukin-10, upon axial diffusivity indicates the potential impacts of peripheral biology upon brain structure. Whilst this exploratory finding requires confirmation in larger cohorts, it points to the importance of considering physical health factors when exploring the pathophysiology of BD.

Development of chronotype in adolescence: implications for brain development and psychopathology.

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Background
A circadian preference for eveningness, a sleep-related behaviour characterized by late sleep and rise times, increases during adolescence. Although eveningness is cross-sectionally associated with internalizing and externalizing psychopathology, few studies have examined within-subject developmental changes in these parameters and their potential biological substrates. Here, we investigated the longitudinal relationships between the trajectory of eveningness preference, internalizing and externalizing psychopathology, and white matter development, across adolescence.
Methods
Two-hundred and seven adolescents (49% male) were assessed longitudinally at four separate time-points between 12 and 19 years of age. Internalizing and externalizing symptoms and preference for morningness/eveningness were assessed at each time point. Diffusion-weighted images were acquired on a subset of participants at the final two time-points to estimate changes in global mean fractional anisotropy (FA). Linear mixed models were performed to estimate the change in eveningness over time. A series of linear regression models assessed the influence of change in eveningness on psychopathology and white matter development at late adolescence.
Results
Across the sample, a preference for eveningness became more predominant by 19 years of age. A steeper slope towards eveningness significantly predicted greater severity in externalizing, but not internalizing, symptoms, at 19 years of age. In contrast, change in psychopathology from early to late adolescence did not predict eveningness at late adolescence. A change towards eveningness predicted an attenuated increase in FA across late adolescence.
Conclusions
This study suggests that developmental changes in sleep-related behaviour may influence both neurodevelopmental and psychological outcomes in adolescents.

Self-reported fatigue was associated with increased white-matter alterations in the long-term trauma survivors.

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Background
Fatigue is one of the major long-lasting side problems associated with both traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD), with a paucity of research investigating the possible associated neurological biomarkers. This study aims at investigating fatigue-related white-matter microstructure differences and their correlations in TBI and/or PTSD patients.
Methods
A total of 153 participants were scanned with diffusion tensor imaging as part of the Department of Defense-Alzheimer's Disease Neuroimaging Initiative, and were divided into four clinical groups including control veterans, PTSD, TBI, and TBI+PTSD. The existence of fatigue was defined by the question, Do you often feel tired, fatigued, or sleepy during the daytime? Tract-based spatial statistics was used to investigate ongoing fatigue related white-matter microstructure alterations in the different clinical groups.
Results
The results showed a significant increase of fatigue reported in the trauma survivors (p < 0.001), with 29.55% in the control veterans' group, 52.17% in the TBI group, 66.67% in the TBI+PTSD group, and 79.25% in the PTSD group reporting fatigue. No white-matter alterations were observed in either the control or TBI groups due to fatigue. Compared to those without fatigue, the fatigued TBI+PTSD patients showed reduced fractional anisotropy and increased diffusivity measures, while the fatigued PTSD patients only showed increased diffusivity measures.
Conclusions
The current results suggest fatigue to be significantly reported in trauma survivors decades post-trauma, and this was associated with the observed white-matter alterations in the TBI+PTSD and PTSD goups. This might suggest that developing PTSD might increase the prevalence of developing fatigue and its underlying alterations of the white-matter tracts.

Transcriptomic and polygenic manifestations of cortical thickness heterogeneity in schizophrenia

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Background
Brain morphology differs markedly between individuals with schizophrenia, but the cellular and genetic basis of this heterogeneity is poorly understood. Here, we sought to determine whether cortical thickness (CTh) heterogeneity in schizophrenia relates to differences in interregional profiles of neural cell types, as inferred from established gene expression data and person-specific genomic variation.
Methods
This study comprised 1849 participants in total, including a discovery (140 cases and 1267 controls) and a validation cohort (335 cases and 185 controls). To characterise CTh heterogeneity, normative ranges were established for 34 cortical regions and the extent of deviation from the ranges was measured for each individual with schizophrenia. Spatial associations between regional CTh deviations and gene expression profiles of neural cell types were used to stratify patients into cell-based subtypes. Subtypes were validated using genomic profiles.
Results
Deviations from normative ranges of CTh were explained by gene expression profiles of five neural cell types: 1) astrocytes; 2) endothelial cells; 3) oligodendrocyte progenitors (OPC); 4) excitatory; and 5) inhibitory neurons. Clustering individuals with schizophrenia based on associations between individual CTh deviations and gene expression profiles distinguished broad cell-based subtypes, which were validated against person-specific genomic variation. In a neuronal subtype (22%), CTh deviations covaried with polygenic risk for schizophrenia (sczPRS) constrained to neuron-linked genes (r=-.40, FDRp=0.009). Whereas, in a mixed astrocyte and OPC subtype (43%), cortical deviations covaried with sczPRS constrained to astrocyte- and OPC-linked genes (r=-.30, FDRp=0.028).
Conclusions
Improving cell type-specific characterisation in schizophrenia facilitates neurobiological interpretation of large-scale MRI phenotypes and may help to prioritise schizophrenia subsets for patient-based disease modeling efforts.

Modulation of the parvalbumin interneuron activity rescues PTSD-like memory formation in autism spectrum disorder.

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Background
Autism Spectrum Disorder (ASD) is not only characterised by deficits in social interactions and increased repetitive movements, but also hypersensitivity to stress. Recent studies in humans have posited a co-occurrence of ASD with Post-Traumatic Stress Disorder (PTSD), a condition resulting from altered memory of a highly stressful event. Yet, the connection between ASD and PTSD remains to be established.
Methods
We exposed two mouse models of ASD – the Contactin-associated protein-like 2 knockout (Cntnap2 KO) and Phosphatase and tensin homolog knockout (Pten cKO) mice – to contextual fear conditioning combined with a 30min-restraint stress. We then optogenetically manipulated the prefrontal cortex during learning and analysed the electrophysiological properties of Parvalbumin interneurons.
Results
Following a single episode of mild stress, Cntnap2 KO and Pten cKO mice formed a pathological memory, which recapitulated all features of PTSD. Remarkably, developing traumatic memories resulted in the exacerbation of the core autistic traits. Furthermore, hyperactivation of the prefrontal cortex was causal to the development of PTSD in stressed Cntnap2 KO mice, and mediated by a deficit in the activity of the parvalbumin interneurons. Specifically, we found a stress-induced shift in parvalbumin interneurons excitability in Cntnap2 KO mice, likely underlying the PFC hyperactivation leading to pathological memory formation.
Conclusions
Given the dramatic impact of PTSD on the severity of the autistic traits, our study, drawing from animal models, highlights the need to consider the sequalae of stress exposure within ASD symptomatology. Furthermore, we provide a therapeutic approach for PTSD-like memory through a behavioural therapy, which also successfully reduces autistic traits. Finally, targeting parvalbumin interneurons of the PFC represents a major therapeutic strategy that could ultimately lead to a better management of the ASD condition.

Sex differences in how metabotropic glutamate 5 receptors modulate morphine reward

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Background
Globally, opioid addiction causes significant health, social and economic costs. Men report a higher lifetime use of opioids; however, women are more likely to relapse during abstinence. Current treatments are limited and do not address biological processes involved in addiction. The metabotropic glutamate 5 receptor (mGlu5) receptor is a potential target for treating addiction. Mice with a genetic deletion (i.e. knockout, KO) of mGlu5 exhibit addiction-like behaviour for psychostimulants and ethanol, but their response to opioids has yet to be examined. Assessing opioid addiction-like behaviour in these mice will determine if mGlu5 could be a treatment target for opioid abuse.
Methods
Here we assessed the effects of morphine conditioned place preference (CPP), which measures opioid reward, in mGlu5 KO mice. Male and female mGlu5 KO and WT mice were conditioned to associate 5 mg/kg morphine with a distinct environment over 4 consecutive days. Following conditioning, preference for the morphine-paired environment (i.e. time spent in the morphine environment) was assessed weekly for 4 weeks during abstinence from morphine, to test the persistence of morphine memory. Persistent preference during abstinence is an indicator of drug craving and risk of relapse. Locomotor data was collected during all conditioning and test sessions.
Results
mGlu5 modulated morphine reward in a sex-specific manner. Male WT mice displayed a persistent preference during abstinence compared to male mGlu5 KO mice. In contrast, female mGlu5 KO mice showed a persistent preference compared to WT females. This suggests mGlu5 increases morphine reward in males and decreases it in females. Morphine administration increased locomotor activity in all WT mice, but acute morphine decreased locomotion in all mGlu5 KO mice. This suggests that mGlu5 receptors decrease sensitivity to morphine-induced locomotion.
Conclusions
There were opposing effects of genotype in each sex for persistence of morphine preference. These results suggest that male mGlu5 KOs are less susceptible to morphine reward than WTs, but female mGlu5 KOs are more susceptible to morphine reward than female WTs. mGlu5 KOs, regardless of sex, are less sensitive than WTs to morphine-induced locomotion, suggesting that morphine reward and locomotion are mediated by different pathways. These results suggest that sex plays a role how mGlu5 modulates addiction-relevant pathology. Future investigations should identify potential mechanisms for the impact of sex on mGlu5 mediation of morphine reward and morphine-induced locomotor activity.

Developmental vitamin D deficiency is associated with impaired adolescent social behaviour and altered gut microbiota in rats

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Background
Vitamin D deficiency during pregnancy, also known as developmental vitamin D (DVD)-deficiency and early neonatal life, is an epidemiologically recognized risk factor of autism. The mounting studies have also begun to show an association of altered gut microbiota with the severity of autism and impaired social behaviour in animal models. Studies have also demonstrated the impact of vitamin D deficiency on gut microbial composition and gut physiology. This study aimed to examine the effect of vitamin D-deficiency during early life on adolescent social behaviour and gut microbial population.
Methods
Our protocol of producing DVD-deficiency involves placing female Sprague-Dawley rats on vitamin D-deficient or control diets before mating (for six weeks), during pregnancy to the birth of pups and up to the postnatal day 35 (P35). At P35, the adolescent rats were assessed for their social play behaviour. After the social play behaviour, the animals were euthanized, gut tissues and colon contents (faecal samples) were collected for the examination of gut histology and 16s amplicon sequencing, respectively.
Results
Our results show that adolescent social behaviour measured by the frequency of pouncing and pinning was reduced in DVD-deficient animals compared with control animals. The histological examination of the jejunal sections showed that villi length was found to be shorter in DVD-deficient animals. Sequencing of the microbial DNA from the colon contents of the adolescent animals showed significant differences in alpha diversity (Pielou's evenness index) and beta diversity (Jaccard distance, Bray-Curtis distance, and Unifrac distance) between DVD-deficient and control animals.
Conclusions
We conclude that Vitamin D deficiency during early life results in alteration of adolescent social behaviour and changes in the composition of the gut microbial population. However, several other factors such as maternal care could also be implicated in the adolescent social behaviour and altered gut microbiota, which need further examination through cross-fostering and gut microbiota transplantation experiments.

Cannabidiol alleviates opioid withdrawal but worsens the development of tolerance to the analgesic effects of opioids

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Background
Amidst the COVID-19 pandemic, opioid overdose deaths have now risen to 250 per day in the United States. The time is now for investigations into new medications for opioid use disorder. A key player in the development and maintenance of opioid use disorder is physical dependence, characterised by the acquisition of tolerance to the analgesic effects of opioids and withdrawal upon cessation of drug use. Emerging evidence suggests a potential role of cannabis for opioid use disorder. However, the current panacea-like view of cannabinoids is problematic given the lack of systematic pre-clinical or clinical studies exploring their efficacy.
Methods
We explored the efficacy of chronic co-administration of cannabidiol (CBD) with oxycodone for the prevention of opioid withdrawal and tolerance to the analgesic effects of opioids in mice. To elicit opioid withdrawal, mice received escalating doses of oxycodone twice daily for 9 days, then underwent a 24hour abstinence period followed by an examination of gastrointestinal, somatic, and negative affective symptoms of opioid withdrawal. To examine opioid tolerance, we administered a consistent dose of oxycodone twice daily over 5 days, followed by tests of thermal pain sensation. CBD was administered prior to each oxycodone injection, excluding test day.
Results
We discovered that chronic co-administration of CBD alongside oxycodone dose dependently inhibited the emergence of opioid withdrawal-induced jumps, an escape behaviour thought to be caused by dysphoria experienced during withdrawal. Surprisingly, CBD co-administration accelerated the development of tolerance to the analgesic effects of oxycodone.
Conclusions
Genetic studies are underway examining the effect of CBD on the expression of genes that code for key receptors involved in the development of opioid tolerance. My findings provide crucial information about the contexts and aspects of opioid addiction for which particular cannabinoids may be beneficial, or indeed, detrimental.

Therapeutic potential of cannabidiol during abstinence from cocaine

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Background
Cocaine addiction is a global health problem with no approved pharmacotherapies. Cannabidiol (CBD) has potential as a pharmacotherapy for cocaine abuse as it has been found to have anti-addiction like properties that can combat relapse risk states in animal models of addiction. While research has shown promising effects of CBD on some cocaine addiction-like behaviours e.g. cocaine reward, cue-induced relapse; there has been no research on how CBD affects abstinence from cocaine.
Methods
This study examined how 10 mg/kg CBD administered during abstinence affected memory of a cocaine-associated environment, using a conditioned place preference (CPP) paradigm. C57BL/6 mice learned to associate 15 mg/kg cocaine with a specific environment across four days, and their preference for the cocaine-paired environment was established at Test. In the following 21 days, mice received daily CBD/vehicle (VEH) injections during home cage abstinence to determine if CBD impaired cocaine reward memory. Preference tests were conducted 7, 14 and 21 days into abstinence. Locomotor data was collected throughout testing.
Results
CBD-treated mice showed a persistent preference for a cocaine-paired environment compared to VEH-treated mice, suggesting CBD facilitated cocaine preference during abstinence. No differences were found between treatment groups for locomotor activity, suggesting that CBD does not affect locomotor activity in a drug-associated environment. We are currently examining protein levels of cannabinoid receptor type 1 (CB1), ionized calcium binding adaptor molecule 1 (IBA1) and N-Methyl-D-aspartic acid (NMDA) in the striatum and hippocampus, to determine molecular mechanisms governing how CBD mediates cocaine memory during abstinence.
Conclusions
This study shows that 10 mg/kg CBD increases persistence of cocaine reward memory compared to VEH-treated controls. This suggests CBD administered during abstinence may not have therapeutic potential. Our findings contrast with previous literature demonstrating therapeutic effects of CBD for cocaine abuse when CBD is administered during acquisition, extinction and prior to reinstatement. Further investigation of CBD's effects on protein expression in addiction-relevant brain regions will help determine why CBD caused cocaine memory to persist in abstinence.

Investigating the Role of Direct and Indirect Spiny Projection Neurons in the Transition to Habits

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Background
Action selection is thought to be governed by two separate systems – a goal-directed system and a habit system. Both systems work together, but play different roles in achieving normal and efficient expression of behavior. In particular, the goal-directed system allows the animal to select actions that are aligned with its current motivations, and the habit system allows an animal to gain efficiency through automaticity. These two systems are governed by two distinct cell populations within the striatum - the direct and indirect spiny projection neurons (SPNs), whose roles are not fully understood for their involvement in these systems.
Methods
We use a well-established behavioral training paradigm whereby rats learn to press a lever for food reward and the outcome-devaluation test to assess if behaviour is habitual or goal-directed. Concurrently, we use an imaging technique known as fibre photometry to record from population dSPNs or iSPNs within the striatum across different stages. To do this, we inject a Cre-dependent virally expressed genetically encoded calcium indicator into the striatum within a D1-Cre or A2a-Cre rat to target either the dSPN or iSPN population, then insert and secure an optic fiber in the target region that is externally connected to allow imaging.
Results
We have found that with extended training, rats begin to respond habitually on the lever even for food rewards and display insensitivity to outcome-devaluation. Moreover, we have demonstrated a capability to record from the dSPNs while the animal is learning a normal habit and during the outcome-devaluation test within the operant chamber. We compare cell activity surrounding different events such as a lever press, across different stages of learning and crucially, between early training (where behaviour is deemed goal-directed) and late training (where behaviour is subsequently deemed habitual).
Conclusions
By studying the neural population activity of these two SPN populations across goal-directed and habitual stages of responding for a reward, we hope to gain an increased understanding of their role in these two systems that are involved in habit and learning. In the near future, we will also study the effect of cocaine on these two populations that govern these two systems, as we expect that cocaine will act on these two populations within the dorsal medial and dorsal lateral striatum to accelerate the transition to habits.

Modulation of Aperiodic Neural Activity Following Convulsive Therapy in Patients with Major Depressive Disorder

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Background
Electroconvulsive therapy (ECT) and magnetic seizure therapy (MST) are effective device-based interventions for treatment-resistant major depressive disorder (MDD). However, understanding of their mechanism(s) of action remains incomplete. Despite being previously disregarded as noise, emerging evidence is beginning to highlight the physiological significance of aperiodic (i.e., non-oscillatory) '1/f-like' activity within neural field recordings, which has recently been linked to excitation-inhibition (E:I) balance within cortical circuits, neuronal population spiking, and cognitive performance. Here, we utilised resting-state electroencephalographic (EEG) recordings to examine the effects of ECT and MST on aperiodic components of the neural power spectrum.
Methods
Resting-state EEG was analysed from a total of 44 patients with treatment-resistant MDD undergoing an acute course of either ECT (n=23; mean no. treatments=13.87, SD=5.32) or MST (n=21; mean no. treatments=21.19, SD=5.12). In addition, baseline data were also collected from 22 healthy controls (HC). Power spectra were computed using Welch’s method and the data were then parametrized into periodic and aperiodic components using the Fitting Oscillations and One over f (FOOOF) algorithm, following which the aperiodic exponent and offset components were extracted for further analysis.
Results
No differences in aperiodic activity were observed between the ECT, MST and HC cohorts at baseline (p> .05). However, following the course of treatment, exponent and offset were found to be enhanced for both the MST and ECT cohorts, when compared to pre-treatment baseline values (all p< .05; i.e., steeper aperiodic slope and greater offset following treatment). Exponent and offset were also larger in patients who received ECT, compared to MST (all p< .05). Finally, we also observed a positive association between the number of ECT treatments received by each patient and the accompanying change in aperiodic offset (r=.48, p=.02).
Conclusions
These findings highlight the ability for convulsive therapies to modulate aperiodic neural activity in patients with TRD. This extends past EEG research which has shown changes in oscillatory dynamics following these therapeutic interventions. Importantly, given recent evidence highlighting the aperiodic exponent as a potential non-invasive index of E:I balance, these results further provide tentative support for a global reduction in E:I ratio within cortical circuits following convulsive therapies.

Temporal and spatial perception of heartbeat sensations in Autism Spectrum Conditions

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Background
The link between interoceptive ability and Autism-Spectrum Condition (ASC) is an ongoing debate, with studies showing varying levels of interoceptive ability in ASCs, relative to neurotypical populations. It is hypothesised, however, that co-morbid alexithymia drives the reduce interoceptive ability, rather than autism itself.
Methods
Using an interoceptive Method of Constant Stimuli (MCS) task, we investigated the difference in heartbeat perception between ASC (N = 52; 35.3 +/- 12.76 years) and neurotypical (N = 56; 30.84 +/- 12.82 years) participants, both categorically and along a transdiagnostic spectrum of alexithymia.
Results
Our results revealed significant group differences across all subclinical measures, but no difference in task performance in terms of precision, heartbeat timing judgement, nor perceived bodily location of heartbeat sensation. We found limited evidence to support a negative correlation between alexithymia and task performance across both groups.
Conclusions
This study suggests that ASC, as a diagnosis, does not necessitate altered interoceptive ability, and that a more nuanced approach in investigating interoception in this population is needed.

Comorbid antisocial personality disorder predicts age of onset of methamphetamine use in people with methamphetamine use disorder

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Background
Methamphetamine is the second most widely abused illicit drug worldwide and represents one of the greatest health threats. More alarming, methamphetamine use typically begins early in life, and over 4% of Australians aged 14-19 have reported using methamphetamine in a given year. This is a major concern as adolescence is a period of heightened vulnerability to substance use disorders. Evidence suggests comorbid psychiatric disorders and cognitive deficits may be contributing factors. We therefore investigated the association between the age of onset of methamphetamine use, psychiatric comorbidities and cognitive performance in people with methamphetamine use disorder.
Methods
We recruited forty people currently using methamphetamine (last use within 7 days) with a DSM-5 diagnosis of stimulant use disorder, methamphetamine-type (moderate or severe). Participants were first administered demographic and drug use questionnaires. They were then administered the MINI International Neuropsychiatric Interview and the Positive and Negative Syndrome Scale interview to assess psychiatric comorbidities, followed by a cognitive task battery assessing speed of processing, cognitive flexibility, working memory, and inhibitory control. A hierarchical multiple regression was conducted to assess whether these factors could predict age of onset of methamphetamine use after controlling for significant demographic variables (i.e. age at test).
Results
Mann-Whitney U tests revealed that people with comorbid antisocial personality disorder started using methamphetamine earlier in life (U=47.50; p<0.001). Inhibitory control performance was also positively associated with age of onset (r=0.432; p=0.011). These variables were therefore entered in the hierarchical regression. The regression revealed that age a test alone explained 28.8% of the variation in age of onset. Addition of antisocial personality disorder diagnosis explained a further 26.1% of the variance, and was a significant predictor of age of onset (β=-0.477; p0.05), and was not a significant predictor (β=0.235; p=0.063).
Conclusions
Our results add to the growing body of literature showing that poor inhibitory control may be associated with earlier age of onset of methamphetamine use. This study also provides further evidence that comorbid diagnosis of antisocial personality disorder is one of the strongest predictors of early onset methamphetamine use. Early interventions in youth at risk of developing methamphetamine use disorders should therefore target these factors. This can be achieved by trialling new psychosocial and/or pharmacological interventions aimed at improving executive functions, and implementation of dual diagnostic treatment streams for young people presenting with personality disorders and co-occurring methamphetamine use problems.

Improving rTMS protocols: Translation from preclinical models to clinical trials targeting depression

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Background
Daily repetitive Transcranial Magnetic Stimulation (rTMS) at 10 Hz is FDA approved for treatment-resistant depression (TRD), however only approximately 30% of patients reach full remission of symptoms under the current protocol. Both the human and animal literature has suggested that this technique still has scope for improvement, with much still unknown about the underlying mechanisms driving the treatment response. Here we outline our bench-to-bedside translational approach: we have identified effective stimulation parameters in preclinical animal models of depression and implemented these evidence-based protocols in a clinical trial involving patients with major depressive disorder.
Methods
We have used two preclinical rodent models of depression to identify optimal stimulation parameters. In a mouse olfactory bulbectomy model of depression, we compared three different rTMS intensities and measured behavioural and neurobiological outcomes. In separate experiments, we used a chronic stress model in rats to study the effect of different rTMS frequencies in rodents of different peri-adolescent ages. Following this, we then implemented a clinical trial (trial number: ACTRN12618001889246) investigating the effectiveness of an altered rTMS intensity in adult patients with TRD.
Results
The olfactory bulbectomy study provided evidence that medium-intensity rTMS (50mT at the cortical surface; 5% of motor-threshold) had long term effects on the brain by increasing neurogenesis. This result was then translated to the ongoing clinical trial investigating the effectiveness of an add-on MI-rTMS treatment, with patients recruited from Sir Charles Gairdner Hospital Mental Health Unit. Severity of clinical symptoms is being determined at baseline, post-treatment, and at a 6 month follow-up to specifically investigate long-term outcomes. Investigations in the rat model are still ongoing but have already identified that young rats respond differently to rTMS compared to adult rats.
Conclusions
Our findings provide evidence to support the use of medium-intensity rTMS to treat depression in human patients, with the current translational approach providing a pathway for the future examination of additional protocol improvements. Furthermore, our bedside - to bench - to bedside approach will include a biomarker exploration in rodents and patients, leading to potential for prognostic and diagnostic innovation. Our preclinical program allows direct investigation of tailored approaches to age and condition, which will inform the development of effective and fast-acting treatment outcomes for individual patients.

Refining a protocol for at-home salivary lithium monitoring

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Background
Lithium prophylaxis has a narrow therapeutic window, necessitating frequent blood tests to regulate the dose. We recently showed that salivary and serum lithium levels are highly correlated (Parkin et al, medRxiv preprint), suggesting that saliva may be a viable alternative to blood for lithium monitoring. As saliva can be self-collected by patients, at-home collection may reduce the need for pathology clinic visits. This study investigated the diurnal variation of salivary lithium levels, as well as the effect of days left at room temperature, to determine factors which may affect readout accuracy, such as time of collection and postage of samples.
Methods
Individuals 65 years and under on lithium medication were recruited from the University of California Irvine Medical Center, and the Veterans Affairs San Diego Mood Disorders Clinic, University of California San Diego. Five saliva samples collected via the passive drool method as part of our parent study were aliquoted, and aliquots were left at room temperature for 0 – 4 days. Participants were also invited to collect saliva samples at home across one 24-hour period, staggered on either side of their usual lithium dose time. Salivary lithium levels were analysed using Inductively-Coupled Plasma Optical Emission Spectrometry.
Results
Salivary lithium levels were not affected by up to 4 days at room temperature (treatment effect p>0.50, intra-subject coefficient of variation: 1.3% - 2.4%). Qualitatively, patient salivary lithium levels displayed a peak following each dose, which returned to pre-dose levels after 12 hours. Only one patient provided saliva samples between 2- and 12- hours post-dose, which showed a salivary lithium level peak at 5- hours post-dose.
Conclusions
These data show that diurnal salivary lithium levels have a 12-hour decline similar to those seen in blood, with a possible peak at 5 hours. As salivary lithium levels were not affected by ≤4 days at room temperature, it will be possible for patients to mail in samples for testing, without impacting the accuracy of the lithium level readout. Further investigation into levels 2-12 hours post-dose, and the potential impact of health and lifestyle factors, such as sleep cycle, food intake, caffeine, smoking, and other medications, will allow us to refine a protocol for at-home saliva collection for lithium monitoring.

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Guide to numbering

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	Tuesday S2, S3,
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Note: reference numbers refer to abstract number, not page number. (*) indicates speaker/presenter.

List of BPA annual scientific meetings

2010	Society Launch at the Royal Society of Victoria, Melbourne
2011	1st meeting at the Melbourne Cricket Ground, Melbourne
2012	2nd meeting at the Melbourne Brain Centre, Melbourne
2013	3rd meeting at the Queensland Brain Institute, Brisbane
2014	4th meeting at the Monash Alfred Psychiatry Research Centre, Melbourne
2015	5th meeting at the Coogee Bay Hotel, Sydney
2016	6th meeting at Noahs on the Beach, Newcaslte
2017	7th meeting at the Novotel, Wollongong
2018	8th meeting at the South Australian Medical Research Institute, Adelaide
2019	9th meeting at the Florey Institute, Melbourne
2020	10th meeting hosted by Neuroscience Research Australia, Sydney (Whova)
2021	11th meeting hosted by the Queensland Brain Institute, Brisbane (Whova)

We look forward to seeing you at the 12th Annual Scientific Meeting of Biological Psychiatry Australia in late 2022 in Newcastle, NSW.

Please check http://www.biolpsychaustralia.com.au/ for details as they are released.