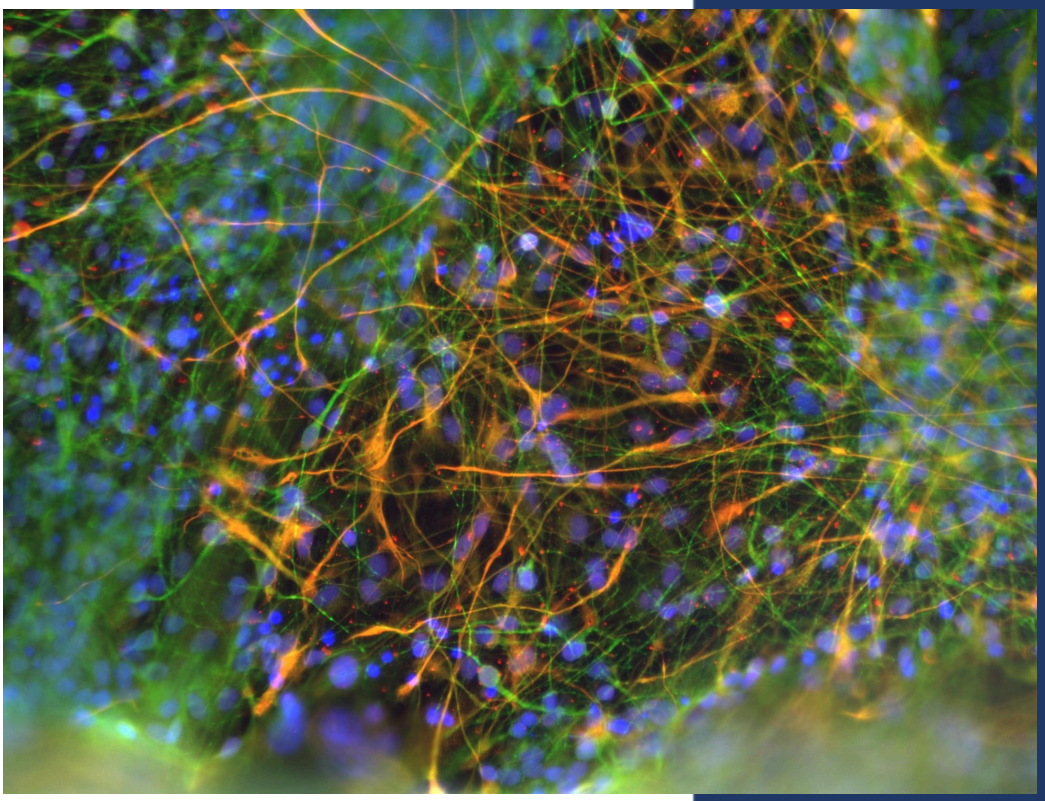
Biological Psychiatry AUSTRALIA

2025



Proceedings of the Biological Psychiatry Australia Scientific Meeting 2025

The Florey
Advancing Brain Research

THEDAXCENTRE

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Enabling precision medicine

Welcome

The 15th Biological Psychiatry Australia Scientific Meeting

26th – 28th October 2025

Dear Friends and Colleagues,

On behalf of the Local Organising Committee, we warmly welcome you to the 15th Annual Biological Psychiatry Australia 2025 (BPA 2025) Scientific Meeting. This year we are back in Melbourne, and we are excited to meet at the Florey Institute in the heart of the University of Melbourne.

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

LOC Co-Chairs: Dr Leigh Walker and Dr Alexandre Guérin

Local Organising Committee: Leigh Walker, Alex Guérin, Tertia Purves-Tyson (President)**,** Roberta Anversa (Treasurer), Carol Gubert (Treasurer) Rachel Hill, Eveline Mu, Elizabeth Haris, Sid Chopra, Georgia Caruana, Vanessa Cropley, Bruna Panizzutti, Lauren Ursich, Catherine Huang, Xavier Maddern, Claire Foldi, Kyna Conn, Sevil Ince

Stay connected with our social media accounts:

Bluesky: @biolpsychaust.bsky.social

Twitter: @biolpsychaust @BPA_ECRN

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

Cover Image by Dr. Bruna Panizzutti Parry

Contents

Acknowledgement of Country

Biological Psychiatry Australia acknowledges the Traditional Owners of the unceded land on which this meeting is taking place: the Wurundjeri Woi Wurrung and Bunurong peoples. We also acknowledge and are grateful to the Traditional Owners, Elders and Knowledge Holders of all Indigenous nations and clans who have been instrumental in our reconciliation journey.

We recognise the unique place held by Aboriginal and Torres Strait Islander peoples as the original owners and custodians of the lands and waterways across the Australian continent, with histories of continuous connection dating back more than 60,000 years. We also acknowledge their enduring cultural practices of caring for Country.

We pay respect to Elders past, present and future, and acknowledge the importance of Indigenous knowledge.

BPA Equity 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, socioeconomics, sexuality, religion, or any other attribute.

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, socioeconomics, sexuality, religion or any other attribute, 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	Tertia Purves-Tyson	Neuroscience Research Australia
Vice-president	Rachel Hill	Monash University
Secretary	Yann Quidé	University of New South Wales
Treasurers	Carol Gubert	Florey Institute of Neuroscience and Mental Health
	Roberta Anversa	Florey Institute of Neuroscience and Mental Health
Webmaster	Lauren Harms	University of Newcastle
ECRN Rep	Samara Walpole	University of Wollongong
Committee members		
	Sarah Cohen-Woods	Flinders University
	Vanessa Cropley	University of Melbourne
	Alexandre Guérin	University of Melbourne
	James Kesby	University of Queensland
	Natalie Matosin	University of Sydney

ECRN Committee

Chair	Samara Walpole	NSW	University of Wollongong
Deputy Chair	Sevil Ince	VIC	University of Melbourne
Secretary	Elizabeth Haris	VIC	University of Melbourne/Orygen
Treasurer	Helen Clunas	NSW	University of Wollongong
Social Media	Juliana Lys de Sousa Alves Neri	NSW	University of Wollongong
	Xavier Maddern	VIC	University of Melbourne/Florey Institute of Neuroscience and Mental Health
Awards subcommittee	Eveline Mu	VIC	Monash University
	Lucy Zhang	VIC	University of Melbourne
	Hollie Byrne	NSW	University of Sydney
	Sidhant Chopra	VIC	University of Melbourne/Orygen
Webinar subcommittee	Emiliana Tonini	NSW	University of Sydney
	Katrina Edmond	NSW	University of Wollongong/University of Sydney
	Jordan Clark	VIC	University of Melbourne
Mentoring subcommittee	Cassie Ma	NSW	University of New South Wales
	Shrujna Patel	NSW	University of Sydney

Society Profile

Scientific Review Committee Chairs: Christina Perry & Robyn Brown

Agustin Cota Coranado, Andrew Gibbons, Anthony Hannan, Ariel Dunn, Aron Hill, Bruna Panizzutti, Claire Foldi, Conor McDonnell, Darryl Eyles, Dylan Kiltschewskij, Elizabeth Haris, Ellen Towers, Elysia Sokolenko, James Kesby, Jamila Iqbal, Jen Cornish, Kyna Conn, Laura Milton, Lauren Harms, Lena Oestreich, Lucy Zhang, Luke Ney, Maria Di Biase, Marta Rapado-Castro, Monokesh Sen, Morgan James, Natalie Matosin, Philip Jean-Richard-dit-Bressel, Anthony Hannan, Rachel Hill, Roberta Anversa, Roger Bitencourt Varela, Samara Walpole, Sarah Cohen Woods, Sylvia Lin, Tertia Purves-Tyson, Tim Karl, Trang Truong, Trevor Steward, Ulysse Thivisol, William Reay, Xavier Maddern, Xiaoying Cui, Yann Quidé

Annual Award Presentations

Isaac Schweitzer Lecture

2010	-
2011	-
2012	-
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
2022	Jayashri Kulkarni
2023	Suresh Sundram
2024	Colleen Loo
2025	Alex Fonito

Aubrey Lewis Award

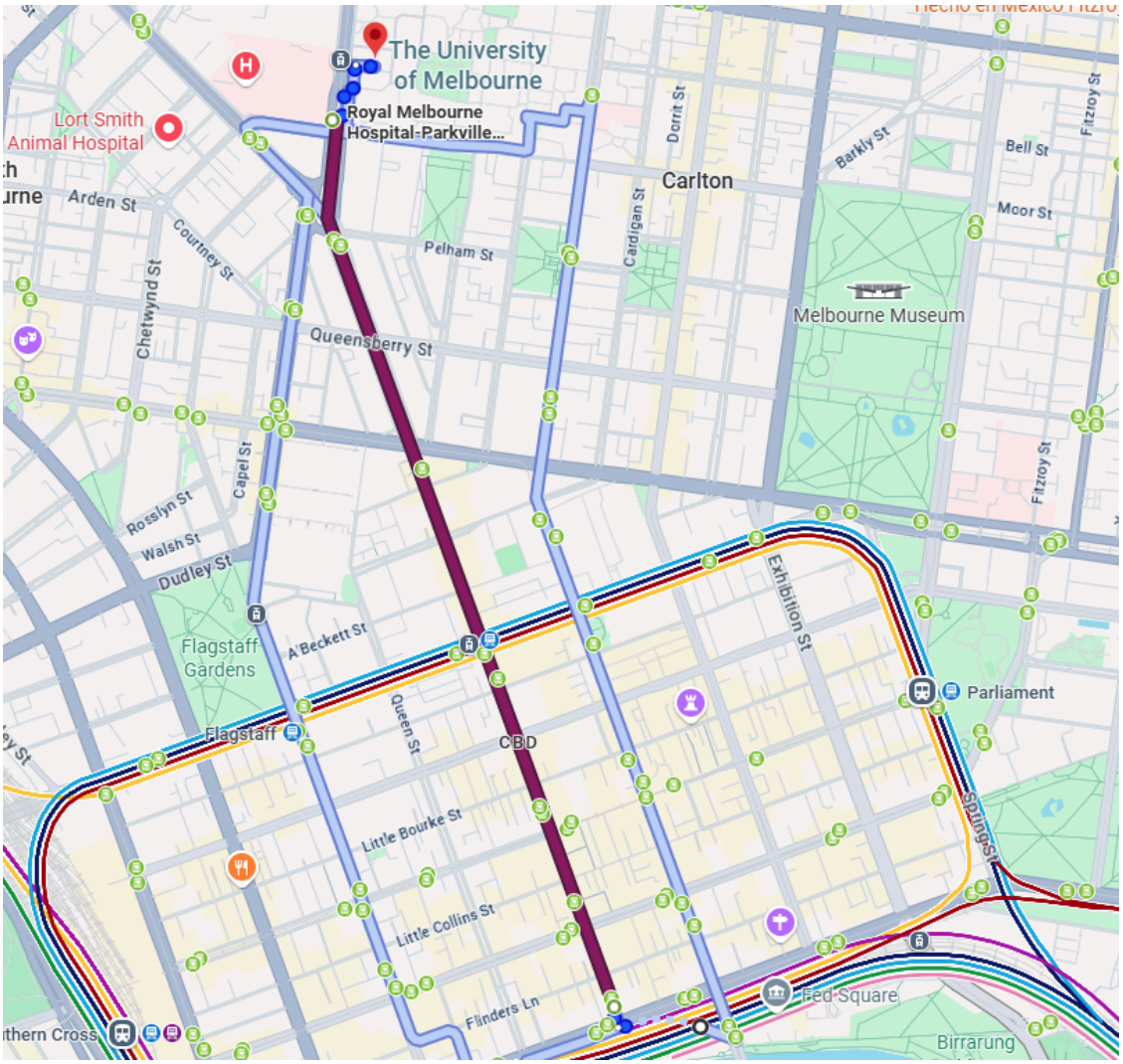
2010	Mark Bellgrove
2011	Melissa Green
2012	Andrea Gogos
2013	Michael Breakspear
2014	Adam Guastella
2015	Irina Voineagu
2016	Andrew Zalesky
2017	Jee Kim
2018	Rachel Hill
2019	Marta Garrido
2020	Bronwyn Graham
2021	Lianne Schmaal
2022	Robyn Brown
2023	Wolfgang Marx
2024	Melissa Sharpe
2025	Natalie Matosin

ECRN Excellence Plenary

2021	Divyangana Rakesh
2022	Luke Ney
2023	Alexandre Guérin
	Cassandra Wannan
2024	Xavier Maddern
	Sidhant Chopra
2025	Georgia Caruana
	Nicola Acevedo

Venue Information

The main conference venue for Sunday 26 to Tuesday 28 October is **the Florey Institute of Neuroscience and Mental Health**, with Monday evening's social event held at the **Clyde Hotel in Carlton (385 Cardigan St)**, a short walk from the Florey).



The Florey is located on the University of Melbourne main campus in Parkville, only a few minutes from the centre of Melbourne. It has many public transport stops within walking distance. To get to the Florey from the city, the 19 tram headed to North Coburg is the fastest option (Stop 11; University of Melbourne/Royal Parade). We recommend staying in one of the many accommodation options in the city or surrounding the University main campus.

To take the tram or any public transport in Melbourne and Victoria, use a Myki card, available in Google Wallet or purchasable at any major train station and 7/11. Note that Apple Wallet does not support e-Myki and iPhone users will need to purchase a physical Myki.

For more information about Public Transport and tram/train schedules, visit the Public Transport Victoria Journey Planner website.

Program at a Glance

Sunday 26 October	
The Florey Institute, 30 Royal Parade, Parkville VIC 3052	
4:30pm – 5:00pm	Registration
5:00pm – 5:30pm	Welcome Social
5:30pm – 6:00pm	**Opening Ceremony**
6:00pm-7:30pm	**Sci Fight Science Comedy Debate** **Topic**: AI will replace mental healthcare **Scientists:** Jess Nithianantharajah, Stephen Wood, Thomas Burne **Comedians**: Pedro Cooray, Elyce Phillips, Jeremiah Detto
7:30pm – 8:30pm	Informal Networking
Monday 27 October	
The Florey Institute, 30 Royal Parade, Parkville VIC 3052	
8:30am – 9:00am	Registration
9:00am – 10:15am	**Symposium 1** How does the hypothalamus contribute to mental illness? Thinking beyond endocrine dysfunction **Chairs & Discussants**: Jacqueline Iredale, Lizzie Manning, Zane Andrews **Speakers:** Christina Perry Shayna O'Connor Jacqueline Iredale Trevor Steward
10:15am – 11:15am	Morning Tea & ECRN Mentoring
11:15am – 12:15pm	**Data Blitz 1** **Chair:** Xavier Maddern **Speakers:** Katherine Drummond Da Lu Xiaoying Cui Po-Han Kung Gabriella Chan Wonyoung Kim Sushma Marla Andrew Gibbons Tamrin Barta Oak Hatzimanolis
12:15pm – 12:45pm	Lunch
12:45pm – 1:45pm	**Poster Session 1 over Lunch**
1:45pm – 2:45pm	**16th Aubrey Lewis Award Lecture – Dr Natalie Matosin** Investigating brain cells to develop personalized therapies for psychiatric and brain illnesses
2:45pm – 3:15pm	Afternoon Tea
3:15pm – 4:30pm	**Data Blitz 2** **Chair:** Bruna Panizzutti

	Speakers: Victoria Edwards-Poulton Dylan Kiltschewskij Nga Yan Tse Sarah Cohen Woods Muskan Khetan Renee Papaluca Pamudika Kiridena Lisanne Jenkins Mitchell Hodgson Samara Walpole Bethany Masson
4:30pm – 5:30pm	**BPA ECR Plenaries** **Chair:** Samara Walpole
	Georgia Caruana Biological correlates of cognition in bipolar disorder – brain, body, and beyond
	Nicola Acevedo Neurobiological treatments for obsessive-compulsive disorder: Modulating Neurocircuitry
The Clyde Hotel, 385 Cardigan St, Carlton VIC 3053	
6:30pm - late	Dinner Social Event
Tuesday 28 October	
The Florey Institute, 30 Royal Parade, Parkville VIC 3052	
8:30am – 9:00am	Registration
9:00am – 10:15am	**Symposium 2** Collecting and evaluating animal models in mental health science and building an online resource for researchers: A Wellcome initiative **Chairs & Discussants**: Rachel Hill and Heather Macpherson **Speakers:** Thomas Burne Claire Foldi Anthony Hannan
10:15am – 11:15am	**Highest Ranked Abstracts** **Chair:** Vanessa Cropley **Speakers:** **Kyna Conn** Psilocybin augments dopamine responses during probabilistic reversal learning in female rats **Heather Macpherson** Investigating the role of melatonin in bipolar disorder using transcriptomics **Xavier Maddern** Sex differences in neural circuits driving binge drinking: A role for the basolateral amygdala
11:15am – 11.45am	Morning Tea

11:45am – 1:00pm	**Symposium 3** Heterogeneity in psychiatric disorders and attempts to identify reliable biological phenotypes **Chairs & Discussants**: Trang Cao, Alex Fornito, Stephen Wood **Speakers:** Enda Byrne Warda Syeda Trang Cao Josselin Houenou
1:00pm – 2:00pm	**13th Isaac Schweitzer Lecture – Professor Alex Fornito** Mapping and modelling the human brain to understand its organization, genetic basis, and disturbances in psychiatric disorders
2:00pm – 2:30pm	Lunch
2:30pm – 3:30pm	**Poster session (including Data Blitz presenters) over Lunch**
3:30pm – 4:45pm	**Symposium 4** Disrupted sleep, disrupted minds: The role of sleep in psychiatric illness across the lifespan **Chairs & Discussants**: Robyn Brown, Morgan James **Speakers:** Morgan James Bei Bei Suzanne Estaphan Rachel Luton
4:45pm – 5:30pm	**AGM, Prizes, Discussion, and Close** **Discussants** Prof Bronwyn Graham Prof Anthony Hannan
Wednesday 29 October	
The Florey Institute, 30 Royal Parade, Parkville VIC 3052	
8:30am – 5:30pm	Addiction Neuroscience Australia (ANA) Satellite Meeting

Presentation Guidelines

Lectures, Oral Presentations, Data Blitz

- Please bring your presentation on a USB drive to upload in the morning on the day of your session in the Ian Potter Auditorium at the Florey Institute
- All presentations will be run from an iMac computer in the auditorium
- You will not be able to connect your own computer to the AV system
- Speakers and Chairs please arrive 15 minutes before your scheduled session. Be sure to run through the presentation after uploading with one of the LOC members to ensure the presentation is displaying properly

Posters

- Posters should be A0 portrait orientation, no more than 90cm wide and 120cm long
- **Posters will be displayed <u>on the day of your presentation only.</u> You can put your poster up when you arrive in the morning, and please remove it at the end of the day.**
    - Posters will primarily be displayed in the DAX Centre Gallery (please refer to the poster map provided on the day)
- We will provide velcro strips and other material to help display your poster, just come ready to present!

Sponsors

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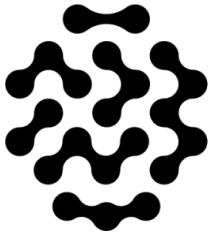

The Florey
Advancing Brain Research

THE DAX CENTRE

Scientific Program

Sunday, 26 October 2025

All events on Sunday 26 October will be held at The Florey Institute – Kenneth Myer Building, 30 Royal Parade, Parkville VIC 3052

Registration desk open
4:30 PM – 5:00 PM

Welcome Social
5:00 PM – 5:30 PM

Opening Event

Opening Ceremony
5:30 PM – 6:00 PM
Dr Tertia Purves-Tyson
Dr Leigh Walker
Dr Alexandre Guérin

Sci Fight Comedy Debate: AI will replace mental healthcare
6:00 PM – 7:30 PM
Scientists: A/Prof Jess Nithianantharajah, Prof Stephen Wood, and Prof Tom Burne
Comedians: Elyce Phillips, Pedro Cooray, and Jeromaia Detto

Monday, 27 October 2025

All events on Monday, 27 October and Tuesday, 28 October will be held at Florey Institute - Kenneth Myer Building, 30 Royal Parade, Parkville VIC 3052

Registration desk open
8:30 AM – 9:00 AM

Symposium 1
9:00 AM – 10:15 AM

How does the hypothalamus contribute to mental illness? Thinking beyond endocrine dysfunction

Chair/Discussant: Dr Jacqueline Iredale (School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle), Dr Lizzie Manning (School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle), and Prof Zane Andrews (Monash Biomedicine Discovery Institute, Monash University)

Speakers: Dr Christina Perry (School of Psychological Sciences, Faculty of Health and Human Sciences, Macquarie University), Shayna O'Connor (Robert Wood Johnson Medical School, Rutgers University (USA)), Dr Jacqueline Iredale (School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle), and Dr Trevor Steward (Melbourne School of Psychological Sciences, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne)

Morning Tea
10:15 AM – 11:15 AM

Mentoring Program
10:30 AM – 11:15 AM

Data Blitz 1
11:15 AM – 12:15 PM
Chair: Xavier Maddern

11:15 AM **Katherine Drummond**
Associations between prenatal exposure to endocrine-disrupting compounds and preschool neurocognitive abilities: an Australian birth cohort

11:21 AM **Da Lu**
Paternal chronic bacterial-like infection induces multigenerational changes in offspring anxiety and cognition related to alterations of sperm small non-coding RNAs

11:27 AM **Xiaoying Cao**
Unravelling the Epitranscriptome: Convergence from Human Postmortem Brain to Preclinical Models

11:33 AM **Po-Han Kung**
Connectivity alterations underpinning negative self-cognition processing in binge eating

11:39 AM **Gabriella Chan**
Genetic and Network-Based Constraints on Gray Matter Volume Changes in Psychosis

11:45 AM **Wonyoung Kim**
Amygdala-PFC and Hippocampus-PFC Functional Connectivity Specialisation in Normal Development and Adversity

11:51 AM **Sushma Marla**
Menstrual Characteristics and Mental Health in Adolescent Girls: Insights from the ABCD Study®

11:57 AM **Andrew Gibbons**
Discrete, cell-specific changes in cortical gene expression in a subgroup of schizophrenia characterised by low levels of the muscarinic receptor, CHRM1.

12:03 AM **Tamrin Barta**
Structure-Function Coupling in Depression in Premanifest Huntington's Disease: A Hierarchical Empirical Bayes Approach

12:09 AM **Oak Hatzimanolis**
Circular RNA expression signatures in Alzheimer's disease highlights dysregulated molecular mechanisms and disease progression

Lunch
12:15 PM – 12:45 PM

Poster Session 1
12:45 PM – 1:45 PM

Posters are located in the DAX Gallery and The Florey Foyer

P_01a **Jacqueline Iredale**
Developing a rodent model for measuring subcortical mechanisms of repetitive transcranial magnetic stimulation

P_02a **Teri Furlong**
Lesions of the lateral hypothalamus-nigral projection result in motor deficits in rats: implications for Parkinson's disease.

P_03a **Maddison Fisher**
Understanding the role of dopamine and impact of methylphenidate on impulsive actions

P_04a **Laisa de Siqueira Umpierrez**
Neural correlates of "Incubation of craving" for alcohol-associated cues.

P_05a **Smruti J Mhalgi**
Midbrain ghrelin signalling regulates conflict behaviour in the Edinger-Westphal nucleus

P_06a **Sujan Kumar Sarkar**
Inhibition of NLRP3 inflammasome by MCC950 administration improves gut health in Huntington's disease mice

P_07a **Thomas M Ferella**
Incubation of alcohol craving: behavioural and psychological factors underlying increased relapse throughout abstinence

P_08a **Kaixin Huang**
Activity-based anorexia in rats: How reward value “drives the wheel”

P_09a **Dr Ariel L. Dunn**
A novel mutation in the Arx gene causes sex-specific behavioural and electrophysiological phenotypes relevant to schizophrenia

P_10a **Jodie Pestana**
The impact of time of day and testosterone on fear extinction in male and female rats

P_11a **Ruchi Jayasinghe**
The impact of transient adolescent food insecurity on metabolism, reward, and mood-related behaviour.

P_12a **Kaspar McCoy**
Beyond Serotonin: Investigating the role of dopamine in psilocybin-induced behavioural and motivational changes

P_13a **Emily Newman-Pace**
Low-Dose Donepezil Modulates Impulsivity but Not Cognitive Flexibility in a Dynamic Strategy Shifting Task

P_14a **Kendall B Raymond**
Assessing Hormonal Drivers of Stress Induced Binge Drinking in Female Mice

P_15a **Kathryn Baker**
Opioid receptor involvement in social and non-social fear extinction in adolescent rats: Effects of naloxone

P_16a **Alicia Bjorksten**
Neurodevelopmental Impairments Following Prenatal DEHP Exposure and Their Partial Reversal by Postnatal MO8 Treatment

P_17a **Anthony Hannan**
Modelling cognitive and psychiatric behavioural traits in a mouse model of Neurofibromatosis type I

P_18a **Elizabeth Manning**
Shifting maladaptive bias in approach-avoidance measured using the platform mediated avoidance task using serotonin 5HT2C receptor antagonists

P_19a **Cassandra Ma**
Cortico-striatal mechanisms differentially mediate punishment and fear suppression in a conditioned punishment task

P_20a **Maria Kuznetsova**
Dissecting the neural circuits of motivation under acute stress: behavioural and circuit-level analysis in rats

P_22a **Ann-Sofie Bjerre**

Neural Signatures of Social Reward: Dopamine and Oxytocin Dynamics in the Nucleus Accumbens

P_23a **Abigail Marcus**
Prenatal methamphetamine exposure causes, and N-Acetyl Cysteine prevents, long-lasting impairments in cognitive control during adulthood

P_24a **Mia Jessica O'Shea**
Investigating the role of orexin in stress-induced binge eating

P_25a **Mia L Langguth**
Can intranasally administered clozapine effectively reduce psychosis-related behaviours and mitigate the debilitating metabolic side effects?

P_26a **Alyssa Tuim**
Novel Betacellulin peptide treatment recovers altered adult Hippocampal Neurogenesis in a BTC-knockout mouse model with relevance to Schizophrenia

P_27a **Brandon RIchards**
RXFP3-expressing lateral hypothalamus/zona incerta cells exhibit projection-specific activity during a conditioned flight paradigm

P_28a **Jodie Naim-Feil**
Patterns in the Brain: Exploring Multiday Cycles in Mood and Anxiety Symptoms

P_29a **Madeleine McCallum**
Gender specific effects of childhood interpersonal trauma on anxiety disorders: a systematic review and meta-analyses

P_30a **Kristiane Yacou Dunbar**
The relationship between neurometabolites and cognitive function in adults with alcohol use disorder: A preliminary proton magnetic resonance spectroscopy study

P_31a **Georgia F. Caruana**
Exploring blood-based biological correlates of cognitive intra-individual variability and other cognitive measures in bipolar disorder

P_32a **Dr Elysia Sokolenko**
A multicentre randomised controlled clinical trial of repetitive transcranial magnetic stimulation for social communication in autism spectrum disorder

P_33a **Helen Clunas**
Region and age specific alterations in endocannabinoid gene expression in major depressive disorder

P_34a **Ricardo De Paoli-Iseppi**
Long Reads, Deep Insights: RNA Isoform Discovery in Neuropsychiatric Risk Genes

P_35a **Angel Yonehara**
Investigating cellular phenotypes and genotypes of a preclinical model relevant to schizophrenia using single-cell RNA sequencing.

P_37a **Tamrin Barta**
Temporal Dynamics of Depression in Premanifest Huntington's Disease: A Network Dysconnection Approach

P_38a **Yingliang Dai**
The Neural Mechanisms Supporting the Updating of Self-Beliefs

P_39a **Lieselotte Claes**
Common and Distinct Neural Correlates of Human Avoidance and Safety Learning

P_40a **Lukas Roell**
Longitudinal functional connectivity markers underlying symptom development in early psychosis

P_41a **Helena Canals Fiol**
If the doors of self were cleansed: effective connectivity of Ego Dissolution

P_42a **Christina M. Suhartono**
18F-FDG PET and Structural MRI Markers of Vulnerability to Diet-Induced Obesity

P_43a **Alfred Pak-Kwan Lo**
Stressful life events with high escape potential induce freezing-like behavior

P_44a **Xuqian Li**
Mental health in the UK Biobank: An updated roadmap for brain-behavior associations

P_45a **Nanfang Pan**
Geometric Resonance Model Underlies ADHD-Related Structural Connectome Deviations

P_46a **Ellen E Towers**
Intrinsic Functional Connectivity Patterns in Comorbid PTSD and Alcohol Use Disorder vs. Alcohol Use Disorder

P_47a **Sarah Manuele**
Cortical thickness associations with adverse life events in youth with non-suicidal self-injury

P_48a **Sarah Cameron**
Transcriptomic profiling of the human habenula in bipolar and major depressive disorder

P_49a **Jessie Sheridan-Moules**
DARPP-32 mRNA in Schizophrenia and Bipolar Disorder: Differential Findings in the Dorsal and Ventral Striatum

P_50a **Carlos M. Opazo**
Links between iron dyshomeostasis, ubiquitin stress, amyloid precursor protein and schizophrenia

P_51a **Alex Stevenson**
Characterising inflammatory and glutamatergic relationships in the nucleus accumbens in schizophrenia: emerging potential for spatial metabolomics with MALDI-MSI

P_52a **Heather K. Macpherson**
Melatonin mitigates oxidative stress and metabolic dysfunction induced by interleukin-6 and dopamine in SH-SY5Y cells

P_53a **Peng Zheng**
Over-activation of Dopamine D2 Receptor Inhibits Mitophagy and Causes Schizophrenia-like Behaviors in Mice

P_55a **Suresh Sundram**

Growth Factors and Schizophrenia Spectrum Disorders: A Splines Modelling Approach

P_56a **Junxuan Zhao**
From Parenting to Brain to Wellbeing: Neural Effects of Emotion-Focused Parenting in Adolescents

P_58a **Chantel Fitzsimmons**
Exploration of the Role of microRNA Expression in Suicidality: A Systematic Review and Bioinformatic Analysis

P_59a **Sue He** *(late-breaking)*
Validating a Translational Approach to Assess Deficits in Motivation in Rodent Models to Enable Novel Drug Discovery

P_61a **Hana McMahon** *(late-breaking)*
Childhood maltreatment and limbic substructure volumes using ultra-high field imaging

P_62a **Amy J Pearl** *(late-breaking)*
Midbrain ghrelin receptor signalling regulates binge drinking in a sex specific manner

P_63a **James Kesby**
Clinician perspectives of treatment priorities and the role of cognitive symptoms in supporting people with schizophrenia

P_64a **Michael D Kendig** *(late-breaking)*
Comparing food addiction phenotypes in animal models of obesity and binge eating

P_65a **Sarah Cohen-Woods** *(late-breaking)*
Development and validation of a methylation profile score for the cortisol response to stress

P_66a **Jasmine Campbell** *(late-breaking)*
Effects of Maternal Immune Activation and Raloxifene on Dopamine-Related Behaviour and Substantia Nigra Gene Expression in Adolescent Male and Female Rats

P_67a **Carolina Gubert** *(late-breaking)*
Uncovering Microbiota-Mediated Benefits of Exercise in a Schizophrenia Mouse Model

16th Aubrey Lewis Award Lecture

1:45 PM – 2:45 PM
Chair: Dr. Robyn Brown

Dr Natalie Matosin
Investigating brain cells to develop personalized therapies for psychiatric and brain illnesses

Afternoon Tea

2:45 PM – 3:15 PM

Data Blitz 2

3:15 PM – 4:30 PM
Chair: Bruna Panizzutti

3:15 PM **Victoria Edwards-Poulton**

Sexually Dimorphic Disruptions to Parvalbumin and Somatostatin Interneurons in Mice Carrying the ArxR264Q Mutation

3:21 PM **Dylan Kiltschewskij**
Harnessing DNA Methylation to Disentangle Heterogeneity in Schizophrenia

3:27 PM **Nga Yan Tse**
Towards Precision Psychiatry: Combining Clinical Complexity and Brain Connectivity for TMS Outcome Prediction

3:33 PM **Sarah Cohen Woods**
Mendelian randomisation and colocalisation reveal pleiotropic effects of CD40/SLC12A5 locus on CD40 protein, depression, and immune disease

3:39 PM **Muskan Khetan**
Role of *oestradiol* and progesterone variability in brain structure and mental health in adolescent females

3:45 PM **Renee Papaluca**
Differential *striatal* gene expression profiles underlies the propensity for depression-like behaviour in a mouse model of vertical sleeve gastrectomy

3:51 PM **Pamudika Kiridena**
Paternal cytokine administration alters sperm small non-coding RNAs and offspring physiology and behaviour in mice

3:57 PM **Lisanne Jenkins**
Grey matter changes observed up to two years prior to the onset of non-suicidal self-injury in male and female youths

4:03 PM **Mitchell Hodgson**
Pinpointing Schizophrenia Mechanisms with Isoform-Resolved Analyses in the Developing Human Brain

4:09 PM **Samara Walpole**
Reductions in Group III Metabotropic Glutamate Receptor Transcripts in Schizophrenia and Bipolar Disorder Midbrain

4:15 PM **Bethany Masson**
Paternal gut microbiota modulation via prebiotics alters sperm small RNAs and impacts offspring physiology and behaviour

BPA ECRN Plenaries

4:30 PM - 5:30 PM
Chair: Dr Samara Walpole

4:30 PM **Ms Georgia Caruana**
Biological correlates of cognition in bipolar disorder – brain, body, and beyond

5:00 PM **Dr Nicola Acevedo**
Neurobiological treatments for obsessive-compulsive disorder: Modulating Neurocircuitry

Dinner Social Event – The Clyde Hotel

6:30 PM – 10:30 PM

Tuesday, 28 October 2025

Registration desk open
8:30 AM – 9:00 AM

Symposium 2
9:00 AM – 10:15 AM

Collecting and evaluating animal models in mental health science and building an online resource for researchers: A Wellcome initiative
Chair/Discussant: A/Prof Rachel Hill (Monash University) and Heather Macpherson (Queensland Brain Institute)

Speakers: Prof Thomas Burne (Queensland Brain Institute), Dr Claire Foldi (Monash University), and Prof Anthony Hannan (Florey Institute for Neuroscience and Mental Health)

Highest Ranked Abstracts
10:15 AM – 11:15 AM
Chair: Vanessa Cropley

10:15 AM **Kyna Conn**
Psilocybin augments dopamine responses during probabilistic reversal learning in female rats

10:35 PM **Heather K Macpherson**
Investigating the role of melatonin in bipolar disorder using transcriptomics

10:55 PM **Xavier Maddern**
Sex differences in neural circuits driving binge drinking: A role for the basolateral amygdala

Morning Tea
11:15 AM - 11:45 AM

Symposium 3
11:45 AM - 1:00 PM

Heterogeneity in psychiatric disorders and attempts to identify reliable biological phenotypes
Chair/Discussant: Dr Trang Cao (Monash University), Prof Alex Fornito (Monash University), and Prof Stephen Wood

Speakers: Dr Enda Byrne (Child Health Research Centre, University of Queensland), Dr Warda Syeda (University of Melbourne), Dr Trang Cao (Monash University), and Prof Josselin Houenou (University of Melbourne; Northern Health)

13th Isaac Schweitzer Lecture
1:00 PM – 2:00 PM
Chair: Tertia Purves-Tyson

Prof Alex Fornito
Mapping and modelling the human brain to understand its organization, genetic basis, and disturbances in psychiatric disorders

Lunch
2:00 PM – 2:30 PM

Poster Session 2 (including Data Blitz Presenters)

2:30 PM – 3:30 PM

Posters are located in the DAX Gallery and The Florey Foyer

P_01b **Bethany Masson**
Paternal gut microbiota modulation via prebiotics alters sperm small RNAs and impacts offspring physiology and behaviour

P_02b **Samara Walpole**
Reductions in Group III Metabotropic Glutamate Receptor Transcripts in Schizophrenia and Bipolar Disorder Midbrain

P_03b **Mitchell Hodgson**
Pinpointing Schizophrenia Mechanisms with Isoform-Resolved Analyses in the Developing Human Brain

P_04b **Lisanne Jenkins**
Grey matter changes observed up to two years prior to the onset of non-suicidal self-injury in male and female youths

P_05b **Pamudika Kiridena**
Paternal cytokine administration alters sperm small non-coding RNAs and offspring physiology and behaviour in mice

P_06b **Renee Papaluca**
Differential striatal gene expression profiles underlies the propensity for depression-like behaviour in a mouse model of vertical sleeve gastrectomy

P_07b **Muskan Khetan**
Role of oestradiol and progesterone variability in brain structure and mental health in adolescent females

P_08b **Sarah Cohen Woods**
Mendelian randomisation and colocalisation reveal pleiotropic effects of CD40/SLC12A5 locus on CD40 protein, depression, and immune disease

P_09b **Nga Yan Tse**
Towards Precision Psychiatry: Combining Clinical Complexity and Brain Connectivity for TMS Outcome Prediction

P_10b **Dylan Kiltschewskij**
Harnessing DNA Methylation to Disentangle Heterogeneity in Schizophrenia

P_11b **Victoria Edwards-Poulton**
Sexually Dimorphic Disruptions to Parvalbumin and Somatostatin Interneurons in Mice Carrying the ArxR264Q Mutation

P_12b **Oak Hatzimanolis**
Circular RNA expression signatures in Alzheimer's disease highlights dysregulated molecular mechanisms and disease progression

P_13b **Tamrin Barta**
Structure-Function Coupling in Depression in Premanifest Huntington's Disease: A Hierarchical Empirical Bayes Approach

P_14b **Andrew Gibbons**
Discrete, cell-specific changes in cortical gene expression in a subgroup of schizophrenia characterised by low levels of the muscarinic receptor, CHRM1.

P_15b **Sushma Marla**
Menstrual Characteristics and Mental Health in Adolescent Girls: Insights from the ABCD Study®

P_16b **Wonyoung Kim**
Amygdala-PFC and Hippocampus-PFC Functional Connectivity Specialisation in Normal Development and Adversity

P_17b **Gabriella Chan**
Genetic and Network-Based Constraints on Gray Matter Volume Changes in Psychosis

P_18b **Po-Han Kung**
Connectivity alterations underpinning negative self-cognition processing in binge eating

P_19b **Xiaoying Cui**
Unravelling the Epitranscriptome: Convergence from Human Postmortem Brain to Preclinical Models

P_20b **Da Lu**
Paternal chronic bacterial-like infection induces multigenerational changes in offspring anxiety and cognition related to alterations of sperm small non-coding RNAs

P_21b **Katherine Drummond**
Associations between prenatal exposure to endocrine-disrupting compounds and preschool neurocognitive abilities: an Australian birth cohort

P_22b **Nicholas van de Garde**
Paternal immune activation via the viral mimic poly I:C leads to epigenetic changes in sperm and results in behavioural and brain changes in offspring

P_23b **Lauren T Ursich**
Assessing the utility of zuranolone to modify alcohol-related behaviours

P_24b **Octavia Soegyono**
Neuroinflammation in the nucleus accumbens core impairs sign-tracking but maintains performance of value-modulated attentional capture

P_25b **Akarshan Sami**
Does epilepsy increase vulnerability to develop alcohol use disorder? A study in the kainic acid model of temporal lobe epilepsy

P_26b **Zoe J. Phelan**
Acute Activation of Serotonergic Neurons in the Dorsal Raphe Nucleus Following Subanaesthetic Ketamine

P_28b **Sheida Shadani**
Sex- and Time-Dependent Effects of Psilocybin on Social Behaviours in Mice

P_29b **Ulysse Thivisol**
Maternal Immune Activation Perturbs the Proteome of the Developing Adolescent Mouse Hippocampus

P_30b **Abdallah Al Siyabi**
Psilocybin Promotes Cognitive Flexibility via Reinforcement Learning Modulation in Rats

P_31b **James W.M.Kang**
Investigating the Development of Fear Avoidance in a Novel Graded Threat Assay in a Preclinical Model of Orofacial Neuropathic Pain.

P_32b **Daria J. Paulis**
AgRP neuron-specific GHSR knockout alters consummatory behaviour in the presence of predator stress

P_33b **Vasilios Drakopoulos**
The role of a cortico-hypothalamic pathway on metabolism and behaviour

P_34b **Alexander G. Athanasopoulos**
Partial 5-HT2A receptor agonism as a treatment against the acutely reinforcing effects of methamphetamine

P_35b **Stella Cardozo**
Chronic nicotine intake initiated during adolescence escalates in adulthood following intermittent access of ethanol.

P_36b **Anna Pangilinan**
Incubation of alcohol craving: Investigating drug-specific neural mechanisms

P_38b **James J Gattuso**
Enhanced Acute Psilocybin Responses and Sex-Specific Long-Term Improvements in Sensorimotor Gating in the Metabotropic Glutamate Receptor 5 Knockout Mouse Model of Schizophrenia

P_39b **Yuting (Heather) Chen**
Molecular Modulation of Cognitive Flexibility: Investigating the Role of Protein Kinase C in Instrumental Reversal Learning

P_40b **Chantel Fitzsimmons**
The neurobehavioral effects of the over-expression of microRNA-219 in the pre-limbic region of the medial prefrontal cortex of rats, towards a predictive model for Schizophrenia.

P_41b **Farideh Ghavidel**
Effects of acute administration of the GLP-1 agonist, semaglutide, on blood glucose levels, incentive motivation and cognitive flexibility in male and female Sprague-Dawley rats

P_42b **Elizabeth Kleeman**
Clearing the Fog: Characterising neurological phenotypes in a Long COVID mouse model to identify biomarkers for Long COVID

P_43b **Bailey Enraght-Moony**
Identifying phenotypic markers to predict mental health outcomes

P_44b **Johnny Park**
Trimetazidine to treat Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: TRI-ME trial

P_45b **Yinuo Shu**
Do complex affect dynamics improve predictive power for psychological and behavioral outcomes?

P_46b **Ramisha Khan**
Clinical trials to treat myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review and meta-analyses of intervention- and measure-specific outcomes

P_47b **Rosalind Ge**
Characterising Sleep and Circadian Rhythm Phenotypes in Young People at Clinical High Risk for Psychosis: A Latent Profile Analysis in the AMPSCZ Cohort

P_48b **Michelle Corrone**
Brain-Derived Neurotrophic Factor Val66met is associated with sex-specific impairment of cognitive flexibility under stress: a reversal learning search strategy analysis in a rat model

P_49b **Anran Li**
Uncovering the RNA isoform landscape in brain development: Insights into neuropsychiatric disorder risk

P_50b **Marcus R. Camilleri**
Elucidating RNA isoform expression in the 2-day old human prefrontal cortex at single-cell resolution

P_51b **Lukas Roell**
Longitudinal hippocampal functional connectivity changes and symptom development in people at psychosis risk

P_52b **Isaac Z. Pope**
Functional Coupling and Longitudinal Outcome Prediction in First-Episode Psychosis

P_53b **Hirotaka Sekiguchi**
A study of frontal bone thickness in patients with schizophrenia

P_54b **Leah J Hudson**
Bidirectional modulatory influences of positive and negative feedback on habenula function

P_56b **Toby Constable**
Psychological Trauma, The Brain, and Psychopathology: No Evidence for Mediation by Grey Matter or Resting State Functional Connectivity

P_57b **Elizabeth Haris**
Between brain circuitry and lived experience: Trauma and self-disturbance in youth at high-risk for psychosis.

P_58b **Soudeh Ashrafipour**
Impact of puberty age gap on resting-state functional connectivity

P_59b **Sandra Luza**
Serum elements and oxidative stress indices are altered in Treatment-Resistant Schizophrenia

P_60b **Jaime Spencer**
Probing interactions between the muscarinic M4 receptor and 'receptor X'

P_61b **Yao Honghong**
Circular RNA biomarker for depression diagnosis

P_63b **Cassie Field**
Repurposing drugs for bipolar disorder using patient-derived cells and a gene expression signature.

P_64b **Alex Reichenbach**
Acute stress regulates AgRP neuronal activity

P_65b **Chiranth Bhagavan** *(late-breaking)*
Sustained Cross-Network Integration Following Low-To-Moderate Psilocybin Doses

P_66b **Sidhant Chopra** *(late-breaking)*
Identifying a synaptic deficit subtype of schizophrenia using in vivo PET imaging

P_67b **Maral Jkorkozian** *(late-breaking)*
The Behavioural Effect of Oxytocin Treatment During Adolescence on Male and Female Offspring Exposed to Maternal Immune Activation

Symposium 4
3:30 PM – 4:45 PM

Disrupted sleep, disrupted minds: The role of sleep in psychiatric illness across the lifespan
Chair/Discussant: A/Prof Robyn Brown (University of Melbourne) and Dr Morgan James (University of Sydney)

Speakers: Dr Morgan James (University of Sydney; Robert Wood Johnson Medical School (USA)), A/Prof Bei Bei (Monash University), Dr Suzanne Estaphan (Australian National University), and Rachel Luton (Australian National University)

AGM, Prizes, Discussion, and Close
4:45 PM – 5:30 PM

Discussants
Prof Bronwyn Graham
Prof Anthony Hannan

AGM, Prizes, and Wrap up
Dr Tertia Purves-Tyson
Dr Leigh Walker
Dr Alexandre Guérin

Conference close
5:30 PM

Wednesday, 29 October 2025

Addiction Neuroscience Australia (ANA) Satellite Meeting

8:30 AM – 5:30 PM

Invited Plenary Speakers

13th Isaac Schweitzer Plenary Lecture

Mapping and modelling the human brain to understand its organization, genetic basis, and disturbances in psychiatric disorders

Prof Alex Fornito, Monash University

Alex Fornito completed his PhD in the Departments of Psychology and Psychiatry at The University of Melbourne before undertaking Post-Doctoral training in the Department of Psychiatry at the University of Cambridge, UK, under the auspices of an NHMRC Training Fellowship. He is currently a Laureate Fellow of the Australian Research Council, Professor in the School of Psychological Sciences, and Head of the Brain Mapping and Modelling Research Program and Neural Systems and Behaviour Lab at the School of Psychological Sciences, Monash University.

Alex's research develops new approaches to mapping and modelling the human brain in health and disease, with a focus on understanding foundational principles of brain organization and their genetic basis, characterizing brain disturbances in psychiatric disorders, and understanding how individual variability in brain structure and function relate to behavior.

His work has received multiple awards, including from the Organization for Human Brain Mapping, the Australian Academy of Science, the Society for Biological Psychiatry, and the British Medical Association. He is co-founding member of the inaugural Executive Committee of Biological Psychiatry Australia and holds editorial positions at Science Advances, eLife, Network Neuroscience, Imaging Neuroscience, Biological Psychiatry, and Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.

Chair: Tertia Purves-Tyson

16th Aubrey Lewis Plenary Award

Investigating brain cells to develop personalized therapies for psychiatric and brain illnesses

Dr Natalie Matosin, University of Sydney

Dr Natalie Matosin is an Al & Val Rosenstrauss Rebecca L Cooper Medical Research Foundation Fellow and Head of the MINDS Lab at the University of Sydney, Australia. She also holds the prestigious Sydney Horizon Fellowship at the University of Sydney.

Dr Matosin was awarded her PhD in neuroscience at the University of Wollongong in 2015. She undertook postdoctoral training at the University of New South Wales and Max Planck Institute of Psychiatry in Munich, where she developed highly specialised expertise in next generation sequencing methods and state- of-the-art histology approaches to analyse postmortem human brain tissue. Dr Matosin established her independent research laboratory in 2018. Her research program investigates brain cells at individual cell resolution with the aim of developing personalised therapies for psychiatric and other brain illnesses.

Chair: Robyn Brown

Early Career Researcher Network Plenary Award

Ms Georgia Caruana, Melbourne Neuropsychiatry Centre, The University of Melbourne

Biological correlates of cognition in bipolar disorder – brain, body, and beyond

Upwards of 60% of people living with bipolar disorder (BD) experience cognitive dysfunction. Despite the prevalence, persistence and psychosocial burden of these symptoms, our characterisation of the cognitive profile of BD, and its biological correlates, remains incomplete. That is, the body of literature examining the link of cognition and neurobiological factors in BD is small, and this existing research has also only broadly assessed cognition using measures of central tendency, at the expense of metrics that index within-person cognitive fluctuations and that may be more sensitive to underlying neurobiological alterations. In this Plenary, Georgia will present the outcomes of her research exploring associations of white matter integrity, peripheral inflammation, and telomere attrition with several indices of within and between-person cognitive variability.

Dr Nicola Acevedo, Swinburne University

Neurobiological Treatments for Obsessive Compulsive Disorder: Modulating Neurocircuitry

This plenary synthesises emerging neurobiological treatments for obsessive compulsive disorder (OCD), a disabling condition with high treatment resistance. Evidence for transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and psilocybin-assisted psychotherapy (PAP) is critically reviewed, including established evidence for TMS, outcomes from a DBS clinical trial and a transdiagnostic PAP protocol. Clinical, neuroimaging, psychosocial and lived-experience perspectives are integrated to highlight therapeutic potential and translational directions. Collectively, these approaches can demonstrate efficacy comparable to standard care while modulating neurobiological underpinnings of OCD. The session will also address barriers to treatment access and the need for personalised, biopsychosocial models of care.

Symposia Abstracts

Symposium 1. How does the hypothalamus contribute to mental illness? Thinking beyond endocrine dysfunction

The hypothalamus is best known for its role in controlling fundamental processes that are important for survival, including feeding, stress responses, mating and metabolism. It does this, in large part, through the actions of subpopulations of neurons that control specific endocrine systems responsible for coordinating responses across the brain and body. While endocrine dysfunction has been implicated in the neurobiology of a variety of mental health disorders, growing evidence suggests that hypothalamic neural activity also controls motivated behaviours on more rapid timescales, acting independently of slow endocrine systems. Given that dysfunction of motivated behaviours is central to the symptoms of a variety of mental illness, detailed investigation of hypothalamic neural activity patterns in patients and animal models of mental health disorders is warranted.

The challenges of investigating the activity and connectivity of neuronal populations in regions such as the hypothalamus, located deep in the brain, has significantly limited research into this important area. However, the ongoing advancement of preclinical and clinical techniques such as optogenetics, chemogenetics, calcium imaging and high resolution (7-Tesla) magnetic resonance imaging have begun to overcome these challenges. In this symposium we will hear from researchers, both clinical and preclinical with a balance of gender and career stage, investigating the hypothalamus in mental health and behaviours relevant to mental health conditions. The research presented will show innovative preclinical and clinical work, highlighting the new techniques and cutting-edge work being undertaken using these approaches to investigate the hypothalamus in mental health beyond endocrine dysfunction.

Chairs and Discussants: Dr Jacqueline Iredale (School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle, Callaghan, NSW, Australia), Dr Lizzie Manning (School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle, Callaghan, NSW, Australia), and Prof. Zane Andrews (Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia)

Dr Christina Perry, School of Psychological Sciences, Faculty of Health and Human Sciences, Macquarie University, NSW, Australia

Biography: Christina Perry is an EMCR and senior lecturer at Macquarie University. She completed her PhD in psychology (behavioural neuroscience) at UNSW, then moved to Melbourne to work for Prof Andrew Lawrence in the Addiction Neuroscience laboratory at the Florey Institute of Neuroscience and Mental Health. Following award of an NHMRC/ARC dementia research fellowship in 2016, she was promoted to team leader, heading a program of research investigating cognitive decline following chronic alcohol use. In 2021 she moved back to Sydney to take up a position with Prof Jen Cornish at Macquarie. There she leads two programs of research, respectively investigating neural mechanisms of relapse in alcohol seeking, and changes in threat response across the threat imminence spectrum; each funded by major competitive government grants. She has active collaborations with Sydney and Deakin Universities, and her track record illustrates the diversity of her expertise in the biological basis of psychiatric disorders. In addition to research and teaching, Dr Perry is actively involved in the Australian research community. She was treasurer for BPA from 2018-2021, and chaired the LOC for the 2024 meeting. In 2023, she co-founded the Addiction Neuroscience Australia group, aimed at promoting collaboration and supporting early career researchers in preclinical addiction neuroscience. She is dedicated to promoting equity and diversity, having chaired the Florey Equality in Science committee between 2017 and 2020, as well as working with the Women in Science Parkville Precinct collaborative to develop more effective and equitable metrics for tracking career progress for researchers.

Abstract: Although the neural circuitry underlying defensive responses has been subject to extensive study, the way that these circuits are integrated to produce changes in defensive behaviour is poorly understood. We recently demonstrated that activating relaxin family peptide receptor-3 (RXFP3)-expressing cells spanning the lateral hypothalamus (LH) and zona incerta (ZI) during retrieval of conditioned fear

caused a switch from freezing to dynamic escape, suggesting not only that memory retrieval was intact, but that there was a heightened sense of danger with respect to the predicted outcome. Interestingly, this only occurred in a subset of mice. Given the heterogeneity of these loci, we hypothesised that different subpopulations of RXFP3+ LH/ZI cells contribute to the choice between active and passive defensive behaviour depending on perceived threat imminence. Using tracing and RNAscope, we identified two putative contributors - GABAergic/RXFP3+ ZI neurons projecting to the ventrolateral periaqueductal gray (vlPAG), and glutamatergic/RXFP3+ LH neurons projecting to the lateral habenula (LHb). To manipulate threat imminence, we used a modified Pavlovian fear conditioning paradigm where footshock is paired with a serial compound stimulus consisting of distinct tone and white noise periods. After conditioning, the tone reliably elicits freezing, while the white noise elicits escape. Pathway-specific fiber photometry showed increased calcium activity in both the ZI-vlPAG and LH-LHb pathways after conditioning. However, the ZI-vlPAG pathway exhibited large calcium transients to footshock, while the LH-LHb pathway was silenced. Overall, this suggests neuroanatomically distinct ensembles which are selectively active during different degrees of threat to dictate adaptive and flexible behavioural responses.

Shayna O'Connor, Robert Wood Johnson Medical School, Rutgers University, New Jersey, USA

Biography: Shayna O'Connor is a fifth-year Ph.D. candidate in Behavioural Neuroscience at Rutgers University (USA) in Dr. Morgan James' lab, where she investigates the neural underpinnings of attention deficits and addiction vulnerability. She is a recipient of the NIH/NIMH T32 Training Fellowship and has been recognized with prestigious awards including the Society for Neuroscience Trainee Professional Development Award and multiple societal and institutional travel and academic awards. Shayna's research explores the role of the orexin system in regulating attention and addiction-related behaviours, using behavioural modelling, pharmacological, histological, and in vivo imaging techniques. Shayna's work has made significant contributions to our understanding of individual differences in addiction risk. Her first-author publications in Neuropharmacology and Addiction Neuroscience distinguished sensation-seeking from novelty-seeking traits, revealing their unique predictive roles in cocaine vulnerability. She has also co-authored high-impact studies, including a Neuropsychopharmacology paper on orexin-1 receptor signalling and a Nature Neuroscience publication on dopaminergic control of cognition. Notably, her recent work in Artificial Intelligence Chemistry applied machine learning to predict orexin-1 receptor ligand binding, exemplifying her multidisciplinary expertise. Shayna earned both her bachelor's and master's degrees at Rutgers University and is on track to complete her Ph.D. in May 2026. Her research bridges attention and addiction neuroscience, aiming to uncover shared neurobiological mechanisms underlying ADHD and substance use disorders and to inform novel therapeutic strategies.

Abstract: Up to 64% of children with ADHD (attention deficit hyperactivity disorder) report recreational cocaine use during adolescence/adulthood, and around 15% go on to develop a diagnosable cocaine use disorder. The biological links underpinning this vulnerability are unclear. In this study, we identified a subpopulation of rats with impaired sustained attention—classified as low performers (LPs) based on consistently poor performance on the rodent psychomotor vigilance task (rPVT). Fiber photometry recordings revealed that LPs exhibit significantly reduced task-related activity in hypothalamic neurons that produce orexin, a neuropeptide critical for arousal. To establish a causal link between orexin function and attentional performance, we inhibited orexin signaling – using both chemogenetic and pharmacological approaches – in high performing rats (HPs); this was sufficient to produce a switch to a LP phenotype. Conversely, increasing orexin signaling in LPs caused a conversion to a HP phenotype. Increasing orexin signaling in HPs did not further enhance performance, rather, it led to impairments, indicating an inverted-U relationship between orexin levels and attentional performance. To assess cocaine vulnerability, we administered daily cocaine injections (10 mg/kg, i.p.) over seven days. LPs exhibited heightened locomotor responses to cocaine relative to HPs, indicating greater sensitivity. Although cocaine elevated orexin levels in both groups, only LPs showed concurrent improvements in attentional performance. These findings indicate that baseline orexin deficits may drive both attentional impairments and heightened cocaine sensitivity—paralleling risk profiles observed in individuals with ADHD. Targeting the orexin system may therefore offer a novel therapeutic avenue for reducing stimulant vulnerability in this population.

Dr Jacqueline Iredale, School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle, Callaghan, NSW, Australia

Biography: Dr Jackie Iredale is a postdoctoral researcher in the Behavioural Neuroscience Group at the University of Newcastle, led by Dr Lizzie Manning, Dr Erin Campbell and Prof. Chris Dayas. The work of the group focuses on understanding the neural mechanisms underlying neuropsychiatric disorders such as depression, substance use disorder and obsessive-compulsive disorder. Jackie's work currently focuses on two projects; investigating the hypothalamic pathways involved in stress and in risk vs. reward decision making, using in vivo calcium imaging approaches; and investigation of the therapeutic mechanisms underlying transcranial magnetic stimulation (TMS) in the treatment of neuropsychiatric disorders. Jackie completed her PhD in 2023 at The University of Newcastle where she developed new in vivo and ex vivo models of pain and optimised novel pharmacological compounds for treatment. Jackie has a total of 5 peer-reviewed publications, 93 citations and a field-weighted citation impact of 0.96. She has secured >$110K in research funding as Chief Investigator and in 2023, she received The Mike and Karin Calford Travel Fellowship from The Hunter Medical Research Institute to travel to leading labs in North America and optimise calcium imaging techniques at The University of Newcastle. Finally, her promise as an emerging leader was recognised in 2023 by an International Brain Research Organization travel award.

Abstract: Recent advancements in preclinical neuroscience have developed valuable tools for studying how the activity of hypothalamic neurons contribute to behaviour, allowing the demonstration of diverse contributions to threat and motivated behaviours relevant to mood disorders. One limitation of much of this research is that hypothalamic neural populations are treated as homogenous groups, however, often subpopulations within a larger, defined population will be activated by different stimuli, potentially driving different responses or behaviours. One approach that has been developed with the capacity to identify and separate the activity of individual subpopulations is in vivo calcium imaging with miniature microscopes (miniscopes). Miniscopes enable visualisation of individual populations of neurons in awake behaving animals. These populations can then be further classified into sub-populations based on individual neuron responses to certain tasks or stimuli. This presentation will discuss work applying miniscopes to measure the activity of individual hypothalamic neurons in models and behaviour tasks relevant to mood disorders. In the first set of studies, the activity of corticotrophin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVNCRH) that control stress hormone release was measured during exposure to chronic mild stress. In a second set of studies, activity of VGlut2+ neurons in the ventromedial hypothalamus was assessed, investigating responses to threatening stimuli and the influence of metabolic state on the activity of these neurons. Advantages and challenges over population imaging approaches like photometry will be highlighted, and the potential for miniscopes in investigating the role hypothalamic neural subpopulations in mental illness discussed.

Dr Trevor Steward, Melbourne School of Psychological Sciences, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia

Biography: Dr. Trevor Steward is a NHRMC Senior Research Fellow at the University of Melbourne School of Psychological Sciences and the Director of the Brain and Mental Health Hub. His research focuses on using ultra high-field 7-Telsa MRI technology to understand how subcortical regions of the brain contribute to common symptoms found across psychiatric disorders. Although the majority of his research to date has examined the neuropsychopathology of eating disorders, he also conducted studies on mood disorders and PTSD. His aim is to leverage neuroimaging tools to inform brain-based treatments and to improve clinical outcomes. He is the co-author of over 100 publications, including in leading journals such as Molecular Psychiatry, Nature Communications, and Biological Psychiatry.

Abstract: Small subcortical structures such as the hypothalamus, bed nucleus of the stria terminalis (BNST), and habenula have remained under-characterized in human neuroscience research largely due to spatial resolution limitations of conventional neuroimaging. Advancements in ultra-high field 7-Tesla (7T) MRI provide the necessary resolution and contrast to interrogate these regions in vivo, enabling mechanistic insights into symptom domains that cut across traditional diagnostic boundaries. This presentation will present a series of studies from our group employing 7T fMRI to examine the role of

subcortical structures in affective and behavioral dysregulation. First, we report findings on the habenula and mediodorsal thalamus during the processing and cognitive restructuring of negatively biased self-referential cognitions. These results implicate thalamocortical and habenular pathways in maladaptive belief updating, with relevance for mood and anxiety disorders. Second, we describe work characterizing BNST activation and connectivity during acute stress exposure and food cue exposure, underscoring its role in ingestive behaviors and arousal dysregulation. Third, we outline an ongoing study investigating hypothalamic functional connectivity in adult women exhibiting binge eating behaviors, with a focus on its integrative role in stress-responsive and appetitive signaling systems. We will discuss methodological considerations unique to ultra-high field imaging, as well as the implications of these findings for biologically informed models of transdiagnostic symptoms. Our aim is to advance the field toward a more precise neurobiological characterization of psychiatric disorders through targeted imaging of previously inaccessible structures.

Symposia Abstracts

Symposium 2. Collecting and evaluating animal models in mental health science and building an online resource for researchers: A Wellcome initiative

Animal models have proved valuable tools to investigate how discrete genetic and environmental risk factors associated with mental illness disrupt brain and behaviour function and for testing novel treatments for psychiatric disorders. However, when we consider the hundreds of genetic, environmental and multi-hit models generated in this field, a major question is how do we know if we are using the most appropriate model? The Consortium for Preclinical Psychiatric Research (CPPR) seeks to provide answers to these questions through a new Wellcome funded initiative to evaluate and rank animal models in mental health science and develop an interactive web-based platform for researchers to identify the best model and/or assay for their specific research question. Diverse representatives of the CPPR at various career stages and from varying institutions will report on novel methods and approaches for generating and evaluating animal models for each domain of depression, anxiety and psychosis. Lived experience researcher Heather MacPherson will guide discussion on the translational validity of animal models.

Chairs and Discussants: Rachel Hill (Monash University) and Heather Macpherson (Queensland Brain Institute)

Thomas Burne, Queensland Brain Institute

Biography: Professor Thomas Burne is a neurobiologist working in the field of biological psychiatry, with a strong interdisciplinary background in behavioural neuroscience and expertise in animal models of neuropsychiatric disorders. He currently holds multiple senior research appointments, including Professorial Research Fellow at the University of Queensland, a group leader at the Queensland Brain Institute (QBI), and a Principal Research Fellow at the Queensland Centre for Mental Health Research. Professor Burne has authored over 150 peer-reviewed publications, with more than 10,000 citations, and in collaboration with national and international partners, he has secured over $8 million in competitive research funding, with continuous funding from the NHMRC from 2007-2028. Since 2003, his research program focuses on understanding the biological mechanisms underlying neurodevelopmental and neuropsychiatric disorders, particularly schizophrenia and autism. His group investigates both genetic and environmental risk factors, during developmental and in adulthood, and he has played a pivotal role in establishing state-of-the-art behavioural testing infrastructure at QBI, enabling high-throughput, automated operant-based cognitive assessments in rodents. In addition to his research leadership, Professor Burne has held several prominent service roles. He is a former President of Biological Psychiatry Australia, the Queensland representative for the Australasian Neuroscience Society, a current member of the NHMRC Animal Welfare Committee and Head of Brain Sciences for the Rebecca L Cooper Foundation.

Abstract: Title: Integrative Approaches to Modelling Neurodevelopmental Disorders in Rodents. A central objective in translational neuroscience is to elucidate the neurobiological mechanisms underlying psychiatric disorders using animal models. While no single model can fully recapitulate the complexity of human mental illness, targeted assays can provide valuable insights into specific pathophysiological processes. Our research program focuses on modelling neurodevelopmental disorders, particularly schizophrenia and autism, by integrating genetic, environmental, and behavioural approaches in rodents. This presentation will highlight three complementary strategies we employ to investigate the neural substrates of psychiatric risk. First, we examine how non-genetic factors, such as vitamin D deficiency, influence brain connectivity and function across developmental stages. Our findings suggest that vitamin D plays a critical role in shaping neural circuits, with implications for schizophrenia-related phenotypes and cognitive dysfunction. Second, we explore the impact of mutations in candidate risk genes identified through genome-wide association studies. Using genetically modified mouse models, we assess how these mutations affect cortical development and behavioural phenotypes relevant to intellectual disability and autism spectrum disorders. Third, we are advancing behavioural neuroscience by developing refined paradigms for assessing cognitive function in rodents. Notably, we have implemented a novel operant-based testing suite, including the Dynamic Strategy Shifting Task (DSST), to probe cognitive flexibility—an executive function often impaired in schizophrenia and related conditions. Together, these

approaches contribute to a mechanistic understanding of psychiatric disorders and support the development of more targeted therapeutic strategies.

Claire Foldi, Monash University

Biography: A/Prof Foldi leads the Neural Mechanisms of Eating Disorders Lab at Monash Biomedicine Discovery Institute (Monash BDI), which is devoted to uncovering the biological underpinnings of eating disorders. She is internationally recognised for her work on anorexia nervosa using a well-established bio-behavioural animal model known as activity-based anorexia (ABA). Her group also works across multiple animal models to understand the mechanisms though which psychedelics may be therapeutic for stress- and anxiety-related disorders. A/Prof Foldi currently sits on the executive of the Australian Eating Disorders Research & Translation Centre (AEDRTC), funded by the Commonwealth Department of Health. This role requires extensive collaboration and knowledge exchange with clinicians, service providers, and individuals with lived experience, ensuring that her research is both scientifically rigorous and socially relevant. Within the AEDRTC, she co-leads the Workforce Development stream through which she is working to develop and implement strategies to expand the capacity and capability of the eating disorders workforce. A/Prof Foldi is chair of the Anxiety working group of the CPPR, where she will support the development of a comprehensive framework for assessing and interpreting preclinical models and assays relevant to anxiety-related conditions.

Abstract: Title: Evaluating Preclinical Models of Anxiety-Related Disorders: Toward a Framework for Rigor, Relevance, and Translation. Preclinical models have been foundational for advancing our understanding of anxiety-related disorders, yet significant challenges remain in translating preclinical insights into new treatments. Our newly established consortium aims to systematically evaluate and catalogue existing models and behavioural assays, in order to develop a shared framework for designing and interpreting preclinical research in anxiety-related behaviours. This talk outlines the initial directions of our group, focusing on three core goals: (1) establishing a comprehensive, searchable library of models and assays; (2) defining quality metrics for preclinical research in anxiety; and (3) identifying opportunities for improved translational alignment. We will explore distinctions and potential redundancies between construct validity (e.g. genetic or environmental manipulations) and outcome measures (e.g. behavioural tasks, molecular markers), and critically evaluate whether such separations advance or hinder model utility. A key priority is the development of ranking criteria and guidelines for model selection based on disorder relevance, translation potential, and symptom-level correspondence with human anxiety presentations. We will also discuss the implementation of AI-based extraction tools to identify, organise, and maintain model data, and propose the use of dimensional, disorder-based clustering to align preclinical models with emerging human data sets. Ultimately, we seek to reconceptualise what makes a model “high quality,” integrating traditional screening outcomes with more nuanced understandings of disease-relevant behaviours and lived experience. This work lays the foundation for a shared resource that will support researchers, funders, and regulators in the selection and interpretation of preclinical anxiety models that are more translatable, transparent, and therapeutically meaningful.

Anthony Hannan, Florey Institute for Neuroscience and Mental Health

Biography: Prof. Hannan is a behavioural neuroscientist and medical researcher at the Florey Institute of Neuroscience and Mental Health, University of Melbourne. His group investigates gene-environment interactions and experience-dependent plasticity in the healthy and diseased brain. The research includes models of specific neurological and psychiatric disorders involving cognitive and affective dysfunction, investigated at behavioural, cellular and molecular levels so as to identify pathogenic mechanisms and novel therapeutic targets. Prof. Hannan provided the first demonstration in any genetic animal model that environmental stimulation can be therapeutic. This has led to new insights into gene-environment interactions in various brain disorders, including Huntington’s disease, depression, dementia, schizophrenia and autism spectrum disorders. Recent discoveries extend to epigenetic inheritance and the microbiota-gut-brain axis as modulators of cognitive and affective function, and dysfunction. Prof. Hannan completed his PhD in neuroscience from the University of Sydney before being awarded a Nuffield Medical Fellowship at the University of Oxford. He subsequently held other research positions before returning to

Australia on an NHMRC RD Wright Career Development Fellowship to establish a laboratory at the Florey Institute. He has won other fellowships and awards, including an ARC FT3 Future Fellowship, NHMRC Senior and Principal Research Fellowships, and the British Council Eureka Prize. He is a Fellow of the International Behavioural Neuroscience Society, Co-Chair of the International Brain Initiative, Co-Chair of the Australian Brain Alliance, and member of the National Committee for Brain and Mind, Australian Academy of Science.

Abstract: Title: Optimising Validity and Translatability in Mouse Models of Cognitive and Affective Disorders. This presentation will integrate what I have learnt from a wide variety of studies using preclinical mouse models, relevant to this symposium. We have examined the role of various molecular and cellular mediators, and environmental modulators, as they influence healthy cognitive and affective function, as well as cognitive and affective disorders. Our findings have revealed key pathways implicated in the therapeutic impacts of environmental stimuli and identified novel therapeutic targets. I will focus here on how we have attempted to optimize construct, face and predictive validity in various mouse models of psychiatric disorders, including schizophrenia, depression and anxiety disorders. I will also address the importance of studying gene-environmental and brain-body interactions, in these preclinical models. For example, using a transgenic mouse model of Huntington's disease (HD) we provided the first evidence for depression-like behaviours (and other endophenotypes) in a preclinical model of HD. This illustrates the utility of using monogenic models to understand complex polygenic psychiatric disorders. Furthermore, we have provided the first evidence of gut dysbiosis (dysregulated gastrointestinal microbiota) in Huntington's disease and a genetic model of schizophrenia. These kinds of approaches emphasize the concept that there may be no such as thing as a 'brain disorder'; they may all ultimately be 'brain-and-body disorders'. In order to understand how gene-environment interactions may sculpt brain development and function between generations, we have also been exploring epigenetic inheritance via the paternal lineage. The effects on offspring, including modulation of brain function and behaviour, via epigenetic inheritance, have particular relevance to the pathogenesis of depression and anxiety disorders. These findings also inform concepts of transgenerational 'epigenopathy', and their therapeutic implications. An overarching message is that all psychiatric disorders have their origins in development, via complex interactions between genetic and environmental factors (mediated by epigenetics and other processes). Optimal preclinical models need to incorporate this understanding, in order to develop (and test) more effective 'precision psychiatry' approaches for prevention and treatment. All of this will be placed in a broader context of how continuous bidirectional interactions between preclinical and clinical psychiatric research can enhance the validity of our animal models. This in turn will increase the likelihood of the discovery, and translation, of novel approaches to the prevention and treatment of psychiatric disorders.

Symposia Abstracts

Symposium 3. Heterogeneity in psychiatric disorders and attempts to identify reliable biological phenotypes

A common assumption in biological psychiatry is that the field will ultimately converge on a core neurobiological phenotype for distinct psychiatric disorders once a sufficient number of well-designed studies have been performed. However, after several decades of research, the field has so far failed to achieve such convergence. Instead, there is an increasing realization that current diagnostic constructs likely refer to multiple disorders that arise from distinct causes. This symposium presents different approaches to identifying more homogeneous subgroups of people with psychiatric disorders and biological underpinnings by investigating genetic heterogeneity in depression (Dr. Enda Byrne), examining brain associations of Affinity Scores across the psychosis continuum (Dr. Warda Syeda), assessing the reproducibility of grey matter differences in psychiatric disorders (Dr. Trang Cao), and reconciling the heterogeneity of bipolar disorder using multi-level models (Prof. Josselin Houenou). Given these approaches, Prof. Stephen Wood will discuss future directions for understanding biological phenotypes in psychiatric disorders.
This symposium has a mix of gender (2 female and 2 male speakers, 1 female chair and 2 male chair and discussant), academic levels (1 early career researcher, 1 senior research fellow, 4 professors), institutions (5 universities and centres), and geographic regions (Brisbane, Sydney, Melbourne) and diverse cultural and scientific background across participants.

Chairs and Discussants: Dr Trang Cao (Monash University), Prof. Alex Fornito (Monash University), and Prof. Stephen Wood (Centre for Youth Mental Health)

Dr. Enda Byrne, Child Health Research Centre, The University of Queensland

Biography: Dr Byrne is a statistical geneticist who leads the Child and Youth Mental Health Group at the University of Queensland. His work focuses on the genetics of psychiatric disorders, with particular interests in depression, neurodevelopmental conditions, and the statistical methods used to study complex traits. A major theme of his group's research is in identifying genetic risk factors for major depression and treatment response and in using genetic data to dissect heterogeneity in depression. This includes investigating the relationship between subtypes of depression such as perinatal depression and seasonal affective disorder. Dr. Byrne has played a key role in large-scale international collaborations, including the Psychiatric Genomics Consortium, contributing to studies that have identified genetic risk factors for a range of mental health conditions. His research also explores the overlap between psychiatric disorders and related behavioural and lifestyle traits, such as sleep and substance use. Furthermore, his group evaluates how polygenic risk scores can be integrated with clinical information to predict the onset and course of mental health problems in young people. He played a key role in establishing the Australian Genetics of Depression Study, one of the largest genetically informative depression cohorts in the world.

Abstract: Depression is a highly prevalent and disabling condition, with its burden expected to rise significantly by 2050. The heterogeneity of depression is evident in the wide variation of symptom presentations and comorbidities, complicating efforts to understand its biological underpinnings and to develop new treatments. Growing evidence suggests that distinct depressive subtypes exhibit unique biological underpinnings, and that these biological differences could potentially be driven by genetic variation. Genome-wide methods allow for investigating the genetic correlations between different subtypes and their application has shown that there is significant genetic heterogeneity at the subtype and symptom level. There are significant differences in heritability, genetic correlation and risk loci by subtype. This presentation will summarise recent findings on genetic heterogeneity in depression from studies in Australia and overseas, how it is linked to variation in clinical presentation and what the implications are for locus discovery, treatment, and understanding the mechanisms of action of identified variants. Findings on depression heterogeneity across five key domains—: symptomatology (including melancholic, atypical, and anxious depression, environmental effects (e.g., trauma, stressful life events), age of onset (early vs. late-onset depression), sex differences (including perinatal depression), and response to treatment— will

be presented. Future research directions needed to advance the field and move toward a more nuanced biological understanding of depression will be discussed.

Dr. Warda Syeda, Melbourne Brain Centre Imaging Unit, University of Melbourne

Biography: Warda Syeda, PhD, is a Research Fellow at the Melbourne Brain Centre Imaging Unit, Department of Radiology, University of Melbourne. Her research focuses on developing computational and neuroimaging approaches to understand brain-behavior relationships in neuropsychiatric and neurodegenerative disorders. She collaborates internationally with the Centre for Neuropsychiatric Schizophrenia Research (CNSR) in Denmark and has co-authored over 15 peer-reviewed publications in advanced MRI and computational psychiatry. Her work integrates quantitative MRI, multivariate modeling, and individualized metrics such as Affinity Scores to identify personalized markers of brain dysfunction across the psychosis spectrum.

Abstract: Psychotic disorders exist along a continuum of symptoms and cognitive impairments with high individual variability, making it difficult to link brain structure with clinical features. To address this, we applied Affinity Scores, an individual-centric framework that quantifies a person's similarity to different psychosis subgroups based on cognitive and clinical data. We analyzed data from 671 participants aged 18–60, including healthy controls, individuals at ultra-high risk, first-episode psychosis, and schizophrenia. Cognitive functioning and clinical symptoms were comprehensively assessed using standardized tools, and T1-weighted MRI data were analyzed using FreeSurfer with ENIGMA-compliant segmentation. Linear regression revealed significant associations between regional brain volumes and Affinity Scores across the psychosis continuum. Frontal, temporal, and parietal regions were linked with affinity to healthy controls, while orbitofrontal, fusiform, lingual, and paracentral regions were associated with higher affinity to clinical groups. These findings suggest that Affinity Scores capture individualized brain–behavior relationships and may serve as a potential neurobiological marker in psychotic disorders.

Dr. Trang Cao, Monash University

Biography: Dr. Trang Cao is currently a Research Fellow, working with Prof Alex Fornito, at School of Psychological Sciences, Monash University. She received her Ph.D. degree in engineering from the University of Melbourne, in 2020. In 2018 and 2019, she was a Visiting Research Scholar with the Friedrich– Alexander Universität Erlangen–Nürnberg, Germany. Her research currently focuses on using MRI to understand brain anatomy and function in both health and disease. She has leveraged her engineering expertise to develop novel mapping tools that examine brain activities and structural changes, based on geometric constraints.

Abstract: Over the past few decades, thousands of magnetic resonance imaging (MRI) studies reporting grey matter alterations in different psychiatric disorders have been published, but the field has failed to converge on a core neuroanatomical phenotype for any specific diagnosis. Here, we systematically investigate whether it is possible to achieve such convergence by evaluating the consistency of grey matter changes across 25 different studies of five distinct psychiatric disorders (schizophrenia, schizoaffective disorder, autism spectrum disorder, major depressive disorder, and bipolar disorder), collectively investigating 2542 people with psychiatric disorders and 2098 controls. We benchmark our consistency estimates to an additional 5 datasets consisting of 654 people with Alzheimer's disease and 937 controls, given the well-described neurodegenerative phenotype associated with this disease. We show that case-control grey matter differences found across sites for the same psychiatric disorder generally show low consistency, with median cross-site correlations for cortical thickness differences ranging between $0.01 \leq r \leq 0.15$ (for comparison, the median cross-site correlation in Alzheimer's disease is $r=0.54$). Moreover, we find that cross-site consistency within each disorder is not associated with heterogeneity in the demographic or clinical characteristics of the patient or control samples. Bootstrapping analyses indicate that consistent results ($r>0.5$) can be obtained for schizophrenia if study-specific sample sizes exceed approximately 250 (for cases and controls), but consistent findings for other disorders are more elusive.

Professor Josselin Houenou

Biography: Prof. Josselin Houenou is a newly appointed Professor of Psychiatry at Northern Health in the Department of Psychiatry, University of Melbourne. Previously to this, he did his medical studies (MD, Psychiatry) in Université Paris Est Créteil, France, as well as his PhD. He is also an alumni visiting school at the Douglas Mental Health Institute (Montréal, Quebec, Canada). He ran a lab of neuroimaging in psychiatry at the ultra high field NeuroSpin neuroimaging Platform from 2013 to 2025. His main focus of interest is on the study of bipolar disorder, schizophrenia and autism using structural and diffusion MRI.

Abstract: Bipolar Disorder(BD) is commonly viewed as a heterogeneous condition. We will demonstrate that this may be because most studies of its pathophysiology are observational and not based on models. For BD, such models usually integrate one or two biological scales (e.g. limbic reactivity and behavior). Models based on MRI have identified abnormal connectivity in limbic networks, either structural or functional as a core component of BD. In parallel, neuronal, synaptic and circadian abnormalities are present in most patients suffering from BD. Last, emotional hyperreactivity has been identified as a key feature of BD. Our aim is thus to build an integrated, multi-scale, whole-brain model of BD to reconcile these different lines of research and biological scales. We integrated the relevant existing literature in BD focusing on axonal reactivity, synaptic plasticity, connectomics, circadian disturbances, and emotional hyperreactivity to build a hypothesis driven framework of BD. We tested different models of BD based on simulation of whole-brain networks and designed a whole-brain model of BD based on anatomical and functional connectivity changes and integrating neuronal hyperexcitability, white matter and myelin changes, hyperexcitability of the amygdala, lack of synchronisation, and abnormal oscillations. Such an approach may reconcile the breadth of symptoms observed in the different patients with BD. Finally, our model is specific to BD (compared with depression and schizophrenia). We here provide a new whole-brain multi-scale model of BD attempting to reconcile heterogeneity in BD. Its predictions can be tested and the models refined and challenged, as in a classical scientific approach.

Symposium 4. Disrupted Sleep, Disrupted Minds: The Role of Sleep in Psychiatric Illness Across the Lifespan

Sleep and circadian rhythms are increasingly implicated in the onset, maintenance, and treatment of psychiatric disorders. Yet sleep remains chronically underrepresented in psychiatric research (and at psychiatric conferences), often regarded as a secondary symptom rather than a primary mechanism. This symposium addresses this gap directly, showcasing cutting-edge work from leading Australian researchers who are redefining the role of sleep across psychiatry. Spanning preclinical models to diverse clinical populations and intervention studies, the session provides an integrative, translational perspective on sleep as a modifiable target for mental health interventions.
In alignment with BPA's Equity and Diversity mission, our panel was intentionally selected to represent diverse career stages (first-year medical student, 2 x Senior Lecturer, 2 x Associate Professor), institutions and geography (USyd, UMelb, ANU, Monash), training (medical and PhD), and to include the perspectives of lived experiences (Luton, Estephan). The majority (80%) of our panel are women, and two out of three talks address sleep in psychiatric conditions relevant to women (postnatal depression and anorexia nervosa).

Chairs and Discussants: Assoc. Prof. Robyn Brown (University of Melbourne) and Dr. Morgan James (University of Sydney)

Dr. Morgan James, University of Sydney and Robert Wood Johnson Medical School (USA)

Biography: Dr. Morgan James Ph.D. is a translational neuroscientist and Horizon Fellow in the School of Psychology at the University of Sydney, where he leads a cross-disciplinary research program investigating how dysregulated arousal systems contribute to psychiatric vulnerability. He also holds a faculty appointment at the Robert Wood Johnson Medical School (Rutgers University, USA), where he maintains an active research lab. Dr. James integrates behavioural neuroscience, pharmacology, and systems-level approaches—including EEG/EMG, fiber photometry, and chemogenetics—to uncover mechanisms linking sleep, addiction, and cognitive dysfunction. A major focus of Dr. James' research is the orexin (hypocretin) system, which regulates arousal, sleep-wake dynamics, and motivated behavior. His lab has been at the forefront of identifying how disrupted orexin signaling contributes to comorbid sleep and psychiatric disturbances, including in substance use and eating disorders. Through both preclinical models and early-stage drug development, Dr. James' work seeks to leverage sleep as a modifiable target for reducing psychiatric risk and enhancing treatment outcomes. Dr. James completed his PhD at the University of Newcastle and postdoctoral training at the Medical University of South Carolina and Rutgers University, supported by NHMRC CJ Martin and Sir Keith Murdoch Fellowships. He established his lab in 2020 with a K99/R00 award from the National Institute on Drug Abuse and is currently supported by multiple NIH grants and foundation funding.

Abstract: Sleep disruption is among the most commonly cited reasons for return to use ('relapse') among cocaine users. Paradoxically, sleep worsens (not improves) across the first month of abstinence, highlighting this period as a critical period for intervention. To probe the brain mechanisms underlying this phenomenon, we developed a rat model that recapitulates abstinence-related sleep disruption observed in humans across a condensed timeline. Rats are trained to develop a cocaine-conditioned place preference (10 mg/kg, i.p.) followed by a 5-day abstinence period. EEG/EMG recordings reveal a progressive increase in wakefulness and a sharp decline in NREM (non-rapid eye movement) sleep across the abstinence period—mirroring human data. Fiber photometry recordings of hypothalamic orexin neurons show increased activity during the sleep (inactive) phase, aligning with EEG/EMG-defined wake events. Molecular analyses confirm elevated orexin mRNA and peptide expression. These changes in orexin levels are causally linked with sleep disturbances: both chemogenetic inhibition of orexin neurons and pharmacological blockade (via suvorexant, a dual orexin receptor antagonist) restore normal sleep architecture. Sleep normalisation also enhanced extinction of cocaine seeking and protected against

relapse triggered by cocaine priming. Further analyses revealed increased orexin innervation and orexin 1 receptor expression in ventral tegmental area (VTA) during abstinence, implicating this circuit in sleep-reward cross-talk. Consistent with this, chemogenetic dampening of orexin-VTA signaling improved sleep and suppressed drug seeking. Together, these findings identify orexin-driven sleep disruption as a mechanistic link between abstinence and relapse, and point to the orexin system as a dual-action therapeutic target to improve sleep and reduce cocaine vulnerability.

Assoc. Prof. Bei Bei, Monash University

Biography: Associate Professor Bei Bei Ph.D. is a Clinical Psychologist and NHMRC Emerging Leadership Fellow (EL2) at Monash University's School of Psychological Sciences and Turner Institute for Brain and Mental Health. She leads the Sleep and Mental Health Laboratory and serves as Head of Behavioural Sleep Medicine at the Monash University Healthy Sleep Clinic—a multidisciplinary service integrating clinical care, research, and professional training. Dr. Bei also holds an Honorary Senior Research Fellowship at the Royal Women's Hospital. Dr. Bei holds a Doctor of Psychology (Clinical) and a PhD from the University of Melbourne. Her research focuses on the interplay between sleep, circadian rhythms, and mental health, with particular emphasis on perinatal and adolescent populations. She has led pioneering studies on sleep variability, insomnia, and mood disorders, and is internationally recognized for advancing cognitive-behavioral treatments for sleep disturbances. She has contributed to global clinical guidelines, including the World Sleep Society's endorsement of behavioral therapies for chronic insomnia, and co-leads an international consortium investigating mechanisms of insomnia treatment. An advocate for public science communication, Dr. Bei regularly engages with media, schools, and community forums to promote evidence-based sleep practices.

Dr. Suzanne Estaphan, Australian National University

Biography: Dr. Suzanne Estaphan, MBBCh, MSc, PhD, SFHEA, is a Senior Lecturer at the Australian National University (ANU) with a longstanding interest in how physiological processes contribute to health, psychiatric, and behavioural outcomes. Her research explores the complex interdisciplinary interplay between biology, psychology, and culture in health and disease, with a particular emphasis on women's health across the lifespan. Suzanne is passionate about bridging basic science with clinical translation to inform holistic, evidence-based healthcare. Prior to her current role, Dr. Estaphan held academic and clinical positions in Egypt and has since established herself as an active researcher and committed educator in Australia. She is a Senior Fellow of the Higher Education Academy (SFHEA), a council member of the Australian Physiological Society (AuPS), and a member of the International Committee of the American Physiological Society (APS). Her international background and dedication to inclusive education underscore her commitment to fostering diversity within the scientific community.

Abstract: Sleep disturbances are increasingly recognised as both a consequence and contributor to the severity and persistence of eating disorders (EDs). Despite compelling epidemiological evidence linking poor sleep to disordered eating behaviours, the causal mechanisms and therapeutic implications remain underexplored. In this presentation, Dr. Estaphan introduce a model that positions sleep as a modifiable biobehavioural target in the treatment of anorexia nervosa (AN)- an eating disorder that, holds a lifetime prevalence rate up to 4% among females, and a mortality rate over five times higher than that of the general population. Drawing on interdisciplinary evidence from neurobiology, circadian science, nutrition, and clinical psychopathology, we present evidence that nutritional modulation of sleep—specifically using alpha-lactalbumin, a tryptophan-rich milk protein—offers a biologically plausible, acceptable, and scalable intervention approach. Ms. Luton will present preliminary qualitative findings from ongoing work exploring the perceptions of clinicians and individuals with lived experience regarding current gaps in sleep support for people with AN. Participants shared views on the acceptability and perceived feasibility of nutritional sleep interventions, preferred delivery formats, and potential implementation barriers. These insights not only support the relevance of our proposed model but also underscore the importance of co-design and contextual sensitivity in the development of novel interventions. Together, the conceptual and qualitative components of this work aim to inform future empirical testing and guide clinical innovation in the field of EDs, where sleep remains an underutilised but promising treatment target.

Ms. Rachel Luton, Australian National University

Biography: Ms. Rachael Luton is a postgraduate medical student at ANU, with a background in public health, psychology, and physiology. She has a strong interest in the neurobiological underpinnings of psychiatric disorders, particularly the role of non-pharmacological interventions in improving clinical outcomes. Supervised by Dr Estaphan and Prof. Rieger, Rachael is currently conducting qualitative research exploring patient and clinician insights into the acceptability and perceived barriers of using nutritional supplements—particularly alpha-lactalbumin—for sleep enhancement in anorexia nervosa. Rachael is committed to amplifying diverse voices in mental health research and to integrating lived experience into future psychiatric care models.

Abstract: Sleep and mental health are deeply intertwined during the perinatal period, yet longitudinal studies exploring their reciprocal influence—particularly in relation to infant sleep—remain scarce. In this presentation, I will share findings from a large, prospective study examining how maternal and infant sleep interact with maternal depressive and anxiety symptoms from late pregnancy to two years postpartum. A community sample of 163 first-time mothers (Mean age = 33.5, SD = 3.5) completed self-report measures of sleep (maternal and infant) and mood (depression and anxiety) across seven timepoints between 30 weeks' gestation and 24 months postpartum. Cross-lagged panel modelling revealed that depressive symptoms in late pregnancy predicted increased insomnia symptoms. Bi-directional associations between maternal sleep and mood were observed throughout the first two years, with maternal sleep at 6 months emerging as a robust predictor of future mental health. Concurrently, maternal and infant sleep were closely linked, though maternal mood was associated only with maternal—not infant—sleep. These associations remained consistent across demographic and clinical subgroups. In addition to these longitudinal findings, I will also present data from a 3-arm randomized controlled trial testing the effects of treating maternal insomnia and supporting infant sleep on maternal depression and anxiety. Together, these findings position maternal sleep as a critical—and modifiable—intervention target, with potential to improve mental health outcomes during the vulnerable perinatal period.

Highest Ranked Abstracts

Chair: Vanessa Cropley

Psilocybin augments dopamine responses during probabilistic reversal learning in female rats

Presenting Author: Kyna Conn (Biomedicine Discovery Institute, Monash University)

Gabriel Wong, *Biomedicine Discovery Institute, Monash University*
Catherine Huang, *Biomedicine Discovery Institute, Monash University*
Laura Milton, *Biomedicine Discovery Institute, Monash University*
Erika Greaves, *Biomedicine Discovery Institute, Monash University*
Claire Foldi, *Biomedicine Discovery Institute, Monash University*

Background
Cognitive inflexibility, i.e., the inability to adapt behavioural strategies when circumstances change, represents a fundamental mechanism underlying depression, anxiety, and eating disorders. Ventral striatal dopamine (DA) orchestrates this adaptive capacity by encoding prediction errors and signalling when established reward contingencies shift, making it essential for successful reversal learning. Despite the promising potential of psilocybin for alleviating mental ill health, and our prior demonstration that psilocybin enhances reversal learning in rats, the precise dopaminergic mechanisms remain unexplored. Understanding how psilocybin modulates DA signalling during cognitive flexibility tasks could unlock targeted interventions for the debilitating cognitive rigidity that perpetuates multiple psychiatric conditions.

Methods
In order to determine whether the cognitive benefits of psilocybin arise from enhanced ventral striatal dopamine signalling, adult female Sprague-Dawley rats (N=17) received viral injections of the dopamine biosensor (GRAB-DA2m) and fiber optic implants targeting the ventral striatum for real-time dopamine monitoring via fiber photometry. Following recovery, rats learned a probabilistic reversal task (80:20 reward contingencies) using nose-poke operant devices. Animals received psilocybin (1.5 mg/kg) or vehicle 24 hours before testing onset. We simultaneously recorded reversal learning performance and ventral striatal dopamine dynamics across 7 consecutive testing sessions to determine whether psilocybin alters trial-by-trial DA responses during flexible learning.

Results
Psilocybin significantly enhanced ventral striatal dopamine transient amplitude and duration following both expected and unexpected rewards ($p<.001$ and $p<.01$, respectively) compared to vehicle controls (n=4/group). Enhanced dopamine responses were also observed following expected losses ($p<.001$), but not unexpected losses. These neurochemical changes occurred alongside improved behavioural performance, with psilocybin-treated rats showing trends toward increased successful trial completion and reversal acquisition ($p=.052$). Dopamine signal modulation was sustained across all seven testing sessions, demonstrating persistent neurochemical effects 24 hours post-administration. This establishes that psilocybin robustly alters ventral striatal dopamine dynamics in a probabilistic reversal learning paradigm.

Conclusions
We show that psilocybin enhances phasic dopamine signalling in response to changing reward contingencies, which may underlie improvements in cognitive flexibility. The ventral striatum plays a critical role in processing reward outcomes by integrating motivational and value-related signals that guide adaptive decision-making. Therefore, dopaminergic tuning offers a plausible mechanism for psilocybin's therapeutic potential in disorders characterized by rigid or perseverative behaviour. Given that cognitive inflexibility perpetuates treatment resistance psychiatric disorders, our data suggest psilocybin may circumvent traditional therapeutic limitations by directly targeting the neurochemical substrates of maladaptive cognitions, potentially enabling breakthrough clinical responses where conventional interventions fail.

Highest Ranked Abstracts

Investigating the role of melatonin in bipolar disorder using transcriptomics

Presenting Author: Heather K Macpherson (Queensland Brain Institute, Asia Pacific Centre for Neuromodulation, The University of Queensland, Brisbane, Australia)

Trang T T Truong - Institute for Innovation in Physical and Mental Health and Clinical Translation, IMPACT, School of Medicine, Deakin University, Geelong, Australia
Michael Berk - Institute for Innovation in Physical and Mental Health and Clinical Translation, IMPACT, School of Medicine, Deakin University, Geelong, Australia
Ken Walder - Institute for Innovation in Physical and Mental Health and Clinical Translation, IMPACT, School of Medicine, Deakin University, Geelong, Australia
Susannah Tye - Queensland Brain Institute, Asia Pacific Centre for Neuromodulation, The University of Queensland, Brisbane, Australia; Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States; Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, United States

Background
Bipolar disorder (BD) is a serious psychiatric disorder characterised by mood and energy dysregulation. Pharmacotherapies are currently the foundation of BD treatment, but are often insufficient at managing psychiatric symptoms and may worsen physical health. Therefore, research is shifting toward repurposing existing medications to more effectively treat BD. Melatonin may be a potential therapeutic target for BD treatment; however, its role in BD pathophysiology remains poorly understood. This study aimed to investigate the therapeutic and mechanistic role of melatonin in BD using transcriptomics.

Methods
RNA-seq data from 216 post-mortem dorsolateral prefrontal cortex samples (156 healthy controls, 60 BD patients) were used to generate gene regulatory networks (GRNs). These were compared to lists of melatonin synthesis, signalling, and degradation genes using gene set enrichment analysis (GSEA) to assess differential expression between BD patients and controls. Furthermore, BD-associated gene regulatory patterns (GRPs) were compared to GRNs induced by melatoninergic agents (melatonin, agomelatine, ramelteon, and GR-135531) to evaluate the repurposing potential of these agents for BD. Finally, RNA-seq data from NT2-N cells treated with lithium, lamotrigine, valproate, or quetiapine were compared to melatonin-related genes using GSEA.

Results
Genes involved in inhibiting melatonin signalling were nominally significantly upregulated in the BD post-mortem gene expression dataset ($p=0.0399$, $q=0.1403$). Transcription factors (TFs) activating melatonin signalling tended to be downregulated in BD females ($p=0.0483$, $q=0.0552$), while TFs inhibiting melatonin signalling were significantly downregulated in BD males ($p=0.0055$, $q=0.0043$). In NT2-N cells, valproate significantly upregulated genes involved in melatonin degradation ($p=0.0003$, $q=0.0026$). The GR-135531 GRN was significantly dissimilar from BD GRPs in all sexes ($p<0.0001$), and in females ($p=0.0076$); and the agomelatine ($p=0.0021$) and ramelteon ($p=0.0478$) GRNs were significantly dissimilar from BD GRPs in males.

Conclusions
BD patients may have a decreased capacity to suppress genes related to oxidative stress, inflammation, and metabolic dysregulation, and melatonin therapy may work in these patients through regulation of the same genes. GSEA identified a significant upregulation of genes related to the degradation of melatonin in valproate-treated cells, which may explain why valproate treatment has been shown to reduce melatonin levels in clinical studies. Overall, this study provides new evidence that dysregulation of genes related to melatonin may play a role in the pathophysiology of BD, and suggests several melatonin receptor agonists as potential therapeutic candidates for BD.

Highest Ranked Abstracts

Sex differences in neural circuits driving binge drinking: A role for the basolateral amygdala

Presenting Author: Xavier Maddern (Florey Institute of Neuroscience and Mental Health, Parkville, 3052, Australia; Florey Department of Neuroscience and Mental Health, University of Melbourne, Parkville, 3052, Australia)

Qian Tan, Florey Institute of Neuroscience and Mental Health, Parkville, 3052, Australia; Biomedicine Discovery Institute and Department of Physiology, Monash University, Clayton, 3168, Australia
Amy J Pearl, *Florey Institute of Neuroscience and Mental Health, Parkville, 3052, Australia*
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Leigh C Walker, *Florey Institute of Neuroscience and Mental Health, Parkville, 3052, Australia; Florey Department of Neuroscience and Mental Health, University of Melbourne, Parkville, 3052, Australia*

Background
Binge drinking is the strongest predictor of alcohol use disorder (AUD). While men have historically had higher rates of alcohol use, binge drinking and AUD compared to women, these rates have converged significantly over recent decades, driven by escalated alcohol use in women. Problematically, despite known sex differences in alcohols neurobiological effects, most previous studies investigating alcohol use and misuse excluded female subjects. Consequently, understanding of sex differences in the neurobiological drivers of binge drinking remains limited, therefore the aim of this study was to map brain activity after binge drinking, and identify and functionally test key nodes and pathways.

Methods
Using Fos-protein immunohistochemistry, we first mapped ‘activation’ of 40 brain regions in male and female alcohol naïve, alcohol-anticipating and binge drinking mice (n=6-7/group/sex). A chemogenetic approach was then used to functionally inhibit the basolateral amygdala (BLA) to determine its role in binge drinking between sexes (n=7-8/group/sex). We then characterised the neurochemical phenotype of Fos-positive cells in the BLA during binge drinking through in situ hybridisation (n=4/sex). Complementarily, we performed retrograde tracing to examine ‘activation’ of BLA projections to the medial prefrontal cortex, nucleus accumbens core and shell, bed nucleus of the stria terminalis and ventral hippocampus during binge drinking (n=4-7/pathway/sex).

Results
Quantification of Fos-protein expression revealed a notable sex-specific increase in ‘activation’ of the BLA in female binge drinking mice compared to male binge drinking ($p=0.047$) and female alcohol naïve ($p=0.003$) counterparts. Further, chemogenetic inhibition of the BLA reduced binge drinking in female ($p=0.012$) but not male mice ($p=0.158$). There were no sex differences in the neurochemical phenotype (vGlut1, vGlut2, vGAT) of Fos-positive cells during binge drinking. However, there was preferential ‘activation’ of the BLA to nucleus accumbens core (AcbC) projection in female, compared to male, binge drinking mice ($p=0.003$).

Conclusions
This series of studies reveals important sex differences in ‘activation’ patterns, and the role of the BLA, in binge drinking. Ongoing work is underway to further add to this, by determining whether the BLA->AcbC projection critically mediates binge drinking in a sex-specific manner. Collectively, this work highlights the importance of considering sex as a biological variable and further contributes to the growing literature that suggests distinct neural circuits may drive alcohol-related behaviours between the sexes. Ultimately, the continued investigation of such sex differences in the field may unveil the need for personalised, sex-tailored treatments for alcohol misuse and AUD.

Data Blitz Abstracts - Session 1

Chair: Xavier Maddern

P_21b Associations between prenatal exposure to endocrine-disrupting compounds and preschool neurocognitive abilities: an Australian birth cohort

Presenting Author: Katherine Drummond

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Barwon Infant Study Investigator Group, Barwon Infant Study Investigator Group

Background
Endocrine-disrupting compounds (EDCs) are exogenous chemicals that interfere with hormonal systems, including environmental pollutants such as plastic-associated phthalates, phenols, and certain metals. EDCs are linked to altered neurodevelopment, including increased risk for autism and learning difficulties. However, studies report variable associations by compound, outcome, and child sex, in part due to heterogeneity in neurodevelopmental assessments. Neurocognition—including executive function (EF), language, and related skills—may offer a unifying framework for interpreting early neurodevelopmental risk. EF reflects core cognitive processes (e.g., inhibitory control) that support goal-directed behaviour. We examined associations between prenatal EDC exposures and preschool neurocognitive abilities.

Methods
Participants were from the Barwon Infant Study, a population-derived pre-birth cohort in regional Victoria, Australia (n=1,074). Maternal third trimester urine was analysed for EDCs, including phthalate and phenol metabolites, metals, and metalloids. At preschool age, children completed a neurocognitive battery (Dog-Koala Go/No-Go, Boy-Girl Stroop, NIH Toolbox® Picture Vocabulary). We used multivariable linear regression to estimate associations between individual EDCs and neurocognitive outcomes. Variable selection techniques were applied to identify key EDCs. To account for combined exposures, Bayesian kernel machine regression (BKMR) was used to assess the joint effects of a prenatal mixture of key EDCs on neurocognitive performance across tasks.

Results
Low molecular weight phthalates (LMWP)—mono-n-butyl phthalate (MnBP), mono-iso-butyl phthalate (MiBP), and mono-ethyl phthalate (MEP)—and metals (zinc, nickel, cobalt), were associated with neurocognitive delays. Higher prenatal exposure to the combined EDC mixture (ψLMWP and metals)—comparing the 90th to the 10th percentile of the mixture distribution—was associated with greater neurocognitive delays. Children with higher exposure showed greater delays in receptive vocabulary ability (NIH Toolbox® Picture Vocabulary Test: –2.94 points; 95% credible interval CI: –5.20, –0.67) and reduced inhibitory control (Boy-Girl Stroop correct responses: –0.61 hits; 95% CI: –0.85, –0.08).

Conclusions
In this population-derived Australian pre-birth cohort, elevated prenatal exposure to a mixture of EDCs—including low molecular weight phthalates and metals—was associated with neurocognitive delays across multiple domains by preschool age. These findings reinforce the prenatal period as a critical window of vulnerability and support the need for strengthened regulation of EDCs during pregnancy.

P_20b Paternal chronic bacterial-like infection induces multigenerational changes in offspring anxiety and cognition related to alterations of sperm small non-coding RNAs

Presenting Author: Da Lu

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Background
Paternal infections can shape behaviour across generations via epigenetic mechanisms including sperm non-coding RNAs, yet the outcomes of sustained immune activation remain poorly understood. While acute lipopolysaccharide (LPS) exposure alters anxiety and depression like responses in offspring, chronic bacterial-like infections, prevalent globally, produce persistent inflammation that may leave deeper multigenerational imprints. We therefore investigated whether prolonged paternal LPS treatment, modelling chronic bacterial-like infection in male C57BL/6J mice, modifies anxiety-related behaviours and cognition across two generations. Understanding how chronic paternal immune stress may program neurobehaviour through non-coding RNA-mediated pathways offers insights into inherited vulnerability and multigenerational transmission of mental health risks.

Methods
Eight-week-old male C57BL/6J mice received weekly intraperitoneal LPS injections (0.33–0.83 mg/kg) over six weeks. Body weight, food intake, and clinical scores were monitored daily. Four weeks post-treatment, males were mated with wild-type females. Sperm samples were collected for small RNA sequencing to profile non-coding RNA landscapes hypothesized to mediate epigenetic inheritance. Offspring underwent anxiety assessments including open-field, light–dark box, elevated plus maze, and novelty-suppressed feeding tests, cognitive evaluation via novel object recognition and Y-maze tasks, and associative learning testing with fear conditioning. Data was analyzed using mixed-effect models accounting for litter variability.

Results
Offspring from LPS-treated sires exhibited reduced anxiety-like behaviour, evidenced by increased exploration in open-field centres, elevated-plus maze open-arms, and light–dark box illuminated areas. Female offspring demonstrated enhanced object-recognition memory. This anxiolytic phenotype persisted transgenerationally, with grand-offspring males showing decreased feeding latency in the novelty-suppressed feeding and increased learning capacities in the fear conditioning test. Small-RNA sequencing of paternal sperm identified one upregulated microRNA, seven upregulated ribosomal-RNA-derived RNAs, and three differentially expressed transfer RNA-derived fragments. Gene ontology analysis of predicted targets further revealed enrichment in neural remodeling and synaptic transmission pathways, providing mechanistic insights into multigenerational behavioural inheritance through epigenetic mechanisms.

Conclusions
Our findings suggest that paternal chronic bacterial-like infection can alter offspring anxiety-like and cognitive behaviours, with altered sperm small-RNA cargos implicating an epigenetic transmission of psychiatric vulnerabilities. These findings identify paternal infection as an important contributor to heritable behaviour risk and highlight sperm non-coding RNAs as promising targets for future preventive interventions to mitigate anxiety-related disorders across generations.

P_19b Unravelling the Epitranscriptome: Convergence from Human Postmortem Brain to Preclinical Models

Presenting Author: Xiaoying Cui

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Background
Schizophrenia is a severe neurodevelopmental disorder characterised by cognitive, emotional, and behavioural impairments. Although its etiology remains unclear, transcriptomic studies of postmortem brain tissue provide valuable insights into disease mechanisms. However, consistent patterns of transcript dysregulation have not been observed, potentially due to the presence of alternatively spliced variants. These splicing events can significantly alter protein function and lead to opposing physiological outcomes. RNA modifications are emerging as key regulators of alternative splicing. To explore how RNA modifications contribute to splicing diversity and disease pathophysiology, we examined epitranscriptomic changes in the caudate nucleus using combined human and dopamine-based preclinical models.

Methods
We performed direct RNA sequencing (dRNA-seq) on postmortem caudate nucleus samples from individuals diagnosed with schizophrenia and age- and sex-matched controls. Sequencing was conducted using the Oxford Nanopore platform, allowing native RNA analysis with full-length isoform resolution. To examine if observed transcriptomic changes were dopamine-dependent, we used the EDiPS rat model (Enhanced Dopamine in Prodromal Schizophrenia), which mimics elevated striatal dopamine levels observed in patients. In parallel, we conducted methylated RNA immunoprecipitation followed by sequencing (MeRIP-seq) on EDiPS striatal tissue to identify dopamine-responsive RNA methylation (m6A) changes.

Results
In human schizophrenia caudate samples, we detected significant alterations in RNA splicing patterns, with differential exon usage in transcripts enriched for postsynaptic dopaminergic, GABAergic, and glutamatergic signalling pathways. These alternative splicing events may reflect underlying changes in RNA modification. In the EDiPS model, MeRIP-seq revealed elevated m6A methylation in transcripts involved in similar synaptic pathways, supporting the hypothesis that dopamine drives the regulation of RNA methylation. Furthermore, several of the genes altered in EDiPS overlapped with those showing splicing variation in schizophrenia samples, suggesting a convergent mechanism linking dopamine dysregulation with epitranscriptomic remodelling.

Conclusions
This is the first study to generate a direct RNA sequencing dataset from postmortem caudate tissue in schizophrenia, offering novel insights into native transcriptome alterations in the disorder. The convergence between human and EDiPS model data strengthens the hypothesis that dopamine dysregulation contributes to altered RNA modification, which may influence synaptic gene expression and splicing outcomes. Our findings suggest that RNA methylation may play a causal role in disease pathogenesis. Furthermore, this work highlights the utility of translational models, such as EDiPS, in linking molecular alterations to schizophrenia-relevant neurobiology, paving the way for RNA-targeted interventions.

P_18b Connectivity alterations underpinning negative self-cognition processing in binge eating

Presenting Author: Po-Han Kung

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Background
Disordered binge eating is often perpetuated by the emotional distress caused by entrenched negative cognitions about the self, food, and body image. Psychotherapy for binge eating therefore aims to identify and restructure these negative cognitions. Despite its clinical significance, the neural mechanisms supporting negative cognition processing and how this may be altered in binge eating remain unexplored.

Methods
Combining ultra-high field 7-Tesla fMRI and a negative cognition paradigm, we mapped and compared whole-brain connectivity during the repetition and cognitive restructuring of negative self- and binge eating-related beliefs in 65 young adults experiencing disordered binge eating (Mean age=27.14; 86.15% female) and 76 healthy control participants (Mean age=26.86; 77.03% female). General psychophysiological interaction (gPPI) analysis was used to estimate the pair-wise functional connectivity between 214 cortical and subcortical regions-of-interest during the repeating versus challenging of negative cognitions (pFDR < .05). LASSO logistic regression with 10-fold cross-validation was then implemented to select the connectivity parameters predictive of binge eating group membership.

Results
The winning LASSO model (λ = 0.076; accuracy = 0.80, AUC = 0.92) identified 23 connectivity parameters that were predictive of binge eating. Most prominently, the binge eating group was characterised by increased functional connectivity between prefrontal nodes of the dorsal attention, cingulo-opercular and salience networks (β = 0.56-1.01) during the repeating of negative cognitions compared to restructuring, as well as decreased connectivity between the superior frontal gyrus and the putamen (β = -0.36).

Conclusions
Increased attentional and salience network engagement during the repeating of negative self-beliefs may contribute to maladaptive thinking patterns in people experiencing binge eating. Whereas the reduced communication between the prefrontal cortex and putamen may underlie impaired integration of goal-directed and habit-related signals, potentially hindering the shift away from negative cognitions. These findings provide novel insights into potential neural vulnerabilities of persistent negative cognitions that reinforce disordered binge eating, thereby expanding neurobiological models of binge eating to consider complex, higher-order mental processes.

P_17b Genetic and Network-Based Constraints on Gray Matter Volume Changes in Psychosis

Presenting Author: Gabriella Chan

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Background
Differences in regional grey matter volumes (GMV) are a common finding in MRI studies of psychotic illness, occurring consistently within disease-related functional networks. However, the mechanisms that shape the spatial patterning of these changes remain unclear. Recent studies suggest that GMV reductions propagate along white matter tracts within brain networks. Here, we expand on existing models of GMV changes by integrating interactions between brain networks and genetic risk factors. Specifically, we apply an epidemiological agent-based spreading model to simulate the movement of pathological gene products along the connectome and predict the resulting spatial pattern of GMV reductions.

Methods
Grey matter volume changes were assessed using voxel-based morphometry analyses on T1-weighted MRI data from 17 scan sites (964 healthy controls and 800 patients). Structural connectivity was derived from diffusion MRI data, producing a group-averaged connectome with 35% binary density. Gene expression profiles across the whole brain were provided by the Allen Human Brain Atlas. Our disease model employed an agent-based Susceptible-Infected-Removed (SIR) model, simulating disease progression based on gene expression within regions and connectivity between regions. Model performance was compared with spatial null models generated using the BrainSMASH toolbox and rewired connectome nulls using the Maslov-Sneppen algorithm.

Results
We simulated pathological processes and subsequent atrophy across all pairwise combinations of potential risk and clearance genes. The resulting simulated atrophy maps were compared with empirical atrophy maps to determine to identify the highest spatial correlation for each gene pair. Across all gene pairs, peak model fit reached r=0.71. Simulated atrophy from gene pairs with high model fit significantly outperformed null models for both spatial and rewired null comparisons. Gene enrichment analysis on highly performing genes revealed significant enrichment in terms associated with synaptic signalling and protein translation.

Conclusions
Our agent-based model integrates genomic and connectomic data to model the spatial distribution of GMV reductions in schizophrenia. Our results indicate that disease processes, shaped by region-specific gene expression, accumulate locally and propagate along the connectome to shape the distribution of GMV changes in psychosis. We identify altered neurotransmission and cytoplasmic translation as key biological processes associated with GMV changes in schizophrenia.

P_16b Amygdala-PFC and Hippocampus-PFC Functional Connectivity Specialisation in Normal Development and Adversity

Presenting Author: Wonyoung Kim

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Background
Childhood adversity is a key risk factor of affective disorders including anxiety and depression. The neurobiological effects of childhood adversity on frontolimbic functional connectivity (FC) are well-established but spatially inconsistent across studies and lacking a developmental benchmark. We aimed to provide a unifying framework by establishing the neurodevelopmental principle of amygdala and hippocampus FC pattern across the frontal cortex.

Methods
In a large developmental cohort (HCP-D; N = 652; ages 5-21), we quantified an individual's amygdala-frontal and hippocampus-frontal FC patterns' resemblance to a normative young adult FC template (HCP-YA; N = 1,084; ages 22-35). Then, to capture the degree to which the frontal FC pattern of a given amygdala or hippocampus voxel is more "amygdala-like" versus "hippocampus-like," we calculated the difference between the two resemblance scores. We used this metric to examine the relationships between specialisation of FC patterns, age, and childhood adversity. Key findings were subsequently tested for replication in an independent cohort (PNC; N = 898; ages 8-23).

Results
FC pattern of the amygdala progressively resembled the amygdala FC template over the hippocampus FC template as individuals aged ($r = 0.357$, $P < 0.001$). Greater exposure to adversity in the past year was associated with advanced maturation in how the amygdala showed more uniquely amygdala-like FC ($r = 0.113$, $P = 0.004$). In the PNC cohort, the spatial pattern of age effects across the amygdala and the hippocampus was replicated ($r = 0.190$, $P_{brainSMASH} < 0.001$). Cumulative exposure to trauma events was correlated with the advanced maturation of the amygdala FC in PNC ($r = 0.071$, $P = 0.034$).

Conclusions
We revealed a neurodevelopmental principle of the frontolimbic circuit, whereby the amygdala and the hippocampus become more spatially specialised in their frontal FC patterns over development. An early maturation of this neurodevelopmental principle is related to prior experience of adversity. This framework may serve as an explanation for the previously reported spatial inconsistencies as well as a generalizable normative developmental model on which childhood adversity can be understood.

P_15b Menstrual Characteristics and Mental Health in Adolescent Girls: Insights from the ABCD Study®

Presenting Author: Sushma Marla

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Background
Adolescence is a critical period for mental health challenges, including depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD). While ADHD typically begins earlier, symptoms may fluctuate during adolescence due to hormonal changes. Menstrual characteristics, such as early menarche, irregular cycles, and pre-menstrual symptoms (PMS), reflect neuroendocrine stress and have been associated with increased psychiatric symptoms. These features are seldom incorporated into longitudinal models of adolescent mental health. Leveraging data from the Adolescent Brain Cognitive Development (ABCD) study, this research investigates whether menstrual characteristics in early adolescence predict internalizing and externalizing symptoms, aiming to identify early biological markers of psychiatric vulnerability in girls.

Methods
This study used data from the ABCD Study® (release 5.1), a large U.S. longitudinal cohort. We included nearly 5,200 female participants aged 9-14 years with data available on menstruation, mental health, BMI, and genetic ancestry. Self-reported menstrual variables included age at menarche, time since menarche, cycle regularity/length, and PMS. Mental health outcomes (ADHD, anxiety, depression) were based on CBCL DSM oriented subscales. Associations between menstrual characteristics and psychopathology were tested using generalized linear mixed-effects models (GLMMs), adjusting for age, BMI, and ancestry. Random intercepts accounted for repeated measures across waves. Analyses were performed in R using harmonized, multi-wave ABCD data.

Results
Earlier menarche was associated with increased depressive and anxiety symptoms. Girls further along in pubertal development, particularly ≥2 years post-menarche, is associated with higher internalizing symptoms, whereas being pre-menarcheal is linked to lower ADHD symptom scores. PMS severity correlated with elevated mental health symptoms: all PMS levels (mild, moderate and severe) were associated with increased depression and heightened anxiety scores. Regardless of age at menarche, girls ≥2 years post-menarche exhibited higher anxiety symptoms and greater PMS severity. The effects of ≥2 years post-menarche and PMS severity remained independent in multiple regression analyses. Menstrual cycle regularity/length was unrelated to symptoms.

Conclusions
This study reveals significant associations between menstrual timing, PMS, and mental health symptoms in adolescent girls. Early menarche and greater PMS severity are linked with increased depression and anxiety, suggesting reproductive factors influence psychiatric risk during adolescence. Incorporating menstrual health into mental health assessments could enhance early detection and intervention strategies.

P_14b Discrete, cell-specific changes in cortical gene expression in a subgroup of schizophrenia characterised by low levels of the muscarinic receptor, CHRM1.

Presenting Author: Andrew Gibbons

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Brian Dean, *Department of Psychiatry, Monash University*
Mohammad Asghari-Jafarabadi, *Department of Psychiatry, Monash University*
Rachel Hill, *Department of Psychiatry, Monash University*
Wittaya Suwakulsiri, *Department of Psychiatry, Monash University*
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Background
The recent FDA approval of Xanomeline/Trospium-Cl for treating schizophrenia highlights an important role for cholinergic muscarinic receptors (CHRM) in mediating the symptoms of schizophrenia. This is significant as we identified a subgroup, comprising approximately one third of individuals with schizophrenia, who have lost over 70% of CHRM1 in the cortex. We termed this group the Muscarinic Receptor Deficit Subgroup of schizophrenia (MRDS). As cortical CHRM1 is predominantly expressed by pyramidal neurons, we hypothesised that individuals with MRDS will have cell-specific differences in gene expression compared with healthy controls and non-MRDS schizophrenia. We used single nuclei (sn)RNASeq to identify these differences.

Methods
Nuclei were isolated from post-mortem, dorsolateral prefrontal cortical tissue from 7 subjects with MRDS schizophrenia, 9 subjects with non-MRDS schizophrenia and 16 non-psychiatric control subjects. snRNASeq was then performed using the 10X Chromium Next GEM system, capturing ~9000 nuclei/sample with a read depth of 70 million reads/sample. Sequencing data was clustered using Cell Ranger and analysed using an R-based pipeline. Clusters were annotated with Seurat using cell and cortical laminae-specific markers and pseudo-bulk differential expression was analysed using EdgeR followed by gene enrichment and pathway analysis.

Results
The MRDS and non-MRDS groups displayed distinct, cell-specific profiles of differentially expressed genes when compared to controls, with only 3.8% ± 0.2% (mean ± SE) of differentially expressed genes in MRDS also being altered in non-MRDS in each identified cell cluster. Pathway analysis revealed that genes involved in glutamatergic signalling were in the top altered pathways in the excitatory neurons of laminae V and VI, and oligodendrocytes in MRDS, but not non-MRDS, compared to controls. Comparing differentially expressed genes between the MRDS and non-MRDS groups, cholinergic-related pathways were altered in the excitatory neurons of lamina V from subjects with MRDS.

Conclusions
Our data suggests that MRDS is a molecularly-distinct subtype of schizophrenia characterised by discrete, cell-specific changes in gene expression within the dorsolateral prefrontal cortex. The prominent changes in glutamatergic signalling pathways in populations of excitatory neurons and the differences in cholinergic pathways seen in Laminae V excitatory neurons suggest that disruptions to excitatory neuronal functioning may be important to the pathology of MRDS. In light of the recent recognition of muscarinic receptors as viable drug targets for the treatment of schizophrenia, our findings have important implications for identifying novel drug targets and directing appropriate treatments for individuals with MRDS.

P_13b Structure-Function Coupling in Depression in Premanifest Huntington's Disease: A Hierarchical Empirical Bayes Approach

Presenting Author: Tamrin Barta

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Matthew Greaves, *Monash University*
Leonardo, *Novelli*
Yifat Glikmann-Johnston, *Monash University*
Adeel Razi, *Monash University*

Background
Depression is one of the most impactful features for Huntington's disease (HD) gene expansion carriers (HDGECs). In HD there is inverse relationship whereby stronger structural connectivity is associated with weaker functional activity (McColgan, Gregory, et al., 2017), and depression in HDGECs is associated with increased functional connectivity within default mode network (DMN) alongside decreased structural connectivity between DMN and basal ganglia (McColgan, Razi, et al., 2017). Structure-function coupling (SFC) has emerged to understand disease-related network reorganization (Fotiadis et al., 2024). We investigated if HD pathogenesis forces depression functional networks to collapse toward structural constraints, or engenders decoupling through compensation.

Methods
We analysed 3T resting-state fMRI and DWI data from 98 HDGECs (30 with a history of depression). DWI data was pre-processed using MRtrix3 (v3.0.3), FSL (v6.0.4), and ANTs (v2.4.3), and fMRI was pre-processed using fMRIPrep (v21.02.2)and MRIQC (v22.0.6). ROIs included medial prefrontal cortex, posterior cingulate and hippocampi for DMN, as well as caudate and putamen for striatum. We employed a novel hierarchical empirical Bayes (HEB) model (Greaves et al., 2025) that leverages structural connectivity-based group level priors for spectral dynamic causal modelling, enabling both between-group structure-function coupling comparisons and refined subject-level posterior estimates through a three-level Bayesian framework.

Results
DWI analysis revealed no significant differences in edge or node strength between HDGECs with depression history versus without. HEB analysis showed HDGECs with depression history demonstrated systematically lower prior variances (range: 0.05-0.25) compared to no-depression (0.1-0.4), indicating stronger structure-function coupling. Mean log-Bayes factors were higher in HDGECs with depression history (29.6) versus no-depression (8.5), indicating stronger model evidence for structure-function coupling relationships. When examining effective connectivity, the structurally-informed HEB model revealed similar directional changes in DMN and striatal connectivity compared to uninformed approaches, but with greater posterior expectations.

Conclusions
Our findings suggest that in HDGECs, disease-related pathogenesis forces depression networks to collapse toward structural constraints rather than operating through compensatory decoupling mechanisms. Additionally, structural priors enhanced the confidence and magnitude of effective connectivity estimates, demonstrating the value of structure-informed modelling approaches in understanding HD-related network reorganization.

P_12b Circular RNA expression signatures in Alzheimer's disease highlights dysregulated molecular mechanisms and disease progression

Presenting Author: Oak Hatzimanolis

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Background
Circular RNAs (circRNAs) are covalently closed, non-coding RNAs increasingly recognised as regulators of gene expression in neurodegenerative disorders, including Alzheimer's disease (AD). Their stability, neural tissue specificity, and regulatory potential make them attractive candidates for biomarker development and therapeutic targeting. Yet, the landscape of circRNA dysregulation in AD, and the prodromal stage of mild cognitive impairment (MCI), remains poorly defined. Human olfactory neurosphere-derived stem (ONS) cells, obtained from patient olfactory mucosa, provide a physiologically relevant and accessible model for studying molecular changes in neurological disease. Here, we investigate circRNA expression patterns in AD and MCI using patient-derived ONS cells.

Methods
We analysed total RNA from 18 ONS cultures representing AD (n=6), MCI (n=6), and healthy controls (n=6). Libraries were generated using ribo-depleted RNA-sequencing and read output was processed through a custom circRNA detection and quantification pipeline optimised for backsplice junction identification. Differential expression analyses were conducted between each disease group and controls, followed by gene ontology and pathway analysis. To assess reproducibility, we compared our results with circRNA datasets from 18 independent previously published datasets spanning postmortem brain and plasma. Cross dataset concordance was evaluated at both circRNA isoform and parent gene levels to identify robust AD associated circRNAs.

Results
We detected 1,584 high confidence circRNAs, and an average of 20 significantly dysregulated in each ONS cell comparison group. CircPICALM and circANKIB1 were consistently upregulated in both AD and MCI. Functional analysis revealed associations with AD-relevant processes, including tau protein binding, glycoprotein metabolism, and endoplasmic reticulum stress. Cross validation with external datasets identified 49 overlapping circRNA-producing genes, encompassing 28 specific isoforms. Several originated from genes implicated in AD pathogenesis, including PICALM, MAN1A2, and ZNF292. Notably, circPICALM demonstrated consistent upregulation across datasets and sample types, reinforcing its potential as a robust biomarker candidate for both early and established stages of AD.

Conclusions
This study provides a comprehensive circRNA expression profile in AD and MCI using patient-derived ONS cells, validating key findings across multiple independent datasets. The consistent dysregulation of circRNAs highlight potential biomarker panels and therapeutic targets in AD. Functional analyses link dysregulated circRNAs to core pathogenic pathways, including protein aggregation, altered glycosylation, and cellular stress responses. Our findings establish ONS cells as a valuable model for mechanistic circRNA studies in neurodegeneration and support the broader application of circRNA profiling for diagnostic and therapeutic development in AD and related disorders.

Data Blitz Abstracts - Session 2

Chair: Bruna Panizzutti

P_11b Sexually Dimorphic Disruptions to Parvalbumin and Somatostatin Interneurons in Mice Carrying the ArxR264Q Mutation

Presenting Author: Victoria Edwards-Poulton

Victoria Edwards-Poulton, *Monash University*
Ariel Dunn, *Monash University*
Suresh Sundram, *Monash University*
Rachel Hill, *Monash University*

Background
Schizophrenia is a severely debilitating psychiatric disorder with strong genetic heritability. Our laboratory identified a novel ARX gene mutation in a female with schizophrenia. ARX is crucial for migration and differentiation of GABAergic interneurons, including subtypes expressing somatostatin or parvalbumin. These interneurons are key modulators of synchronised neural network firing and are reduced in patients with schizophrenia. In order to understand the specific role of the ARX mutation that we identified, we generated a mouse model called ArxR264Q. ArxR264Q mice exhibited sex-specific sensorimotor, cognitive and socialisation phenotypes relevant to schizophrenia.

Methods
We now aimed to assess how the ARXR264Q genotype affected parvalbumin and somatostatin interneuron densities, and whether this affect was specific to sex. We postulated that parvalbumin and somatostatin interneuron subtype densities would be affected by genotype - and potentially also by sex - given the X-linked location of the ARX gene, in brain regions relevant to schizophrenia symptom domains. To elucidate cellular density changes, immunohistochemical procedures and IMARIS-assisted quantification were performed to analyse PV and SST interneuron densities (cells/mm2) in regions pertinent to schizophrenia, namely the prefrontal cortex, striatum, pallidum, hippocampus, amygdala, subiculum as well as white matter tracts.

Results
A sex-specific effect of genotype is present on SST and PV interneurons in the PFC, striatum and white matter tracts where male ArxR264Q mice demonstrate significant increases in PV ($p<0.05$) and SST ($p<0.05$) densities whilst females show decreases ($p<0.05$) or no change. In the amygdala, PV deficits were male-specific ($p<0.001$), yet, both sexes show deficits in SST density ($p<0.0001$). In the pallidum, a region critical for rodent social recognition, SST reductions were female-specific ($p<0.001$) while both sexes of ArxR264Q mice displayed decreased PV density ($p<0.0001$). Hippocampal PV and SST densities were decreased in ArxR264Q mice ($p<0.05$), irrespective of sex.

Conclusions
The results suggest the mutation has disrupted PV and SST interneuron cell density across all regions studied, excluding the subiculum. These cellular alterations may contribute to the behavioural phenotypes observed in the model, which are relevant to symptom domains of psychiatric disorders such as schizophrenia. In addition, we identified striking sex-specific effects on cell densities in the PFC, striatum, pallidum, amygdala, hippocampus, and white matter tracts, highlighting the clearly sexually dimorphic role of this gene. Overall, the findings suggest sex-specific and region-specific regulation of PV and SST interneuron cell densities in ARXR264Q mutant mice.

P_10b Harnessing DNA Methylation to Disentangle Heterogeneity in Schizophrenia

Presenting Author: Dylan Kiltschewskij

Dylan Kiltschewskij, *The University of Newcastle*
William Reay, *Menzies Institute for Medical Research*
Murray Cairns, *The University of Newcastle*

Background
Schizophrenia is a debilitating psychiatric condition marked by profound heterogeneity in onset, progression, severity and treatment response. This heterogeneity poses a major challenge for effective intervention, as it necessitates personalised approaches to treatment that account for each individual's unique combination of genetic and environmental risk factors. DNA methylation offers a powerful lens for capturing these influences, as it reflects dynamic interactions between genetic predisposition and environmental exposures. While altered DNA methylation has been observed in schizophrenia, its potential for elucidating heterogeneity remains underexplored.

Methods
To address this, we recently conducted the first meta-analysis of DNA methylation variability in schizophrenia to pinpoint genomic loci with significantly higher or lower variance compared to non-psychiatric controls. This was conducted using blood methylation data from three publicly available cohorts (Nsz = 1036, NCtrl = 954). Changes in DNA methylation variability were determined via Levene's test and meta-analysed across cohorts using Stouffer's weighted method. Methylation sites with significantly altered variance between cases and controls were subject to a battery of analyses assessing their genomic organisation, brain enrichment, and association with schizophrenia progression and severity.

Results
We identified 213 variably methylated positions (VMPs) after correction for multiple testing. Interestingly, VMPs with increased variance in schizophrenia were significantly overrepresented among brain-enriched genes, and in several cases exhibited concordant changes in post-mortem cerebellum, hippocampus, prefrontal cortex and striatum. These loci also revealed individual-level methylation outliers among schizophrenia cases, suggesting that VMPs may mark biologically relevant sites of dysregulation in specific individuals. Furthermore, these VMPs correlated with methylation patterns previously linked to clinical measures of progression and severity, such as cognitive deficits and global assessment of function scores.

Conclusions
Collectively, our findings highlight specific genomic loci that may contribute to schizophrenia risk in a subset of individuals, rather than uniformly across the population. This work positions DNA methylation variability as a compelling molecular signature for reconciling clinical and biological heterogeneity in schizophrenia.

Data Blitz Abstracts - Session 2

P_9b Towards Precision Psychiatry: Combining Clinical Complexity and Brain Connectivity for TMS Outcome Prediction

Presenting Author: Nga Yan Tse

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Background
Clinical factors and brain connectivity are well-established predictors of transcranial magnetic stimulation (TMS) treatment outcomes. Increasing evidence suggests that these two factors may interact to influence antidepressant response; however, they are seldom examined concurrently in past TMS prediction studies.

Methods
In a large, combined sample of 96 adults with treatment-resistant depression who received either optimised connectivity-guided (Brisbane cohort; n=59) or conventional (Melbourne cohort; n=37) TMS treatment, we evaluated the predictive performance of models based on: 1) whole-brain functional connectivity maps of symptom improvement (i.e., R-map), 2) clinical complexity factors, and 3) the combination of both, controlling for the effect of site.

Results
The integrated model combining clinical complexity and functional connectivity characteristics yielded the best prediction accuracy with the highest robustness against inter-site variability, outperforming the univariate models based on clinical or functional connectivity factors alone. Notably, total illness duration (r=.21; p=.036) and prior treatment failures (r=.22; p=.035) emerged as the only significant factors driving the superior outcome prediction, overall pointing towards treatment refractoriness as a key clinical determinant of TMS outcome. Further, whole-brain voxel-wise analysis revealed a significant interaction effect between symptom improvement and clinical complexity (FWE-corrected p =.037), with the stringent inclusion of site, symptom improvement, and clinical complexity as covariates. Specifically, negative connectivity between the stimulation site and select regions including the subgenual anterior cingulate cortex (sgACC), caudate, and ventromedial prefrontal cortex (vmPFC) was associated with greater symptom improvement, selective to those with high clinical complexity (r =-.40; p =.005).

Conclusions
Together, these findings underscore the prognostic significance of integrating clinical and neurobiological factors in TMS outcome prediction. We also identify a connectivity marker of symptom improvement specific to high clinical complexity. Expansion of targeting beyond the canonical DLPFC-sgACC circuit to include the vmPFC and caudate may enhance treatment response in complex presentations via potentially more targeted engagement of the fronto-striatal-limbic circuitry.

Data Blitz Abstracts - Session 2

P_8b Mendelian randomisation and colocalisation reveal pleiotropic effects of CD40/SLC12A5 locus on CD40 protein, depression, and immune disease

Presenting Author: Sarah Cohen-Woods

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Background
Depression is a leading cause of global disease burden, yet the biological mechanisms contributing to the disorder remain unclear. Inflammatory pathways have been implicated; however, the causal roles of specific immune proteins and variants are not well established. Determining causality is challenging, and while genome-wide association studies have linked immune-related loci to depression, identifying precise effector genes remains difficult. Mendelian randomisation (MR) can help elucidate causal effects by using genetic variants as instrumental variables and integrating functional data. Here, we apply MR methods to leverage large-scale GWAS and proteomic data to disentangle the relationship between immune factors and depression.

Methods
We conducted a two-sample Mendelian randomisation (MR) analysis using generalised summary Mendelian randomisation (GSMR) to investigate causal relationships between 91 immune-related plasma proteins and depression. Genetic instruments were derived from a large-scale protein quantitative trait locus (pQTL) meta-analysis and applied to a genome-wide association study (GWAS) of depression (n = 294,322 cases, 741,438 controls). Primary findings were validated via an independent replication cohort, and sensitivity analyses using alternative MR methods. Pairwise and multi-trait colocalisation analyses assessed potential confounding by linkage disequilibrium (LD) and shared genetic architecture. A phenome-wide association study (PheWAS) explored downstream biological pathways associated with identified variants.

Results
We identified a robust association between CD40 protein levels and depression (OR: 0.95, 95% CI: 0.94 - 0.97, $p = 1.71 \times 10^{-11}$), driven primarily by cis-acting variants. Pairwise colocalisation analyses indicated distinct – though not independent – lead variants for CD40 protein and depression, suggesting linkage disequilibrium was driving the effect. eQTL analyses prioritised SLC12A5 as the likely effector gene for depression risk at this locus. A phenome-scan demonstrated that the CD40 protein lead variant was predominantly associated with inflammatory disorders, whereas the depression lead variant showed stronger links to psychiatric conditions, revealing distinct biological pathways at this locus.

Conclusions
Our findings demonstrate pleiotropic effects at the CD40/SLC12A5 locus and emphasise the importance of combining mendelian randomisation with colocalisation analyses to disentangle shared genetic effects at loci with complex genetic architecture. While our results do not support a causal role for plasma CD40 protein levels in depression, SLC12A5-mediated effects may contribute to its pathophysiology, likely acting through brain-specific mechanisms. These findings refine the pathophysiological model of depression and highlight the relevance of immune-brain interactions. SLC12A5 emerges as a promising effector gene and priority target for future functional and multi-omic studies to advance mechanistic insight and therapeutic development.

P_7b Role of oestradiol and progesterone variability in brain structure and mental health in adolescent females

Presenting Author: Muskan Khetan

Muskan Khetan, *University of Melbourne*
Nandita Vijayakumar, *Deakin University*
Ye Tian, *University of Melbourne*
Sarah Whittle, *University of Melbourne*

Background
Adolescent females are particularly vulnerable to mental health symptoms and emotional dysregulation. During puberty, oestradiol (E2) and progesterone (P4) begin to cycle, but show high variability pre-menarche and in the early years post-menarche, similar to other transitional life stages. Although hormone variability during postpartum and perimenopause has been linked to brain structure and mental health symptoms in adults, little is known about how hormone variability affects the adolescent brain. We examined how within-individual variability in E2 and P4 relates to brain structure and mental health/emotion dysregulation, to better understand risk for mood and mental health disorders in adolescent females.

Methods
Participants (N = 147 females, aged 11–16) were from the cross-sectional Puberty and NeuroDevelopment in Adolescents (PANDA) study. Salivary E2/P4 were assayed weekly for one month, and variability was calculated as the within-subject standard deviation. MRI was conducted on the day of the final saliva sample. Depressive and anxiety symptoms, and emotional dysregulation were assessed using self-report questionnaires. Externalising symptoms were parent-reported. Cortical thickness and surface area, and subcortical volume, were estimated using FreeSurfer v7.3.2. Regression and mediation analyses tested associations between E2/P4 variability, brain structure and mental health/emotion dysregulation. All models included age, menarche, race, and income-to-needs ratio.

Results
There was a significant negative association between P4 variability and left thalamus volume (Cohen's d = -0.26, pFDR = 0.031), indicating that greater P4 variability was linked to smaller thalamus volume. In addition, we found a negative association between E2 variability and anxiety (Cohen's d = -0.170; pFDR = 0.043) and depressive symptoms (Cohen's d = -0.179; pFDR = 0.036) and emotion dysregulation (Cohen's d = -0.179; pFDR = 0.036). These associations were stronger among pre-menarche participants, suggesting that greater E2 fluctuations may relate to reduced depression, anxiety, and emotion dysregulation, particularly in earlier stages of puberty.

Conclusions
Findings indicate that greater monthly variation in P4 may influence volume in the left thalamus—a region involved in emotion and cognition and rich in P4 receptors. Additionally, increased monthly variation in E2 was linked to reduced depressive and anxiety symptoms and emotion dysregulation, especially among pre-menarche girls. These findings suggest that early adolescent hormone variability may shape brain and behaviour in ways distinct from adult transitions like postpartum or perimenopause. Our study is among the few exploring hormone variability during adolescence, highlighting the need for future longitudinal work in larger samples to better understand these developmental processes.

Data Blitz Abstracts - Session 2

P_6b Differential striatal gene expression profiles underlies the propensity for depression-like behaviour in a mouse model of vertical sleeve gastrectomy

Presenting Author: Renee Papaluca

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Background
Bariatric surgery is the most effective long-term obesity treatment, driven by gut-brain axis changes that reduce appetite and improve glycaemic control. However, a patient subset experiences adverse mental health outcomes post-surgery, like depression and suicidality. While clinical studies are ongoing, research exploring how gut-brain axis alterations may mechanistically contribute to these outcomes is lacking. Therefore, this study used a mouse model of vertical sleeve gastrectomy (VSG) to investigate individual differences in depressive-like behaviour following surgery. We hypothesized that while VSG improves metabolic outcomes, a subset would exhibit increased susceptibility to depressive-like behaviour and distinct transcriptional changes in reward-related brain regions.

Methods
Male and female C57BL/6 mice (n=57) were fed a high-fat, high-sugar diet (11 weeks) before undergoing VSG or sham surgery. Depression-like behaviour was assessed both pre- and post-surgery. VSG mice were stratified post hoc into tertiles based on behavioural changes; the top and bottom tertiles were classified as ‘depression-susceptible’ and ‘depression-resilient’. From these subgroups, RNA was extracted from tissue punches of the dorsal striatum and nucleus accumbens, key components of brain circuitry known to be dysregulated in major depressive disorder. Bulk RNA-sequencing was performed on these samples to identify differential gene expression patterns associated with post-surgical vulnerability to depression-like behaviour.

Results
VSG resulted in significant and sustained weight loss and reduced food intake compared to sham controls. Differential gene expression analysis revealed downregulated neuroinflammation and tight junction-related genes. Further gene set enrichment analysis shows depression-susceptible VSG mice display an upregulation of TNF-α-NF-κB and PI3K-AKT/mTOR pathways. Additional chow-diet cohort data and further RNA-seq validation are currently ongoing, and preliminary findings will be presented.

Conclusions
These findings, although preliminary, suggest that individual variability in depressive outcomes following bariatric surgery may be underpinned by differential activation of inflammatory and metabolic signalling pathways in key brain regions. This study provides foundational insight into the neurobiological mechanisms underlying post-surgical affective vulnerability and may inform future clinical screening and intervention strategies in bariatric populations.

Data Blitz Abstracts - Session 2

P_5b Paternal cytokine administration alters sperm small non-coding RNAs and offspring physiology and behaviour in mice

Presenting Author: Pamudika Kiridena

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Background
Paternal pre-conceptual exposure to parasitic, bacterial, and viral infections are all known to impact offspring phenotype via sperm epigenetic changes. Even in the absence of infection, paternal immune activation (PIA) can alter offspring behaviour and physiology through changes to sperm small RNAs. While this implicates the immune response, the specific component responsible for this phenomenon remains unknown. Cytokines offer a potential mechanism as they are a shared factor across different types of immune activation. As such, we investigated whether key pro-inflammatory cytokines elevated during PIA could recapitulate changes to offspring phenotype.

Methods
C57BL/6J mice were injected with either TNF-α or IL-1β; or saline at 8-weeks old. Following one spermatogenesis cycle (4-weeks), F0 male mice (fathers) were mated with age matched naïve female mice to produce F1 mice (offspring). F1 mice underwent a series of behavioural tests to assess anxiety-like, depression-like, and cognitive behavioural changes. Paternal sperm was collected following breeding and analysed to identify differentially expressed small RNAs.

Results
Offspring from cytokine treated fathers showed increased anxiety-like behaviour in the elevated plus maze and lost significantly more bodyweight following a 24-hour fast during the novelty suppressed feeding test. Despite no difference in whole brain weight, hypothalamus weights for cytokine offspring were significantly less than controls. Analysis of paternal sperm small non-coding RNA showed that miRNA, tsRNA, and piRNA clusters were significantly downregulated in response to IL-1β, while paternal TNF-α significantly downregulated a single piRNA cluster.

Conclusions
These findings suggest that paternal cytokine treatment with IL-1β and TNF-α have differential effects on offspring. Interestingly, offspring phenotype and sperm epigenetics are altered in a way which partially recapitulates viral-like PIA via Poly I:C. This study provides the first evidence of how elevated paternal cytokine levels can alter offspring phenotype. This adds to our understanding of paternal immune activation as an important pre-conceptual factor for offspring health and risk of neuropsychiatric disorders.

P_4b Grey matter changes observed up to two years prior to the onset of non-suicidal self-injury in male and female youths

Presenting Author: Lisanne Jenkins

Lisanne Jenkins, *University of Melbourne; Monash University; Northwestern University; Alfred Health*
Maryam Kouchakidivkolaei, *Simon Fraser University*
Sera Manuele, *Monash University*
Mindy Westlund Schreiner, *Ohio State University; Nationwide Children's Hospital*
Karteek Popuri, *Memorial University of Newfoundland*
Leo Chen, *University of Melbourne; St Vincent's Hospital Melbourne*
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Stewart Shankman, *Northwestern University*
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Lei Wang, *Ohio State University*

Background
Non-suicidal self-injury (NSSI), the deliberate destruction of one's own body tissue without suicidal intent, has an 18% lifetime prevalence and is a risk factor for future suicidality. We leveraged data from the longitudinal Adolescent Brain Cognitive DevelopmentSM Study to identify gray matter abnormalities in youths who between baseline (mean age=10) and Year 2 engaged in NSSI for the first time (premorbid NSSI; pNSSI).

Methods
Participants were 275 youths with pNSSI (63% female), T1 MRI and puberty data and 275 controls individually matched on 30 demographic and clinical variables. Two-group comparisons were performed separately for males and females. Covariates were puberty stage, intracranial volume and MRI manufacturer. Subcortical analysis was performed using FreeSurfer-initiated large deformation diffeomorphic metric mapping in N=548 (n=344 female, n=204 male). Cortical thickness (CT) analysis was performed using permutation analysis of linear models (n=10,000) in N=470 (n=290 female, n=180 male).

Results
In females, lower CT in the pNSSI group compared to controls was present in bilateral anterior cingulate, left lateral orbitofrontal and auditory association cortex, and right ventromedial prefrontal cortex. Greater CT in females with pNSSI was seen in left visual cortex, right auditory cortex, piriform cortex, hippocampus and entorhinal cortex. Subcortically there was inward deformation in the pNSSI group compared to controls in the bilateral caudate nucleus accumbens, putamen and thalamus.
For males, the pNSSI group showed greater CT than controls in left premotor, primary somatosensory and parietal cortex, and right retrosplenial cortex, precuneus, inferior parietal cortex and entorhinal cortex.

Conclusions
Few studies of NSSI include males, which is problematic as we demonstrated males and females show different patterns of group differences. Females showed the expected reduced gray matter in regions involved in cognitive control and reward valuation in the pNSSI group, however males did not. Both males and females with pNSSI showed greater cortical thickness compared to controls in the entorhinal cortex, an area that is beginning to emerge as important for NSSI.Our study contributes and increased neurobiological understanding of NSSI, which is needed to inform treatments.

Data Blitz Abstracts - Session 2

P_3b Pinpointing Schizophrenia Mechanisms with Isoform-Resolved Analyses in the Developing Human Brain

Presenting Author: Mitchell Hodgson

Mitchell Hodgson, *The University of Melbourne*
Mike Clark, *The University of Melbourne*

Background
Most genetic studies of neuropsychiatric disorders focus solely on disease risk at the gene level. However, nearly all genes expressed in the brain routinely produce multiple transcript isoforms. Recent large-scale analyses have shown that examining the effect of disease variants on isoforms doubled the detection of risk signals, suggesting isoforms are often the targets of disease variants. Despite this progress, we have limited understanding of which isoforms cause disease and how they do so, which hampers efforts to uncover disease mechanisms and develop therapies. We aimed to address this gap by identifying and characterising disease-associated isoforms in neuropsychiatric disorders.

Methods
A systematic search of PubMed and Scopus (screening 456 titles) identified two isoform-aware whole-transcriptome resources from the developing human brain. To find high-confidence disease-linked isoforms, we created a database that captured GWAS traits, prenatal timepoints (trimester), effect size, association method, and cross-study replication count. As schizophrenia GWAS provides the greatest statistical power, a larger number of high-confidence isoform associations (n=2373) were identified for this trait, which we focused on in our cross-study analysis. We then conducted detailed analyses of the structural, molecular, functional, evolutionary, and expression features of the highest-confidence isoforms with significant effect sizes.

Results
We identified 57 genes comprising 73 high-confidence risk isoforms that were corroborated across different methods and/or studies. Fine-mapping further refined the signal for 10 of these isoforms to a single, high-confidence variant that appears to influence both their expression and schizophrenia risk—for example, STAB1-205 (rs7612511), ABCB9-215 (rs1716183), and YWHAE-206 (rs9905529). These implicated isoforms are predicted to feature distinct proteoforms for STAB1, YWHAE, and an alternative 5′ UTR in ABCB9. Notably, AlphaFold modelling of the YWHAE risk isoform predicts the loss of 6 of 9 α-helices, disrupting the canonical 14-3-3 dimer interface—consistent with a loss of function.

Conclusions
By curating 2,373 prenatal schizophrenia isoform–trait associations and prioritising those replicated across methods and studies, we nominate 73 high-confidence risk isoforms spanning 57 genes. Nineteen genes converge on a single risk isoform, and fine-mapping suggests likely causal variants for 10 of these, linking specific transcriptomic changes to predicted functional effects (e.g., structural disruption of the 14-3-3ε dimer interface in YWHAE-206). These findings provide precise, testable targets for experimental follow-up and demonstrate that isoform-resolved analyses reveal actionable biology often missed by gene-level approaches.

Data Blitz Abstracts - Session 2

P_2b Reductions in Group III Metabotropic Glutamate Receptor Transcripts in Schizophrenia and Bipolar Disorder Midbrain

Presenting Author: Samara Walpole

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Background
Group III metabotropic glutamate receptors (mGluRs) (consisting of mGluR4, 7 and 8) are of increasing interest in the pathophysiology and treatment of schizophrenia. These receptors are largely thought to sit on presynaptic terminals where they regulate neurotransmitter release. However, their specific cellular expression and subsequent potential for downstream signalling impacts in the midbrain is unknown. The midbrain is a crucial hub for dopaminergic and glutamatergic signalling which are disrupted in schizophrenia and bipolar disorder, with neuroinflammation found in half of the cases. Due to their involvement across several neurotransmitter systems, group III mGluRs are a promising target for novel antipsychotics.

Methods
To determine transcript expression and cellular localisation of group III mGluRs, RNA was extracted from postmortem midbrain from 35 schizophrenia, 33 bipolar disorder and 33 non-psychiatric control subjects. Gene expression of the group III mGluRs (GRM4, GRM7, GRM8) was measured via qRT-PCR using TaqMan Gene Expression Assays and analysed by diagnosis and pre-defined inflammatory subgroups. The neuroinflammatory subgroups were categorised based on elevated expression levels of a combination of pro-inflammatory transcripts (SERPINA3, IL6, IL1β and TNFα) and defined using 2-step recursive clustering. Cellular expression of the mGluRs was investigated by single-nucleus RNA sequencing (snRNAseq) of postmortem human midbrain tissue (n=34).

Results
SnRNAseq showed that GRM4 was primarily localised to inhibitory interneurons, GRM7 was diversely expressed across glutamatergic, GABAergic and dopaminergic neurons as well as mesenchymal stem cells (MSCs), and GRM8 was predominantly expressed in pericytes, glutamatergic neurons and dopaminergic neurons. Analysis by inflammation subgroup revealed significant reductions in group III mGluR mRNAs. High neuroinflammation schizophrenia subjects show reduced GRM4, GRM7 and GRM8 mRNAs compared to both controls and low neuroinflammation schizophrenia subjects. Bipolar disorder subjects with high neuroinflammation show reduced GRM4 and GRM8 mRNAs compared to controls and reduced GRM4 mRNA compared to low neuroinflammation bipolar disorder subjects.

Conclusions
We reveal significant transcriptional reductions in group III mGluRs in a subgroup of schizophrenia and bipolar disorder subjects with elevated inflammation, linking glutamatergic dysfunction with neuroinflammation. Activation of group III mGluRs inhibits both GABAergic and glutamatergic transmission in the midbrain. The presence of GRM7 and GRM8 mRNAs in dopaminergic neurons, coupled with the observed reductions in their mRNA, suggests a potential mechanism whereby glutamatergic signalling regulates dopamine. However, our findings suggest additional non-neuronal roles of the group III mGluRs due to the marked expression of GRM7 and GRM8 in MSCs and pericytes, respectively, which warrants further investigation.

Data Blitz Abstracts - Session 2

P_1b Paternal gut microbiota modulation via prebiotics alters sperm small RNAs and impacts offspring physiology and behaviour

Presenting Author: Bethany Masson

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Anthony Hannan, *Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, 3010, Australia; Department of Anatomy and Physiology, University of Melbourne, Parkville, VIC, 3010, Australia*

Background
Parental environmental exposures, including models of stress, immune activation and Western diet can alter offspring phenotypes via germline epigenetic modifications. Such environmental stimuli interact with the gastrointestinal (GI) tract either directly or indirectly via the gut microbiota—the commensal microorganisms that colonize the GI tract. The maternal gut microbiota has been demonstrated to impact offspring, however, the influence of the paternal gut microbiota on offspring is only beginning to be understood. Our lab aims to investigate the impact of paternal gut microbiota modulation on offspring physiology, gut microbiota, and cognitive and affective behaviour.

Methods
The gut microbiota of male C57BL/6J mice was modulated using a combination of two prebiotics, administered via drinking water. After approximately one spermatogenic cycle in the presence of the prebiotic modulated gut microbiota, these mice were bred with naïve female mice to produce offspring which were investigated for physiological and behavioural changes. To investigate potential mediators of epigenetic inheritance the paternal sperm small non-coding RNAs (sncRNAs) were profiled.

Results
Paternal gut microbiota modulation via prebiotics resulted in a transient increased body weight in both male and female offspring following weaning. Additionally, male and female offspring showed morphological changes in their gastrointestinal tract, with an increase in colon length. Offspring also had an altered GI transit time. Male and female offspring showed altered cognitive performance, spending an increased duration in the novel arm of the Y-maze. The offspring gut microbiome diversity measures were not altered by paternal prebiotic administration, however there were 3 differentially abundant taxa. Analysis of sperm sncRNAs revealed fathers administered prebiotics had differentially expressed sncRNAs.

Conclusions
Our lab presents further evidence of the role of the paternal gut microbiota in modulating offspring phenotypes, specifically in offspring physiology and cognitive behaviour. Previously environmental stimuli, such as diet and stress, known to influence the gut microbiota, have been implicated in paternal epigenetic inheritance and alterations in the sperm epigenome. We currently report changes to the sncRNA profile of sperm from prebiotic administered males, providing further evidence the gut-germline axis may play an influential role in intergenerational epigenetic inheritance.

Poster Abstracts

Please note that Poster Abstracts are displayed in alphabetical order by first name and by day.

P_51a Characterising inflammatory and glutamatergic relationships in the nucleus accumbens in schizophrenia: emerging potential for spatial metabolomics with MALDI-MSI

Presenting Author: Alex Stevenson

Alex Stevenson, *School of Science, University of Wollongong; Molecular Horizons Research Entity, Faculty of Science, Medicine and Health, University of Wollongong*
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Background
Glutamatergic dysfunction and neuroinflammation are implicated in the pathophysiology of schizophrenia. Evidence has associated subcortical structures, including the nucleus accumbens (NAc), with a glutamatergic pathology. Metabolic regulation of the glutamate system, particularly the mechanisms of synaptic packaging and uptake, appears to be perturbed in the NAc in schizophrenia. Although neuroinflammation is known to exacerbate changes in glutamate receptor expression, it remains unknown how it affects the mechanisms of glutamate uptake and synaptic packaging. We aimed to measure the gene expression of glutamate transporters in schizophrenia subjects with and without neuroinflammation, and develop a pipeline for quantifying glutamate/glutamine concentrations using MALDI-MSI.

Methods
Postmortem human NAc tissue was obtained from individuals who lived with schizophrenia (n=30) and matched nonpsychiatric controls (n=30). The relative gene expression of excitatory amino acid transporters 1 and 2 (EAATs) was quantified using RT-qPCR. To examine the distribution of glutamate and glutamine, fresh frozen NAc tissue sections were coated with a matrix using an automatic TM-Sprayer and analysed via matrix-assisted laser desorption/ionisation mass spectrometry imaging (MALD-MSI). Data was acquired using an Orbitrap Elite mass spectrometer coupled to an intermediate pressure MALDI source and visualised/analysed using Lipostar MSI software.

Results
We report no effect of schizophrenia diagnosis or midbrain-inflammation status on EAAT1 and 2 gene expression in the NAc. However, when analysing by NAc-inflammation status, high inflammation controls had significantly higher EAAT1 mRNA compared to low inflammation controls (39.96%; p=0.008). MALDI-MSI was successfully employed in non-psychiatric human striatal tissue to map the distributions and relative concentrations of numerous small metabolites. This included, but is not limited to, glutamate, glutamine, aspartate, glutathione, and taurine. Glutamine was highly localised white matter structures (such as the internal capsule), whilst glutamate was more diffusely distributed across grey matter.

Conclusions
In the current study, we have found no significant diagnostic differences in the mRNA expression of EAAT1 and 2 mRNAs in the NAc in schizophrenia. However, subgroup analyses revealed that inflammation may modulate specific gene expression profiles, particularly EAAT1 mRNA. Additionally, this is the first study to utilise MALDI-MSI for neurotransmitter analysis in the context of a psychiatric disorder. The use of this technology for future postmortem schizophrenia studies will provide an opportunity to explore the glutamatergic system in greater molecular and spatial detail than previously possible, targeting specific anatomical regions such as the NAc.

P_43a Stressful life events with high escape potential induce freezing-like behavior

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Background
Stressful life events have long been considered to play an important role in the development of Functional Neurological Disorder (FND). Theories suggest that events which have an escape potential (i.e., the type of events that could be avoided by getting ill) may be central to inducing FND pathology. However, it remains unclear how these stressors may interact specifically with the motor system, a key domain affected by FND. The current study examines the neurobehavioral patterns triggered by the recall of these stressors in healthy individuals.

Methods
Twenty-two healthy adult participants recruited from the community completed a novel autobiographical motor task in an ultra-high field (7 Telsa) MRI scanner. All participants were interviewed to identify stressful and neutral events which had occurred within the preceding year. During the task, participants were asked to maintain a pinch force at 10% of maximum voluntary contraction while viewing cues related to their personal events, namely stressful events with high and low escape potential, as well as a neutral event. Visual feedback was given before the cues appeared to ensure every trial started from the target force level.

Results
Behaviorally, participants showed a decay in force across all conditions. However, this effect was attenuated during the high escape condition. That is, participants were better in keeping the previous behavioral pattern when recalling their stressful events with high escape potential. At a whole brain level, participants showed increased activity in temporal pole and anterior prefrontal cortex during the high escape compared with both the low escape and neutral conditions.

Conclusions
The behavioral results demonstrate that stressful events with high escape potential induce transient freezing-like responses in a non-clinical population. Neurobiologically this effect is associated with changes to the activity of paralimbic and frontal regions. These results suggest the unique link between stressors with escape potential and defensive motor behavior, which can be the target for future investigations in the pathogenesis of FND.

P_16a Neurodevelopmental Impairments Following Prenatal DEHP Exposure and Their Partial Reversal by Postnatal MO8 Treatment

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Background
Diethylhexyl phthalate (DEHP) is a widely used plastic additive chemical ubiquitous in the modern environment. Given increasing epidemiological evidence of a link between prenatal DEHP exposure and adverse neurodevelopmental outcomes in children (including autism and ADHD symptoms), we used a humanized Val66Met BDNF mouse model to investigate the effect of prenatal DEHP exposure at an environmentally relevant dose within the daily allowable range. The Val66Met polymorphism is the most common mutation in human BDNF, a gene integral to neuronal development, and has been associated with neuropsychiatric disorders including schizophrenia.

Methods
We examined prenatal DEHP effects in Val66Met mice. Pregnant dams received 0µg/kg/day or 20µg/kg/day DEHP orally during mid-gestation (embryonic day 10.5-14.5). Offspring underwent a battery of behavioural tests. Synaptic function was assessed using a multiple electrode array to measure field potentials and gene expression analysis of synaptic scaffolding proteins was conducted. This was repeated in wildtype C57Bl/6 mice who were treated with an estrogenic medium-chain fatty acid drug postnatally (1mg/kg/day MO8, orally, from 8-14-weeks-of-age) to assess reversal of DEHP-induced effects. Linear mixed models were used with litter as a random effect to account for within-litter similarities.

Results
Prenatal DEHP exposure caused a prepulse-inhibition deficit in female offspring only ($p=0.0092$) which did not interact with Val66Met BDNF genotype ($p=0.50$). This DEHP-induced prepulse-inhibition deficit was replicated in C57Bl/6 females ($p=0.011$) who exhibited overexpression of Homer1a ($p=0.0082$) and a decrease in excitatory post-synaptic potential (EPSP) in the right hippocampus ($p<0.0001$) compared to vehicle-exposed females, resulting in a loss of electrophysiological hippocampal asymmetry. Postnatal treatment with MO8 in DEHP-exposed females reduced brain Homer1a expression ($p=0.034$), increased right hippocampal EPSP ($p=0.047$) and restored ~71% of the prepulse-inhibition deficit, although this effect was not statistically significant ($p=0.066$).

Conclusions
Our study highlights neurodevelopmental risks of prenatal DEHP exposure, particularly in females, marked by prepulse inhibition deficits and altered synaptic function. These effects were not modulated by the Val66Met BDNF genotype, suggesting a broad vulnerability. Elevated Homer1a expression paralleling findings in autism models and schizophrenia, points to synaptic disruption and impaired postsynaptic signalling as potential mechanisms. Postnatal MO8 treatment showed partial rescue of these phenotypes. Together, these findings support the need to reassess environmental DEHP exposure limits to better protect brain development.

P_26a Novel Betacellulin peptide treatment recovers altered adult Hippocampal Neurogenesis in a BTC-knockout mouse model with relevance to Schizophrenia

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Background
Clozapine, an atypical antipsychotic with low dopamine-D2 receptor affinity, uniquely phosphorylates the epidermal growth factor (EGF) signalling pathway, and remains the most effective treatment for 60% of individuals who exhibit limited or no response to conventional antipsychotics. Whilst previously associated with schizophrenia, the mechanism through which EGF signalling may underlie clozapine's superior efficacy remains poorly understood. Our laboratory has previously demonstrated that knocking out Betacellulin (BTC), an EGF ligand, impairs Adult Hippocampal neurogenesis, which is rescued by treatment with clozapine. We therefore hypothesised that administering recombinant BTC to BTC knockout (KO) mice would similarly rescue hippocampal neurogenic deficits.

Methods
BTC knockout (KO) and wild-type (WT) mice (n=40; balanced for sex) randomly received either BTC peptide (500ug/uL) or vehicle via intracerebroventricular osmotic mini-pump infusion over 14 days, resulting in four experimental groups. Tissue was then collected, frozen fresh and sectioned at 20µm in ventral to mid dentate gyral regions for immunofluorescence. Cell proliferation, neuronal differentiation and progenitor identity were assessed using Ki67, NeuroD1, and Nestin immunohistochemistry, respectively. The primary outcome measures were the neuronal counts of colocalised Ki67+ and NeuroD+ cells within the subgranular zone (SGZ) of the dentate gyrus, quantified using Qupath imaging and analysis software

Results
There was a significant reduction in the number of Ki67+ proliferating cells and NeuroD+ differentiating neurons in the dentate gyrus in the BTC KO mice compared to wild-type (WT) littermate controls (main effect of genotype Ki67 P = 0.0012; NeuroD P = 0.0047). The BTC peptide infusion significantly increased the number of Ki67+ proliferating cells and NeuroD+ differentiating neurons, rescuing neurogenic deficits (main effect treatment Ki67 P = 0.0001; NeuroD P = 0.0076).

Conclusions
These findings indicate that BTC peptide supplementation can rescue cell proliferation (Ki67) and neuronal differentiation (NeuroD) deficits in BTC KO mice. With significant main effects of both markers, this proof-of-concept study supports a role for BTC-EGF signalling in mediating hippocampal neurogenesis. It also highlights BTC as a potential therapeutic target that can replicate Clozapine's unique mode of action without inducing its adverse effects, specifically for schizophrenia-related neurogenesis dysfunction.

P_22a Neural Signatures of Social Reward: Dopamine and Oxytocin Dynamics in the Nucleus Accumbens

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Background
Social dysfunction is a core feature of many psychiatric conditions, including depression, schizophrenia, and dementia. A key contributor to this dysfunction stems from disrupted social reward processing. Neuromodulators, particularly dopamine and oxytocin, play vital roles in motivation and reward integration, yet the mechanisms underpinning social reward remain poorly understood. This reflects previous limitations in monitoring and manipulating endogenous neuromodulator dynamics, as well as paradigms lacking volitional engagement – a critical aspect of social motivation. Understanding when and how neuromodulators support volitional social behaviour is essential for dissecting the neural basis of social deficits and guiding the development of targeted therapeutics.

Methods
To investigate the temporal dynamics of neuromodulator signalling during social interaction, we used fiber photometry to record real-time dopamine activity in the nucleus accumbens of rats performing a volitional social operant task. This task was designed to separate anticipatory and consummatory phases of social reward, allowing neuromodulator signals to be precisely aligned to specific behavioural events. To understand the role of oxytocin receptors in social learning, motivation, and reward, we used AAV-guided CRISPR/Cas9 to selectively disrupt oxytocin receptor expression in the nucleus accumbens and prefrontal cortex.

Results
Preliminary results show that nucleus accumbens dopamine is robustly engaged by social-predictive cues and the consumption of social reward but responds only weakly to the goal-directed action required to obtain the reward. However, dopamine responses to the social-predictive cue are markedly stronger when social access is contingent on the goal-directed action. These findings point to a functional dissociation within the social reward circuitry, with social motivation amplifying dopaminergic signalling. In parallel, experiments targeting oxytocin receptor function are underway to assess how oxytocin shapes volitional social learning and behaviour.

Conclusions
Our findings demonstrate a functional separation of action and outcome within the nucleus accumbens dopamine response. Signalling is amplified when social access is contingent on a goal-directed action, suggesting that motivational context enhances dopaminergic encoding of the social-predictive cue at the transition from expectation to reward. Building on this, CRISPR/Cas9-mediated disruption of oxytocin receptor expression in the nucleus accumbens and prefrontal cortex is underway to probe its role in modulating social learning and behaviour. By integrating circuit-level recordings with targeted neuromodulator manipulation, this work provides a mechanistic framework for understanding volitional social behaviour and guides therapeutic strategies for social dysfunction.

P_2a Lesions of the lateral hypothalamus-nigral projection result in motor deficits in rats: implications for Parkinson's disease.

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Background
The lateral hypothalamus (LH) is emerging as a brain region of interest in Parkinson's disease (PD) as LH neurons have been shown to degenerate in PD. Degeneration of the substantia nigra (SN) is a defining feature of PD and is thought to underlie observed motor symptoms. Interestingly, the LH has strong anatomical projections to the SN, but the behavioural functions associated with this projection have not been determined. We have recently shown that the LH is involved in spontaneous locomotor activity in rats and thus sought to determine whether the LH regulates motor activity via the SN.

Methods
We utilised female rats (n=16) to functionally disconnect the LH and SN by intracranial infusion of a shRNA virus and a 6-hydroxydopamine toxin, respectively. An open field test was used to assess spontaneous locomotion and meth-induced hyperlocomotion. Other motor abilities were assessed using tests typically used to model PD-motor deficits (balance beam, rota rod, cylinder test). Rats were also tested for the ability to develop habits in an instrumental learning task, as we have also recently shown that the LH is involved in habitual learning; a task long known to depend on the SN.

Results
Contralateral targeting of the LH and SN did not disrupt goal-directed or habit-motor learning compared to ipsilateral targeting (control group). Motor coordination on the balance beam and rota rod was also not altered. However, functional disconnection of the LH and SN significantly reduced spontaneous locomotor and meth-induced hyperlocomotion in the open-field test. Furthermore, it also reduced spontaneous rearing in the cylinder test and total lever responses in the progressive ratio test (but not body weight or free-feeding consumption).

Conclusions
Our findings suggest that the LH and SN work together to regulate spontaneous and meth-induced locomotion in rats. We also demonstrated that the LH-SN connection is not involved in motor co-ordination or habit-motor learning, and thus the LH and SN do not work together for all aspects of motor activity known to be controlled by the SN. Our findings suggest that it is possible that the degeneration of the LH seen in PD may also contribute to some of the motor symptoms of the disease, as reduced spontaneous locomotion is a key feature of PD.

P_27a RXFP3-expressing lateral hypothalamus/zona incerta cells exhibit projection-specific activity during a conditioned flight paradigm

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Background
Fear-related disorders such as post-traumatic stress disorder involve deficits in threat imminence perception, causing exaggerated fear responses relative to the actual degree of threat. Rodent fear models typically measure defensive freezing behaviour, but rodents exhibit a range of defensive behaviours from increased vigilance to uncoordinated flight depending on perceived threat severity. We recently found that activating RXFP3-expressing cells in the mouse zona incerta (ZI) and lateral hypothalamus (LH) induced active flight in a subset of mice following fear conditioning. Therefore, we sought to determine how different subpopulations of these cells respond to stimuli that differ in their perceived threat imminence.

Methods
To assess how mice respond to different degrees of perceived threat, we used a modified fear conditioning paradigm where footshock is paired with a serial compound stimulus (SCS) consisting of distinct tone and white noise periods. After conditioning, the tone reliably elicits freezing (less imminent), while white noise elicits flight (more imminent). We previously identified a RXFP3+ LH to lateral habenula (LHb) pathway and RXFP3+ ZI to ventrolateral periaqueductal gray (vlPAG) pathway as putative contributors to these behaviours. Consequently, we used fiber photometry to measure the calcium activity of these pathways in RXFP3-Cre mice during the SCS fear conditioning protocol.

Results
Both RXFP3+ ZI-vlPAG and RXFP3+ LH-LHb pathways were recruited as SCS fear conditioning progressed, but only to the more threatening white noise, and not to the less threatening tone. Interestingly, both pathways exhibited unique activity patterns to footshock: the RXFP3+ ZI-vlPAG pathway exhibited a large calcium transient that decayed slowly in the post-shock period, while the RXFP3+ LH-LHb pathway was rapidly silenced immediately after footshock.

Conclusions
We have identified two distinct RXFP3-expressing LH/ZI populations with unique activity during SCS fear conditioning. Though both pathways responded to increasing threat imminence, the RXFP3+ LH-LHb pathway was rapidly silenced after threat passed, suggesting that it encodes a relief signal. As the RXFP3+ ZI-vlPAG pathway was insensitive to the removal of aversive stimuli during the post-shock period, this pathway may encode the perceived danger of a presented stimulus. These findings work towards uncovering the circuitry that mediate complex responses to perceived threats. Understanding these circuits will help us understand how individual differences cause maladaptive responses to cues that signal danger.

P_50a Links between iron dyshomeostasis, ubiquitin stress, amyloid precursor protein and schizophrenia

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Background
Schizophrenia is a neuropsychiatric disorder that is often disabling and associated with brain changes, which have been linked to oxidative stress. Iron is critical for key neurobehavioral pathways. However, iron is redox-sensitive, and its excess can provoke neuronal damage. Recently, we have identified iron dyshomeostasis and ubiquitin stress in the prefrontal cortex (PFC) of a group of individuals with schizophrenia. This study aims to evaluate whether the Amyloid Precursor Protein (APP), a protein that facilitates export of iron, is altered in PFC of individuals with schizophrenia, and to examine behavioural, brain structural and protein changes in APP knock out mice.

Methods
Specimens from the PFC of individuals with schizophrenia (n=86) and matched controls (n=85) were obtained from three independent brain tissue resources. Metals, and relevant proteins (APP and glutathione peroxidase 4 (GPX4)) were quantified in brain supernatant fractions by ICP-MS and infrared Western blots, respectively. We also analyzed

the iron levels in brain samples from age-matched control and APP knock out (APP-KO) mice by ICP-MS. Protein levels were assessed by Western blot. The behavior of these animals was monitored by prepulse inhibition assessment and clasping scores. Brain structural changes in mice were monitored by magnetic resonance imaging.

Results

Protein levels of APP were decreased in schizophrenia cases (-0.49 SDs, p=0.001), and the iron-APP relationship was grossly distorted in the patient group (t160=-3.44, p=0.0008). Moreover, protein levels of GPX4, which serves as the checkpoint for ferroptosis, were lower in patients (-0.326 SDs, p=0.031). The inspection of the frontal cortex of APP-KO mice informed elevated iron in the soluble fraction and accumulation of ubiquitinated proteins in the insoluble fraction. Surprisingly, we observed that male APP-KO mice displayed increased startle response and high clasping scores. Importantly, these animals expressed a specific and significant decrease in the volume of thalamus.

Conclusions

We previously reported an elevation of labile iron in PFC tissue of schizophrenia individuals. Iron dyshomeostasis can disrupt neurodevelopment, leading to oxidative and protein stress, which in turn may lead to neuronal dysfunction. 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 during the early phases of schizophrenia. Here we also identify novel schizophrenia-like endophenotypes in APP-KO animal model exhibiting brain iron accumulation. These results suggest that stressors in ubiquitin signalling, iron metabolism and APP homeostasis could impact the neurobiology of schizophrenia.

P_19a Cortico-striatal mechanisms differentially mediate punishment and fear suppression in a conditioned punishment task

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Background
Aversive events in our environment shape our behaviour and how we respond to them. An instrumental behaviour is punished when the outcome is aversive, which can then be avoided if the behaviour is suppressed. Yet there are instances where behaviours appear inappropriately sensitive to potential threats. The neural underpinnings of these inappropriate behaviours are poorly understood. The cortico-striatal circuit, including the prelimbic (PL) and infralimbic (IL) cortices, and the nucleus accumbens core (AcbC) and shell (AcbSh), have been implicated in motivated behaviours in response to fear and rewarding outcomes respectively, but not in choice behaviours dependent on punishment contingencies.

Methods
In a conditioned punishment task, we initially trained rats to press two levers for pellets. Their responding suppressed on one lever when it also earned a conditioned stimulus (CS+) that was paired with a footshock, whilst responding continued on the other lever that earned a neutral conditioned stimulus (CS-) that did not elicit a footshock. Following learned conditioned punishment and fear, animals were micro-infused with the GABA agonist, muscimol, or saline into either the PL, IL AcbC or AcbSh prior to an expression test. Using an ipsilateral vs contralateral approach, the PL-AcbC and IL-AcbSh pathways were also tested.

Results
Here, we show that regions of the cortico-striatal pathway are implicated in punishment and fear expression in different ways. Inhibiting the IL or PL increased responding on the punished, whilst inhibiting the AcbC or AcbSh decreased responding on the unpunished lever. Suppressed responding to both levers during the CS+ was abolished following inhibition of the PL and AcbSh, but not the IL and AcbC. Inhibiting the IL-AcbSh pathway resulted in a similar pattern of findings compared to cortical inhibitions only, whilst inhibiting the PL-AcbC pathway resulted in similar findings to striatal inhibitions, but to a lesser extent.

Conclusions
These results suggest there is an effect of cued punishment expression that is distinct from non-cued punishment and fear expression to the same cue, that is mediated by cortico-striatal mechanisms. The IL-AcbSh pathway is selectively identified as being necessary for inferring the aversive valence of the instrumental punisher, as well as fear expression to the CS+. The PL-AcbC pathway is likely involved, but only due to receiving inputs from other regions, potentially from the amygdala.

P_18a Shifting maladaptive bias in approach-avoidance measured using the platform mediated avoidance task using serotonin 5HT2C receptor antagonists

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Background
Obsessive compulsive disorder (OCD) involve shifts in the balance between approach and avoidance behaviours under conflict, with a bias towards avoidance responses that impact the ability to pursue rewarding activities. Although selective serotonin reuptake inhibitors are used to treat these disorder, acute treatment can increase anxiety symptoms in part via 5HT2C receptors. The platform mediated avoidance task in rodents provides a translational approach for studying neural mechanisms underlying this behaviour and testing new treatments that restore balance during approach-avoidance.

Methods
Sapap3 knockout (KO) mice (n=12, 6 males), a leading preclinical OCD model, were compared to controls (n=34, 19 males) and trained in the platform mediated avoidance task for 10 days, to associate a tone with foot-shock, which can be avoided using a platform in the opposite side of the chamber to a reward lever. Mice then underwent 2 days of extinction with response prevention (ERP), with a barrier preventing platform access and no foot-shock after the tone, followed by an extinction test where mice were injected with control or 5HT2C antagonist (SB242084 1mg/kg) 30 minutes prior to testing.

Results
In controls, females showed higher suppression of lever pressing during the tone ($p=0.03$). In Sapap3-KOs, males showed a genotype effect with higher suppression of pressing than WT, which was absent in females (sex x genotype x day $p=0.0015$). Following ERP, Sapap3-KOs ($p=0.0022$) and females ($p<0.0001$) showed persistent fear, with higher suppression of pressing during the tone. These factors interacted with 5HT2C antagonist treatment ($p=0.0495$), with Sapap3-KO males showing the largest decrease in suppression of pressing following SB242084.

Conclusions
These findings highlight 5HT2C antagonists as a promising target for treating OCD and anxiety, and the utility of platform avoidance for screening drugs that re-balance approach-avoidance conflict.

P_42a 18F-FDG PET and Structural MRI Markers of Vulnerability to Diet-Induced Obesity

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Background
Individual differences in the propensity to overconsume high-fat/high-sugar ("junk") foods and develop obesity remain poorly understood. Behavioural traits with shared genetic and/or biological underpinnings, alongside dysfunction in the brain's reward circuitry, are thought to interact with the environment to drive diet-induced obesity (DIO). In an established rat model of DIO, we previously showed for the first time that lower cognitive flexibility, measured by the reversal learning parameter α before diet exposure, predicted later development of DIO. Building on this, the present study examines FDG-PET and structural neuroimaging markers that both precede and persist throughout the development of DIO.

Methods
Outbred male Sprague Dawley rats (n = 34) were provided free access to a high-fat/high-sugar diet for 10 weeks, then separated into DIO-prone and diet-resistant subgroups based on weight gain. Neuroimaging markers of DIO were assessed using 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) and structural magnetic resonance imaging (MRI), conducted both before and after high-fat/high-sugar diet exposure. An a priori volume-of-interest (VOI) analysis compared neurometabolic activity across 28 predefined brain regions. Additionally, exploratory voxel-wise analysis using Statistical Parametric Mapping (SPM) examined group differences in whole-brain neurometabolic activity.

Results
Prior to diet exposure, DIO-prone rats exhibited significantly higher global neurometabolic activation than diet-resistant rats ($p < 0.001$), with regional differences in the nucleus accumbens and lateral hypothalamus ($p = 0.027$). Voxel-wise analysis showed greater hypothalamic activation in DIO-prone rats regardless of timepoint ($p = 0.014$). Following prolonged high-fat/high-sugar diet consumption, both groups demonstrated marked hypoactivation in the nucleus accumbens ($p < 0.001$), with diet-resistant rats showing a significantly larger reduction from pre- to post-diet ($p = 0.028$). Volume-of-interest mapping and clustering further identified distinct pre-diet coactivation patterns that converged after diet exposure.

Conclusions
Increased activation in reward-related brain regions emerged as a key neuroimaging predictor of vulnerability to overeating and diet-induced obesity. Post-diet findings emphasise the lasting impact of high-fat/high-sugar diets on brain function. Notably, DIO-prone rats showed smaller reductions in neurometabolic activation after diet exposure, suggesting resistance to diet-induced neural changes. Ongoing structural MRI analyses will further clarify neuroanatomical differences. Together, these findings provide critical groundwork for future studies exploring neurobehavioral mechanisms underlying pathological overeating and obesity, and identify potential early markers for individuals at risk.

P_9a A novel mutation in the Arx gene causes sex-specific behavioural and electrophysiological phenotypes relevant to schizophrenia

Presenting Author: Dr Ariel L. Dunn

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Background
Schizophrenia is a complex psychiatric disorder with distinct sex differences. While sex hormones undoubtedly modify such differences, sex chromosome genes likely also contribute. We identified a novel missense mutation in X chromosome gene, ARX, in a female with schizophrenia. Previously identified ARX mutations cause sex-specific phenotypes, including intellectual disability and epilepsy in males, and 'milder' psychiatric symptoms in females. The ARX gene encodes a transcription factor integral to GABAergic interneuron development. Given GABAergic interneurons regulate neural network activity, and both are disrupted in schizophrenia, we hypothesised that our novel ARX mutation may cause sex-specific phenotypes relevant to schizophrenia.

Methods
We generated a mouse using CRISPR-Cas 9 technology with our identified ARX mutation, termed the ArxR264Q mouse. Adult ArxR264Q mutant mice (both sexes) were tested on a broad behavioural battery from postnatal day 70, including 'anxiety' and risk-taking in the elevated plus maze (EPM), a three-chamber social novelty task, locomotion and sensorimotor gating via pre-pulse inhibition (PPI) with drug challenges, and cognitive flexibility using a touchscreen-based paired discrimination task. In vivo local field potentials (LFPs) in the prefrontal cortex and hippocampus were recorded simultaneously during these tasks as a measure of neural network activity aligned to the behavioural output.

Results
ArxR264Q females show impaired socialisation versus wild-type mice, with simultaneously reduced gamma power during the task. ArxR264Q males, but not females, show altered startle response, startle habituation, and PPI following MK-801, suggesting sex-specific sensory processing deficits. ArxR264Q mice show increased open arm and cliff exploration in the EPM versus wild-type mice, indicating risk-taking in both sexes. Wild-type mice show increased gamma and theta power when exploring EPM open arms, while ArxR264Q mice do not. This may explain failure of ArxR264Q mice to recognise, and therefore fear, EPM open arms. ArxR264Q females show reduced reversal learning accuracy, indicative of cognitive rigidity.

Conclusions
Overall, this study uncovered striking convergent network level disruptions which directly underlie sex-specific behavioural disruptions in ArxR264Q mice. The innovative technique of simultaneous neural network recordings aligned with behavioural outcomes is a highly valuable tool enabling a deeper understanding of the functional changes that help to explain behavioural phenotypes. These data provide important new insights into the origins of mature circuit dysfunction and adult behavioural abnormalities relevant to schizophrenia. The ArxR264Q mouse therefore represents a novel genetic risk model enabling the targeted investigation of new treatment options for symptoms relevant to schizophrenia and other neurodevelopmental disorders with GABAergic dysfunction.

P_32a A multicentre randomised controlled clinical trial of repetitive transcranial magnetic stimulation for social communication in autism spectrum disorder

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Background
A small number of studies have indicated that repetitive transcranial magnetic stimulation (rTMS) may improve social outcomes in autism spectrum disorder (ASD). In a large multicentre, double-blind randomised controlled trial involving five sites, we investigated whether rTMS to the right temporoparietal junction (rTPJ) can improve social communication in adolescents and young adults (aged 14-40 years) with ASD. The study evaluated the safety and efficacy of a 4-week course of active intermittent theta burst stimulation (iTBS) compared to sham iTBS (each consecutive weekday, 20 sessions).

Methods
Participants underwent a 3T T1 MRI and stereotactic neuronavigation was used to target the rTPJ (Montreal Neurological Institute coordinates x=56, y=−56, z=18). iTBS was delivered at 70% of resting motor threshold, with a total of 600 pulses delivered each session (bursts 3 pulses at 50Hz, repeated at 5Hz intervals for 2 seconds, with 8 seconds between trains). The primary outcome for this study is self-report social function as assessed using the Social Responsiveness Scale (SRS-2) at one-month post-intervention completion. Other clinical, cognitive, genetic, epigenetic, and neuropsychology assessment outcomes were assessed over a 6-month follow-up period.

Results
101 participants (44 females, mean age 22.28 (SD=7.42)) were enrolled into the study between September 2021 and February 2025. SRS-2 scores at one-month post-intervention were collected from 84 participants. Seventy-six participants have completed the trial. Seven participants are currently enrolled and due to complete by the beginning of October 2025. Initial data analysis has begun, and data collection will be finalised by the beginning of October 2025.

Conclusions
The findings from this trial will provide insight to the efficacy of a potential novel biomedical intervention to improve social communication symptoms in ASD.

P_46a Intrinsic Functional Connectivity Patterns in Comorbid PTSD and Alcohol Use Disorder vs. Alcohol Use Disorder

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Background
Co-occurring posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) is highly prevalent and associated with worse psychiatric health and social outcomes than either disorder alone. Despite this, the neurobiology of this comorbidity remains understudied. We investigated group differences in intrinsic functional connectivity (IFC) between those with PTSD&AUD and AUD-alone.

Methods
In this study, 20 individuals with PTSD&AUD and 25 individuals with AUD-alone underwent resting-state functional magnetic resonance imaging (fMRI). This data was preprocessed and post-processed (using fMRIPrep and XCP-D, respectively) to correct for artifacts and improve signal-to-noise ratio. Differences in IFC between PTSD&AUD and AUD-alone was evaluated using 430 node ROI-to-ROI matrices derived from XCP-D. Second-level analyses used a GLM model which included age, sex, medication use, and drinking history as covariates.

Results
A significant group difference was found in the right Default_PFCdPFCm_8 seed (Default Mode Network B (DMN); MVPA PFDR = 0.049). In the PTSD&AUD group, reduced connectivity was observed with Default_PFCdPFCm_8 seed and regions in the dorsal attention A (3/10 connections), limbic B (2/10), salience-ventral, temporal parietal, cerebellar, and default B/C networks. In contrast, increased connectivity was seen with regions in the default A (10/30), somato-motor A/B (12/30), executive control A/C (CEN) (4/30), salience/ventral attention (2/30), the dorsal attentional B networks and the left ventral pallidum, when compared to AUD-alone.

Conclusions
These findings suggest that individuals with PTSD&AUD show altered IFC compared to AUD-alone. This pattern of between-group differences may reflect difficulties in regulating internal states and external attention, which could help explain the greater emotional and cognitive challenges observed clinically in individuals with PTSD&AUD compared to those with AUD alone.

P_13a Low-Dose Donepezil Modulates Impulsivity but Not Cognitive Flexibility in a Dynamic Strategy Shifting Task

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Background
Cognitive flexibility—encompassing vigilance, inhibitory control, reversal learning, and working memory—is significantly impaired in schizophrenia and strongly predicts functional outcomes. Although drugs designed to enhance cognition are available, their effects on flexibility, impulsivity, processing speed, and goal-directed behaviour vary with dosage and depend on the behavioural test used. This study evaluated the effects of acute administration of low-dose Donepezil in rats using a dynamic strategy shifting task (DSST), which incorporates multiple aspects of cognitive performance.

Methods
Sprague-Dawley rats of both sexes (N=24) were trained to nose poke a central aperture and press a lever for food rewards. During rule training, they learned to discriminate between spatial and non-spatial rules, requiring six consecutive correct responses (CCR) to progress. In the test phase, a within-subject Latin-square design was used to administer Donepezil (0, 0.3, 1, 3 mg/kg), with rats completing up to seven dynamically shifting rules per session. Measures included CCR, response duration, premature nose pokes, and perseverative magazine entries.

Results
All rats successfully completed training. Donepezil had a biphasic effect on speed of processing, as measured by response duration—slower at 0.3 mg/kg and faster at 3 mg/kg. Low doses (0.3, 1 mg/kg) reduced impulsivity, as measured by premature responses, while 0.3 mg/kg increased goal-directed behaviours, as measured by perseverative magazine entries. However, Donepezil did not significantly affect strategy shifting performance in terms of trials to criterion or number of rules completed within a single session.

Conclusions
This study examined the behavioural effects of low-dose Donepezil in rats engaged in a complex learning task. Although the drug did not enhance strategy-shifting ability, it influenced other cognitive domains. Lower doses reduced impulsive actions and promoted goal-directed behaviour, while processing speed showed a dose-dependent pattern—slower at 0.3 mg/kg and faster at 3 mg/kg. These results suggest Donepezil can selectively affect components of cognitive function, such as attention and behavioural regulation, without improving overall flexibility. The findings underscore the importance of dosage and task design when assessing the impact of cognitive enhancers in preclinical models.

P_31a Exploring blood-based biological correlates of cognitive intra-individual variability and other cognitive measures in bipolar disorder

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Background
Cognitive impairment is a common and functionally meaningful characteristic of bipolar disorder (BD), but its biological underpinnings are yet to be fully established. Emerging evidence posits telomere length and peripheral inflammation as prospective factors of interest. In this study, we examined the independent and synergistic associations between these biological factors and cognition in BD.

Methods
One hundred and forty-nine participants (n=92 people with BD and n=57 healthy controls) completed cognitive assessments of processing speed, sustained attention, working memory, executive function, and neurocognitive intraindividual variability. Whole-blood and plasma were also provided by subsamples within this, from which genomic DNA was extracted to measure telomere length, and several inflammatory cytokines and chemokines were examined with composite scores. Multivariate regression analyses explored associations of these variables.

Results
Poorer cognition, higher intraindividual variability, and shorter telomeres were found in the BD group compared to healthy controls. No significant group differences in either of the inflammatory composites were identified, and no independent associations of cognition with telomere length or either inflammatory composite were observed. However, a synergistic interaction of the biological variables was evident in the BD group, whereby BD patients with a combination of shorter telomeres and high levels of inflammatory cytokines and chemokines demonstrated poorer processing speed.

Conclusions
The relationship between cognition and blood-based biological markers in BD is complex. This work provides preliminary evidence that poor processing speed in BD is influenced by the combined, rather than the isolated effects, of telomere length and inflammation.

P_52a Melatonin mitigates oxidative stress and metabolic dysfunction induced by interleukin-6 and dopamine in SH-SY5Y cells

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Background
Melatonin has emerged as a promising pharmacological candidate for bipolar disorder (BD). The mechanisms of action underpinning this therapeutic utility remain incompletely understood, but may be a result of its antioxidant, anti-inflammatory and anti-dopaminergic properties. This study investigated melatonin's effects on dopamine signalling, metabolism, and oxidative stress under inflammatory and hyperdopaminergic conditions in differentiated SH-SY5Y neuronal cells.

Methods
SH-SY5Y cells were differentiated for seven days with 10μM retinoic acid. 100nM melatonin or vehicle was administered for two hours, then 20ng/ml interleukin-6 (IL-6), 5μM dopamine, 500μM dopamine, or vehicle for 12 or 24 hours. Dopaminergic markers were quantified using HPLC and RT-PCR; metabolic markers with in-cell Westerns, carbon central metabolism (CCM) metabolomics, Seahorse Mito Stress assay, and glucose uptake assay; and oxidative stress with reactive oxygen species / superoxide (ROS/SOX) and total antioxidant capacity (TAC) assays.

Results
IL-6 increased dopamine content, TAC, p-AMPK/AMPK, p-Erk1/2/Erk1/2, and nucleoside mono- and diphosphate levels; and decreased dopamine turnover, SV2C, and spare respiratory capacity. Melatonin independently increased nucleoside mono- and diphosphate levels and NADH, and decreased dopamine turnover, ROS, and glucose-1-phosphate. Melatonin pretreatment prior to IL-6 significantly increased spare respiratory capacity, glucose uptake, and NADH; and reduced dopamine content, TAC, p-AMPK/AMPK, p-GSK3β/GSK3β, and non-mitochondrial oxygen consumption. 500μM dopamine significantly increased SOX, p-Erk/Erk, insulin receptor alpha, GLUT1, spare respiratory capacity, non-mitochondrial oxygen consumption, maximal respiration, and basal glycolytic ATP production. Melatonin pretreatment prior to 500μM dopamine administration significantly reduced p-Erk1/2/Erk1/2 and GLUT1.

Conclusions
IL-6 induces hyperdopaminergia, metabolic stress, and mitochondrial impairment in differentiated SH-SY5Y cells, and melatonin reverses IL-6-induced hyperdopaminergia, oxidative stress, and metabolic reprogramming. Furthermore, excess dopamine induces a glycolytic high-energy state in a similar manner to what is seen in mania, and melatonin has a partial protective effect against dopamine-induced metabolic reprogramming. Melatonin may therefore have a mitigating effect on manic symptomology in BD patients directly by reducing dopamine, and indirectly by moderating the metabolic effects of inflammation.

P_33a Region and age specific alterations in endocannabinoid gene expression in major depressive disorder

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Background
The endocannabinoid system (ECS) represents a promising therapeutic target for major depressive disorder (MDD), yet its role in MDD pathophysiology remains poorly characterised. Findings in the prefrontal cortex consistently report increased CB1 receptor expression in MDD; however, there has been limited examination of other ECS components or brain regions. The anterior cingulate cortex (ACC) and hippocampus are particularly relevant given their established roles in depression pathophysiology and documented structural abnormalities in MDD patients. Given that both aging and depression independently affect endocannabinoid signalling, this study examined ECS gene expression in both regions across different age groups.

Methods
ACC (Brodmann's area 24, n=39) and hippocampus (CA1, n=26) tissue from post-mortem MDD subjects and age-matched controls were obtained from the National Institute of Health, USA. Subjects were stratified by age (<65 vs ≥65 years). Total RNA was extracted and synthesised into cDNA. Using Fluidigm techniques, mRNA expression of receptor genes (CNR1, TRPV1, TRPV4) and endocannabinoid metabolising enzyme genes (FAAH1, NAAA, DAGLA, DAGLB, MGLL) were measured. Statistical analyses controlled for age, post-mortem interval, and RNA integrity number where correlations were significant.

Results
In the ACC, CNR1 gene expression was significantly reduced in MDD subjects over 65 years compared to age-matched controls (-65%, p=0.026), while in the hippocampus, CNR1 expression decreased with age regardless of diagnosis (-52%, p=0.014). TRPV4 expression was significantly elevated in the ACC in MDD (+26%, p=0.007) but showed no diagnostic differences in the hippocampus. For endocannabinoid metabolising enzymes, NAAA expression was significantly increased in the hippocampus in MDD (+55%, p=0.050), independent of age, but remained unchanged in the ACC.

Conclusions
This study provides the first evidence of brain region-specific ECS gene expression alterations in MDD. The ACC showed age-dependent CNR1 downregulation and elevated TRPV4 in MDD, suggesting impaired cannabinoid receptor signaling in executive control regions. Conversely, the hippocampus exhibited NAAA upregulation in MDD, indicating disrupted endocannabinoid metabolism in memory circuits. These region-specific molecular signatures provide important mechanistic insights into MDD pathophysiology. Further studies to examine the cell specific nature of these changes and whether these changes extend to the protein level will be important.

P_41a If the doors of self were cleansed: effective connectivity of Ego Dissolution

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Background
Ego Dissolution (ED) is a profound experience consistently identified as a key factor mediating positive clinical outcomes following psychedelic-assisted therapy. It also provides a unique lens through which to study the neural basis of self-related processing. While previous neuroimaging studies have investigated ED using functional connectivity, they have not addressed effective connectivity —that is, the directed causal influences between regions. This project aims to characterize effective connectivity differences, using a generative modelling approach, between individuals who report experiencing ED and those who do not, thereby advancing mechanistic understanding of self-disintegration under psychedelics.

Methods
Data are drawn from the PsiConnect trial (ACTRN 12621001375842), the largest psilocybin dataset in healthy participants to date (N = 64). To estimate effective connectivity from resting-state fMRI data, Spectral Dynamic Causal Modelling (spDCM) is used, a Bayesian approach that infers effective connectivity by fitting a biophysical generative model to the cross-spectral density of BOLD signals. The model includes five key regions implicated in self-processing and memory: parahippocampal cortex (PHC), hippocampus (HP), retrosplenial cortex (RSC), posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC).

Results
We expect to observe a breakdown in directed connectivity between the PHC and RSC in participants reporting high ED, leading to reduced top-down influence from the mPFC and PCC to the HP. These patterns are hypothesized to associate with MEQ Mystical subscale scores. By contrast, individuals with lower ED scores are expected to show stronger PHC–RSC connectivity and preserved network integration. Pre-drug connectivity may also predict ED susceptibility, with lower baseline RSC-PHC connectivity associated with increased likelihood of experiencing ED.

Conclusions
The anticipated findings support a mechanistic account of ED as a breakdown between key nodes of the autobiographical memory system. Specifically, ED may reflect a sequential decoupling: first between the PHC and RSC, then between higher-order cortical hubs (PCC and mPFC) and the HP. This cascade may underlie the subjective loss of self, conceptualized as impaired access to autobiographical memory. Given the PHC's central role in contextual binding, its disconnection may also disrupt the integration of sensory information with higher cognitive representations – further contributing to the dissolution of self-boundaries.

P_1a Developing a rodent model for measuring subcortical mechanisms of repetitive transcranial magnetic stimulation

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Background
Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique involving the delivery of electromagnetic pulses to targeted brain regions, altering neuronal activity within the target region and associated brain circuits. Despite its increasing use across a range of neuropsychiatric conditions, optimal treatment paradigms are yet to be determined due to a lack of understanding regarding the mechanisms underlying rTMS treatment. The aim of this study was to pilot combining the use of a custom rodent rTMS device with in vivo imaging to record the activity of reward-related brain regions, specifically the striatum, before, during and after rTMS.

Methods
Optimisation of custom 3D-printed coil support was undertaken in order to facilitate paired rTMS and fibre photometry recording. This approach was then used to investigate rTMS induced subcortical activity changes, examining dopamine activity using DLight1.2 (n=8) with photometry recording from posterior dorsomedial striatum (pDMS). Photometry recordings were taken before, during and after frontal pole rTMS application, testing the acute effects of 3 different rTMS protocols in a repeated measures design. Operant testing was performed in the post-rTMS recording period, using a probabilistic reward dose-response paradigm to characterise any immediate changes to dopamine signalling following rTMS.

Results
Trialling a custom 3D-printed rTMS coil support, the combined use of rTMS and fibre photometry in rats was achieved in a small pilot cohort. Preliminary results from the small pilot cohort establishing this showed paired rTMS and photometry could be successfully undertaken, recording continuously before, during and after rTMS application. Additionally, cFos activity mapping was performed following a final rTMS stimulation, with analysis indicating changes in striatal activity. Photometry recording and operant testing investigating the effects of different rTMS protocols on dopamine activity in the pDMS is ongoing.

Conclusions
By pairing miniaturised rodent rTMS devices with in vivo imaging, the novel rTMS/photometry approach developed here facilitates measurement of rTMS effects on brain function in awake behaving rodents. This provides a platform to understand the mechanisms underlying the direct and downstream effects of rTMS. Work is ongoing using this approach to investigate the effect of rTMS on striatal function, specifically changes in dopamine activity in the pDMS. Moving forward we aim to assess the effect of various rTMS protocols on other brain regions and targets, as well as in models of neuropsychiatric disorders.

P_63a Clinician perspectives of treatment priorities and the role of cognitive symptoms in supporting people with schizophrenia

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Background
Schizophrenia is a highly disabling and life limiting mental disorder. The historical treatment focus has been remission of positive symptoms (i.e., hallucinations/delusional thinking). However, neurocognitive impairments better predict functional outcomes in people affected by schizophrenia. Cognitive remediation (CR) is the only intervention for schizophrenia which has a substantial evidence base supporting reliable improvements in cognition. Despite this, CR is not widely available or utilised due to bottlenecks in service delivery and inadequate cognitive testing access. Understanding the barriers limiting CR and cognitive testing is critical to improving treatment outcomes in schizophrenia.

Methods
A voluntary anonymous online cross-sectional survey (Qualtrics platform) of Australian psychiatrists to explore their treatment priorities and access to common referral services (including cognitive testing and CR). The survey focussed on the clinical priorities, referral practices, and experience/confidence in treating people experiencing psychosis. Participants included registrars (n=28) and practicing psychiatrists (n=68) in Australia (N=96). Exploratory analyses were completed using a variety of statistical approaches based on the data type (linear mixed-methods regression, chi-squared analyses and ANOVA's).

Results
Overall, clinicians were confident in their ability to treat those with psychosis, but neutral with regards to their ability to identify/treat cognitive symptoms. Despite clinicians acknowledging that cognitive symptoms were most predictive of functional outcomes (>75%), they reported that consumer concerns were primarily positive symptoms (>60%). In accordance with consumer concerns, treating positive symptoms was the highest priority in managing early psychosis (~90%), with cognitive symptoms the lowest. Moreover, only the minority of clinicians made referrals for cognitive testing or CR (both <30%). Access to cognitive testing was a substantial factor limiting referrals (only 40% with access).

Conclusions
Despite the acknowledged relationship between cognitive symptoms and functional outcomes, and the evidence base for CR efficacy, access to formal testing and referral rates are far from optimal. These findings should motivate efforts to develop simple, quick cognitive screening and testing protocols. By supporting clinicians to prioritise cognitive symptoms and providing easy access to cognitive readouts, these screens would help guide clinician decision making and referral to CR. Moreover, better education of consumers and the functional burdens cognitive symptoms represent are required to help drive consumer-led demand for cognitive assessment and CR referrals.

P_49a DARPP-32 mRNA in Schizophrenia and Bipolar Disorder: Differential Findings in the Dorsal and Ventral Striatum

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Background
DARPP-32 (dopamine- and cAMP-related phosphoprotein of 32 kDa) is a cytosolic protein highly expressed in the medium spiny neurons of the striatum. It is a key integrator between dopaminergic and glutamatergic signaling processes, modulating downstream cascades critical for synaptic plasticity and neurotransmission. Dysregulation of DARPP-32 has been implicated in the pathophysiology of schizophrenia and bipolar disorder, particularly in relation to dopamine imbalance and cognitive dysfunction. However, region-specific alterations, inflammatory influence, and subgroup specific analyses remain largely underexplored.

Methods
To determine changes in DARPP-32 mRNA in individuals with schizophrenia (SCZ), bipolar disorder (BD), and matched non-psychiatric controls (CTR), RNA was extracted from human postmortem nucleus accumbens (NAc; ventral striatum) (CTR = 30, SCZ = 30), midbrain (MB) (CTR = 33, SCZ = 35, BD = 33), and caudate nucleus (CN; dorsal striatum) (CTR = 52, SCZ = 54, BD = 29). Gene expression of DARPP-32 was measured using RT-qPCR and analyzed by diagnosis, pre-defined inflammatory subgroups, and cause of death.

Results
In the CN, DARPP-32 mRNA was decreased in both low inflammation SCZ and high inflammation SCZ groups compared to controls. Similarly, BD subjects had lower DARPP-32 mRNA in the CN, but specifically in the low inflammation group compared to high inflammation BD subjects and controls. In contrast, DARPP-32 mRNA did not differ between diagnostic and inflammatory groups in the NAc or MB. When comparing cause of death, SCZ subjects who died by suicide showed increased DARPP-32 mRNA in the NAc compared to those who died from other causes.

Conclusions
We reveal transcriptional alterations in DARPP-32 in the CN in SCZ and BD. The reduction in DARPP-32 in both SCZ and BD suggests diminished dopaminergic and glutamatergic modulation in the CN across diagnoses. Elevated DARPP-32 in the NAc specifically in SCZ subjects who died by suicide suggests potential involvement in suicidality and warrants further investigation. Overall, these findings support DARPP-32's involvement in psychiatric pathophysiology but highlight the region-specific nature of its involvement across the dorsal and ventral striatum and warrant further investigation at the protein and cell level.

P_10a The impact of time of day and testosterone on fear extinction in male and female rats

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Background
Sex hormones play a critical role in fear extinction, the laboratory basis of exposure therapy for anxiety disorders. For example, fear extinction varies markedly across the estrous cycle in female rats, and the menstrual cycle in healthy and clinically anxious women, with worse extinction retention during phases of low oestradiol and progesterone. Fewer studies have examined the effects of testosterone on fear extinction in males, and findings are mixed. No studies have examined the effects of testosterone on fear extinction in females. The present study aimed to clarify the effects of testosterone on fear extinction in male and female rats.

Methods
In Experiment 1, male rats (n=48) underwent a fear conditioning and extinction protocol during the morning (8am, when testosterone levels are low) or midday (12pm, when testosterone levels are higher). In Experiment 2, female rats (n=64) underwent an identical protocol as Experiment 1 except they were also extinguished during either the metestrus (low estradiol/progesterone) or proestrus (high estradiol/progesterone) phase of the estrous cycle. In Experiment 3, male (n=23) and female rats (n=24) underwent fear conditioning, and then received a s.c. injection of antide (a gonadotropin-releasing hormone receptor antagonist, which suppresses testosterone within 24h) or vehicle 24h before extinction.

Results
The time of day influenced fear extinction in males and females, such that rats extinguished during the morning exhibited worse extinction retention than those extinguished at midday. In males, serum testosterone levels were lower in the morning relative to midday. Testosterone levels at the time of euthanasia were not correlated with any behavioral measure. Serum testosterone and estradiol levels are still being analyzed in females. In contrast to past research, the estrous cycle did not influence fear extinction in females at either time. Reducing testosterone levels via systemic administration of antide had no effect on fear extinction in either sex.

Conclusions
This study demonstrates that circulating levels of testosterone may produce differing effects on fear extinction depending on specific factors. That is, while natural fluctuations in testosterone across the day may influence fear extinction, systemically reducing testosterone levels has no effect. These findings are consistent with previous mixed reports on testosterone effects on fear extinction. Given that our current knowledge on fear extinction is mostly based on studies conducted primarily in male animals, and the impact of sex hormones has been relatively ignored in both sexes, this study highlights the importance of considering the impact of sex hormones in both sexes.

P_28a Patterns in the Brain: Exploring Multiday Cycles in Mood and Anxiety Symptoms

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Background
Psychiatric disorders such as Major Depressive Disorder are characterised by recurrent relapse. While early intervention can mitigate risks, a major challenge is estimating when symptoms will increase. Studies in neurology show that longer-term biological rhythms (>24hrs) influence brain excitability, heart rate, and stress, yet their impact on psychiatric symptoms remains unknown. Advances in wearable technologies enable continuous, long-term monitoring of physiological signals. Using Rhythmo, a platform we developed to extract multiday cycles from heart rate signals, this study evaluates whether depressive and anxiety symptoms oscillate over multiday cycles, offering initial insight into long-term patterns underlying symptom fluctuation in psychiatry.

Methods
Data was extracted from the NetHealth study and included heart rate signals from Fitbit smartwatches of 193 colleague students, each completing up to 8 assessments of Beck's Depression Inventory (BDI) and Beck's Anxiety Inventory (BAI) scheduled across academic terms over the 4 year study. Multiday cycles were extracted from the heart rate signals using a range of signal processing techniques (via Rhythmo) including Morlet wavelet transform to identify prominent peaks. Once a significant cycle was identified, there was a retrospective assessment of whether testing occurred during the peak or trough of the individual participant's multiday cycle.

Results
Linear mixed-effects models were applied to investigate whether multiday heart rate cycles predict fluctuations in depressive and anxiety symptoms in healthy controls. For both BDI
and BAI, symptoms were significantly elevated during the Peak phase of the multiday cycle (BDI: β=3.38, p=.022; BAI: β=3.27, p=.031). Higher daily mean heart rate was also associated with increased symptom severity (BDI: β=0.18, p = .022; BAI: β=0.17, p=.033), though weaker effects than multiday cycles. Interaction between sex * cycle phase was significant for BAI (p=.040). Models included a random intercept to account for repeated measures within participants.

Conclusions
This study provides initial evidence that self-reported depressive and anxiety symptoms fluctuate across personalised multiday cycles, with cycle peak showing the strongest association with increased symptom severity. These findings also demonstrate the sensitivity of wearable-based monitoring for capturing longer-term rhythms relevant to mental health. The next step is to track these cycles and symptom fluctuations in clinical cohorts. This approach holds immense potential for developing predictive models to identify high symptom risk periods and support proactive, personalised early-intervention models. This novel framework could advance precision-medicine and digital health solutions for psychiatry.

P_56a From Parenting to Brain to Wellbeing: Neural Effects of Emotion-Focused Parenting in Adolescents

Presenting Author: Junxuan Zhao

Junxuan Zhao, *University of Melbourne*

Background
Parental emotion socialisation is theorised to influence the development of internalising disorders in adolescents through its impact on emotion regulation. However, the underlying neural mechanisms have not been investigated.

Methods
In a randomised controlled trial, sixty female adolescents aged 10-12 with elevated internalising symptoms and their mothers were assigned to either the intervention group or the waitlist control group. An emotion-focused parenting intervention was implemented to manipulate parenting and examine its effect on adolescent internalising symptoms and the underlying neural mechanisms. Adolescents completed affect labelling and cognitive reappraisal fMRI tasks at pre-intervention and at 6-month follow-up. Brain effective connectivity between key nodes of limbic and cortical brain networks during emotion regulation was assessed using dynamic causal modelling. Mother- and adolescent-reported internalising symptoms were collected at pre-intervention and at 8-month follow-up.

Results
Previous analyses using this dataset have shown that the intervention led to significant improvements in maternal emotion socialisation behaviours. We anticipate that the intervention will also improve adolescent internalising symptoms, with improved effective connectivity between limbic and cortical brain network during emotion regulation mediating this effect.

Conclusions
The current study contributes to understanding how parental emotion socialisation influences adolescent neural and emotional development. The findings will provide evidence that intervening with parenting may enhance brain development and mental health outcomes in female adolescents at risk of internalising disorders.

P_8a Activity-based anorexia in rats: How reward value “drives the wheel”

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Background
Compulsive exercise is reported in up to 80% of patients with anorexia nervosa (AN) and is an essential component of the activity-based anorexia (ABA) rodent model. Based on the shared genetic and phenotypic features of AN and obsessive-compulsive disorder, there may be similar underlying biological mechanisms, including disrupted activity in dorsal striatum (DStr). However, the specific effect of disrupted DStr activity on compulsive exercise remains unknown. We have previously observed that DStr activity is involved in both excessive exercise and goal-directed instrumental learning. However, whether this is related to actions at specific dopamine receptor expressing neurons in DStr remains unclear.

Methods
To determine the involvement of DStr D2 receptor expressing (D2R) neurons in compulsive exercise and operant behaviour in ABA, we stereotactically injected D2-Cre driven inhibitory DREADDs into DStr. Female Sprague-Dawley rats (n=25; 9 weeks of age) were exposed to ABA conditions, which combined unlimited voluntary running wheel access with time-limited (90 min) food access, followed by the outcome-specific devaluation task (ODT). In addition, we conducted operant-paired fibre photometry with D2-Cre driven GCaMP during instrumental training of ODT in a separate cohort of female rats (n=7; 13 weeks old).

Results
We showed that the suppression of D2R neurons in DStr reduced pathological weight loss in ABA (p=0.0260), whereas selective suppression of these neurons in the medial subcompartment (dorsomedial striatum; DMS) had no effect on body weight maintenance (p=0.4261). However, compulsive exercise correlated with compulsive responding only when D2R neurons in DMS were suppressed (r=0.86, p=0.004), suggesting that DMS D2 neurons align these behaviours. Moreover, changes in calcium release during instrumental learning showed distinct patterns within D2R neurons in DMS compared to the lateral subcompartment (dorsolateral striatum; DLS), with DLS activity increasing over training and peaking at pellet retrieval.

Conclusions
These findings reveal distinct roles for D2R neurons across DStr subregions in compulsive exercise pathology. While broad DStr D2R suppression reduces pathological weight loss in ABA, DMS-specific D2R neurons uniquely coordinate the relationship between compulsive exercise and operant behaviours. The differential dynamics between DMS and DLS D2R neurons during instrumental learning support functional specialisation within the dorsal striatum. This research advances our understanding of the neurobiological mechanisms underlying compulsive exercise in AN and highlights the therapeutic potential of targeting specific striatal circuits. Future investigations should explore how these manipulations might translate to clinical interventions for AN patients with compulsive exercise.

P_12a Beyond Serotonin: Investigating the role of dopamine in psilocybin-induced behavioural and motivational changes

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Background
The resurgence of research into psilocybin has been spurred by promising results demonstrating rapid-acting therapeutic potential across psychiatric conditions. While investigations have traditionally focused on serotonergic mechanisms, the promiscuous binding profile of psilocybin suggests other neurotransmitter systems may contribute to its therapeutic effects. The dopaminergic system represents a compelling target given its role in motivation and reward value, domains frequently disrupted in psychiatric disorders. In the present study, we investigated dopamine's role in the effects of psilocybin using C57Bl/6J mice.

Methods
We examined the effect of dopamine receptor antagonism (D1, SCH2390, 0.01 mg/kg; D2, raclopride, 0.5 mg/kg) on psilocybin-induced (1.5 mg/kg) head-twitch response (HTR) in females and assessed acute effects on effort-based responding using progressive ratio tasks. To examine stimulus-evoked dopamine release in motivational circuits using fibre photometry, we virally expressed dopamine biosensors in the nucleus accumbens core (NAcc) and medial prefrontal cortex (mPFC), GRAB DA2m and 3m, respectively, and examined dopamine release to a sucrose reward.

Results
We demonstrate that dopaminergic signalling contributes to psilocybin's acute behavioural effects. Both D1- and D2-receptor blockade attenuated psilocybin-induced HTR, with D2-antagonism producing significant suppression ($p = 0.001$, $n = 9$) while D1-effects showed trends ($p = 0.07$, $n = 9$). Psilocybin acutely reduced progressive ratio breakpoint performance ($p = 0.076$, $n = 6$), indicating decreased effort-based responding. Surprisingly, direct measurement using genetically-encoded biosensors, in males, revealed no significant changes in stimulus-evoked dopamine release in the NAcc ($p = 0.75$, $n = 4$) but a slight, no significant decrease in the mPFC ($p = 0.064$, $n = 4$).

Conclusions
The dissociation between behavioural dopaminergic effects and measured dopamine release suggests complex, potentially sex-specific mechanisms underlying psilocybin's interaction with dopaminergic circuits, providing important targets for future investigations aimed at elucidating the neurobiological substrates of psilocybin's therapeutic actions.

P_15a Opioid receptor involvement in social and non-social fear extinction in adolescent rats: Effects of naloxone

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Background
In social species, the presence of another individual can reduce stress reactions to adverse stimuli, a phenomenon known as social buffering. Social buffering dampens fear responses during the extinction of learned fear in adolescent rats. Adolescence is characterised by diminished fear inhibition and heightened social engagement, making it a critical period for investigating mechanisms underlying social modulation of fear extinction. Although endogenous opioids are implicated in enhanced fear extinction learning by social buffering, their role in adolescent rats remains untested. In this study, we investigated whether opioid receptors are necessary for extinction under social and alone conditions.

Methods
Male and female 5–6-week-old adolescent rats were fear conditioned and then given one or two days of extinction training either in the presence of a same-age, same-sex rat or alone. Some male rats received two days of extinction training alone, as this produces better extinction retention in adolescents than a single session. Animals received the opioid receptor antagonist naloxone (5 mg/kg) or saline 10 minutes before extinction training. One day later, animals were tested alone for extinction retention.

Results
The presence of a conspecific reduced conditioned fear responses during extinction training. Naloxone increased fear expression during social extinction in male but not female rats. However, this effect was not observed during the extinction retention test. In contrast, when extinction training was conducted alone, naloxone elevated fear expression in males during both extended extinction and the extinction retention test, indicating impaired extinction learning and retention.

Conclusions
These results replicate previous findings that opioid receptors are required for extinction learning and retention in adolescent male rats when extinction training is extended to enhance retention. The findings suggest that opioid receptors contribute to socially mediated fear reduction in adolescent males during extinction, but their influence does not extend to long-term extinction retention.

P_14a Assessing Hormonal Drivers of Stress Induced Binge Drinking in Female Mice

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Background
Using alcohol to self-medicate during times of stress is an increasingly common problem, and in recent years, has emerged as a major women's health issue. Despite these epidemiologic trends, the interactions between stress, alcohol and hormones have not yet been sufficiently investigated. Surges of hormones during puberty, a critical developmental period experienced by all, often coincide with the onset of mental health disorders (anxiety/depression) and alcohol misuse, making this an important area for investigation. Therefore, to address this important gap in the literature, we assessed the role of pubertal hormones in stress and alcohol consumption in female mice.

Methods
At P28, a group of pre-pubertal female mice underwent ovarectomisation (OVX, n =19) surgeries to prevent hormone-associated organisation of the brain during puberty. A control group (n=18) underwent parallel sham surgeries and remained gonadally intact. During adulthood (P63), a modified stress-enhanced fear learning (SEFL) paradigm was used to administer unpredictable foot shocks (11 x 1 mA over 2 days), modelling PTSD-like stress (n=9-10/group). These mice, as well as shock-naive controls (n=9/group), then underwent four weeks of drinking-in-the-dark (DiD) to assess the potential impact of stress, and/or disruption of organisational hormones on binge-like alcohol drinking patterns.

Results
Pre-pubertal OVX significantly decreased alcohol consumption, independent of stress history ($p<0.0001$). Administration of a PTSD-like shock did not correspond with increased alcohol consumption ($p=0.3431$). While mice had comparable baseline body weights prior to intervention, OVX resulted in greater weight gain throughout experimentation compared to sham mice (p-value). Interestingly, preliminary results suggest no changes in food consumption. Whole brain light sheet imaging to assess differences in neural activity and estrogenic signalling are now underway.

Conclusions
These findings suggest that hormonal surges during puberty may increase drinking behaviour, with this effect being independent of unpredictable stress exposure.but this change in alcohol consumption is not significantly modulated by unpredictable stress. Prior research has shown that estrogen, a gonadal hormone produced in the female body during and after puberty, modulates the neurotransmitter systems associated with alcohol's rewarding properties, which may in part underpin our findings. Further research using adult OVX mice and pre-pubertal OVX mice with exogenous hormone treatment (estrogen/progesterone) will allow us to parse whether the effects of sex hormones on alcohol consumption are organisational or activational.

P_30a The relationship between neurometabolites and cognitive function in adults with alcohol use disorder: A preliminary proton magnetic resonance spectroscopy study

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Background
Chronic alcohol use disorder (AUD) is associated with altered levels of brain neurometabolites, including total N-acetylaspartate (tNAA), glutathione (GSH), and glutamate, which may contribute to cognitive impairments. This preliminary study investigated baseline neurometabolite concentrations in the anterior cingulate cortex (ACC) and their association with cognitive performance in individuals diagnosed with AUD.

Methods
Forty-one participants (mean age=48; 61% male) meeting DSM-5 criteria for moderate to severe AUD underwent proton magnetic resonance spectroscopy (1H-MRS) to quantify neurometabolite concentrations (tNAA, GSH, glutamate) in the ACC. Cognitive functioning was assessed using the N-back task (working memory), Number-Letter task (cognitive flexibility), Stroop Colour Word Test (SCWT; distractor interference and cognitive control), and Trail Making Test (TMT; set-shifting ability). Linear regression analyses controlled for age, alcohol consumption, and antidepressant use.

Results
Higher baseline GSH levels significantly predicted better performance on the N-back task ($p = 0.048$, CI: 0.14–29.87). No significant associations were found between baseline tNAA ($p = 0.054$, CI: -0.10–10.60) or glutamate ($p = 0.56$, CI: -4.62–2.58) and N-back performance. Additionally, neurometabolite levels were not significantly associated with performance on the Number-Letter task (tNAA: $p = 0.09$; GSH: $p = 0.849$; glutamate: $p = 0.475$), SCWT (tNAA: $p = 0.09$; GSH: $p = 0.849$; glutamate: $p = 0.606$), or TMT (tNAA: $p = 0.753$; GSH: $p = 0.976$; glutamate: $p = 0.366$).

Conclusions
These preliminary findings suggest that elevated baseline GSH concentrations in the ACC are associated with improved working memory performance in individuals with AUD. However, baseline levels of tNAA and glutamate did not show significant relationships with cognitive outcomes assessed by the N-back, Number-Letter task, SCWT, or TMT.

P_4a Neural correlates of “Incubation of craving” for alcohol-associated cues.

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Background
Alcohol use disorder (AUD) is characterised by high relapse rates and intense cravings, often triggered by alcohol-associated cues. This cue-elicited craving intensifies over a period of abstinence, a phenomenon known as “incubation of craving”. We have replicated this phenomenon in an animal model, however the specific role of the discrete cues in relapse behaviour during abstinence remains unclear. Additionally, findings from our lab have shown increased activity in reward circuits following abstinence, but the specific pathways involved have yet to be identified. This study aimed to investigate the corticostriatal pathways recruited during relapse in both cue and no-cue conditions.

Methods
Prior to self-administration training, Long Evans rats received unilateral injections of a retrograde tracer (Cholera Toxin β subunit) into the nucleus accumbens (NAc) core or shell. After recovery, rats were trained to lever press for alcohol associated with a discrete cue light. Relapse to alcohol-seeking was tested before (No Abstinence), or after 28 days of abstinence (Abstinence), in the presence or absence of cues. Rats were perfused 90 minutes after each test and brains processed for c-fos immunoreactivity to estimate neural activation. Recruitment of corticostriatal pathways was assessed by quantifying c-fos in retrogradely labelled cell bodies in the prefrontal cortex.

Results
Increases in alcohol-seeking occur after abstinence regardless of the presence of cues. Preliminary results indicate that the largest corticostriatal projections recruited during incubation of craving are the cingulate cortex to NAc shell and core, and prelimbic to NAc core. Data from the no-cue condition groups are still under analysis.

Conclusions
These findings suggest that although alcohol-associated cues significantly increase the likelihood of relapse-like behaviour after a period of abstinence, incubation of craving does not seem to be solely cue-dependent. Additionally, alcohol withdrawal induces neural adaptations that magnify the recruitment of specific reward circuits. Ongoing experiments are looking at ways of preventing or reversing these adaptations to develop treatments that reduce relapse risk in AUD.

P_39a Common and Distinct Neural Correlates of Human Avoidance and Safety Learning

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Background
Persistent avoidance and deficits in safety learning play a major role in maintaining anxiety disorders. Limited studies investigated the neural correlates of avoidance, implicating ventromedial prefrontal cortex (vmPFC), amygdala and striatum. However, these studies examined the neural circuitry of instructed avoidance behaviours rather than of actual avoidance learning. At the brain circuitry level, safety learning has been broadly linked to activity in the vmPFC, hippocampus and posterior cingulate cortex (PCC). Whether this neural circuitry also drives avoidance learning and associated safety behaviours remains unclear. Our aim was to answer this question using a novel avoidance and safety learning paradigm combined with 7T functional magnetic resonance imaging (fMRI).

Methods
84 healthy control participants were recruited (age: 22.71 ±4.15 years, 56% female). The paradigm consisted of 2 main task phases, ‘conditioning’ and ‘avoidance’. Participants were first conditioned to two threat stimuli (A+, D+) and a compound safety stimulus (AX-). Participants were then trained to successfully avoid the D+ (avoidable) versus A+ (unavoidable) stimuli. Participant expectancy rating and avoidance responses confirmed their successful learning of the task contingencies. General linear models were used to characterise brain responses to 1) successful avoidance vs unsuccessful avoidance, 2) successful avoidance vs safety learning, and 3) successful early vs late successful avoidance learning.

Results
Successful avoidance versus unsuccessful avoidance learning was associated with significant activation of the lateral frontopolar cortex, posterior vmPFC, dorsolateral prefrontal cortex, primary somatosensory cortex, dorsal PCC, and intraparietal sulcus, among other areas. Successful avoidance versus safety learning also demonstrated broad activation differences including involvement of the anterior and posterior vmPFC, rostral and dorsal anterior cingulate cortex, PCC, dorsolateral prefrontal cortex, and ventral caudate nucleus/accumbens. When comparing early to late avoidance learning, early learning was distinctly associated with activation of the periaqueductal grey (PAG), mediodorsal thalamus, right anterior insular cortex, and right ventrolateral putamen.

Conclusions
This is the first study showing that avoidance learning appears to rely on both shared and distinct brain mechanisms when compared to safety learning, with notable shared involvement of the vmPFC and PCC, but apparent distinct involvement of threat-responsive regions during early avoidance, including PAG, thalamus and insular cortex. To what extent this underlying circuitry of avoidance is altered in psychopathology will be important questions for ongoing work.

P_40a Longitudinal functional connectivity markers underlying symptom development in early psychosis

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Background
Psychotic disorders comprise a wide spectrum of different symptoms such as delusions, hallucinations, negative symptoms and cognitive impairments with a typical onset in late adolescence or early adulthood. Current treatment options are limited, particularly due to a lacking mechanistic understanding of certain symptom domains resulting in a lack of targeted therapies. Hence, we aimed to identify longitudinal functional neuroimaging-based markers that drive the course of certain symptom domains at an early disease stage to leverage the development of new therapeutic options.

Methods
We used longitudinal clinical and resting-state fMRI data from two independent large-scale observational studies comprising a total sample size of more than 750 patients at clinical high-risk for psychosis. We computed functional connectivity in several brain networks and pathways that have been described to be relevant in psychosis and used structural equation modelling to study clinically-relevant functional connectivity changes in early psychosis.

Results
Our results demonstrate that increases in functional connectivity in the limbic network drive an attenuation of negative symptoms in people at clinical high-risk for psychosis.

Conclusions
These findings reveal that strengthening functional connectivity within the limbic network at an early disease stage may yield the potential to mitigate the development of negative symptoms in early psychosis. Based on these results, we propose to evaluate non-invasive deep brain stimulation techniques such as focused ultrasound in terms of their ability to modulate functional connectivity within the limbic network. This may pave the way toward the development of more targeted early intervention approaches to improve the long-term outcomes in psychosis.

P_3a Understanding the role of dopamine and impact of methylphenidate on impulsive actions

Presenting Author: Maddison Fisher

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Background
The neurobiological and psychological processes driving impulsive behaviours are poorly understood. Impulsive symptoms of ADHD are commonly treated with the psychostimulant methylphenidate (MPH), which increases synaptic dopamine, suggesting an important role of dopamine signaling. However, it is unclear how dopamine signaling differs at baseline during different components of decision-making, or why reducing reuptake with MPH improves impulse control.

Methods
Here we examined the differences between high and low impulsive Long Evan rats in dopamine dynamics and behavioural responses to MPH administration. Using fiber photometry, we recorded neuronal activity (GCaMP) and dopamine transients (dLight) in the nucleus accumbens while rats performed a task that requires response inhibition. We also conducted two pharmacology studies to determine the doses that were most effective at reducing impulsive behaviour (0.1mg/kg, 1.0mg/kg, 3.0mg/kg), and a sub-chronic study to better reflect the daily dosing schedule required for efficacy in humans.

Results
Experiment 1 found that high impulsive rats had elevated dopamine release to reward as compared to low impulsive rats, linking differences in behaviour and neurobiological signaling. Experiment 2 revealed that the lowest dose of MPH decreased impulsivity in both high and low impulsive rats, while Experiment 3 found sub-chronic administration of this dose did not decrease impulsive behaviour.

Conclusions
Overall, these findings provide new evidence for the link between impulsive behaviour and aberrant dopamine release to anticipated rewards. However, these results indicate that there are likely several factors influencing individual responses to MPH treatment and suggests further refinement is needed when measuring impulsivity in preclinical research.

P_29a Gender specific effects of childhood interpersonal trauma on anxiety disorders: a systematic review and meta-analyses

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Background
Anxiety disorders are the most prevalent mental illnesses globally, typically arising during adolescence and more commonly diagnosed in women. To investigate early life predictors of anxiety disorders and gender differences, we conducted a systematic review and meta-analyses investigating the impact of gender in the relationship between childhood interpersonal trauma (e.g., sexual abuse, physical abuse, emotional/psychological abuse, physical/emotional neglect, poly-victimization, and parental substance use/mental illness/domestic violence and separation) and the risk of developing anxiety disorders. We hypothesized that the higher diagnosis of anxiety disorders in females may be due to gender differences in the type of childhood trauma experienced.

Methods
Collaborative screening of 2063 abstracts identified 18 eligible studies conducted in eight different countries. Quality control was assessed by two independent scorers from Deakin University and ISN Psychology. The quality and the risk of bias for each eligible study was evaluated using the National Heart, Lung, and Blood Institute (NHLBI) guideline on systematic reviews. Separate meta-analyses were conducted for childhood physical and sexual abuse, stratified by sex. All studies only reported males and females and referred to no other sex.

Results
All studies reported a positive relationship between at least one form of childhood abuse and an anxiety disorder. While the odds ratio for any anxiety disorder following childhood physical abuse was similar in females (95% confidence interval (CI) 1.88, 2.56) and males (95% CI 1.52, 2.12), the pooled odds ratio (OR) for any anxiety disorders following childhood sexual abuse was greater for females (95% CI 3.33, 4.35) than males (95% CI 1.05, 2.00). Notably, sexual abuse findings had significant heterogeneity (females I squared = 98% and males I squared = 92%) and should be interpreted with caution.

Conclusions
By highlighting the importance of trauma history, type, and sex in the development of anxiety disorders, this review emphasizes the need for gender-sensitive trauma-informed care. Sexist stigma surrounding sexual abuse may contribute to increased anxiety amongst female survivors. However, sexual abuse of boys may similarly be underreported based on perceived contradictions of male gender-roles. Biological differences in Hypothalamic-pituitary-adrenal (HPA) axis activity and sex hormones may also play a role. Future research examining gender identity distinct from reported sex at birth will help to delineate sex-related biology from psychosocial contributions and further our understanding of childhood trauma and anxiety disorders.

P_58a Exploration of the Role of microRNA Expression in Suicidality: A Systematic Review and Bioinformatic Analysis

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Background
Suicide, a global concern causing approximately 800,000 deaths annually, is influenced by complex and multifaceted factors, including biological, and environmental aspects. MicroRNA (miRNA) play a crucial role in modulating gene expression related to psychiatric disorders. This study aims to review the role of miRNA in suicide, providing insights into the molecular mechanisms influencing suicidality.

Methods
We performed an extensive literature review using Web of Science, PubMed, Scopus, Embase, and Ovid databases up to and including September 8, 2024, focusing on case-control studies involving humans, with a history of suicide and non-suicidal controls. We assessed the risk of bias in the included studies using the Newcastle Ottawa Scale. Identified miRNA were subjected to bioinformatics analysis to find their brain-specific gene targets, followed by enrichment analysis to identify affected pathways and associated diseases.

Results
Our systematic review of 1,437 studies led to the inclusion of 13 studies that collectively examined 285 suicidal subjects and 291 controls. We identified 43 unique miRNA with significant differential expression between cases and controls, with miR-30a, miR-30e, and miR-218 being consistently dysregulated in suicidal patients. Bioinformatics analysis revealed that these miRNA target several genes in the brain and are associated with various biological processes and diseases. Enrichment analysis further highlighted their potential roles in pathways related to DNA transcription, forkhead box O (FoxO) signaling, Ras-associated protein-1 (Rap1) signaling, long-term depression and dopaminergic synapse.

Conclusions
Our study revealed the significant role of miR-30a, miR-30e, and miR-218 as key cellular mediators in the pathophysiology of suicide. These findings provide promising directions for positioning these miRNAs as potential biomarkers or targets for therapeutic intervention.

P_23a Prenatal methamphetamine exposure causes, and N-Acetyl Cysteine prevents, long-lasting impairments in cognitive control during adulthood

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Background
Methamphetamine (MA) use during pregnancy is an increasing problem in Australia, with hundreds of children exposed in-utero each year. However, the long-term impacts for these children are poorly defined, and there are no FDA-approved treatments. To provide better insight into these impacts, and explore the therapeutic efficacy of N-Acetyl Cysteine (NAC), we employed an animal model of prenatal MA exposure with concurrent NAC treatment to measure outcomes experienced by offspring across development, and whether these could be prevented with pharmaceutical intervention.

Methods
Pregnant Long-Evans rats were administered methamphetamine (5 mg/kg/day) or saline via subcutaneous injections from gestational day (G) 10 through to postnatal day (P) 21. In their home-cages, rats also received bottles of NAC (1% w/v) or regular drinking water across the same administration period (i.e., G10-P21). There were four experimental groups: MA only (MA), saline only (SAL), concurrent MA and NAC (MA*NAC), and saline with NAC (SAL*NAC). These dams and their offspring were run across 3 experimental cohorts.
Male and female offspring were tested on physical and behavioural measures from birth (P0) through to adulthood (P60+).

Results
Prenatal MA and NAC independently cause reductions in weight gain across infancy. Prenatal MA and NAC do not affect the acquisition of physical milestones across early infancy. Prenatal MA impairs the expression, but not the acquisition, of sign-tracking in adulthood, while NAC affects neither. Prenatal MA impairs associative interference in a latent inhibition task during adulthood, and NAC prevents this.

Conclusions
Infant rats prenatally exposed to MA and also to NAC showed reduced weight gain, suggesting independent negative effects on growth. In adulthood, rats prenatally exposed to MA demonstrated impaired expression of sign-tracking, potentially reflecting dopaminergic dysfunction or impaired reward circuitry. Also in adulthood, prenatal MA impaired associative interference in the latent inhibition task, suggesting long-lasting deficits in cognitive control. However, concurrent prenatal NAC preserved performance, indicating protection via antioxidant pathways. These findings highlight oxidative stress as a mechanism underlying MA-related cognitive deficits and support the potential of NAC as a prenatal intervention to prevent long-term harm from prenatal MA exposure.

P_20a Dissecting the neural circuits of motivation under acute stress: behavioural and circuit-level analysis in rats

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Background
Disruption of motivation is a critical feature of psychiatric disorders including depression. Motivated behaviour involves multiple processes, including the capacity to sustain effort and evaluate effort–reward trade-offs. However much preclinical research aimed at understanding motivation and reward dysfunction in psychiatric disorders uses simpler paradigms that lack these features. This study aimed to compare different approaches for examining effort related choice in rats, for future studies examining underlying neural circuitry and effects of acute stress.

Methods
Adult male Wistar rats were trained in progressive ratio (PR) and effort discounting (ED) operant tasks that both test the preference for a low-effort/low-reward and a high-effort/high-reward outcome. The PR task measures sustained motivation by increasing the number of lever presses required for a fixed reward (1 sucrose pellet) until responding ceases (breakpoint), with a low effort (free) chow outcome available at all times. The ED task assessed cost–benefit decisions by offering a choice between a low-effort/low-reward and a high-effort/high-reward lever, with effort requirements increasing across blocks within session.

Results
PR task performance (collected under baseline conditions) revealed individual variability in persistence, highlighting complementary aspects of motivated behaviour captured by each paradigm. Optogenetics and fibre photometry are being used in ongoing studies to examine the role of infralimbic cortex (IL) and its projections to the nucleus accumbens (NAc) in these behaviours at baseline and following acute stress (60 minutes restraint).

Conclusions
While the PR and ED tasks target distinct motivational processes, stress-induced alterations were specific to cost–benefit decision-making. These findings lay the groundwork for upcoming in vivo fibre photometry and optogenetic experiments targeting IL–NAc projections to determine how this pathway controls motivation at baseline and following acute stress. Understanding these mechanisms will advance our knowledge of stress-related disruptions in decision-making and effortful behaviour, with translational relevance for stress-related disorders such as depression.

P_24a Investigating the role of orexin in stress-induced binge eating

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Background
Negative emotions such as stress are major antecedents to binge eating, which impacts up to 15% of young adults globally. Yet, the neurobiological mechanisms underpinning stress-driven binge eating remain to be elucidated. Here, we identify the orexin neuropeptide system, in its known capacity to influence stress and feeding-related behaviours, as a promising candidate. We aimed to characterise the role of orexin in stress-induced bingeing using a cross-species approach.

Methods
We used an established preclinical model, comprising repeated cycles of exposure to a mild stressor and intermittent access to palatable food, to induce binge-like eating in mice. Animals were administered either SB-334867 (15 mg/kg, s.c.) or vehicle (5% DMSO in saline, s.c.) prior to stress binge testing. Immunohistochemistry was performed to assess both orexin levels in the lateral hypothalamus and Fos expression throughout the brain (Fos is a marker of neuronal activity). In humans, fasted plasma samples were collected in 75 individuals with binge eating and 89 healthy controls. Orexin concentrations were analysed using enzyme-linked immunosorbent assay.

Results
In our preclinical work, immunohistochemistry revealed activation of lateral hypothalamic orexin neurons in stress binge mice compared to controls and a specific recruitment of orexin immunoreactive cells. Further, systemic antagonism of the orexin-1 receptor with SB-334867 reduced stress-induced binge eating. This effect was associated with reduced activation of the nucleus accumbens core, and increased activation of the bed nucleus of the stria terminalis (BNST) compared to vehicle-treated mice. In our clinical sample, participants with binge eating exhibited significantly higher fasting plasma orexin A levels than matched controls, as determined by Mann Whitney U test.

Conclusions
Our data implicates orexin signaling through the orexin-1 receptor in stress-induced binge eating, likely via a network involving components of the limbic system (nucleus accumbens core and BNST). Further, our results indicate that repeated cycles of stress-induced binge eating recruit the orexin system (i.e. evidencing engagement of the orexin 'reserve'). Together with our clinical evidence of elevated plasma orexin in humans with binge eating, we demonstrate that orexins impact is conserved across species and, further, may represent an exciting target for pharmacotherapeutic development.

P_25a Can intranasally administered clozapine effectively reduce psychosis-related behaviours and mitigate the debilitating metabolic side effects?

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Background
Clozapine is the most effectively anti-psychotic treatment in treatment-resistant schizophrenia. However, chronic administration of clozapine causes metabolic syndrome - a combination of increased weight, elevated triglyceride levels, low levels of high-density lipoproteins, hypertension and elevated blood glucose - leading to diabetes and cardiovascular complications. This, together with the heightened risk of developing life-threatening agranulosis and neutropenia, means the monitoring and management of the debilitating side effects of the drug results in clozapine being under-utilised in the treatment of schizophrenia.

Methods
We have developed a poloxamer-based clozapine-infused sol-gel engineered for sustained and controlled nose-to-brain drug delivery. Previously we showed intranasal clozapine achieves high concentrations in brain with minimal distribution to blood and produces an industry-standard antipsychotic effect in suppressing conditioned avoidance response at a fraction (3.5%) of the oral dose required to achieve the same effect. Here we have established that chronic administration of intranasal clozapine reduces amphetamine-induced locomotion and increases pre-pulse inhibition, key preclinical antipsychotic outcomes.

Results
In parallel, we now demonstrate a greatly reduced potential of intranasally-administered clozapine to elevate blood glucose. Acute administration of clozapine increases blood glucose concentrations in both treatment conditions relative to controls ($F(3,36) = 7.5$ $p<0.0005$, $n=10$) however this effect is only significant at each time point in orally administered animals ($p<0.05$). Following six-weeks chronic clozapine administration, animals administered intranasal clozapine have a blood glucose profile that is indistinguishable from controls across a two-hour period following a 20% glucose challenge, however orally administered animals have significant blood glucose elevation for 60-min post-challenge before returning to baseline.

Conclusions
Together with the pending outcome of our Phase I clinical trial examining the tolerability of administering vehicle sol-gel intranasally in healthy participants and patients, our latest metabolic findings bring us closer to the potential of intranasal clozapine in greatly reducing the debilitating and life-threatening side effects of the drug in those with treatment resistant schizophrenia.

P_55a Growth Factors and Schizophrenia Spectrum Disorders: A Splines Modelling Approach

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Background
Schizophrenia and related disorders (schizophreniform; schizoaffective disorders) are complex psychiatric disorders involving disruptions in neurodevelopmental processes. Growth factors—critical regulators of neuronal development, plasticity, and survival—have been implicated in the schizophrenia spectrum disorders (SSD), yet most studies rely on linear models that may overlook biologically relevant nonlinear relationships. We applied restricted cubic spline modelling to evaluate the associations between serum levels of various growth factors and SSD risk. This method allows for detection of complex patterns that may reflect underlying physiological thresholds or saturation effects, offering a more nuanced understanding of how deviations in growth factor concentrations relate to disease risk.

Methods
This case-control study included 501 individuals with SSD and 646 healthy controls, aged 18–65, drawn from the Australian Schizophrenia Research Bank. Serum concentrations of 14 growth factors from the epidermal growth factor (EGF) and insulin-like growth factor (IGF) systems, basic fibroblast growth factor (bFGF), resistin, BDNF and vascular endothelial growth factor (VEGF), were measured using multiplex immunoassays. Associations between Z-transformed growth factor levels and SSD risk were assessed using restricted cubic spline regression, adjusting for demographic and behavioural variables. Sensitivity analyses using truncated Z-scores were performed to assess the robustness of observed relationships across different biomarker value thresholds.

Results
Significant nonlinear associations were observed between several growth factors and SSD risk. Amphiregulin and neuregulin1-β1 (EGF system ligands) showed inverted-U shaped relationships, indicating elevated risk at moderate levels. bFGF displayed a positive linear trend, while the EGF receptor showed complex quadratic and cubic patterns, with risk elevated at both low and high levels. Resistin and VEGF also exhibited nonlinear relationships. These effects persisted across sensitivity analyses. No significant associations were found for IGF system ligands, suggesting selective pathway involvement. The spline approach uncovered patterns that would likely be missed using conventional linear models, highlighting its value in psychiatric biomarker research.

Conclusions
Our findings reveal distinct nonlinear relationships between specific serum growth factors and SSD risk, supporting the hypothesis of disrupted neurodevelopmental signalling in these disorders. The use of restricted cubic splines allowed for a more precise interpretation of biomarker patterns, identifying physiologically plausible dose-response curves. These results suggest that serum levels of EGF system factors, resistin, and VEGF may reflect underlying biological vulnerability to SSD. While not definitive biomarkers, these growth factors warrant further longitudinal investigation as part of multi-modal models aimed at early detection and therapeutic targeting of neurodevelopmental dysregulation in schizophrenia.

P_45a Geometric Resonance Model Underlies ADHD-Related Structural Connectome Deviations

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Background
Attention-deficit/hyperactivity disorder (ADHD), as a prevalent neurodevelopmental disorder, exhibits aberrant brain structural connectome compared to neurotypical controls, yet the mechanisms underpinning the connectome architecture remain elusive. The geometric resonance model (GRM) derived from Neural Field Theory offers promising mechanistic insights into these phenomena by incorporating geometrical constraints that govern brain dynamics. This framework preferentially interconnects cortical regions that facilitate resonant excitation of geometric eigenmodes. Herein, we employed the GRM to characterize ADHD-related alterations in white matter network architecture and examined the heterogeneity in model parameters and performance to elucidate underlying pathophysiological mechanisms.

Methods
We leveraged multisite datasets encompassing 713 ADHD children and 261 neurotypical controls. Empirical structural connectomes were constructed using probabilistic tractography with Schaefer400 parcellation. Individual geometric eigenmodes of the left hemisphere were obtained by solving the eigenvalue problem associated with the Helmholtz equation of the cortical midthickness meshes. Using the GRM, we generated connectome models for each participant using their geometric modes and eigenvalues. We identified optimal model parameter combinations [number of modes (k) and axonal length scale (rs)] that maximized model performance. Case-control differences in these parameters and their associations with topological deviations relative to normative model ranges were assessed.

Results
GRM recapitulated empirical structural connectomes across our sample (binary degree correlation: 0.38, weighted degree: 0.45, edge weights correlation: 0.52) in optimal parameter combinations. Nevertheless, ADHD structural connectomes demonstrated reduced constraint by geometric eigenmodes (summed metrics: 1.34±0.12 vs. 1.40±0.14, F=-18.28, p<.001). ADHD children exhibited elevated k (56.51±40.15 vs. 51.18±36.24, F=1.13, p=.287) and significantly increased rs (12.50±6.72 vs. 11.14±6.39, F=4.15, p=.042) relative to controls. Furthermore, ADHD cases showed greater deviated global efficiency (mean positive deviation: 0.96 vs. 0.81; mean negative deviation: -0.91 vs. -0.82) compared to normative range, and individual rs correlated with deviations in global efficiency (r=-0.16, p<.001).

Conclusions
Pediatric brain connectivity patterns appear to follow organizational principles that promote shortcuts enabling resonant excitation of cortical geometric eigenmodes, as evidenced by our model's capacity to recapitulate landmark features of topology and topography. Atypical geometric constraint patterns revealed through GRM analysis may contribute to ADHD-related structural connectome abnormalities on cortex, highlighting its potential for elucidating mechanistic foundations of altered brain structural connectivity in the realm of psychiatry.

P_53a Over-activation of Dopamine D2 Receptor Inhibits Mitophagy and Causes Schizophrenia-like Behaviors in Mice

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Background
Oxidative stress emerges early in schizophrenia pathogenesis, particularly in first-episode, drug-naïve patients. Despite the established role of dopamine D2 receptor (D2R) dysfunction in schizophrenia, the mechanistic link between D2R signaling, mitochondrial dysfunction, and oxidative stress-mediated cellular damage remains unclear.

Methods
We applied cryogenic electron microscopy (Cryo-EM) to examine mitochondrial ultrastructure in cultured striatal neurons and established a schizophrenia mouse model using the D2R-specific agonist quinpirole. Primary striatal neurons and adult mice were assessed for mitochondrial function, oxidative stress markers, and behavioral outcomes.

Results
We demonstrated that D2R over-activation caused: (1) significant reduction in mitochondrial cristae number and length in primary striatal neurons; (2) exacerbated oxidative stress with elevated ROS and malondialdehyde (MDA) levels; (3) upregulated expression of marker for autophagolysosome formation, indicating impaired mitophagy in primary striatal neurons; (4) working memory deficits and stereotyped behaviors characteristic of schizophrenia in adult mice. (5) mitochondrial localization of D2R in primary striatal neurons.

Conclusions
Our findings demonstrate a novel mechanistic pathway linking D2R over-activation to mitochondrial dysfunction and schizophrenia-like phenotypes. This work establishes mitochondrial dysfunction as a critical mediator between dopaminergic dysregulation and behavioral abnormalities, highlighting mitochondrial quality control mechanisms as promising therapeutic targets for oxidative stress-related pathology in schizophrenia.

P_34a Long Reads, Deep Insights: RNA Isoform Discovery in Neuropsychiatric Risk Genes

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Background
Neuropsychiatric disorders are highly complex conditions and the risk of developing a disorder has been tied to hundreds of genomic variants that alter the expression and/or RNA isoforms made by risk genes. However, the RNA isoforms expressed by these risk genes and how they contribute to disease risk and onset is not well understood. To address this gap, we aimed to profile the entire coding sequence of several risk genes using nanopore long-read sequencing.

Methods
Neuropsychiatric risk genes from GWAS loci were identified based upon collated expression, association and pathway information. Genes with multiple lines of evidence for schizophrenia, bipolar disorder, depression and autism spectrum disorder risk were prioritised. Combining our new bioinformatic pipeline IsoLamp with nanopore long-read amplicon sequencing, we deeply profiled the RNA isoform repertoire of 31 high-confidence neuropsychiatric disorder risk genes in seven human brain regions.

Results
We show most risk genes are more complex than previously reported, identifying 363 novel isoforms and 28 novel exons, including isoforms which alter protein domains, and genes such as ATG13 and CSMD1 where most expression was from previously undiscovered isoforms. The greatest isoform diversity was detected in the schizophrenia risk gene ITIH4. Mass spectrometry of brain protein isolates confirms translation of a novel exon skipping event in ITIH4 and GABBR2, suggesting new regulatory mechanism for these genes in the brain.

Conclusions
Our results emphasize the widespread presence of previously undetected RNA and protein isoforms in the human brain and provide an effective approach to address this knowledge gap. Uncovering the isoform repertoire of candidate neuropsychiatric risk genes will underpin future analyses of the functional impact these isoforms have on neuropsychiatric disorders, enabling the translation of genomic findings into a pathophysiological understanding of disease.

P_11a The impact of transient adolescent food insecurity on metabolism, reward, and mood-related behaviour.

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Background
Food insecurity is defined as inadequate access to nutritionally sufficient sustenance and affects over 800 million individuals globally. Escalating prevalence driven by socioeconomic disparities, geopolitical instability, and climate perturbations necessitates urgent mechanistic investigation. While food insecurity profoundly disrupts weight homeostasis and cognitive function, the underlying neurobiological drivers remain enigmatic. We established a mouse model of transient food insecurity during adolescence to elucidate its impact on adult metabolic programming, feeding behaviours, and cognitive function. We hypothesised that food insecurity during this critical period of brain development would induce sexually dimorphic phenotypes, providing critical insights into vulnerability mechanisms

Methods
Five-week-old C57Bl/6 mice (N= 64; both sexes) underwent transient food insecurity paradigm involving unpredictable chow access with variable quantity and timing across four weeks. Comprehensive metabolic assessment encompassed body composition analysis, glucose tolerance testing, and insulin sensitivity evaluation. Behavioural phenotyping in adulthood included maze-based anxiety assessments followed by intermittent high-fat, high-sugar diet exposure. Motivation was evaluated using progressive ratio tasks via home-cage Feeding Experimentation Device 3 (FED3) operant systems. Concurrent in-vivo fiber photometry monitored dopamine dynamics within nucleus accumbens during food reward presentation, enabling real-time assessment of mesolimbic reward circuit function following developmental food insecurity exposure.

Results
Adolescent food insecurity (FI) induced excessive weight gain in both sexes in adulthood, with females exhibiting greater susceptibility (females: $p=0.0004$; males: $p=0.0089$). Sex-divergent effects emerged during palatable food access, whereby FI females demonstrated binge-like consumption ($p=0.0001$) and FI males showed reduced intake ($p=0.0060$). Increased “risky” exploration of the open arm of the elevated plus maze was observed in males exposed to adolescent FI ($p<0.0001$), concomitant with reduced rearing ($p=0.0104$), grooming ($p=0.0015$) and a trend toward increased motivation ($p=0.0684$). Preliminary fibre photometry revealed sexually dimorphic dopamine responses: heightened signal variability in FI males contrasted with attenuated dopamine release in FI females.

Conclusions
This study reveals that transient food insecurity experienced during adolescence precipitates profound, sexually dimorphic alterations in metabolic programming, feeding behaviours, and risk taking that persist into adulthood. The striking sex differences in binge-eating susceptibility highlight critical vulnerabilities requiring targeted interventions. These findings illuminate previously unrecognized mechanisms linking early-life nutritional adversity to lifelong health disparities. Future investigations integrating advanced neurobiological techniques with hormonal manipulations will elucidate the molecular underpinnings of sex-specific vulnerabilities. Understanding these mechanisms is paramount for developing precision medicine approaches to mitigate food insecurity's devastating consequences on global health outcomes.

P_47a Cortical thickness associations with adverse life events in youth with non-suicidal self-injury

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Background
Adverse life events (ALEs) are risk factors for non-suicidal self-injury (NSSI), the intentional destruction of one's body tissue without suicidal intent. Little is known of NSSIs neurobiological mechanisms, particularly in males. Early home and school environments are critical in youth brain development and psychopathology, and may moderate NSSI risk. A better understanding of these mechanisms will support novel treatments and interventions for NSSI. Using Adolescent Brain Cognitive Development study, we identified 235 youths without NSSI history at baseline (age 10) who developed NSSI by Year 2 (age 12) and 235 controls matched on demographic and psychological features without NSSI.

Methods
We anticipated associations between ALEs and cortical thickness (CT) in regions involved in emotion learning, regulation, inhibition and reward and may differ for NSSIs versus controls, and males versus females. Vertex-wise CT was regressed onto youth-reported ALEs from the Life Events Scale separate for males (n=180) and females (n=290), covarying pubertal stage, intracranial volume and MRI manufacturer. We averaged the CT of clusters positively and negatively associated with ALE ($P<0.05$ corrected) and conducted Structural Equation Models to examine whether measures of family conflict, caregiver acceptance and school environment influenced these CT by ALE clusters.

Results
ALEs were negatively associated with the left hippocampus, presubiculum, and entorhinal, parahippocampal, and orbitofrontal cortices and positively associated with CT in the right superior and inferior lateral parietal lobe and posterior cingulate for females, and right OFC, left dorsolateral prefrontal cortex and V1 for males. Interaction models found caregiver acceptance moderated the effect of positive school environment on CT clusters positively associated with ALE for NSSI males and females.family conflict moderated the effect of school environment on CT clusters positively associated with ALE for NSSI and controls (stronger effects for NSSI), and negatively associated for female controls.

Conclusions
Home and school environments contributed to ALE associations with altered CT, with sex differences likely due to pubertal influence on neurodevelopment. Findings align with existing research that found gray matter volume and CT associations with ALEs, and our work showing associations between ALEs and subcortical shape, in adolescents. We demonstrate the interplay between home and school environments has a greater impact on CT clusters associated with ALE in adolescents who develop NSSI. Results highlight the importance of adaptive environments as protective factors for brain changes associated with ALEs, and a need for preventative early family and school interventions.

P_48a Transcriptomic profiling of the human habenula in bipolar and major depressive disorder

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Background
The habenula is a small, epithalamic brain structure that acts as a neuroanatomical hub connecting the limbic forebrain to the major monoamine centres. Preclinical evidence has established habenula hyperactivity as a driver of depressive-like behaviours, reversible by novel therapeutics such as ketamine and deep brain stimulation. These findings suggest the habenula as a promising target for novel antidepressant treatments. However, the human habenula remains largely unexplored, and it is unclear whether these remarkable preclinical advancements translate to the clinical field.

Methods
We applied whole RNA sequencing to comprehensively profile gene expression in the human habenula and assess transcriptomic alterations in major depressive disorder (MDD) and bipolar disorder (BPD). Postmortem habenula-enriched tissue from control (n=6), BPD (n=6), and MDD (n=6) cases was obtained from the Netherlands Brain Bank. Libraries were prepared using the Illumina Stranded Total RNA Prep with RiboZero Plus and sequenced at the Ramaciotti Centre for Genomics (UNSW Sydney, Australia). Reads were processed with the nf-core/RNAseq pipeline and aligned to the human genome (GRCh38.109). Differential expression analysis was performed in R using DESeq2, and enrichment analysis with g:Profiler.

Results
Counts were generated for 39,451 genes across each sample. Exploratory differential expression analysis identified 62 genes altered in BPD and 25 in MDD (FDR<0.1), with high-confidence hits generating 28 and 12 genes, respectively (FDR<0.05). Results from differential expression and enrichment analyses revealed pathways involved in inflammation, calcium and potassium signalling, and epigenetic regulation, consistent with preclinical models. Notably, novel alterations in genes related to metal ion homeostasis suggest previously unrecognised mechanisms of habenula dysfunction in mood disorders.

Conclusions
These findings provide the first transcriptomic characterisation of the human habenula in MDD and BPD, advancing our understanding of its role in mood disorders and identifying potential novel targets for future therapeutics. Further research is needed to validate these findings in larger cohorts. Single-cell and spatial transcriptomic approaches will be critical for identifying the specific cell types driving these changes and further elucidating the mechanisms underlying habenula dysfunction in mood disorders.

P_5a Midbrain ghrelin signalling regulates conflict behaviour in the Edinger-Westphal nucleus

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Background
Adaptive decision-making during threat to survival, like choosing to forage in a dangerous environment, is influenced by physiological states such as hunger. The centrally projecting Edinger-Westphal nucleus (EWcp) integrates stress, arousal, and energy cues and expresses receptors for ghrelin, a hunger hormone known to influence feeding and anxiety-like behaviours. However, little is known about the role of EWGHSR or whether ghrelin directly accesses this midbrain site. Our project explores how ghrelin influences decision-making via the EWcp, and how the integrity of the blood-brain barrier (BBB) in this region may permit metabolic hormone access to the brain.

Methods
To investigate ghrelin signalling in the EWcp, we use a combination of viral-mediated knockdown (short hairpin RNA), histological analyses, and behavioural testing including the light-dark box, elevated plus maze, and baited large open field (n=8/sex). Mice were tested under fed or fasted conditions to assess how conflict decision-making changes under metabolic pressure. To investigate how peripheral ghrelin may access this midbrain site, we use fluorescently labelled dextran, lectin-based histochemistry, and confocal imaging to characterise vascular density and blood-brain barrier integrity in the EWcp.

Results
We show that EWcpGHSR knockdown increases anxiety-like behaviours in the light-dark box and elevated plus maze in mice compared to scramble-shRNA controls under fed conditions. Interestingly, fasting and the introduction of a palatable food reward reversed the anxiety-like phenotype observed in EWcpGHSR knockdown mice. Specifically, EWcpGHSR knockdown mice spent longer within the food zone and consumed more palatable food than scramble-shRNA controls. This change in behaviour was not driven by increased “hunger,” as mice showed similar feeding responses to familiar and novel palatable foods within their home cage.

Conclusions
Our research suggests that the EWcp plays a crucial role in mediating conflict decision-making when experiencing hunger, through ghrelin receptor signalling. We are now examining EWcp vascularisation to determine potential routes of hormone access and metabolic consequences of EWcpGHSR knockdown. Early histological data suggest an atypical vascular profile in the EWcp, raising the possibility that it may be more permeable to peripheral signals than surrounding regions. Together, these findings may help uncover neurobiological mechanisms linking hunger, anxiety, and decision-making, with implications for understanding stress-related disorders and the metabolic modulation of brain circuits.

P_17a Modelling cognitive and psychiatric behavioural traits in a mouse model of Neurofibromatosis type I

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Background
Neurofibromatosis type I (NF1) is caused by a mutation in one copy of the neurofibromin 1 gene. Patients exhibit diverse symptoms, including tumour formation, hyperpigmentation, and vision disorders. A majority also experience learning difficulties and psychiatric conditions like ADHD, autism, anxiety, or depression, which standard therapies do not address.
In this research we aimed to replicate and expand the currently published behavioural characterisation of the heterozygous Nf1 mouse model (Nf1 +/-), in order to establish its suitability in future preclinical drug trials specifically targeting cognitive and neuropsychiatric symptoms in NF1 patients.

Methods
The initial approach involved the phenotypic characterisation of the Nf1 +/- mouse model using a broad battery of standard rodent behavioural tests, and then a set of touchscreen-based tests, to examine specific aspects of cognition (including attention, working memory, short-term memory, spatial memory, associative memory, cognitive flexibility), social function, and psychiatric traits (including anxiety and depression-like behaviours). We also measured whole brain weight upon dissection.

Results
Male and female Nf1 +/- mice showed reduced cognitive performance and an increase in traits relevant to autism, but no changes in emotionality or locomotion, according to integrative behavioural analyses. Sustained attention was evaluated using the touchscreen-based rodent continuous performance test (rCPT). Initial evaluation of performance in this task revealed specific attentional deficits in Nf1 +/- mice. This was not confounded by differential reward motivation, as shown by the progressive ratio task. Brain weights of Nf1 +/- mice were significantly higher compared to controls, and several behavioural measures correlated with brain weights, providing support for a mechanistic link.

Conclusions
We were able to build on published findings regarding behavioural alterations in the Nf1 +/- mouse model, and found important additional phenotypes relevant to NF1. As consistent evidence shows higher brain volumes in NF1 patients, the +/- mouse model will be extremely useful in investigating the underlying neurobiological mechanisms. Furthermore, the alterations in behaviour relevant to cognition and psychiatric phenotypes support the use of this mouse model in future trials testing pharmacological therapeutics for these symptom complexes in NF1 patients.

P_6a Inhibition of NLRP3 inflammasome by MCC950 administration improves gut health in Huntington's disease mice

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Background
Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by psychiatric (particularly depression), cognitive (culminating in dementia) and motor dysfunction, and is caused by a tandem-repeat gene mutation encoding an expanded polyglutamine tract in the huntingtin protein. Recent evidence suggested that HD affects entire body including gut. Neuroinflammation has been reported in HD pathogenesis and our group firstly discovered gut dysbiosis in HD. NLRP3 inflammasome has been implicated in various psychiatric disorders and may contribute to HD pathogenesis, including neuroinflammation. However, its involvement in gut inflammation and gut microbiota alterations, as well as cognitive and behavioural symptoms, remain unexplored.

Methods
This study aims to investigate the contribution of NLRP3 inflammasomes to microbiota-gut-brain axis function by targeting inhibition of these inflammasomes, focusing on the amelioration of behavioural impairment and gut dysbiosis, along with other associated molecular and cellular abnormalities. NLRP3 inflammasome inhibitor MCC950 was administered to R6/1 transgenic HD mice, and their randomized wild-type (WT) littermate controls, from 6 to 20 weeks of age. We conducted behavioural tests and assessed growth performances and gut health parameters. We also collected fecal samples for microbial evaluation, and brain and gut tissues to assess NLRP3 inflammasomes, IL-1β and IL-18 levels.

Results
HD mice showed lower body weight and brain weight, increased water consumption, impaired memory along with motor abnormalities and worsened gastrointestinal parameters. MCC950 did not alter growth parameters, nor remarkably improve behavioural function of HD mice. However, MCC950 exhibited beneficial effects on gut health of HD mice by improving the faecal water content, faecal consistency, faecal output and gut transit time.

Conclusions
Our findings are promising, especially considering the significant gastrointestinal dysfunction experienced by HD patients. We have identified a novel avenue for investigating these debilitating symptoms by targeting inflammasome. This approach has the potential to restore gut dysbiosis and improve gastrointestinal health in HD. Positive effects of MCC950 on gut function could be linked to the altered gut microbiota and/or their molecular products, which can signal to other organs including the brain. To explore this link, we are investigating 16S analysis of gut microbiome and

characterizing the NLRP3 inflammasome, IL-1β, IL-18 and caspase-1 from gut and brain tissues, by Western analyses.

P_37a Temporal Dynamics of Depression in Premanifest Huntington's Disease: A Network Dysconnection Approach

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Background
Depression emerges years before motor signs in Huntington's disease gene expansion carriers (HDGECs) (Epping & Paulsen, 2011; McAllister et al., 2021; Pla et al., 2014), yet the neural mechanisms underlying this temporal relationship remain unclear. A growing body of evidence links depression in HDGECs to striatal and default mode network (DMN) regions (Barta et al., 2024; Garcia-Gorro et al., 2019; McColgan, Razi, et al., 2017). Our previous findings suggested posterior DMN as the driver of depression for HDGECs, with compensatory mechanisms of right DMN. How these directional connectivity patterns evolve over time and relate to depression trajectories remains unknown.

Methods
The study included 105 HDGECs (53 Females, Mage = 43, Mean CAG repeat length = 43) from the largest longitudinal study of premanifest HD, TrackOn-HD. Here, we applied spectral dynamic causal modelling (spDCM; Friston et al., 2014; Novelli et al., 2024; Razi et al., 2015) to examine effective connectivity changes over 24 months, alongside voxel-based morphometry of grey matter atrophy and linear mixed models of depressive symptoms, including volumetry. ROIs were constrained to DMN hubs of posterior cingulate, medial prefrontal cortex, and bilateral hippocampus, as well as striatal regions of bilateral caudate and putamen.

Results
Depression-related network dysconnection operated independently of regional grey matter atrophy, with HDGECs exhibiting widespread striatal volume loss but no differential atrophy patterns. Larger posterior cingulate cortex volumes predicted increased depression severity in HDGECs with depression history, across BDI-II ($p = .041$) and HADS-D($p = .002$). Longitudinal spDCM analyses revealed distinct dysconnection profiles: HDGECs with depression history showed widespread interhemispheric alterations including progressive disinhibition of striatal-DMN circuits and aberrant hippocampal regulatory control, while those without depression exhibited more focal frontostriatal dysconnection. Clinically elevated depressive symptoms associated with differential connectivity patterns of PCC and hippocampus depending on depression history.

Conclusions
Findings suggest depression for HDGECs emerges through network dysconnection operating independently of regional atrophy. Increased PCC volume in association with depression symptom severity for HDGECs with depression history may represent compensation. Our findings reveal functional network reorganization in relatively preserved regions (hippocampus, PCC) drives depression vulnerability in premanifest HD. As HD progresses, compensatory mechanisms of proposed disease epicentres in those without depression may break down and become maladaptive as neurodegenerative burden increases. Functional alterations precede structural breakdown in DMN and represent compensatory responses to subclinical neurodegenerative processes.

P_7a Incubation of alcohol craving: behavioural and psychological factors underlying increased relapse throughout abstinence

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Background
Incubation of craving refers to the increase in physiological and psychological responses to alcohol- and drug-associated cues across abstinence. This is modelled in rodents by an increase in cue-elicited drug-seeking responses across abstinence. Our lab has found that incubation can be robustly produced in rats trained to lever press for alcohol. However, understanding what parameters affect the behavioural changes observed is critical for developing translatable models. Here we assessed: (1) the impact of other stressors (social isolation) during abstinence (2) the importance of active inhibitory training (extinction) and (3) the impact of different alcohol access schedules (intermittent vs fixed ratio).

Methods
Experiment 1 tested inhibitory training and social isolation. Male and female Long Evans rats (N=29) were trained to self-administer alcohol, then alcohol-seeking was tested before and after abstinence. Half the rats received extinction training before abstinence, while the other half did not. Throughout abstinence, rats either remained in their homecage, or were placed into individual chambers (4hrs/day). Experiment 2 tested the effect of an intermittent-access schedule, known to produce addictive phenotypes. Once stable self-administration was established, rats (N=32) progressed through intermittent-access schedules (final schedule - 6x 5-mins access/25-mins no-access) or remained under fixed-ratio. Seeking was tested before and after abstinence.

Results
Experiment 1 found that the increase in alcohol-seeking was only evident in rats that had received extinction. This may reflect a ceiling effect, as initial responding was high in the no-extinction group. No difference was found between individual and homecage abstinence conditions. However, simple effects analyses indicated that responding only increased at late compared to early test for individually housed rats that had extinction training. In experiment 2, the intermittent-access schedule resulted in escalation in seeking responses and alcohol consumption (g/kg) compared to rats that remained on the fixed-ratio schedule.

Conclusions
While housing conditions throughout abstinence do not drive increased responding overall, our data suggest social isolation may facilitate incubation. This highlights the influence of stress on relapse propensity. Incubation was only evident when rats had undergone extinction training prior to abstinence, at least where alcohol access was on a fixed-ratio schedule. While this may reflect a ceiling effect, it may also indicate that subjects are not fully alcohol dependent. In complement, the intermittent-access training produced escalation of both alcohol consumption and alcohol-seeking. Our ongoing research will use these refined parameters as a translatable tool to understand and prevent relapse.

P_44a Mental health in the UK Biobank: An updated roadmap for brain-behavior associations

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Background
The UK Biobank (UKB) is a key resource for population mental health research. With thousands of imaging-derived phenotypes (IDPs) and a broad range of mental health phenotypes (MHPs), covering psychiatric disorders, transdiagnostic symptoms, and environmental exposures, UKB enables large-scale investigation of brain-mental health associations. However, a systematic overview of these associations, including their robustness and effect sizes across time, has been lacking. In this study, we aimed to provide an up-to-date roadmap for clinical neuroimaging research by leveraging the UKB dataset to quantify and update both cross-sectional and longitudinal effect sizes for brain-mental health associations.

Methods
We included 4,939 participants who completed the initial imaging visit (2014+) and the first repeat imaging visit (2019+), as well as the Mental Health Questionnaire (2016+) and the Mental Well-being Questionnaire (2022+) administered online. During the imaging visits, participants underwent MRI scans and completed touchscreen questionnaires that included questions on mental health. To assess the robustness of associations, we randomly split the sample into two equal subsets. Pearson's correlations were conducted between 4,554 IDPs from different MRI modalities and 356 self-reported MHPs within each subset. Repeated measures correlations were performed between 2,227 IDPs and 95 MHPs measured at two timepoints.

Results
Across 1,621,224 Pearson's correlations, the absolute median effect size was |0.02|, with the top 1% exceeding |0.21|. Of these, 670 were significant after FDR correction and 393 were replicated. For the 211,565 repeated measures correlations, the median effect size was |0.04|, with the top 1% exceeding |0.41|; 45,306 were significant after correction and 37,111 were replicated. To make the results more accessible, we developed a web-based tool to summarise and visualise our findings. This tool allows users to explore the availability, typical and top effect sizes, and replicability of associations across 17 MHP categories and 6 IDP modalities.

Conclusions
Our large-scale analysis of the UKB dataset reveals that associations between brain imaging and mental health phenotypes are, on average, small in magnitude. Nevertheless, a substantial number of associations remained significant after correction for multiple comparisons and demonstrated replicability across independent subsets and timepoints. The web-based tool we developed provides a practical roadmap for both clinicians and researchers interested in the UKB or mental health research in general. We hope this resource will promote transparency and support future study planning by helping researchers justify their choices of variables and analytic approaches and set realistic benchmarks for power calculations.

P_38a The Neural Mechanisms Supporting the Updating of Self-Beliefs

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Background
People update their beliefs preferentially in response to favorable versus unfavorable information - a process known as ‘positivity bias’. At a brain systems level, belief updating has been associated with activity in the default mode network (DMN) and salience network (SN) regions. This study aims to test positivity bias in belief updating as related to beliefs about oneself (i.e. self-belief updating), and to examine dynamic interactions between key DMN and SN regions.

Methods
We developed a novel self-belief updating paradigm that was completed during 7-Tesla functional magnetic resonance imaging (fMRI) scanning by 48 healthy adults. Using Bayesian inference, we behaviorally modeled self-belief updating and tested for positivity bias. Dynamic causal modelling (DCM) inferred directed causal influences (i.e. effective connectivity) between key DMN and SN regions modulated by valence and the magnitude of self-belief updating.

Results
Computational modeling results indicated that the positively biased model was the winning model in explaining updating behaviors. Neurobiologically, DCM showed that the activity of posterior cingulate cortex (PCC) had an excitatory influence on left anterior insular-opercular cortex activity during overall belief updating, whereas this influence became inhibitory as update magnitude increased. Greater belief updating was also associated with stronger inhibitory effects from the ventral anterior cingulate cortex (VACC) to the dorsal medial prefrontal cortex (DMPFC) and PCC. VACC activity demonstrated a strong excitatory influence on the DMPFC activity during favorable updating.

Conclusions
Participants broadly showed greater updating for favorable versus unfavorable information, confirming positivity bias when assessing oneself. Our DCM findings establish how large-scale dynamic brain network interactions enable the encoding of valence-specific information to maintain optimistic, yet adaptable, self-concepts. This approach could provide valuable insights into the biological basis of entrenched negatively biased thinking patterns which contribute to depression.

P_35a Investigating cellular phenotypes and genotypes of a preclinical model relevant to schizophrenia using single-cell RNA sequencing.

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Background
The X-linked homeobox gene Arx encodes a transcription factor essential for embryonic brain development, regulating cell fate and neuronal positioning. Mutations in Arx are associated with intellectual disability, epilepsy, autism spectrum disorder, and schizophrenia. Our lab identified an ArxR264Q mutation, where a proline is replaced by glutamine, in a female patient with schizophrenia and generated a corresponding mouse model. ArxR264Q mice exhibit altered GABAergic interneuron density, particularly in parvalbumin and somatostatin populations, alongside behavioural deficits including impaired social interaction, disrupted sensorimotor processing, and increased risk-taking. This model provides insight into the functional impact of Arx mutations on neurodevelopment and behaviour.

Methods
To investigate how the ArxR264Q mutation drives cellular and behavioural phenotypes, we performed single-cell RNA sequencing (scRNA-seq) to identify differentially expressed genes (DEGs) in distinct brain cell types of mutant versus wildtype littermates. We hypothesised that the mutation would induce cell-type-specific transcriptional changes, particularly in GABAergic interneurons, including parvalbumin and somatostatin populations. Brain-wide single-cell transcriptomes were profiled at postnatal day 3 using fresh mouse tissue (~4,500 cells per sample) processed with 10x Genomics Chromium Next GEM Single Cell 3', enabling cell-specific analysis of downstream Arx transcriptional effects.

Results
We identified 16 brain cell types, including GABAergic, glutamatergic, neural precursor, oligodendrocyte precursor, and astrocyte populations. GABAergic cells showed the most differentially expressed genes (1,876 DEGs), including known Arx targets Lmo1 and Dlx5. Sub-clustering revealed medial (MGE) and caudal (CGE) ganglionic eminence–derived
subtypes. Immature MGE cells showed downregulation of complement pathway genes (C1qa, C1qb, C1qc) and immune modulators (Apoe, Tyrobp, Fcer1g). Sex-specific analyses revealed 685 DEGs in females and 13 in males, with only six overlapping, suggesting the Arx R264Q mutation affects distinct biological pathways in each sex.

Conclusions
scRNA-seq analysis of the Arx R264Q mouse model revealed altered expression of complement-related genes in immature MGE-derived GABAergic neurons. Given the previously identified role of complement proteins in regulating GABAergic migration and the strong association between the complement pathway and schizophrenia, these transcriptional changes may underlie the GABAergic cell density reductions and behavioural phenotypes observed in adulthood, supporting a link between early complement pathway dysregulation and neurodevelopmental outcomes in this model.

P_30b Psilocybin Promotes Cognitive Flexibility via Reinforcement Learning Modulation in Rats

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Background
While psychedelics like psilocybin demonstrate remarkable therapeutic potential for depression and other psychiatric conditions, the computational principles governing their cognitive effects remain elusive. Cognitive inflexibility—a core feature of affective disorders—represents a critical therapeutic target, yet current mechanistic understanding is insufficient to optimize treatment. Probabilistic reversal learning in ethologically-valid home-cage environments provides unprecedented opportunities to quantify psilocybin's effects on adaptive flexibility in freely-behaving animals. Computational modelling of these learning dynamics is essential to decode how psilocybin restructures decision-making algorithms and identify the specific cognitive processes underlying its therapeutic efficacy.

Methods
Nine female rats were trained on a two-choice probabilistic reversal learning task (80% vs 20%) in the home-cage. Following acquisition of stable performance, animals received psilocybin (n = 5) or saline control (n = 4) via single injection. Behavioural data spanning three baseline and seven post-treatment sessions were analysed. A Rescorla-Wagner reinforcement learning algorithm captured trial-by-trial choice dynamics, incorporating binary reward feedback across two available actions. Session-wise maximum-likelihood parameter estimation quantified individual learning rates (α), decision noise (inverse-temperature β), and initial action biases (V_0). Within-subject pre/post treatment comparisons employed non-parametric Wilcoxon signed-rank tests, with effect sizes calculated using Cohen's d.

Results
Psilocybin induced striking computational changes: learning rates increased substantially (α: $\Delta = +0.24$, $d = 1.1$, $p = .125$) while prior action values dropped markedly (V_0: $\Delta = –0.35$, $d = –1.16$, $p = .125$). Decision noise showed a moderate increase (β: $\Delta = –0.50$, $d = –0.58$, $p = .31$), suggesting enhanced exploration. Saline controls exhibited negligible parameter shifts across all measures ($|\Delta| \leq 0.03$, $|d| \leq 0.11$, $p \geq .88$). These pharmacologically-specific effects—independent of session length or baseline performance—reveal psilocybin fundamentally alters reinforcement learning computations by accelerating adaptation while reducing behavioural perseveration and increasing exploratory flexibility.

Conclusions
These computational signatures—accelerated learning rates and diminished behavioural priors—demonstrate how algorithmic modelling can decode psilocybin's cognitive mechanisms with unprecedented precision. Machine learning approaches leveraging these parameter profiles offer transformative potential for predicting individual treatment responses and optimizing dosing protocols. By quantifying flexibility enhancement through reinforcement learning frameworks, we can develop predictive models that identify which patients will benefit most from psychedelic interventions. This computational psychiatry approach promises personalised treatment selection for rigidity-characterised disorders, moving beyond one-size-fits-all therapeutics toward precision psychedelic medicine guided by individualised learning signatures.

P_25b Does epilepsy increase vulnerability to develop alcohol use disorder? A study in the kainic acid model of temporal lobe epilepsy

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Background
Alcohol use disorder (AUD) and epilepsy are frequently comorbid, but their causal relationship remains unclear. One possibility is that both conditions share underlying neuropsychiatric vulnerabilities, particularly anxiety and depression, which are common in temporal lobe epilepsy (TLE). These affective disturbances may contribute to the expression of maladaptive behaviours, including problematic alcohol use. Preclinical models allow investigation of these interactions in a controlled setting. This study used the kainic acid-induced status epilepticus (KASE) rat model of TLE to examine whether epilepsy increases vulnerability to AUD-like behaviours, and to explore how these behaviours relate to anxiety- and depression-like traits.

Methods
Adult male Wistar rats were randomly assigned to receive kainic acid-induced status epilepticus (KASE, n=14) or sham treatment (n=10). Epilepsy development was confirmed via video-EEG monitoring eight weeks post-induction. Prior to alcohol exposure, rats were evaluated on anxiety- and depression-like behaviour using the elevated plus maze, open field, and forced swim test. Animals then underwent 12 weeks of chronic intermittent access to ethanol. AUD-like behaviours assessed included escalation of intake across sessions, consumption of quinine-adulterated ethanol (to measure punishment resistance), and intake following abstinence (to model relapse-like behaviour). Data were analysed using ANOVA and correlation analyses.

Results
KASE rats exhibited reduced escalation of ethanol intake and decreased consumption of quinine-adulterated ethanol, suggesting lower punishment resistance, compared to sham controls. However, KASE rats demonstrated a significant increase in relapse-like drinking following a period of abstinence. The proportion of rats classified as high in AUD-like behaviour (top 25% in at least two of three domains) was similar between groups. Among controls, anxiety-like behaviour positively correlated with punishment resistance, but this relationship was absent in the KASE group. These findings suggest complex, potentially dissociable relationships between epilepsy, affective behaviours, and distinct components of AUD-like phenotypes.

Conclusions
This study provides evidence that chronic epilepsy may alter the expression of AUD-like behaviours in a domain-specific manner. While epileptic rats exhibited reduced escalation and punishment-resistant drinking, they displayed enhanced relapse-like behaviour, suggesting a unique vulnerability profile. The dissociation between anxiety and drinking behaviour in KASE rats further supports the notion that temporal lobe epilepsy may disrupt typical affect-drug relationships. These findings challenge the assumption that TLE uniformly increases AUD risk and instead suggest that seizure-related factors or prior alcohol exposure may play a stronger role. Further studies are needed to clarify the directionality of this comorbidity.

P_34b Partial 5-HT2A receptor agonism as a treatment against the acutely reinforcing effects of methamphetamine

Presenting Author: Alexander G. Athanasopoulos

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Background
Psychedelics show therapeutic promise via agonism at the 5-HT_2A receptor. Recent findings suggest that partial 5-HT2A receptor agonists may retain these therapeutic benefits without hallucinogenic effects. Beyond this, we hypothesise that partial agonists may also act as functional antagonists—blunting the downstream effects of elevated endogenous neurotransmitters, as observed in methamphetamine use disorder. Methamphetamine increases 5-HT release from dorsal raphe projections to mPFC pyramidal neurons expressing 5-HT_2A receptors, ultimately driving dopamine release in the NAc - a key substrate for acute drug reinforcement. We test whether 6-F-DET, a non-hallucinogenic 5-HT_2A partial agonist, reduces methamphetamine's reinforcing properties in a self-administration model.

Methods
20 Sprague-Dawley rats (10M/10F) will be trained to self-administer methamphetamine (0.1 mg/kg/infusion) under an FR1 schedule until stable responding is achieved. Rats will then receive the 5-HT_2A receptor antagonist MDL-100907 (0.01, 0.03, 0.1, 0.3 mg/kg, i.p.) in a counterbalanced design, 15 minutes prior to methamphetamine sessions. To assess the functional antagonist hypothesis, rats will receive a single dose of 6-F-DET (1.25 or 2.5 mg/kg, i.p.) 15 minutes prior to self-administration, followed by six additional sessions without drug to evaluate post-acute effects. After 30 days of forced abstinence, cue- and meth-primed reinstatement tests will be conducted with 6-F-DET administered beforehand.

Results
This experiment is currently underway; however, based on prior literature we have several key hypotheses. We expect that methamphetamine self-administration will be reduced following pretreatment with the 5-HT_2A receptor antagonist MDL-100907, consistent with studies showing its ability to attenuate methamphetamine-induced hyperlocomotion, conditioned place preference, and MDMA-evoked dopamine release in the NAc. Similarly, we hypothesise that 6-F-DET will act as a functional antagonist under conditions of elevated serotonin tone and reduce methamphetamine self-administration. Together, these findings may support a role for 5-HT_2A modulation in dampening the acute reinforcing effects of methamphetamine.

Conclusions
This study may provide critical insight into targeting the 5-HT_2A receptor for the treatment of methamphetamine-use disorder. While psychedelics offer robust post-acute therapeutic effects likely through neuroplastic mechanisms, their acute utility is limited by hallucinogenic side effects. If our hypothesis holds, non-hallucinogenic partial 5-HT_2A receptor agonists like 6-F-DET may offer dual therapeutic utility: attenuating the acute reinforcing effects of methamphetamine while preserving the post-acute therapeutic benefits observed with classical psychedelics. Ultimately these findings may support the development of a safer and more scalable alternative to classical psychedelics for the treatment of methamphetamine-use disorder.

P_14b Discrete, cell-specific changes in cortical gene expression in a subgroup of schizophrenia characterised by low levels of the muscarinic receptor, CHRM1.

Presenting Author: Andrew Gibbons

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Background
The recent FDA approval of Xanomeline/Trospium-Cl for treating schizophrenia highlights an important role for cholinergic muscarinic receptors (CHRM) in mediating the symptoms of schizophrenia. This is significant as we identified a subgroup, comprising approximately one third of individuals with schizophrenia, who have lost over 70% of CHRM1 in the cortex. We termed this group the Muscarinic Receptor Deficit Subgroup of schizophrenia (MRDS). As cortical CHRM1 is predominantly expressed by pyramidal neurons, we hypothesised that individuals with MRDS will have cell-specific differences in gene expression compared with healthy controls and non-MRDS schizophrenia. We used single nuclei (sn)RNASeq to identify these differences.

Methods
Nuclei were isolated from post-mortem, dorsolateral prefrontal cortical tissue from 7 subjects with MRDS schizophrenia, 9 subjects with non-MRDS schizophrenia and 16 non-psychiatric control subjects. snRNASeq was then performed using the 10X Chromium Next GEM system, capturing ~9000 nuclei/sample with a read depth of 70 million reads/sample. Sequencing data was clustered using Cell Ranger and analysed using an R-based pipeline. Clusters were annotated with Seurat using cell and cortical laminae-specific markers and pseudo-bulk differential expression was analysed using EdgeR followed by gene enrichment and pathway analysis.

Results
The MRDS and non-MRDS groups displayed distinct, cell-specific profiles of differentially expressed genes when compared to controls, with only 3.8% ± 0.2% (mean ± SE) of differentially expressed genes in MRDS also being altered in non-MRDS in each identified cell cluster. Pathway analysis revealed that genes involved in glutamatergic signalling were in the top altered pathways in the excitatory neurons of laminae V and VI, and oligodendrocytes in MRDS, but not non-MRDS, compared to controls. Comparing differentially expressed genes between the MRDS and non-MRDS groups, cholinergic-related pathways were altered in the excitatory neurons of lamina V from subjects with MRDS.

Conclusions
Our data suggests that MRDS is a molecularly-distinct subtype of schizophrenia characterised by discrete, cell-specific changes in gene expression within the dorsolateral prefrontal cortex. The prominent changes in glutamatergic signalling pathways in populations of excitatory neurons and the differences in cholinergic pathways seen in Laminae V excitatory neurons suggest that disruptions to excitatory neuronal functioning may be important to the pathology of MRDS. In light of the recent recognition of muscarinic receptors as viable drug targets for the treatment of schizophrenia, our findings have important implications for identifying novel drug targets and directing appropriate treatments for individuals with MRDS.

P_36b Incubation of alcohol craving: Investigating drug-specific neural mechanisms

Presenting Author: Anna Pangilinan

Anna Pangilinan, *Macquarie University*

Background
Incubation of craving, the increase in cue-induced drug-seeking over the course of abstinence, is thought to be a key contributor to relapse in many drug use disorders. Glutamatergic pathways from the medial prefrontal cortex to the nucleus accumbens, and synaptic plasticity in the nucleus accumbens have both been implicated in relapse-like behaviour for psychostimulant drugs in animal models. There is some evidence to suggest that similar mechanisms could underpin incubation of alcohol craving, however current literature is limited. As such, we aim to identify and characterise neural pathways and neuroplasticity that relate to and potentially cause increased alcohol-seeking after abstinence.

Methods
Rats will be trained to self-administer alcohol, with a cued alcohol-seeking test before and after abstinence to model incubation of alcohol craving. With the brains of these rats, we will start by using synaptic tracing and RNAScope to identify and characterise neural circuitry that is active during each alcohol-seeking test. Then, synaptic plasticity during abstinence will be evaluated using synaptic spine modelling, and cellular protein fractionation and qPCR. These methods will identify morphological changes, and alterations to AMPA receptor expression, respectively. Finally, we intend to use optogenetics to determine the functional role of described neural pathways on alcohol-seeking after abstinence.

Results
We are presently in the process of conducting a literature review of research describing the neural mechanisms underlying incubation of drug craving, focussing on the limited published research on alcohol. Existing research in psychostimulants has informed the specific methods that we will use to examine alcohol-specific pathways and plasticity. Investigation into identifying projections to the nucleus accumbens core and shell is underway, utilising tissue that has already been collected in the lab.

Conclusions
From this research, we expect to elucidate neural pathways and plasticity that causally contribute to the incubation of alcohol craving in a rodent model. This will aid in the identification of potential therapeutic targets to prevent relapse in people with Alcohol Use Disorder.

P_49b Uncovering the RNA isoform landscape in brain development: Insights into neuropsychiatric disorder risk

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Background
The origins of neuropsychiatric disorders often trace back to prenatal brain development, a process governed by intricate genetic regulation. Alternative splicing enables genes to produce multiple RNA isoforms with diverse functions, vastly expanding transcriptomic and proteomic complexity. Despite their critical role in brain physiology, the contribution of specific risk gene isoforms remains poorly understood. Therefore, this research aims to characterize key isoforms of neuropsychiatric risk genes during early brain development, laying the foundation for future investigations into isoform-specific functions and the molecular mechanisms underlying diseases.

Methods
To model human prenatal brain development, we utilized a range of in vitro systems, including neuronal cell cultures, human pluripotent stem cell (hPSC)-derived neurons, and 3D cortical organoids. RNA was extracted at 3-4 key timepoints to recapitulate early neurodevelopmental trajectories. Targeted long-read sequencing using Oxford Nanopore technology was performed to profile isoforms of seven neuropsychiatric risk genes. Isoform identification and characterization, including structure and expression quantification, were analyzed using the IsoLamp pipeline. Candidate isoforms were prioritized for future functional studies based on novelty, expression levels, and temporal changes during development.

Results
Across the seven risk genes, 313 isoforms were identified, of which 274 are non-annotated. These novel isoforms on average contribute to 43% of the total gene expression, highlighting how risk gene isoforms are more variable and complex than previously acknowledged. Notably, multiple novel isoforms in risk genes such as CACNA1C, KLC1, and DOC2A, exhibited high usage and dynamic developmental expression, suggesting potential involvement in key neurodevelopmental processes. For example, a highly expressed novel DOC2A isoform was downregulated in cortical organoids at 6 months, while other novel isoforms utilising an alternative transcriptional start site were upregulated, implying isoform-specific roles in neurodevelopment.

Conclusions
This study profiled and characterized RNA isoforms of seven neuropsychiatric risk genes during human brain development using long-read sequencing and hPSC–derived neuronal models. A substantial number of novel isoforms were identified, many of which exhibited dynamic developmental usage and high levels of expression. These findings reveal the transcriptomic complexity in the developing brain and highlight candidate isoforms with potential functional relevance. The results lay the foundation for future work aimed at understanding isoform-specific mechanisms in neurodevelopment and identifying novel targets for therapeutic intervention in neuropsychiatric disorders.

P_43b Identifying phenotypic markers to predict mental health outcomes

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Background
Mental health conditions are a major contributor to the global burden of disease, with significant treatment gaps worldwide. In Australia, mental health disorders account for 15% of Disability-Adjusted Life Years (DALYs). Psychotherapies have been shown to be effective in treating these conditions, but access to these supports remains limited due to geographic, financial, and systemic barriers. Artificial intelligence (AI) advances offer new ways to address these challenges through machine learning, natural language processing (NLP), chatbots, and digital phenotyping. These technologies enable the ongoing collection and analysis of data to forecast, monitor, and intervene in mental health conditions in real-time.

Methods
This study aims to examine and integrate AI-driven phenotypic and morphological data within the SHAE mobile health application to evaluate mental health outcomes in a corporate wellness context. A longitudinal design was implemented with 300 participants who engaged with SHAE over a period of 10 to 30 days. The phenotypic traits will be assessed at two time points and compared to investigate their predictive values in measuring depression, anxiety, and stress. Correlation analyses will be used to determine predictive validity.

Results
The analysis of the initial data set provided by industry partner (Precision Health Alliance) is underway, with preliminary findings suggesting a link between age, gender, and adiposity markers and the subjective well-being measure of the DASS-21 (Depression, Anxiety, and Stress). Additional phenotypic data are being compiled by the industry partner at present. These markers will be utilised in a longitudinal study to examine phenotypic variations and changes in subjective well-being through an AI intervention, thereby indicating the effectiveness of the intervention. The analysis is currently underway and will be presented at the conference.

Conclusions
The development of understanding how phenotypic and morphological traits are linked with the predictive ability of mental health outcomes will allow for a preliminary understanding to pre-emptively determine the risk of developing more serious conditions. This will inform treatment before the clinical manifestation of impactful symptoms, enabling the opportunity for the earliest intervention. The indication of phenotypic traits that best predict mental health outcomes may also be illuminated for future study. This will form the foundation that can be further utilised in future research to target specific populations, such as elite athletes or populations that undergo high levels of stress.

P_1b Paternal gut microbiota modulation via prebiotics alters sperm small RNAs and impacts offspring physiology and behaviour

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Background
Parental environmental exposures, including models of stress, immune activation and Western diet can alter offspring phenotypes via germline epigenetic modifications. Such environmental stimuli interact with the gastrointestinal (GI) tract either directly or indirectly via the gut microbiota—the commensal microorganisms that colonize the GI tract. The maternal gut microbiota has been demonstrated to impact offspring, however, the influence of the paternal gut microbiota on offspring is only beginning to be understood. Our lab aims to investigate the impact of paternal gut microbiota modulation on offspring physiology, gut microbiota, and cognitive and affective behaviour.

Methods
The gut microbiota of male C57BL/6J mice was modulated using a combination of two prebiotics, administered via drinking water. After approximately one spermatogenic cycle in the presence of the prebiotic modulated gut microbiota, these mice were bred with naïve female mice to produce offspring which were investigated for physiological and behavioural changes. To investigate potential mediators of epigenetic inheritance the paternal sperm small non-coding RNAs (sncRNAs) were profiled.

Results
Paternal gut microbiota modulation via prebiotics resulted in a transient increased body weight in both male and female offspring following weaning. Additionally, male and female offspring showed morphological changes in their gastrointestinal tract, with an increase in colon length. Offspring also had an altered GI transit time. Male and female offspring showed altered cognitive performance, spending an increased duration in the novel arm of the Y-maze. The offspring gut microbiome diversity measures were not altered by paternal prebiotic administration, however there were 3 differentially abundant taxa. Analysis of sperm sncRNAs revealed fathers administered prebiotics had differentially expressed sncRNAs.

Conclusions
Our lab presents further evidence of the role of the paternal gut microbiota in modulating offspring phenotypes, specifically in offspring physiology and cognitive behaviour. Previously environmental stimuli, such as diet and stress, known to influence the gut microbiota, have been implicated in paternal epigenetic inheritance and alterations in the sperm epigenome. We currently report changes to the sncRNA profile of sperm from prebiotic administered males, providing further evidence the gut-germline axis may play an influential role in intergenerational epigenetic inheritance.

P_63b Repurposing drugs for bipolar disorder using patient-derived cells and a gene expression signature.

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Background
Drug discovery is lackluster for bipolar disorder (BD) partly due to the limited understanding of the mechanisms of the disease. Alternative approaches for advancements in treatment are urgently required. Utilising a novel in-vitro cell model and an in-silico drug screen we provide a promising avenue of drug repurposing to accelerate the discovery of new treatments.

Methods
People with BD (n=12) and unaffected individuals (n=10) were recruited. Blood samples were collected from participants to generate neural progenitor cells to provide a biologically plausible model of BD. RNA sequencing was performed to measure global gene expression, and a signature was created consisting of genes that best describe the overall differences in gene expression between the groups. This gene expression signature was used to perform an in-silico drug screen using The Library of Integrated Network Based Cellular Signatures.

Results
29 genes were identified with differential expression between the two groups (adj. $p < 0.05$). The in-silico drug screen identified drugs that reverted the gene expression signature in the BD cohort to look most similar to that of the healthy control cohort. A list of the top 15 drugs was generated, which included quetiapine and lovastatin, validating our method due to the presence of prior confirmatory or suggestive preclinical, epidemiological and clinical data in BD. Novel drugs were also identified, including nimodipine, pirfenidone and calcitriol.

Conclusions
Our analysis identified drugs with the potential to be repurposed for BD. These drugs should be prioritised for further investigations to provide essential alternative treatments for BD.

P_40b The neurobehavioral effects of the over-expression of microRNA-219 in the pre-limbic region of the medial prefrontal cortex of rats, towards a predictive model for Schizophrenia.

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Background
Schizophrenia is a severe psychiatric disorder affecting ~1% of the population, with significant societal and healthcare burdens. While genetic factors contribute, recent evidence highlights the role of epigenetic regulators, such as microRNAs (miRNAs). miR-219, a brain-enriched miRNA, has emerged as a critical modulator of glutamatergic signalling, particularly via N-methyl-D-aspartate receptor (NMDA-R) pathways. Disruption of NMDA-R function mimics schizophrenia-like behaviours in animal models. miR-219 is rapidly downregulated following NMDA-R antagonism and is dysregulated in schizophrenia patient brains. This project investigates the role of miR-219 in schizophrenia pathogenesis in rats, proposing it as a potential diagnostic biomarker and therapeutic target

Methods
To evaluate the effects of miR-219 on neurobehavior, lentiviral constructs encoding miR-219 were stereotaxically injected into the prelimbic region of the medial prefrontal cortex of Sprague Dawley rats. Behavioural testing was conducted post-injection using a battery of standardized tests: the open-field maze and elevated plus maze assessed anxiety and locomotor activity; the novel object recognition test evaluated memory and cognitive function, and the pre-pulse inhibition paradigm measured sensorimotor gating. Post-mortem tissue analysis confirmed miR-219 expression levels via RT-PCR.

Results
Rats overexpressing miR-219 showed significantly increased anxiety-like behaviour in both the open-field and elevated plus maze tests, with greater time spent in the periphery and closed arms, respectively. Sensorimotor gating was impaired, evidenced by reduced PPI at the 8 dB pre-pulse level, aligning with schizophrenia-associated deficits. However, there were no significant differences in total locomotor activity or in cognitive performance during novel object recognition tasks, suggesting preserved working memory. These findings indicate selective behavioural changes relevant to schizophrenia phenotypes following miR-219 overexpression

Conclusions
This study demonstrates that targeted overexpression of miR-219 in the medial prefrontal cortex of rats induces behavioural changes consistent with symptoms observed in schizophrenia, particularly heightened anxiety and impaired sensorimotor gating. While cognitive performance and locomotor activity remained unaffected, the selective deficits observed provide compelling evidence for miR-219's role in the modulation of neural circuits involved in psychiatric disorders. These results support the hypothesis that miR-219 dysregulation contributes to schizophrenia pathophysiology and may represent a promising molecular target for therapeutic intervention. The model established here also offers a useful platform for studying miRNA-driven mechanisms of psychiatric disease.

P_20b Paternal chronic bacterial-like infection induces multigenerational changes in offspring anxiety and cognition related to alterations of sperm small non-coding RNAs

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Background
Paternal infections can shape behaviour across generations via epigenetic mechanisms including sperm non-coding RNAs, yet the outcomes of sustained immune activation remain poorly understood. While acute lipopolysaccharide (LPS) exposure alters anxiety and depression like responses in offspring, chronic bacterial-like infections, prevalent globally, produce persistent inflammation that may leave deeper multigenerational imprints. We therefore investigated whether prolonged paternal LPS treatment, modelling chronic bacterial-like infection in male C57BL/6J mice, modifies anxiety-related behaviours and cognition across two generations. Understanding how chronic paternal immune stress may program neurobehaviour through non-coding RNA-mediated pathways offers insights into inherited vulnerability and multigenerational transmission of mental health risks.

Methods
Eight-week-old male C57BL/6J mice received weekly intraperitoneal LPS injections (0.33–0.83 mg/kg) over six weeks. Body weight, food intake, and clinical scores were monitored daily. Four weeks post-treatment, males were mated with wild-type females. Sperm samples were collected for small RNA sequencing to profile non-coding RNA landscapes hypothesized to mediate epigenetic inheritance. Offspring underwent anxiety assessments including open-field, light–dark box, elevated plus maze, and novelty-suppressed feeding tests, cognitive evaluation via novel object recognition and Y-maze tasks, and associative learning testing with fear conditioning. Data was analyzed using mixed-effect models accounting for litter variability.

Results
Offspring from LPS-treated sires exhibited reduced anxiety-like behaviour, evidenced by increased exploration in open-field centres, elevated-plus maze open-arms, and light–dark box illuminated areas. Female offspring demonstrated enhanced object-recognition memory. This anxiolytic phenotype persisted transgenerationally, with grand-offspring males showing decreased feeding latency in the novelty-suppressed feeding and increased learning capacities in the fear conditioning test. Small-RNA sequencing of paternal sperm identified one upregulated microRNA, seven upregulated ribosomal-RNA-derived RNAs, and three differentially expressed transfer RNA-derived fragments. Gene ontology analysis of predicted targets further revealed enrichment in neural remodeling and synaptic transmission pathways, providing mechanistic insights into multigenerational behavioural inheritance through epigenetic mechanisms.

Conclusions
Our findings suggest that paternal chronic bacterial-like infection can alter offspring anxiety-like and cognitive behaviours, with altered sperm small-RNA cargos implicating an epigenetic transmission of psychiatric vulnerabilities. These findings identify paternal infection as an important contributor to heritable behaviour risk and highlight sperm non-coding RNAs as promising targets for future preventive interventions to mitigate anxiety-related disorders across generations.

P_32b AgRP neuron-specific GHSR knockout alters consummatory behaviour in the presence of predator stress

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Background
The arcuate nucleus of the hypothalamus is seen as the center for the homeostatic control of food intake, where agouti-related protein (AgRP) neurons drive feeding behaviour by integrating hunger cues. Ghrelin, secreted from the gut, activates AgRP neurons to drive hunger by activating the growth hormone secretagogue receptor (GHSR). In the context of foraging, animals have to be able to balance food-seeking behaviour with predator evasion, making dynamic signals that attenuate hunger cues essential for survival. Ghrelin may play a role in modulating stress responses, making it a novel target for understanding hunger signals in the context of acute stressors.

Methods
Here, we subject AgRP GHSR knockout mice to a live rat stress behaviour assay, where knockout mice are missing the GHSR from AgRP neurons.

Results
We show that knockouts consume less food than wild types under control conditions. Interestingly, knockout mice consume the same amount of food in the presence of both the live and control rat following an overnight fast, while wild type mice consume significantly less food in the presence of the live rat versus the control. Additionally, we see differences in time spent interacting with the rat between genotypes.

Conclusions
Overall, our results suggest that ghrelin signaling on AgRP neurons is important in modulating hunger cues under acute threat conditions. Further work is needed to understand whether this holds true in the context of palatable food intake without a metabolic need for food consumption.

P_10b Harnessing DNA Methylation to Disentangle Heterogeneity in Schizophrenia

Presenting Author: Dylan Kiltschewskij

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Background
Schizophrenia is a debilitating psychiatric condition marked by profound heterogeneity in onset, progression, severity and treatment response. This heterogeneity poses a major challenge for effective intervention, as it necessitates personalised approaches to treatment that account for each individual's unique combination of genetic and environmental risk factors. DNA methylation offers a powerful lens for capturing these influences, as it reflects dynamic interactions between genetic predisposition and environmental exposures. While altered DNA methylation has been observed in schizophrenia, its potential for elucidating heterogeneity remains underexplored.

Methods
To address this, we recently conducted the first meta-analysis of DNA methylation variability in schizophrenia to pinpoint genomic loci with significantly higher or lower variance compared to non-psychiatric controls. This was conducted using blood methylation data from three publicly available cohorts (Nsz = 1036, NCtrl = 954). Changes in DNA methylation variability were determined via Levene's test and meta-analysed across cohorts using Stouffer's weighted method. Methylation sites with significantly altered variance between cases and controls were subject to a battery of analyses assessing their genomic organisation, brain enrichment, and association with schizophrenia progression and severity.

Results
We identified 213 variably methylated positions (VMPs) after correction for multiple testing. Interestingly, VMPs with increased variance in schizophrenia were significantly overrepresented among brain-enriched genes, and in several cases exhibited concordant changes in post-mortem cerebellum, hippocampus, prefrontal cortex and striatum. These loci also revealed individual-level methylation outliers among schizophrenia cases, suggesting that VMPs may mark biologically relevant sites of dysregulation in specific individuals. Furthermore, these VMPs correlated with methylation patterns previously linked to clinical measures of progression and severity, such as cognitive deficits and global assessment of function scores.

Conclusions
Collectively, our findings highlight specific genomic loci that may contribute to schizophrenia risk in a subset of individuals, rather than uniformly across the population. This work positions DNA methylation variability as a compelling molecular signature for reconciling clinical and biological heterogeneity in schizophrenia.

P_42b Clearing the Fog: Characterising neurological phenotypes in a Long COVID mouse model to identify biomarkers for Long COVID

Presenting Author: Elizabeth Kleeman

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Background
The national inquiry into Long COVID and Repeated COVID infections identified that around 30% of patients with Long COVID in Australia suffer from neurological and neuropsychiatric symptoms. These neurological manifestations vary widely and fluctuate in terms of severity and duration across patients. Yet the cause and pathophysiology of neurological PASC remains largely unclear. While an increasing number of large clinical Long COVID studies investigate neurological symptoms, they mostly rely on the participants self-diagnosis of Long COVID which provides limited insights into disease mechanisms due to their lack of powerful invasive experimental paradigms.

Methods
We aim to uncover the mechanistic underpinnings of neurological and psychiatric of Long COVID in a preclinical C57BL/6J mouse model of Long COVID. In this model, young adult wildtype C57BL6/J mice (both males and females) are intranasally infected with a mouse adapted SARS-CoV-2 virus or mock infected with PBS as the control group. Four weeks after the infection, we ran a behavioural battery of tests looking at cognition, depression, and anxiety in the Long COVID mice. Furthermore, we performed 16S rRNA sequencing on the DNA extracted from mouse faeces to look at the composition of their gut microbiome.

Results
We found that the Long COVID mice showed significantly decreased novel object exploration time in the novel object recognition task compared to mock control mice. The female Long COVID mice also showed reduced distance travelled overall in this task compared to mock control female mice, suggesting reduced locomotion. However, Long COVID mice showed no significant differences in the light/dark box, open field test, novelty-suppressed feeding test, and sucrose preference test. In terms of their gut microbiome, female Long COVID mice show reduced alpha diversity (Shannon Index) and significantly different beta diversity when compared to mock control female mice.

Conclusions
Overall, the Long COVID mice show reduced short-term memory in the novel object recognition task, suggesting that they have cognitive impairment. Additionally, the female Long COVID mice show reduced locomotion and reduced gut biodiversity. There were no detectable signs of anxiety or depression in these Long COVID mice. The cognitive impairment is in line with clinical studies which suggest that many Long COVID patients experience "brain fog". Additionally, the reduced locomotion may indicate that the female Long COVID mice may be experiencing fatigue. Furthermore, the gut microbiome changes suggest that this could be a potential target for future therapeutics.

P_57b Between brain circuitry and lived experience: Trauma and self-disturbance in youth at high-risk for psychosis.

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Background
Trauma is a well-established risk factor for psychosis, yet the mechanisms linking early adversity to symptom onset remain unclear. One proposed pathway is through self-disturbance—a disruption in one's basic experience (phenomenology) of a sense of self. While self-disturbance is common in individuals at clinical high-risk (CHR) for psychosis, the associated functional connectivity changes remain largely unexamined, despite evidence from schizophrenia spectrum disorders showing alterations in networks associated with self-referential processing. To address this gap, we conducted whole-brain functional connectivity analyses using data from two studies: the global Accelerating Medicines Partnership Schizophrenia study and a Melbourne-based study of self-disturbance in CHR.

Methods
Data from 158 participants were analysed to examine associations between the neurophenomenology of trauma and self-disturbance in CHR. Self-disturbance was measured using the Examination of Anomalous Self-Experience (EASE). Trauma was assessed using scales from the Psychosis Polyrisk Score measure. Resting-state fMRI data were analysed using data-driven machine learning models, including connectome-based predictive modelling, Network-Based-Statistics (NBS), NBS-Predict, and logistic ridge regression, to test whether EASE and trauma scores were associated with and could be predicted from functional connectivity profiles. Additional analyses examined whether EASE scores mediated the relationship between trauma and CHR status.

Results
Analyses are ongoing, with results to be presented at the conference. We hypothesise that the severity of self-disturbance in CHR will be associated with altered functional connectivity, particularly within the DMN (i.e., the network associated with self-referential processing). We also expect overlap with trauma-related functional connectivity, especially involving the DMN and emotion-related brain regions such as the amygdala.

Conclusions
By integrating predictive modelling with causal inference, this approach aims to clarify how brain connectivity relates to self-disturbance and how self-disturbance may mediate trauma-related psychosis risk.

P_41b Effects of acute administration of the GLP-1 agonist, semaglutide, on blood glucose levels, incentive motivation and cognitive flexibility in male and female Sprague-Dawley rats

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Background
Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) agonist used to treat diabetes and manage weight gain. This compound is also used in improving metabolic disturbances caused by antipsychotic drugs in people with schizophrenia. Cognitive deficits, one of the main features highlighted in people with schizophrenia, plays a prominent role in the occurrence of functional impairment in daily life. However, there is limited evidence that GLP-1 agonists improve cognitive symptoms in schizophrenia patients. In this study, we aimed to investigate effects of an acute dose of semaglutide on blood glucose levels, incentive motivation and cognitive flexibility in rats.

Methods
Adult Sprague-Dawley rats (18 males and 18 females) housed in groups of three in wire-top cages, had restricted access to food prior testing. Rats underwent instrumental training to nose poke and lever press for a 45 mg pellet reward. Next, they were tested on a series of spatial and non-spatial rules to visual or auditory cues. After passing 5 consecutive rules, semaglutide was injected (0.1 mg/kg, s.c.) and dynamic strategy shifting task was performed comprising 7 distinct rules. Repeated blood samples (baseline and 30 min intervals after oral dosing of 2g/kg glucose) were collected 24 h after injection.

Results
Semaglutide induced a significant weight loss for four days after treatment, and an increase in blood glucose levels at baseline in males, and in males and females after oral dosing of glucose. Semaglutide reduced incentive motivation (sign tracking behaviour) in both males and females. Goal directed behaviours were reduced in female but not male rats in response to semaglutide. There were no significant effects of semaglutide on measures of cognitive flexibility, including the trials to criteria and number of rules passed.

Conclusions
Acute dosing of semaglutide significantly increased blood glucose levels (hyperglycemia) and reduced incentive motivation in both male and female Sprague-Dawley rats, with a sex-specific reduction in goal-directed behaviour observed only in females. However, it did not improve cognitive flexibility, suggesting limited potential for acute dosing to address cognitive deficits in schizophrenia. Future studies should examine chronic administration of GLP-1 agonists on cognitive function.

P_17b Genetic and Network-Based Constraints on Gray Matter Volume Changes in Psychosis

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Background
Differences in regional grey matter volumes (GMV) are a common finding in MRI studies of psychotic illness, occurring consistently within disease-related functional networks. However, the mechanisms that shape the spatial patterning of these changes remain unclear. Recent studies suggest that GMV reductions propagate along white matter tracts within brain networks. Here, we expand on existing models of GMV changes by integrating interactions between brain networks and genetic risk factors. Specifically, we apply an epidemiological agent-based spreading model to simulate the movement of pathological gene products along the connectome and predict the resulting spatial pattern of GMV reductions.

Methods
Grey matter volume changes were assessed using voxel-based morphometry analyses on T1-weighted MRI data from 17 scan sites (964 healthy controls and 800 patients). Structural connectivity was derived from diffusion MRI data, producing a group-averaged connectome with 35% binary density. Gene expression profiles across the whole brain were provided by the Allen Human Brain Atlas. Our disease model employed an agent-based Susceptible-Infected-Removed (SIR) model, simulating disease progression based on gene expression within regions and connectivity between regions. Model performance was compared with spatial null models generated using the BrainSMASH toolbox and rewired connectome nulls using the Maslov-Sneppen algorithm.

Results
We simulated pathological processes and subsequent atrophy across all pairwise combinations of potential risk and clearance genes. The resulting simulated atrophy maps were compared with empirical atrophy maps to determine to identify the highest spatial correlation for each gene pair. Across all gene pairs, peak model fit reached r=0.71. Simulated atrophy from gene pairs with high model fit significantly outperformed null models for both spatial and rewired null comparisons. Gene enrichment analysis on highly performing genes revealed significant enrichment in terms associated with synaptic signalling and protein translation.

Conclusions
Our agent-based model integrates genomic and connectomic data to model the spatial distribution of GMV reductions in schizophrenia. Our results indicate that disease processes, shaped by region-specific gene expression, accumulate locally and propagate along the connectome to shape the distribution of GMV changes in psychosis. We identify altered neurotransmission and cytoplasmic translation as key biological processes associated with GMV changes in schizophrenia.

P_53b A study of frontal bone thickness in patients with schizophrenia

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Background
It is often said “Patients with mental disorders have thick skulls” by neuropathologist, forensic pathologist, anatomist and radiologist. In clinical practice, psychiatrists sometimes encounter cases which have those findings in neuroimaging such as computed tomography (CT). However, the evidence to date remains unclear. In this study, we examined skull thickness in patients with schizophrenia.

Methods
The thickness of the frontal bone was measured in subjects without psychiatric disorders and patients with schizophrenia. The patients with schizophrenia were divided into two groups: treatment response and treatment resistant schizophrenia. The head CT images were taken with a 5 mm slice, and the thickness was measured in every 1 cm up to 5 cm from the midline to both outside at a height of 4 cm above the orbito-auricular line. The average of the thickness from 1 to 5 cm was compared among three cohorts. This study was approved by the Ethics Committee of Fujita Kokoro Care Centre.

Results
128 subjects in the control, 93 subjects in the treatment response, and 51 subjects in the treatment resistance group were assigned in this study. Mean age was 42.4±11.6, 43.6±14.8, and 47.9±12.1 years, respectively, with no differences between groups. Frontal bone thickness was 7.6 ± 1.4 cm, 7.7 ± 1.5 cm, and 9.2 ± 1.6 cm on the right side and 8.0 ± 1.6 cm, 8.1 ± 1.9 cm, and 9.5 ± 1.8 cm on the left side, respectively. Bonferroni's test showed a statistically significant difference in the treatment resistance group versus the control group and the treatment response group.

Conclusions
We showed that the frontal bone was thicker by 1.5 mm in the treatment resistant group than the control and treatment response groups. Future studies are needed to determine whether the frontal bone thickness is related to the pathophysiology of treatment resistant schizophrenia or whether it is an effect of medication and are also needed for other psychiatric disorders besides schizophrenia.

P_52b Functional Coupling and Longitudinal Outcome Prediction in First-Episode Psychosis

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Background
Clinical outcomes following a first episode of psychosis are highly heterogeneous between patients. The identification of prognostic biomarkers would greatly facilitate personalized treatments. Psychosis patients often display brain-wide disruptions of inter-regional functional coupling (FC), with some being linked to symptom severity and remission. FC may thus hold prognostic potential for people experiencing psychosis.

Methods
Fifty-five antipsychotic-naïve first-episode psychosis patients (51% female, 15-25 years) were randomized to receive either antipsychotic or placebo tablets for 6 months alongside psychosocial interventions. Functional magnetic resonance imaging was conducted at baseline and after 3 months to evaluate whether baseline FC, or 3-month change in FC, could predict 6- and 12-month changes in symptoms and functioning, quantified using the Brief Psychiatric Rating Scale and the Social and Occupational Functioning Assessment Scale, respectively. We considered three different cross-validated prediction algorithms: (i) connectome-based predictive modelling; (ii) kernel ridge regression; and (iii) multilayer meta-matching. Each prediction model comprised 35 to 49 individuals.

Results
All models showed poor performance in predicting patients' 6- and 12-month changes in symptoms and functioning (all mean r0.05).

Conclusions
Our findings suggest that brain-wide measures of FC may not be suitable for predicting extended clinical outcomes over a 6- to 12-month period in first-episode psychosis patients.

P_60b Probing interactions between the muscarinic M4 receptor and 'receptor X'

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Background
Alcohol use disorder is an undertreated health issue that has a substantial negative impact on the individual, community, and societal level. Novel treatments with improved efficacy and reduced side effect profiles are needed. Combining available drugs that act to counterbalance key dysregulations is a promising avenue to fast-track new options. Here, we investigate- in vitro- the potential mechanism underlying a behaviourally relevant interaction following coactivation of the M4 muscarinic acetylcholine receptor (mAChR) and an ion channel ("receptor X") in rodent models of alcohol use disorder.

Methods
HEK293-T cells were transiently transfected with the human receptor X alone, or in conjunction with the human M4 mAChR (or vice versa). Functional effects of co-expressing and co-stimulating these two receptors was determined by measuring intracellular calcium- utilising a GCaMP sensor- and an adapted BRET assay for Gαi protein dissociation. Cell-surface expression levels of the M4 receptor under both conditions were assessed through flow cytometry.

Results
Co-expressing the M4 receptor attenuated the ability of selective receptor X ligands to elicit calcium mobilisation in a concentration-dependent manner. This effect appears to be specific to the M4 receptor relative to the M2 receptor; however, this will be confirmed in further studies. There was no effect of receptor X expression or stimulation on the efficacy or potency of muscarinic ligands, an observation supported by the lack of ability of receptor X expression or stimulation to modulate M4 expression, as determined with flow cytometry.

Conclusions
M4 receptor expression in HEK293-T cells dampens the calcium response findings provide rationale to further interrogate interactions between muscarinic M4 receptors and receptor X that may inform future treatment options.

P_31b Investigating the Development of Fear Avoidance in a Novel Graded Threat Assay in a Preclinical Model of Orofacial Neuropathic Pain.

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Background
Following injury, acute pain triggers withdrawal from the damaging stimuli and promotes risk assessment and avoidance learning. These fear avoidance behaviours are argued to be an adaptive survival mechanism to ensure recovery. Such behaviours usually subside as the initial injury heals, but in some circumstances fear avoidance is sustained and is reported to be a key behavioural characteristic of people with chronic pain. This study sought to develop a preclinical model of fear avoidance in chronic orofacial neuropathic pain.

Methods
We investigated the temporal development of fear avoidance behaviours in male Sprague-Dawley rats (n=80) in a novel 3-chamber apparatus over a 35-day period. Our behavioural test used exposure to predator odour or bright light to create graded threat levels, to assess safety seeking and vigilance, which are core fear avoidance behaviours, over a 10-minute test period. The 3-chamber apparatus consisted of: (i) an aversive open area with a food reward in the presence of predator odour (high threat zone); (ii) a mildly aversive corridor connected to; (iii) an enclosed dark box accessible through a door (safe zone).

Results
Our data revealed that with repeated exposure to the test chamber there was a significant effect on time spent in the high threat zone ($F_{5, 263}$ (time) = 2.261, $P<0.05$; $F_{3, 263}$ (surgery) = 12.79, $P<0.0001$). This effect was attributed to uninjured rats spending increasingly more time in the high threat zone. In contrast, rats with a trigeminal neuropathic injury maintained the amount of time they spent in the high threat zone from first to last exposure.

Conclusions
Our data suggest that fear avoidance is not heightened following neuropathic injury, rather it fails to habituate and is maintained at the same level to that seen on initial exposure to threat. Our graded threat assay provides a valuable tool to investigate the neural correlates underpinning maladaptive affective behaviours.

P_38b Enhanced Acute Psilocybin Responses and Sex-Specific Long-Term Improvements in Sensorimotor Gating in the Metabotropic Glutamate Receptor 5 Knockout Mouse Model of Schizophrenia

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Background
Schizophrenia affects 1% of the global population and is characterized by a combination of positive symptoms (e.g., hallucinations), negative symptoms (e.g., anhedonia), and cognitive impairments. While dopaminergic dysfunction has historically dominated explanatory models, increasing evidence implicates disruptions in glutamatergic and serotonergic signalling. Genetic deletion of metabotropic glutamate receptor 5 (mGluR5) produces schizophrenia-relevant phenotypes in mice, including hyperlocomotion and sensorimotor gating deficits. Previous studies suggested functional interactions between mGluR5 and 5-HT2A receptors, the latter being the main target of psilocybin, a psychedelic with emerging therapeutic applications. However, the effects of psilocybin in the context of glutamatergic dysfunction remain poorly understood.

Methods
Here, we investigated the acute and long-term behavioural effects of psilocybin (1 mg/kg) in metabotropic glutamate receptor 5 (mGluR5) knockout (KO) and wild-type (WT) mice.

Results
Psilocybin robustly increased locomotor activity and head-twitch responses (HTR), with both effects significantly enhanced in mGluR5 KO mice, particularly in males. While psilocybin did not alter anxiety-like behaviour in the light–dark box, it increased immobility time in the Porsolt swim test in male mice, potentially reflecting adaptive behavioural adjustment rather than depressive-like states. Notably, psilocybin produced a sustained enhancement in sensorimotor gating, as measured by prepulse inhibition (PPI), specifically in female mGluR5 KO mice. This effect was not correlated with acute HTR magnitude, suggesting that psilocybin's long-term therapeutic actions may be dissociable from its hallucinogenic acute effects.

Conclusions
These findings suggest that mGluR5 deletion enhances sensitivity to 5-HT2A-mediated stimulation and identify mGluR5 as a key modulator of psilocybin's behavioural profile and raise the possibility that individuals with altered glutamatergic signalling may exhibit differential responses to psychedelic treatment. Moreover, the sex-specific and long-lasting improvements in sensorimotor gating highlight the need to consider sex as a biological variable and support further investigation into neuroplasticity as a potential mechanism underlying psilocybin's long-term effects. Together, these findings provide insight into glutamatergic–serotonergic interactions and support the continued evaluation of psilocybin in models relevant to schizophrenia and related disorders.

P_44b Trimetazidine to treat Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: TRI-ME trial

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Background
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) causes debilitating symptoms including intense fatigue, post-exertional malaise and others. While 1% of Australians are diagnosed with ME/CFS, its true prevalence and burden may to be higher due to its diagnostic complexity and significant symptomatic overlap with other complex illnesses (e.g. Long-COVID). While there are currently no FDA/TGA approved evidence-based treatments for ME/CFS, we have a promising new candidate - trimetazidine.Trimetazidine allows mitochondrial energy generation to be more efficient without overexerting this mechanism, which addresses the key pathophysiological mechanisms of ME/CFS: mitochondrial dysfunction and reduced mitochondrial energy generation.

Methods
An a priori consumer co-design process was initially conducted, working together with a group of individuals with lived experience of ME/CFS through the Barwon Health Lived Experience Team. The TRI-ME trial is then designed and approved as an 8-week, double-blind, randomised, placebo-controlled Phase 2 clinical trial. The primary aim of the trial is to assess the efficacy of trimetazidine in reducing fatigue in ME/CFS, measured by Chalder Fatigue Scale. The secondary aims assess trimetazidine's efficacy in improving other ME/CFS symptoms, self-reported physical activity, cognitive functioning, cost-effectiveness and quality of life.

Results
The trial is currently recruiting at the Barwon Health site, Geelong. As the trial is currently ongoing and there is no results to be reported at present.

Conclusions
We received over 400 expressions of interest within the first three weeks of trial commencement, highlighting the major unmet need for a novel treatment for ME/CFS. Trimetazidine is an accessible, affordable, tolerable and off-patent medication, approved to treat angina in Europe and Asia. If the trial is successful, it will facilitate rapid translation to clinical use of trimetazidine for treating ME/CFS.

P_21b Associations between prenatal exposure to endocrine-disrupting compounds and preschool neurocognitive abilities: an Australian birth cohort

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Barwon Infant Study Investigator Group, Barwon Infant Study Investigator Group

Background
Endocrine-disrupting compounds (EDCs) are exogenous chemicals that interfere with hormonal systems, including environmental pollutants such as plastic-associated phthalates, phenols, and certain metals. EDCs are linked to altered neurodevelopment, including increased risk for autism and learning difficulties. However, studies report variable associations by compound, outcome, and child sex, in part due to heterogeneity in neurodevelopmental assessments. Neurocognition—including executive function (EF), language, and related skills—may offer a unifying framework for interpreting early neurodevelopmental risk. EF reflects core cognitive processes (e.g., inhibitory control) that support goal-directed behaviour. We examined associations between prenatal EDC exposures and preschool neurocognitive abilities.

Methods
Participants were from the Barwon Infant Study, a population-derived pre-birth cohort in regional Victoria, Australia (n=1,074). Maternal third trimester urine was analysed for EDCs, including phthalate and phenol metabolites, metals, and metalloids. At preschool age, children completed a neurocognitive battery (Dog-Koala Go/No-Go, Boy-Girl Stroop, NIH Toolbox® Picture Vocabulary). We used multivariable linear regression to estimate associations between individual EDCs and neurocognitive outcomes. Variable selection techniques were applied to identify key EDCs. To account for combined exposures, Bayesian kernel machine regression (BKMR) was used to assess the joint effects of a prenatal mixture of key EDCs on neurocognitive performance across tasks.

Results
Low molecular weight phthalates (LMWP)—mono-n-butyl phthalate (MnBP), mono-iso-butyl phthalate (MiBP), and mono-ethyl phthalate (MEP)—and metals (zinc, nickel, cobalt), were associated with neurocognitive delays. Higher prenatal exposure to the combined EDC mixture (ψLMWP and metals)—comparing the 90th to the 10th percentile of the mixture distribution—was associated with greater neurocognitive delays. Children with higher exposure showed greater delays in receptive vocabulary ability (NIH Toolbox® Picture Vocabulary Test: –2.94 points; 95% credible interval CI: –5.20, –0.67) and reduced inhibitory control (Boy-Girl Stroop correct responses: –0.61 hits; 95% CI: –0.85, –0.08).

Conclusions
In this population-derived Australian pre-birth cohort, elevated prenatal exposure to a mixture of EDCs—including low molecular weight phthalates and metals—was associated with neurocognitive delays across multiple domains by preschool age. These findings reinforce the prenatal period as a critical window of vulnerability and support the need for strengthened regulation of EDCs during pregnancy.

P_46b Clinical trials to treat myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review and meta-analyses of intervention- and measure-specific outcomes

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Background
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disabling condition characterised by persistent fatigue, cognitive impairment, and post exertional malaise. Despite its rising burden, evidence-based treatment options are lacking. To address this, we formed a team with diverse expertise (e.g., trials, pharmacology, psychology, biomarkers) to conduct a systematic review and meta-analyses of pharmacological, behavioural, and nutraceutical clinical trial outcomes in people with ME/CFS, with a particular focus on the use of objective and subjective outcome measures.

Methods
The review included all peer-reviewed studies with human participants diagnosed with ME/CFS that report pre- and post-intervention quantitative fatigue-related outcomes (e.g., Fatigue Severity Scale, Chalder Fatigue Scale, Multidimensional Fatigue Inventory, Visual Analogue Scale for Fatigue, Checklist Individual Strength), published in English. Data extraction is ongoing, capturing intervention details, diagnostic criteria, and outcome metrics including any biomarker assessment. Two reviewers will independently assess study quality using the Cochrane risk of bias tools to assess clinical trials. Similar interventions will be meta-analysed to yield overall effect sizes as odds ratios for dichotomous outcomes and standard mean differences for continuous outcomes.

Results
Following removal of duplicates, 837 abstracts were screened, followed by full-text assessment by three reviewers, resulting in 182 eligible studies to be included. Data extracted to date revealed the diverse interventions trialled, including pharmacological agents (e.g., hydrocortisone, moclobemide, L-Carnitine), behavioural therapies (e.g., graded exercise therapy, cognitive behavioural therapy), “alternative” approaches (e.g., acupuncture, Qigong, Tuina), dietary supplements (e.g., ginseng), homeopathic remedies, and novel procedures such as RNA-based treatments and autohemotherapy. Despite a wide variety of outcome measures tested (e.g., fatigue severity, physical function, psychological wellbeing, cognitive profile and biological markers), most treatments appear ineffective in alleviating symptoms of ME/CFS.

Conclusions
By synthesising a large collection of independent studies, this review explores the biological and psychological foundations of ME/CFS treatments and highlights evolving intervention trends. Earlier trials (1980s–early 2000s) focused mostly on pharmacological approaches such as immunoglobulins, steroids, and supplements, which yielded limited success. Since the early 2000s, the focus has shifted toward behavioural therapies, with cognitive behavioural therapy and graded exercise therapy showing some improvements. However, these therapies are met with low

acceptance and tolerability by people with lived experience. Cognitive outcomes remain underexplored in the literature, highlighting an important gap for future research.

P_23b Assessing the utility of zuranolone to modify alcohol-related behaviours

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Background
Alcohol is the leading cause of death worldwide among people aged 15–49, with rates of alcohol use disorder (AUD) rising, particularly in women. Neurosteroids, synthesised in the brain from sex hormones or cholesterol, are promising candidates for neuropsychiatric treatment. Zuranolone, a synthetic form of the neurosteroid allopregnanolone, was recently FDA-approved for postpartum depression, and previous studies have shown allopregnanolone reduces alcohol consumption. Here, we investigated zuranolone's effects on alcohol-related behaviours in a rodent model to determine whether it holds an opportunity for drug repurposing.

Methods
Male and female C57BL/6J mice underwent a drinking-in-the-dark (DID) binge drinking protocol (n=12/sex), and locomotor behaviour assessed in alcohol-naive cohorts (n=8/sex). Mice received zuranolone (0–3 mg/kg, i.p.) 30 minutes or allopregnanolone (0–50 mg/kg, i.p.) immediately before testing; allopregnanolone serving as a positive control. An additional cohort (n=20/sex) received daily oral zuranolone (3 mg/kg) or vehicle gelatin pellet for 14 days during the DID protocol. Data were analysed using two-way repeated- or mixed-measures ANOVA with Bonferroni post-hoc analysis where appropriate.

Results
High-dose allopregnanolone (24 mg/kg) moderately reduced alcohol consumption in male ($p0.05$) mice, whereas zuranolone had no effect in either sex ($p>0.05$). Repeated oral zuranolone administration transiently reduced binge drinking in males during the first week (main effect treatment x time, $p0.05$). Allopregnanolone (3–24 mg/kg) produced a dose-dependent increase (main effect treatment, $p<0.05$) in locomotor activity but significantly suppressed activity at the highest dose (50 mg/kg) in both sexes. In contrast to allopregnanolone, high-dose zuranolone (3 mg/kg) produced significant hyperactivity in both sexes ($p<0.01$), with females eliciting an attenuated response.

Conclusions
Zuranolone demonstrates sex-dependent effects on binge drinking and locomotion. Despite its structural similarity to endogenous allopregnanolone, zuranolone elicited distinct behavioural responses, suggesting a unique pharmacological profile warranting further investigation. However, no results suggest zuranolone should be perused for repurposing in AUD. Further, these findings underscore the importance of considering sex as a biological variable in developing targeted effective treatments for AUD.

P_54b Bidirectional modulatory influences of positive and negative feedback on habenula function

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Background
The habenula (Hb) is a highly conserved epithalamic region that is hyperactive in those with depression. It has a key hypothesised role in the encoding of negative reward prediction error and has been shown in animal studies to be bidirectionally modulated by aversive vs appetitive stimuli: the former increasing and the latter decreasing its activity. Despite growing interest in human Hb function, there have been few neuroimaging studies that have addressed the 'bidirectional modulation' hypothesis. This study aimed to better understand Hb function in healthy individuals with hopes to apply this knowledge to a clinical sample in the future.

Methods
Sixty-six healthy volunteers (mean age ± SD = 29.4 ± 9.1; 37 females) were scanned using a Siemens 7-Tesla research scanner. Participants completed two tasks that were designed to model Hb responses to negative and positive feedback: a reversal learning task and a prediction uncertainty task. We used conventional fMRI general linear models to assess whether both tasks evoked common Hb activation (PFDR <0.05) when directly comparing negative and positive feedback conditions. We used a validated Hb anatomical parcellation to confirm the specific nature of Hb activity changes in response to the feedback types as compared to non-task (resting) baseline.

Results
For both tasks, we observed robust activation of the Hb and extended regions (including the ventral tegmental area, dorsal raphe nucleus, anterior cingulate cortex and medial prefrontal cortex) when comparing the negative vs positive feedback conditions.
Our post-hoc 'region of interest' analyses indicated that these differential effects for both tasks were driven by greater Hb responses to the negative feedback condition. The Hb was also positively modulated during positive feedback.

Conclusions
Supporting prevailing evidence from animal studies, we observed bidirectional responses of the Hb to both negative and positive feedback. Consistent with these models, the Hb was more prominently engaged during negative feedback. How these dynamics influence the Hb's broader circuity function will be important to clarify in ongoing work especially in reference to clinical populations.

P_4b Grey matter changes observed up to two years prior to the onset of non-suicidal self-injury in male and female youths

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Background
Non-suicidal self-injury (NSSI), the deliberate destruction of one's own body tissue without suicidal intent, has an 18% lifetime prevalence and is a risk factor for future suicidality. We leveraged data from the longitudinal Adolescent Brain Cognitive DevelopmentSM Study to identify gray matter abnormalities in youths who between baseline (mean age=10) and Year 2 engaged in NSSI for the first time (premorbid NSSI; pNSSI).

Methods
Participants were 275 youths with pNSSI (63% female), T1 MRI and puberty data and 275 controls individually matched on 30 demographic and clinical variables. Two-group comparisons were performed separately for males and females. Covariates were puberty stage, intracranial volume and MRI manufacturer. Subcortical analysis was performed using FreeSurfer-initiated large deformation diffeomorphic metric mapping in N=548 (n=344 female, n=204 male). Cortical thickness (CT) analysis was performed using permutation analysis of linear models (n=10,000) in N=470 (n=290 female, n=180 male).

Results
In females, lower CT in the pNSSI group compared to controls was present in bilateral anterior cingulate, left lateral orbitofrontal and auditory association cortex, and right ventromedial prefrontal cortex. Greater CT in females with pNSSI was seen in left visual cortex, right auditory cortex, piriform cortex, hippocampus and entorhinal cortex. Subcortically there was inward deformation in the pNSSI group compared to controls in the bilateral caudate nucleus accumbens, putamen and thalamus.
For males, the pNSSI group showed greater CT than controls in left premotor, primary somatosensory and parietal cortex, and right retrosplenial cortex, precuneus, inferior parietal cortex and entorhinal cortex.

Conclusions
Few studies of NSSI include males, which is problematic as we demonstrated males and females show different patterns of group differences. Females showed the expected reduced gray matter in regions involved in cognitive control and reward valuation in the pNSSI group, however males did not. Both males and females with pNSSI showed greater cortical thickness compared to controls in the entorhinal cortex, an area that is beginning to emerge as important for NSSI.Our study contributes and increased neurobiological understanding of NSSI, which is needed to inform treatments.

P_51b Longitudinal hippocampal functional connectivity changes and symptom development in people at psychosis risk

Presenting Author: Lukas Roell

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Background
The hippocampus is suggested to be the epicenter of gray matter volume decline in psychosis, while functional dysconnectivity of the hippocampal lesion network plays a fundamental role in several symptom domains. Hence, we examined how longitudinal changes in hippocampal functional connectivity are intertwined with the early symptom development in individuals at risk for psychosis, aiming at exploring the hippocampus as a potential treatment target for novel non-invasive deep brain stimulation techniques such as focused ultrasound.

Methods
We used data from the North American Prodrome Longitudinal Study (NAPLS 3) - a large-scale longitudinal observational study in young individuals at risk for psychosis conducted at multiple sites in the US. We included comprehensive clinical and resting-state fMRI data from more than 500 subjects acquired at five different measurement timepoints. Using structural equation modelling and machine learning approaches, we studied the interrelations between hippocampal functional connectivity changes and symptom development at an early psychosis stage.

Results
Our results demonstrate that increases of functional connectivity within the hippocampus are linked to improvements in negative symptom severity in early psychosis and also predict the outcome of early negative symptoms.

Conclusions
Based on these findings, we propose that increasing functional connectivity within the hippocampus through focused ultrasound stimulation may represent a promising early treatment target to prevent the development of negative symptoms in people at risk for psychosis.

P_50b Elucidating RNA isoform expression in the 2-day old human prefrontal cortex at single-cell resolution

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Background
Most neuropsychiatric disorders have a developmental origin and many risk genes have been identified. In addition, processes like alternative splicing enable almost all genes to produce multiple mRNA products (isoforms), some of which are specifically linked to neuropsychiatric disorder risk. However, our knowledge of RNA isoforms during human neurodevelopment and the cell-type expression profiles of risk isoforms are limited. Addressing this fundamental knowledge gap would deepen our understanding of how risk gene isoforms can either facilitate healthy brain development or contribute to neuropsychiatric disorders.

Methods
As an initial step toward characterising RNA isoform expression trajectories across human brain development, we performed long-read single-nuclei RNA-sequencing (LR-snRNA-seq) on 9,988 cells from the pre-frontal cortex (PFC) of a 2-day-old female post-mortem sample. Single nuclei were captured using the 10x Chromium Next GEM Single Cell 3' kit (v3.1) and sequenced using Oxford Nanopore long-read sequencing (ONT). Data was analysed using FLAMES, our custom LR-snRNA-seq bioinformatics pipeline, and Seurat. These tools enabled us to uncover trends in isoform expression as well as addressing broader questions, such as which cell types have greater RNA isoform diversity.

Results
LR-snRNA-seq identified 19 major cell types, with three broad groups including excitatory neurons (e.g. layer 2-3-CUX2 cells), GABAergic interneurons (e.g. ID2+ cells) and non-neuronal cells (e.g. oligodendrocytes and microglia). We detected 38,825 expressed genes and 141,111 isoforms (~3.6 isoforms per gene), including 156 novel isoforms. Isoform expression varied greatly between cell-types, 38% of isoforms were differentially expressed between cell-types, including 75 novel isoforms, whilst excitatory neurons expressed the highest numbers of both known and novel isoforms. We also found neuropsychiatric risk genes typically expressed many mRNA isoforms, including ANK2 and KMT2C.

Conclusions
This is the first study of RNA isoforms in the post-natal developing human brain at the single-cell level. Using long-read ONT sequencing, we have identified the expected cell types and characterised the expression profiles of hundreds of thousands of RNA isoforms within individual cells and cell-types. We have confirmed neuropsychiatric risk genes have particularly complex RNA isoform profiles and elucidated isoforms of high biological interest. Future expansion of this study across a wider developmental window will help bridge the knowledge gap of how RNA diversity and RNA isoforms contribute to neurological health and neuropsychiatric disease.

P_48b Brain-Derived Neurotrophic Factor Val66met is associated with sex-specific impairment of cognitive flexibility under stress: a reversal learning search strategy analysis in a rat model

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Background
Cognitive flexibility is a core executive function vital for adaptation and adjustment to new information. The brain-derived neurotrophic factor (BDNF) single nucleotide polymorphism, val66met, has been suggested to modulate cognitive flexibility but it remains unclear how confounding variables such as stress and sex influence this relationship. Environmental enrichment (EE) may protect against stress-induced effects. The aim of this study was to test whether BDNF val66met alters reversal learning, a key component of cognitive flexibility, when tested under stressful water maze conditions.

Methods
We used a Sprague Dawley val66met rat model where pregnant val/met dams were moved to either low or high EE environments. Dams and offspring stayed in these environments until weaning, after which the offspring was moved to standard, moderate enrichment housing. Adult male and female val/val, val/met and met/met offspring then underwent a water maze reversal learning protocol.

Results
All groups rapidly learned the new location of the platform. Mediation analysis showed the relationship between val66met and cognitive flexibility was mediated by differential use of spatial strategies. Sequential clustering analysis demonstrated that val66met interacted with sex to predict cognitive flexibility performance with lower flexibility in met/met males and val/met females compared to other genotypes. EE was not a strong promotor of cognitive flexibility. Water maze testing increased corticosterone levels, confirming the stressful nature of the test.

Conclusions
This study demonstrates the importance of considering stress and sex when investigating the role of BDNF val66met in cognitive flexibility.

P_3b Pinpointing Schizophrenia Mechanisms with Isoform-Resolved Analyses in the Developing Human Brain

Presenting Author: Mitchell Hodgson

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Mike Clark, *The University of Melbourne*

Background
Most genetic studies of neuropsychiatric disorders focus solely on disease risk at the gene level. However, nearly all genes expressed in the brain routinely produce multiple transcript isoforms. Recent large-scale analyses have shown that examining the effect of disease variants on isoforms doubled the detection of risk signals, suggesting isoforms are often the targets of disease variants. Despite this progress, we have limited understanding of which isoforms cause disease and how they do so, which hampers efforts to uncover disease mechanisms and develop therapies. We aimed to address this gap by identifying and characterising disease-associated isoforms in neuropsychiatric disorders.

Methods
A systematic search of PubMed and Scopus (screening 456 titles) identified two isoform-aware whole-transcriptome resources from the developing human brain. To find high-confidence disease-linked isoforms, we created a database that captured GWAS traits, prenatal timepoints (trimester), effect size, association method, and cross-study replication count. As schizophrenia GWAS provides the greatest statistical power, a larger number of high-confidence isoform associations (n=2373) were identified for this trait, which we focused on in our cross-study analysis. We then conducted detailed analyses of the structural, molecular, functional, evolutionary, and expression features of the highest-confidence isoforms with significant effect sizes.

Results
We identified 57 genes comprising 73 high-confidence risk isoforms that were corroborated across different methods and/or studies. Fine-mapping further refined the signal for 10 of these isoforms to a single, high-confidence variant that appears to influence both their expression and schizophrenia risk—for example, STAB1-205 (rs7612511), ABCB9-215 (rs1716183), and YWHAE-206 (rs9905529). These implicated isoforms are predicted to feature distinct proteoforms for STAB1, YWHAE, and an alternative 5′ UTR in ABCB9. Notably, AlphaFold modelling of the YWHAE risk isoform predicts the loss of 6 of 9 α-helices, disrupting the canonical 14-3-3 dimer interface—consistent with a loss of function.

Conclusions
By curating 2,373 prenatal schizophrenia isoform–trait associations and prioritising those replicated across methods and studies, we nominate 73 high-confidence risk isoforms spanning 57 genes. Nineteen genes converge on a single risk isoform, and fine-mapping suggests likely causal variants for 10 of these, linking specific transcriptomic changes to predicted functional effects (e.g., structural disruption of the 14-3-3ε dimer interface in YWHAE-206). These findings provide precise, testable targets for experimental follow-up and demonstrate that isoform-resolved analyses reveal actionable biology often missed by gene-level approaches.

P_7b Role of oestradiol and progesterone variability in brain structure and mental health in adolescent females

Presenting Author: Muskan Khetan

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Background
Adolescent females are particularly vulnerable to mental health symptoms and emotional dysregulation. During puberty, oestradiol (E2) and progesterone (P4) begin to cycle, but show high variability pre-menarche and in the early years post-menarche, similar to other transitional life stages. Although hormone variability during postpartum and perimenopause has been linked to brain structure and mental health symptoms in adults, little is known about how hormone variability affects the adolescent brain. We examined how within-individual variability in E2 and P4 relates to brain structure and mental health/emotion dysregulation, to better understand risk for mood and mental health disorders in adolescent females.

Methods
Participants (N = 147 females, aged 11–16) were from the cross-sectional Puberty and NeuroDevelopment in Adolescents (PANDA) study. Salivary E2/P4 were assayed weekly for one month, and variability was calculated as the within-subject standard deviation. MRI was conducted on the day of the final saliva sample. Depressive and anxiety symptoms, and emotional dysregulation were assessed using self-report questionnaires. Externalising symptoms were parent-reported. Cortical thickness and surface area, and subcortical volume, were estimated using FreeSurfer v7.3.2. Regression and mediation analyses tested associations between E2/P4 variability, brain structure and mental health/emotion dysregulation. All models included age, menarche, race, and income-to-needs ratio.

Results
There was a significant negative association between P4 variability and left thalamus volume (Cohen's d = -0.26, pFDR = 0.031), indicating that greater P4 variability was linked to smaller thalamus volume. In addition, we found a negative association between E2 variability and anxiety (Cohen's d = -0.170; pFDR = 0.043) and depressive symptoms (Cohen's d = -0.179; pFDR = 0.036) and emotion dysregulation (Cohen's d = -0.179; pFDR = 0.036). These associations were stronger among pre-menarche participants, suggesting that greater E2 fluctuations may relate to reduced depression, anxiety, and emotion dysregulation, particularly in earlier stages of puberty.

Conclusions
Findings indicate that greater monthly variation in P4 may influence volume in the left thalamus—a region involved in emotion and cognition and rich in P4 receptors. Additionally, increased monthly variation in E2 was linked to reduced depressive and anxiety symptoms and emotion dysregulation, especially among pre-menarche girls. These findings suggest that early adolescent hormone variability may shape brain and behaviour in ways distinct from adult transitions like postpartum or perimenopause. Our study is among the few exploring hormone variability during adolescence, highlighting the need for future longitudinal work in larger samples to better understand these developmental processes.

P_9b Towards Precision Psychiatry: Combining Clinical Complexity and Brain Connectivity for TMS Outcome Prediction

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Background
Clinical factors and brain connectivity are well-established predictors of transcranial magnetic stimulation (TMS) treatment outcomes. Increasing evidence suggests that these two factors may interact to influence antidepressant response; however, they are seldom examined concurrently in past TMS prediction studies.

Methods
In a large, combined sample of 96 adults with treatment-resistant depression who received either optimised connectivity-guided (Brisbane cohort; n=59) or conventional (Melbourne cohort; n=37) TMS treatment, we evaluated the predictive performance of models based on: 1) whole-brain functional connectivity maps of symptom improvement (i.e., R-map), 2) clinical complexity factors, and 3) the combination of both, controlling for the effect of site.

Results
The integrated model combining clinical complexity and functional connectivity characteristics yielded the best prediction accuracy with the highest robustness against inter-site variability, outperforming the univariate models based on clinical or functional connectivity factors alone. Notably, total illness duration (r=.21; p=.036) and prior treatment failures (r=.22; p=.035) emerged as the only significant factors driving the superior outcome prediction, overall pointing towards treatment refractoriness as a key clinical determinant of TMS outcome. Further, whole-brain voxel-wise analysis revealed a significant interaction effect between symptom improvement and clinical complexity (FWE-corrected p =.037), with the stringent inclusion of site, symptom improvement, and clinical complexity as covariates. Specifically, negative connectivity between the stimulation site and select regions including the subgenual anterior cingulate cortex (sgACC), caudate, and ventromedial prefrontal cortex (vmPFC) was associated with greater symptom improvement, selective to those with high clinical complexity (r =-.40; p =.005).

Conclusions
Together, these findings underscore the prognostic significance of integrating clinical and neurobiological factors in TMS outcome prediction. We also identify a connectivity marker of symptom improvement specific to high clinical complexity. Expansion of targeting beyond the canonical DLPFC-sgACC circuit to include the vmPFC and caudate may enhance treatment response in complex presentations via potentially more targeted engagement of the fronto-striatal-limbic circuitry.

P_22b Paternal immune activation via the viral mimic poly I:C leads to epigenetic changes in sperm and results in behavioural and brain changes in offspring

Presenting Author: Nicholas van de Garde

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Background
The paternal pre-conception environment has been shown to impact offspring behaviour and physiology in models of stress, diet, infection and other types of environmental exposures. These altered offspring phenotypes implicate the sperm epigenome as the likely signal carrying these heritable changes. Many pre-clinical models of such paternal pre-conception environmental exposures demonstrate altered affective behavioural phenotypes in offspring, relevant to psychiatric disorders. The mechanisms underlying how environmental exposures lead to epigenetic germ-line changes are not fully characterised, particularly in the context of infection and immune activation.

Methods
8-week-old male C57BL/6J mice received a 12mg/kg dose of the double-stranded RNA mimic poly I:C, leading to a non-pathogenic viral-like innate immune response, or vehicle control. After four weeks, mice were mated with age-matched naïve females. Immunohistochemistry was performed on post-natal day 21 and 9-week-old offspring, with a parallel cohort being assessed from 9 weeks of ages in a battery of behavioural tests to examine affective, social and cognitive behaviours. The paternal sperm short non-coding RNA (sncRNA) profile was assessed to explore alterations in the epigenome that may carry the signal leading to offspring phenotypic changes.

Results
Paternal administration of poly I:C resulted in a delayed time to interact with a stranger mouse without impacting other social parameters in the 3-chamber social interaction test, and a male specific reduction and delay in fear conditioning and reduced striatum mass. Offspring additionally showed thinning of the somatosensory cortex and corpus callosum as per histology. These offspring behaviour and neurological changes were correlated with altered paternal sncRNA cargo, including the upregulated tRNA fragment Glu-CTC-1 and downregulated expression of 6 piRNA clusters.

Conclusions
These results implicate the paternal immune system as one potential driver of epigenetic inheritance by altering the paternal sncRNA cargo that is delivered into the oocyte at conception. The altered sncRNA cargo may drive developmental changes, resulting in phenotypic changes in behaviour and brain parameters in adult offspring, including a male-specific dysregulation of fear conditioning and striatum mass reduction. These results could have broad implications for the intergenerational impacts of viral infections on public health, with particular relevance to mental health.

P_12b Circular RNA expression signatures in Alzheimer's disease highlights dysregulated molecular mechanisms and disease progression

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Background
Circular RNAs (circRNAs) are covalently closed, non-coding RNAs increasingly recognised as regulators of gene expression in neurodegenerative disorders, including Alzheimer's disease (AD). Their stability, neural tissue specificity, and regulatory potential make them attractive candidates for biomarker development and therapeutic targeting. Yet, the landscape of circRNA dysregulation in AD, and the prodromal stage of mild cognitive impairment (MCI), remains poorly defined. Human olfactory neurosphere-derived stem (ONS) cells, obtained from patient olfactory mucosa, provide a physiologically relevant and accessible model for studying molecular changes in neurological disease. Here, we investigate circRNA expression patterns in AD and MCI using patient-derived ONS cells.

Methods
We analysed total RNA from 18 ONS cultures representing AD (n=6), MCI (n=6), and healthy controls (n=6). Libraries were generated using ribo-depleted RNA-sequencing and read output was processed through a custom circRNA detection and quantification pipeline optimised for backsplice junction identification. Differential expression analyses were conducted between each disease group and controls, followed by gene ontology and pathway analysis. To assess reproducibility, we compared our results with circRNA datasets from 18 independent previously published datasets spanning postmortem brain and plasma. Cross dataset concordance was evaluated at both circRNA isoform and parent gene levels to identify robust AD associated circRNAs.

Results
We detected 1,584 high confidence circRNAs, and an average of 20 significantly dysregulated in each ONS cell comparison group. CircPICALM and circANKIB1 were consistently upregulated in both AD and MCI. Functional analysis revealed associations with AD-relevant processes, including tau protein binding, glycoprotein metabolism, and endoplasmic reticulum stress. Cross validation with external datasets identified 49 overlapping circRNA-producing genes, encompassing 28 specific isoforms. Several originated from genes implicated in AD pathogenesis, including PICALM, MAN1A2, and ZNF292. Notably, circPICALM demonstrated consistent upregulation across datasets and sample types, reinforcing its potential as a robust biomarker candidate for both early and established stages of AD.

Conclusions
This study provides a comprehensive circRNA expression profile in AD and MCI using patient-derived ONS cells, validating key findings across multiple independent datasets. The consistent dysregulation of circRNAs highlight potential biomarker panels and therapeutic targets in AD. Functional analyses link dysregulated circRNAs to core pathogenic pathways, including protein aggregation, altered glycosylation, and cellular stress responses. Our findings establish ONS cells as a valuable model for mechanistic circRNA studies in neurodegeneration and support the broader application of circRNA profiling for diagnostic and therapeutic development in AD and related disorders.

P_24b Neuroinflammation in the nucleus accumbens core impairs sign-tracking but maintains performance of value-modulated attentional capture

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Background
Neuroinflammation in the nucleus accumbens (NAC) core has been linked to heightened sensitivity to drug-related cues, an effect that can precede relapse susceptibility in conditions such as substance-use disorder. Recent findings from our laboratory indicate that neuroinflammation in the NAC core of rats similarly amplifies sensitivity to food-associated cues. Here, I investigated whether lipopolysaccharide (LPS)-induced neuroinflammation in the NAC core altered cue sensitivity by affecting attentional processes, using value-modulated attentional capture (VMAC), a task reliably associated with compulsive and compulsive-like actions in humans and recently back-translated to rats.

Methods
Male and female Long-Evans rats received bilateral infusions of LPS or saline into the NAC core. They were then trained to sign-track towards a left or right lever, associated with the delivery of a low- (1 pellet) or high-value (3 pellets) reward (counterbalanced). Next, rats were trained to nose-poke an illuminated port on the opposite side of the operant chamber for a single pellet. During the VMAC test, rats were required to continue correctly nose-poking in the presence of the high- or low-value lever distractor.

Results
Sham controls displayed the typical pattern of responding, making more ‘active omissions’ (i.e. pressing the lever) during the high- relative to the low-value distractor trials. By contrast, LPS in the NAC core prevented rats from forming the sign-tracking response such that these rats did not differentially lever press on either trial type. Nevertheless, LPS-treated rats exhibited a VMAC effect assessed via an alternate measure, making fewer correct nose-pokes during high- relative to low-value trials.

Conclusions
Together, these results suggest that mimicking this neuroinflammatory feature of compulsivity maintains the learning of attentional bias towards high-value cues, despite preventing cue-approach learning. Additionally, these results demonstrate that VMAC performance and sign-tracking behaviours are dissociable. That is, the VMAC effect, which is driven by attention, is independent of lever pressing. This supports inconsistencies found in human sign-tracking studies and supports the finding that VMAC is more reliably associated with compulsivity compared to classic sign-tracking behaviours.

P_5b Paternal cytokine administration alters sperm small non-coding RNAs and offspring physiology and behaviour in mice

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Background
Paternal pre-conceptual exposure to parasitic, bacterial, and viral infections are all known to impact offspring phenotype via sperm epigenetic changes. Even in the absence of infection, paternal immune activation (PIA) can alter offspring behaviour and physiology through changes to sperm small RNAs. While this implicates the immune response, the specific component responsible for this phenomenon remains unknown. Cytokines offer a potential mechanism as they are a shared factor across different types of immune activation. As such, we investigated whether key pro-inflammatory cytokines elevated during PIA could recapitulate changes to offspring phenotype.

Methods
C57BL/6J mice were injected with either TNF-α or IL-1β; or saline at 8-weeks old. Following one spermatogenesis cycle (4-weeks), F0 male mice (fathers) were mated with age matched naïve female mice to produce F1 mice (offspring). F1 mice underwent a series of behavioural tests to assess anxiety-like, depression-like, and cognitive behavioural changes. Paternal sperm was collected following breeding and analysed to identify differentially expressed small RNAs.

Results
Offspring from cytokine treated fathers showed increased anxiety-like behaviour in the elevated plus maze and lost significantly more bodyweight following a 24-hour fast during the novelty suppressed feeding test. Despite no difference in whole brain weight, hypothalamus weights for cytokine offspring were significantly less than controls. Analysis of paternal sperm small non-coding RNA showed that miRNA, tsRNA, and piRNA clusters were significantly downregulated in response to IL-1β, while paternal TNF-α significantly downregulated a single piRNA cluster.

Conclusions
These findings suggest that paternal cytokine treatment with IL-1β and TNF-α have differential effects on offspring. Interestingly, offspring phenotype and sperm epigenetics are altered in a way which partially recapitulates viral-like PIA via Poly I:C. This study provides the first evidence of how elevated paternal cytokine levels can alter offspring phenotype. This adds to our understanding of paternal immune activation as an important pre-conceptual factor for offspring health and risk of neuropsychiatric disorders.

P_18b Connectivity alterations underpinning negative self-cognition processing in binge eating

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Background
Disordered binge eating is often perpetuated by the emotional distress caused by entrenched negative cognitions about the self, food, and body image. Psychotherapy for binge eating therefore aims to identify and restructure these negative cognitions. Despite its clinical significance, the neural mechanisms supporting negative cognition processing and how this may be altered in binge eating remain unexplored.

Methods
Combining ultra-high field 7-Tesla fMRI and a negative cognition paradigm, we mapped and compared whole-brain connectivity during the repetition and cognitive restructuring of negative self- and binge eating-related beliefs in 65 young adults experiencing disordered binge eating (Mean age=27.14; 86.15% female) and 76 healthy control participants (Mean age=26.86; 77.03% female). General psychophysiological interaction (gPPI) analysis was used to estimate the pair-wise functional connectivity between 214 cortical and subcortical regions-of-interest during the repeating versus challenging of negative cognitions (pFDR < .05). LASSO logistic regression with 10-fold cross-validation was then implemented to select the connectivity parameters predictive of binge eating group membership.

Results
The winning LASSO model (λ = 0.076; accuracy = 0.80, AUC = 0.92) identified 23 connectivity parameters that were predictive of binge eating. Most prominently, the binge eating group was characterised by increased functional connectivity between prefrontal nodes of the dorsal attention, cingulo-opercular and salience networks (β = 0.56-1.01) during the repeating of negative cognitions compared to restructuring, as well as decreased connectivity between the superior frontal gyrus and the putamen (β = -0.36).

Conclusions
Increased attentional and salience network engagement during the repeating of negative self-beliefs may contribute to maladaptive thinking patterns in people experiencing binge eating. Whereas the reduced communication between the prefrontal cortex and putamen may underlie impaired integration of goal-directed and habit-related signals, potentially hindering the shift away from negative cognitions. These findings provide novel insights into potential neural vulnerabilities of persistent negative cognitions that reinforce disordered binge eating, thereby expanding neurobiological models of binge eating to consider complex, higher-order mental processes.

P_8b Mendelian randomisation and colocalisation reveal pleiotropic effects of CD40/SLC12A5 locus on CD40 protein, depression, and immune disease

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Background
Depression is a leading cause of global disease burden, yet the biological mechanisms contributing to the disorder remain unclear. Inflammatory pathways have been implicated; however, the causal roles of specific immune proteins and variants are not well established. Determining causality is challenging, and while genome-wide association studies have linked immune-related loci to depression, identifying precise effector genes remains difficult. Mendelian randomisation (MR) can help elucidate causal effects by using genetic variants as instrumental variables and integrating functional data. Here, we apply MR methods to leverage large-scale GWAS and proteomic data to disentangle the relationship between immune factors and depression.

Methods
We conducted a two-sample Mendelian randomisation (MR) analysis using generalised summary Mendelian randomisation (GSMR) to investigate causal relationships between 91 immune-related plasma proteins and depression. Genetic instruments were derived from a large-scale protein quantitative trait locus (pQTL) meta-analysis and applied to a genome-wide association study (GWAS) of depression (n = 294,322 cases, 741,438 controls). Primary findings were validated via an independent replication cohort, and sensitivity analyses using alternative MR methods. Pairwise and multi-trait colocalisation analyses assessed potential confounding by linkage disequilibrium (LD) and shared genetic architecture. A phenome-wide association study (PheWAS) explored downstream biological pathways associated with identified variants.

Results
We identified a robust association between CD40 protein levels and depression (OR: 0.95, 95% CI: 0.94 - 0.97, $p = 1.71 \times 10^{-11}$), driven primarily by cis-acting variants. Pairwise colocalisation analyses indicated distinct – though not independent – lead variants for CD40 protein and depression, suggesting linkage disequilibrium was driving the effect. eQTL analyses prioritised SLC12A5 as the likely effector gene for depression risk at this locus. A phenome-scan demonstrated that the CD40 protein lead variant was predominantly associated with inflammatory disorders, whereas the depression lead variant showed stronger links to psychiatric conditions, revealing distinct biological pathways at this locus.

Conclusions
Our findings demonstrate pleiotropic effects at the CD40/SLC12A5 locus and emphasise the importance of combining mendelian randomisation with colocalisation analyses to disentangle shared genetic effects at loci with complex genetic architecture. While our results do not support a causal role for plasma CD40 protein levels in depression, SLC12A5-mediated effects may contribute to its pathophysiology, likely acting through brain-specific mechanisms. These findings refine the pathophysiological model of depression and highlight the relevance of immune-brain interactions. SLC12A5 emerges as a promising effector gene and priority target for future functional and multi-omic studies to advance mechanistic insight and therapeutic development.

P_64b Acute stress regulates AgRP neuronal activity

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Background
Agouti-related peptide (AgRP) neurons in the hypothalamus sense hunger and promote feeding, however when food is unavailable, AgRP neurons promote adaptive behaviours by reducing anxiety and increasing food-seeking. Thus, AgRP neurons respond to environmental stimuli that convey information relevant to food seeking and food detection. But, when foraging, food is not the only potential environmental stimulus to be encountered; other such stimuli include stressors signalling risk, threat or danger. This study aimed to investigate the effects of stressors on AgRP neural activity and whether optogenetic control of AgRP neurons can simulate the stressful event.

Methods
To do this, we combined fibre photometry with various stress paradigms. We recorded AgRP neuronal responses using GCaMP7s in fed and fasted mice during restraint stress, looming object and elevated zero maze.

Results
In both, fed and fasted mice, AgRP activity dropped when exposed to stress but less compared to food. Our experiments show that AgRP neurons are transiently inhibited by acute stressors but rebound immediately once the stressful event has passed and can pinpoint GABAergic neurons in the DMH providing this inhibitory input. With this insight, we demonstrated that mice learn to avoid the Y-maze arm paired with optogenetically suppressed AgRP activity.

Conclusions
Together our results suggest that a transient decrease in AgRP neural activity encodes a broader “stop foraging” signal that has differential outcomes for food consumption based on the presence of stressful stimuli.

P_6b Differential striatal gene expression profiles underlies the propensity for depression-like behaviour in a mouse model of vertical sleeve gastrectomy

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Background
Bariatric surgery is the most effective long-term obesity treatment, driven by gut-brain axis changes that reduce appetite and improve glycaemic control. However, a patient subset experiences adverse mental health outcomes post-surgery, like depression and suicidality. While clinical studies are ongoing, research exploring how gut-brain axis alterations may mechanistically contribute to these outcomes is lacking. Therefore, this study used a mouse model of vertical sleeve gastrectomy (VSG) to investigate individual differences in depressive-like behaviour following surgery. We hypothesized that while VSG improves metabolic outcomes, a subset would exhibit increased susceptibility to depressive-like behaviour and distinct transcriptional changes in reward-related brain regions.

Methods
Male and female C57BL/6 mice (n=57) were fed a high-fat, high-sugar diet (11 weeks) before undergoing VSG or sham surgery. Depression-like behaviour was assessed both pre- and post-surgery. VSG mice were stratified post hoc into tertiles based on behavioural changes; the top and bottom tertiles were classified as ‘depression-susceptible’ and ‘depression-resilient’. From these subgroups, RNA was extracted from tissue punches of the dorsal striatum and nucleus accumbens, key components of brain circuitry known to be dysregulated in major depressive disorder. Bulk RNA-sequencing was performed on these samples to identify differential gene expression patterns associated with post-surgical vulnerability to depression-like behaviour.

Results
VSG resulted in significant and sustained weight loss and reduced food intake compared to sham controls. Differential gene expression analysis revealed downregulated neuroinflammation and tight junction-related genes. Further gene set enrichment analysis shows depression-susceptible VSG mice display an upregulation of TNF-α-NF-κB and PI3K-AKT/mTOR pathways. Additional chow-diet cohort data and further RNA-seq validation are currently ongoing, and preliminary findings will be presented.

Conclusions
These findings, although preliminary, suggest that individual variability in depressive outcomes following bariatric surgery may be underpinned by differential activation of inflammatory and metabolic signalling pathways in key brain regions. This study provides foundational insight into the neurobiological mechanisms underlying post-surgical affective vulnerability and may inform future clinical screening and intervention strategies in bariatric populations.

P_47b Characterising Sleep and Circadian Rhythm Phenotypes in Young People at Clinical High Risk for Psychosis: A Latent Profile Analysis in the AMPSCZ Cohort

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Background
Sleep-circadian rhythm (SCR) disturbances frequently precede psychosis onset and may serve as early risk markers in clinical high-risk (CHR) youth. However, to date, most studies have relied on subjective sleep complaints and 'group-average' approaches that may obscure the heterogeneity of SCR patterns and symptom trajectories characteristic of CHR youth. Latent Profile Analysis (LPA) offers an individual-centered approach to identify distinct subgroups based on SCR characteristics. Integrating both subjective and actigraphy-derived sleep-wake behaviour, this study aims to examine whether distinct SCR profiles exist in CHR youth and their associations with clinical outcomes.

Methods
We conducted a preliminary analysis using Latent Profile Analysis (LPA) on data from the Accelerating Medicines Partnership Schizophrenia (AMP SCZ) study. The sample included clinical high-risk (CHR) young people aged 12-30 years (n=508) and healthy controls (HC; n=64). Analysis utilised baseline sleep quality questionnaire and actigraphic measures including sleep duration, efficiency, timing, regularity, interdaily stability, intradaily variability, and relative amplitude. Multiple-group LPA evaluated measurement invariance across CHR and HC groups.

Results
Three distinct sleep-circadian rhythm classes were identified: Class 1 (13.6%): "Severely Disrupted Sleepers" exhibited poorest sleep quality, shortest duration, lowest efficiency, and most circadian disruptions; Class 2 (42.1%): "Average Sleepers" showed typical patterns; Class 3 (44.2%): "Good Sleepers" demonstrated morning chronotype with least disruption. The 3-class structure demonstrated measurement invariance across groups. HC were predominantly Average or Good Sleepers, while CHR showed greater representation in Severely Disrupted Sleepers. Functional outcomes varied by class: Average and Good Sleepers had higher functioning scores compared to Severely Disrupted Sleepers, suggesting severe sleep-circadian disruption associates with poorer functional outcomes, particularly in CHR youth.

Conclusions
These preliminary findings identify distinct SCR profiles across the sample of CHR and healthy controls. Such phenotyping approaches may inform the development of personalised clinical trajectories and targeted intervention strategies for youth at risk for psychosis.

P_2b Reductions in Group III Metabotropic Glutamate Receptor Transcripts in Schizophrenia and Bipolar Disorder Midbrain

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Background
Group III metabotropic glutamate receptors (mGluRs) (consisting of mGluR4, 7 and 8) are of increasing interest in the pathophysiology and treatment of schizophrenia. These receptors are largely thought to sit on presynaptic terminals where they regulate neurotransmitter release. However, their specific cellular expression and subsequent potential for downstream signalling impacts in the midbrain is unknown. The midbrain is a crucial hub for dopaminergic and glutamatergic signalling which are disrupted in schizophrenia and bipolar disorder, with neuroinflammation found in half of the cases. Due to their involvement across several neurotransmitter systems, group III mGluRs are a promising target for novel antipsychotics.

Methods
To determine transcript expression and cellular localisation of group III mGluRs, RNA was extracted from postmortem midbrain from 35 schizophrenia, 33 bipolar disorder and 33 non-psychiatric control subjects. Gene expression of the group III mGluRs (GRM4, GRM7, GRM8) was measured via qRT-PCR using TaqMan Gene Expression Assays and analysed by diagnosis and pre-defined inflammatory subgroups. The neuroinflammatory subgroups were categorised based on elevated expression levels of a combination of pro-inflammatory transcripts (SERPINA3, IL6, IL1β and TNFα) and defined using 2-step recursive clustering. Cellular expression of the mGluRs was investigated by single-nucleus RNA sequencing (snRNAseq) of postmortem human midbrain tissue (n=34).

Results
SnRNAseq showed that GRM4 was primarily localised to inhibitory interneurons, GRM7 was diversely expressed across glutamatergic, GABAergic and dopaminergic neurons as well as mesenchymal stem cells (MSCs), and GRM8 was predominantly expressed in pericytes, glutamatergic neurons and dopaminergic neurons. Analysis by inflammation subgroup revealed significant reductions in group III mGluR mRNAs. High neuroinflammation schizophrenia subjects show reduced GRM4, GRM7 and GRM8 mRNAs compared to both controls and low neuroinflammation schizophrenia subjects. Bipolar disorder subjects with high neuroinflammation show reduced GRM4 and GRM8 mRNAs compared to controls and reduced GRM4 mRNA compared to low neuroinflammation bipolar disorder subjects.

Conclusions
We reveal significant transcriptional reductions in group III mGluRs in a subgroup of schizophrenia and bipolar disorder subjects with elevated inflammation, linking glutamatergic dysfunction with neuroinflammation. Activation of group III mGluRs inhibits both GABAergic and glutamatergic transmission in the midbrain. The presence of GRM7 and GRM8 mRNAs in dopaminergic neurons, coupled with the observed reductions in their mRNA, suggests a potential mechanism whereby glutamatergic signalling regulates dopamine. However, our findings suggest additional non-neuronal roles of the group III mGluRs due to the marked expression of GRM7 and GRM8 in MSCs and pericytes, respectively, which warrants further investigation.

P_59b Serum elements and oxidative stress indices are altered in Treatment-Resistant Schizophrenia

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Background
The molecular basis of schizophrenia (Sz) is explained by genetics and environmental factors. Around 30% of individuals with Sz have chronic illness and are often treatment-resistant (TRS). Our postmortem and MRI studies identified disturbances in brain iron in cortical and subcortical regions of individuals with chronic Sz. These changes may reflect elevated oxidative stress that may promote brain changes in the disorder. However, there are no consistent reports of changes in serum levels of elements in Sz. This work aimed to examine serum levels of elements and indices of oxidative stress in a cohort of TRS compared to control individuals.

Methods
Individuals with TRS (N=70) and matched controls (N=53) were recruited from clinics in North-Western Melbourne. Complete hematologic analyses were performed on blood samples. Metals and trace elements were determined by ICP-MS; proteins assessed by Western blot; GPX3 activity by NADPH oxidation assay, and total Antioxidant Capacity (AOX) by a Radical Trapping Antioxidant Assay. An ELISA and a multi-Plex ELISA assay assessed the determination of Hepcidin, IL-6 and TNF-α, respectively. Statistical analyses were performed using GraphPad Prism 11 and IBM SPSS 29 software.

Results
Serum iron and selenium are significantly decreased in TRS individuals compared to controls. In addition, the TRS group showed elevated levels of pro-inflammatory cytokines and hepcidin and low GPX3 activity is involved in the antioxidant response. However, AOX was significantly increased in TRS compared to controls. The changes in serum elements were not affected by age, gender, or Clozapine dose.

Conclusions
We propose that the decrease in selenium may explain the reduction in GPX3 activity and the elevation in pro-inflammatory cytokines, which in turn would trigger hepcidin secretion. Thus, hepcidin promotes the degradation of Ferroportin-1 and the decrease in serum iron as observed in the TRS cohort examined in this study. We also conclude that the increase in total antioxidant activity in the TRS group may be part of a compensatory response against the decrease in GPX3 activity.

P_28b Sex- and Time-Dependent Effects of Psilocybin on Social Behaviours in Mice

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Background
Social behaviour plays a crucial role in shaping and maintaining societal structures and relationships. Impairments in social behaviour are hallmark symptoms of various psychiatric conditions. While a single dose of psilocybin has previously been shown to enhance social reward learning in male mice, the effects of psilocybin on a broader range of social behaviours, particularly over varying timeframes and importantly in females, remain unknown. Using the 3-chamber sociability paradigm and the barrier climbing test we assessed sociability and social motivation, respectively. We evaluated the effects of psilocybin on core body temperature, investigating the involvement of serotonin receptors in these behaviours.

Methods
Male and female C57BL/6J mice were implanted with temperature-sensitive RFID transponders and pretreated with either a 5-HT1A (WAY-100635) or 5-HT2A (MDL-100907) receptor antagonist 30 minutes before psilocybin or saline administration. Acute body temperature and home-cage behaviour were recorded post-treatment. 3-chamber test was conducted at 4 hours, 24 hours, and 7 days, including 10-minute trials for habituation, sociability, and social novelty. Social motivation was assessed using a barrier climbing test, measuring latency to cross a semi-obstructive barrier to interact with either a familiar or novel mouse during a 25-minute session. Each treatment group included 8 males and 8 females.

Results
Female, but not male mice, exhibited an increase in huddling (social contact) behaviour immediately after a single dose of psilocybin ($p = .014$). Four hours post-administration, females showed an enhanced preference for social novelty ($p = .013$), which was not observed at 24 hours. Males displayed reduced aggressive behaviour immediately following psilocybin administration ($p = .016$) and showed a preference for familiarity at 24 hours ($p = .008$). During the social novelty trial, males also exhibited reduced grooming ($p = .001$) and rearing ($p = .001$).

Conclusions
Together, these data highlight the importance of using both sexes in preclinical research models and suggest that the effects of one dose of psilocybin in mice are time- and sex-dependent. Future studies aim to record dopamine release dynamics in the prefrontal cortex and nucleus accumbens during social interactions using GRAB DA and fiber photometry.

P_58b Impact of puberty age gap on resting-state functional connectivity

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Background
Although adolescents progress through the same stages of puberty, there is significant inter-individual variability regarding the timing of these stages [2]. Pubertal timing (PT) has important implications for social and emotional outcomes, as well as underlying brain structure, however, the influence of PT on brain functional connectivity (FC) remains understudied [5]. This study aims to identify how resting-state FC (rs-FC) links to PT, including the timing of adrenal and gonadal development.

Methods
Participants were drawn from the ABCD study (n=3,493; 1,626 females; ages 9–10 at baseline), with data from baseline and 2-year follow-up. One time point per participant was randomly selected. Pubertal timing was indexed using Puberty Age Gap (PAG), estimating deviation from age- and sex-specific developmental norms. We analyzed preprocessed cortical resting-state functional connectivity (rs-FC) between 12 networks (Gordon atlas). Inter- and intra-network correlations were examined. Ordinary least squares regressions tested associations between PAG and rs-FC, separately by sex and controlling for age. False Discovery Rate correction was applied to account for multiple comparisons.

Results
In males, hormone-, PDS-, and total PAGs were linked to rs-FC in VTA–FO, CA–FO, SMM–AD, SA–CGC, FO–DT, and SA–SMM, with VTA–FO showing the strongest positive (hormone/PDS) and strongest negative (total) associations. In females, PDS PAG showed no significant effects, but hormone PAG was associated with DT–DT, DT–DLA, DT–VS, and VS–DLA, with the strongest positive (DT–DT) and negative (VS–DT) links. Total PAG was associated with DLA–CGC and SMM–AD. Adrenarche PAG showed only negative associations in both sexes, strongest in AD–VTA (females) and SA–CGC (males). Gonadarche PAG was largely negative, except for SMM-related (males) and SA–VS (females) connections.

Conclusions
Our findings reveal sex-specific associations between PT and rs-FC, and highlight the distinct influence of adrenal and gonadal processes on brain networks. In males, PT was significantly associated with rs-FC, particularly in cognitive control and sensorimotor networks. In females, PT showed associations with rs-FC in attention, sensory processing, and memory-related networks. These results suggest that PT contributes to neural organisation in a sex-dependent manner, potentially shaping differences in cognitive and emotional development. Examining this association longitudinally could be an important future direction.

P_35b Chronic nicotine intake initiated during adolescence escalates in adulthood following intermittent access of ethanol.

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Background
The widespread use of electronic cigarettes by adolescents in Australia has contributed to an increase in the prevalence of alcohol use, with age and sex influencing patterns of co-use—factors that may complicate treatment approaches later in life. Here, we investigated whether a background of chronic nicotine use during adolescence followed by intermittent alcohol intake during adulthood facilitates subsequent escalation of nicotine intake.

Methods
Animals were divided into five groups: water only, vape mix only, vape mix + nicotine (90 µg), 10% v/v ethanol in water, and ethanol + nicotine. Tuesday, Thursday, Saturday, and Sunday, animals had unrestricted 24-hour access to their assigned solutions, but the ethanol group, which received water. After two weeks of home-cage exposure, binge-like sessions were introduced on Mondays, Wednesdays, and Fridays. Mice received access to their respective substances, while the ethanol group had one water bottle replaced by ethanol and the ethanol + nicotine group received ethanol added to the nicotine-containing bottle.

Results
Using a newly established binge drinking protocol in C57BL/6 mice (n = 50/5 per group/sex), our results revealed a significant treatment effect where ethanol increased nicotine consumption in both females ($p = 0.0085$) and males ($p = 0.0016$) in the co-access group compared to vape mix + nicotine group. No significant differences were observed in alcohol intake on binge days (vs water; $p = 0.7192$ females/$p = 0.500$ males) and nicotine ($p = 0.9776$/$p = 0.9855$ males vs vape mix). Although no main effect of sex was found, a trend to higher consumption in females was observed.

Conclusions
These findings provide important insights into the dynamics of ethanol-nicotine co-use, supporting the hypothesis that ethanol facilitates nicotine intake. This experimental model can help us better understand the mechanisms behind co-use during adolescence and support the development of better prevention and treatment strategies in adulthood.

P_15b Menstrual Characteristics and Mental Health in Adolescent Girls: Insights from the ABCD Study®

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Background
Adolescence is a critical period for mental health challenges, including depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD). While ADHD typically begins earlier, symptoms may fluctuate during adolescence due to hormonal changes. Menstrual characteristics, such as early menarche, irregular cycles, and pre-menstrual symptoms (PMS), reflect neuroendocrine stress and have been associated with increased psychiatric symptoms. These features are seldom incorporated into longitudinal models of adolescent mental health. Leveraging data from the Adolescent Brain Cognitive Development (ABCD) study, this research investigates whether menstrual characteristics in early adolescence predict internalizing and externalizing symptoms, aiming to identify early biological markers of psychiatric vulnerability in girls.

Methods
This study used data from the ABCD Study® (release 5.1), a large U.S. longitudinal cohort. We included nearly 5,200 female participants aged 9-14 years with data available on menstruation, mental health, BMI, and genetic ancestry. Self-reported menstrual variables included age at menarche, time since menarche, cycle regularity/length, and PMS. Mental health outcomes (ADHD, anxiety, depression) were based on CBCL DSM oriented subscales. Associations between menstrual characteristics and psychopathology were tested using generalized linear mixed-effects models (GLMMs), adjusting for age, BMI, and ancestry. Random intercepts accounted for repeated measures across waves. Analyses were performed in R using harmonized, multi-wave ABCD data.

Results
Earlier menarche was associated with increased depressive and anxiety symptoms. Girls further along in pubertal development, particularly ≥2 years post-menarche, is associated with higher internalizing symptoms, whereas being pre-menarcheal is linked to lower ADHD symptom scores. PMS severity correlated with elevated mental health symptoms: all PMS levels (mild, moderate and severe) were associated with increased depression and heightened anxiety scores. Regardless of age at menarche, girls ≥2 years post-menarche exhibited higher anxiety symptoms and greater PMS severity. The effects of ≥2 years post-menarche and PMS severity remained independent in multiple regression analyses. Menstrual cycle regularity/length was unrelated to symptoms.

Conclusions
This study reveals significant associations between menstrual timing, PMS, and mental health symptoms in adolescent girls. Early menarche and greater PMS severity are linked with increased depression and anxiety, suggesting reproductive factors influence psychiatric risk during adolescence. Incorporating menstrual health into mental health assessments could enhance early detection and intervention strategies.

P_13b Structure-Function Coupling in Depression in Premanifest Huntington's Disease: A Hierarchical Empirical Bayes Approach

Presenting Author: Tamrin Barta

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Background
Depression is one of the most impactful features for Huntington's disease (HD) gene expansion carriers (HDGECs). In HD there is inverse relationship whereby stronger structural connectivity is associated with weaker functional activity (McColgan, Gregory, et al., 2017), and depression in HDGECs is associated with increased functional connectivity within default mode network (DMN) alongside decreased structural connectivity between DMN and basal ganglia (McColgan, Razi, et al., 2017). Structure-function coupling (SFC) has emerged to understand disease-related network reorganization (Fotiadis et al., 2024). We investigated if HD pathogenesis forces depression functional networks to collapse toward structural constraints, or engenders decoupling through compensation.

Methods
We analysed 3T resting-state fMRI and DWI data from 98 HDGECs (30 with a history of depression). DWI data was pre-processed using MRtrix3 (v3.0.3), FSL (v6.0.4), and ANTs (v2.4.3), and fMRI was pre-processed using fMRIPrep (v21.02.2)and MRIQC (v22.0.6). ROIs included medial prefrontal cortex, posterior cingulate and hippocampi for DMN, as well as caudate and putamen for striatum. We employed a novel hierarchical empirical Bayes (HEB) model (Greaves et al., 2025) that leverages structural connectivity-based group level priors for spectral dynamic causal modelling, enabling both between-group structure-function coupling comparisons and refined subject-level posterior estimates through a three-level Bayesian framework.

Results
DWI analysis revealed no significant differences in edge or node strength between HDGECs with depression history versus without. HEB analysis showed HDGECs with depression history demonstrated systematically lower prior variances (range: 0.05-0.25) compared to no-depression (0.1-0.4), indicating stronger structure-function coupling. Mean log-Bayes factors were higher in HDGECs with depression history (29.6) versus no-depression (8.5), indicating stronger model evidence for structure-function coupling relationships. When examining effective connectivity, the structurally-informed HEB model revealed similar directional changes in DMN and striatal connectivity compared to uninformed approaches, but with greater posterior expectations.

Conclusions
Our findings suggest that in HDGECs, disease-related pathogenesis forces depression networks to collapse toward structural constraints rather than operating through compensatory decoupling mechanisms. Additionally, structural priors enhanced the confidence and magnitude of effective connectivity estimates, demonstrating the value of structure-informed modelling approaches in understanding HD-related network reorganization.

P_56b Psychological Trauma, The Brain, and Psychopathology: No Evidence for Mediation by Grey Matter or Resting State Functional Connectivity

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Background
Many contemporary models assume that at least part of the influence of trauma on psychopathology is mediated by the brain, but few studies have explicitly tested this mediation hypothesis using appropriate statistical methods that account for heterogeneity in different types of trauma, survivor characteristics (e.g., age of onset, sex), and psychopathological outcomes. In this study, we structural equation modelling to formally test whether measures of grey matter volume (GMV) of inter-regional functional coupling (FC) measured with magnetic resonance imaging (MRI) mediate the influence of sexual and/or interpersonal violence trauma on both dimensional and categorical measures of psychopathological outcomes.

Methods
1,110 (30.63% male; 18–45 years, M = 29.58, SD = 7.75) individuals with diverse psychiatric histories were recruited from the community. Complete behavioural and GMV/resting-state FC were available for 670 and 538 individuals, respectively. 252 path models were tested, systematically varying exposure (sexual/interpersonal physical violence), mediator (principal components describing variance in GMV or resting-state FC), and outcome (negative affectivity, antisocial schizotypy, or lifetime PTSD), stratifying by age of trauma and survivor sex. Models adjusted for age, family SES and co-occurring trauma types. Monte Carlo simulations estimated the significance of indirect (i.e., mediation) effects across both liberal and conservative thresholds.

Results
Exposure to interpersonal physical violence predicted GMV in frontoparietal and subcortical regions, with dose–response patterns moderated by sex and developmental timing. Both females and males showed distinct neural correlates with increasing rates of exposure. Sexual trauma was not associated with either GMV or FC across the 252 models. Crucially, no neurobiological metric significantly mediated trauma–psychopathology associations, even at liberal thresholds, regardless of how psychopathology was operationalised.

Conclusions
We find no evidence to support the hypothesis that the effects of trauma on psychopathology are mediated by GMV or FC. Instead, we find that trauma exerts independent effects on both neurobiology and psychopathology, in a way that depends on survivor sex, age of onset, and trauma frequency. As such, trauma-related neurobiological changes may reflect adaptations or correlates of exposure that lack mechanistic psychiatric significance.

P_29b Maternal Immune Activation Perturbs the Proteome of the Developing Adolescent Mouse Hippocampus

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Background
Prenatal immune insult, including influenza infection, may predispose individuals towards the emergence of neuropsychiatric disorders such as schizophrenia in late adolescence. Rodent maternal immune activation (MIA) models have shown that a prenatal immune insult can perturb early development, yet few studies have examined its consequences on adolescent neurodevelopment. Our research group has demonstrated schizophrenia-relevant structural, morphological, behavioural, and gene expression abnormalities in MIA offspring, particularly in the hippocampus, yet proteomic abnormalities remain to be examined.

Methods
We sought to investigate how MIA affects the total- and phospho-proteome of the mouse hippocampus in late adolescence (8 weeks; 8W) to young adulthood (14 weeks; 14W), and whether these effects are sex-specific. Pregnant C57BL/6J dams were incubated with either influenza or saline control. Hippocampi were excised from their female and male offspring at 8W and 14W of age. Samples were prepared for total- and phospho-proteomic analysis with 18-plex tandem mass tag and liquid chromatography-facilitated mass spectrometry. Bioinformatic analysis was performed using a proteomics-modified Searchlight2 pipeline.

Results
Total-proteomic analysis revealed that normally sexually dimorphic Serpin A proteins (1e, 1a/c, 1b/d, and 3k) are centrally dysregulated in the hippocampi of MIA offspring. Notably, Serpin A proteins appear upregulated in adolescent (8W) MIA females and young adult (14W) MIA males. Our phospho-proteomic analysis revealed further sex-specific changes in adolescent MIA hippocampi and female-specific changes in young adult MIA hippocampi. These were largely postsynaptic proteins, with important roles in synaptic plasticity, cytoskeletal structure, inflammation, cell signalling, and cell metabolism. Almost all significant
phospho-proteins were upregulated.

Conclusions
These findings highlight Serpin A protein dysregulation in MIA offspring, relevant to sex-dependant Serpina A dysregulation reported in schizophrenia patients. Female engagement of an otherwise male-biased Serpin A pathway during adolescence may serve as a protective immunoregulatory response to prenatal insult. These findings also reveal the sexually dimorphic dysregulation of phosphorylated proteins important for synaptic plasticity. Abnormal phosphorylation of proteins such as Ank1, Arhgap5, Camk2b, Cldn11, Jph3, Mbp, Speg, and Tmcc2 may disproportionately contribute to functional impairments in the hippocampus of MIA offspring. Pharmaceutically

targeting these protein and phosphorylation pathways may have therapeutic benefit in neurodevelopmental disorders like schizophrenia.

P_33b The role of a cortico-hypothalamic pathway on metabolism and behaviour

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Background
The neural mechanisms controlling food intake and bodyweight have been ascribed to neuroendocrine and nutrient feedback. Within this framework, agouti-related peptide (AgRP) neurons increase food intake in response to signals of energy deprivation. Recent studies show that AgRP neurons receive sensory input from other brain regions. This sensory input provides important learned external information about food availability and palatability, which is integrated with mood levels. Although these neural circuits transmitting sensory information to hypothalamic feeding centres remain unknown, they may drive excessive consumption when satiated or suppress feeding in the presence of hunger, as presented in obesity or anorexia nervosa.

Methods
Recently a novel stress-sensitive neural pathway from the medial prefrontal cortex (mPFC) to lateral hypothalamus (LH) was identified to suppress feeding behaviour. Hence, we hypothesised an interaction between the mPFC-LH pathway and AgRP neurons that may affect food intake, feeding behaviour, and body weight. Furthermore, we used two chronic approaches of either caspase mediated deletion or NaChBac excitation of this pathway to examine metabolic and behavioural differences.

Results
We show sex-dependent differences in bodyweight and metabolism. A long with differences in stress, anhedonia and social behaviour.

Conclusions
Our findings establish a novel sex-dependent top-down, cortico-hypothalamic network controlling metabolism and behaviours related to feeding and reward-seeking. Future experiments will examine other neural nodes influencing this circuit and establish its role underlying different pathological states characterised by abnormal feeding behaviour such as obesity or anorexia nervosa.

P_11b Sexually Dimorphic Disruptions to Parvalbumin and Somatostatin Interneurons in Mice Carrying the ArxR264Q Mutation

Presenting Author: Victoria Edwards-Poulton

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Ariel Dunn, *Monash University*
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Rachel Hill, *Monash University*

Background
Schizophrenia is a severely debilitating psychiatric disorder with strong genetic heritability. Our laboratory identified a novel ARX gene mutation in a female with schizophrenia. ARX is crucial for migration and differentiation of GABAergic interneurons, including subtypes expressing somatostatin or parvalbumin. These interneurons are key modulators of synchronised neural network firing and are reduced in patients with schizophrenia. In order to understand the specific role of the ARX mutation that we identified, we generated a mouse model called ArxR264Q. ArxR264Q mice exhibited sex-specific sensorimotor, cognitive and socialisation phenotypes relevant to schizophrenia.

Methods
We now aimed to assess how the ARXR264Q genotype affected parvalbumin and somatostatin interneuron densities, and whether this affect was specific to sex. We postulated that parvalbumin and somatostatin interneuron subtype densities would be affected by genotype - and potentially also by sex - given the X-linked location of the ARX gene, in brain regions relevant to schizophrenia symptom domains. To elucidate cellular density changes, immunohistochemical procedures and IMARIS-assisted quantification were performed to analyse PV and SST interneuron densities (cells/mm2) in regions pertinent to schizophrenia, namely the prefrontal cortex, striatum, pallidum, hippocampus, amygdala, subiculum as well as white matter tracts.

Results
A sex-specific effect of genotype is present on SST and PV interneurons in the PFC, striatum and white matter tracts where male ArxR264Q mice demonstrate significant increases in PV ($p<0.05$) and SST ($p<0.05$) densities whilst females show decreases ($p<0.05$) or no change. In the amygdala, PV deficits were male-specific ($p<0.001$), yet, both sexes show deficits in SST density ($p<0.0001$). In the pallidum, a region critical for rodent social recognition, SST reductions were female-specific ($p<0.001$) while both sexes of ArxR264Q mice displayed decreased PV density ($p<0.0001$). Hippocampal PV and SST densities were decreased in ArxR264Q mice ($p<0.05$), irrespective of sex.

Conclusions
The results suggest the mutation has disrupted PV and SST interneuron cell density across all regions studied, excluding the subiculum. These cellular alterations may contribute to the behavioural phenotypes observed in the model, which are relevant to symptom domains of psychiatric disorders such as schizophrenia. In addition, we identified striking sex-specific effects on cell densities in the PFC, striatum, pallidum, amygdala, hippocampus, and white matter tracts, highlighting the clearly sexually dimorphic role of this gene. Overall, the findings suggest sex-specific and region-specific regulation of PV and SST interneuron cell densities in ARXR264Q mutant mice.

P_16b Amygdala-PFC and Hippocampus-PFC Functional Connectivity Specialisation in Normal Development and Adversity

Presenting Author: Wonyoung Kim

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Andrew Zalesky, *University of Melbourne, Department of Biomedical Engineering*

Background
Childhood adversity is a key risk factor of affective disorders including anxiety and depression. The neurobiological effects of childhood adversity on frontolimbic functional connectivity (FC) are well-established but spatially inconsistent across studies and lacking a developmental benchmark. We aimed to provide a unifying framework by establishing the neurodevelopmental principle of amygdala and hippocampus FC pattern across the frontal cortex.

Methods
In a large developmental cohort (HCP-D; N = 652; ages 5-21), we quantified an individual's amygdala-frontal and hippocampus-frontal FC patterns' resemblance to a normative young adult FC template (HCP-YA; N = 1,084; ages 22-35). Then, to capture the degree to which the frontal FC pattern of a given amygdala or hippocampus voxel is more "amygdala-like" versus "hippocampus-like," we calculated the difference between the two resemblance scores. We used this metric to examine the relationships between specialisation of FC patterns, age, and childhood adversity. Key findings were subsequently tested for replication in an independent cohort (PNC; N = 898; ages 8-23).

Results
FC pattern of the amygdala progressively resembled the amygdala FC template over the hippocampus FC template as individuals aged ($r = 0.357$, $P < 0.001$). Greater exposure to adversity in the past year was associated with advanced maturation in how the amygdala showed more uniquely amygdala-like FC ($r = 0.113$, $P = 0.004$). In the PNC cohort, the spatial pattern of age effects across the amygdala and the hippocampus was replicated ($r = 0.190$, $P_{brainSMASH} < 0.001$). Cumulative exposure to trauma events was correlated with the advanced maturation of the amygdala FC in PNC ($r = 0.071$, $P = 0.034$).

Conclusions
We revealed a neurodevelopmental principle of the frontolimbic circuit, whereby the amygdala and the hippocampus become more spatially specialised in their frontal FC patterns over development. An early maturation of this neurodevelopmental principle is related to prior experience of adversity. This framework may serve as an explanation for the previously reported spatial inconsistencies as well as a generalizable normative developmental model on which childhood adversity can be understood.

P_19b Unravelling the Epitranscriptome: Convergence from Human Postmortem Brain to Preclinical Models

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Background
Schizophrenia is a severe neurodevelopmental disorder characterised by cognitive, emotional, and behavioural impairments. Although its etiology remains unclear, transcriptomic studies of postmortem brain tissue provide valuable insights into disease mechanisms. However, consistent patterns of transcript dysregulation have not been observed, potentially due to the presence of alternatively spliced variants. These splicing events can significantly alter protein function and lead to opposing physiological outcomes. RNA modifications are emerging as key regulators of alternative splicing. To explore how RNA modifications contribute to splicing diversity and disease pathophysiology, we examined epitranscriptomic changes in the caudate nucleus using combined human and dopamine-based preclinical models.

Methods
We performed direct RNA sequencing (dRNA-seq) on postmortem caudate nucleus samples from individuals diagnosed with schizophrenia and age- and sex-matched controls. Sequencing was conducted using the Oxford Nanopore platform, allowing native RNA analysis with full-length isoform resolution. To examine if observed transcriptomic changes were dopamine-dependent, we used the EDiPS rat model (Enhanced Dopamine in Prodromal Schizophrenia), which mimics elevated striatal dopamine levels observed in patients. In parallel, we conducted methylated RNA immunoprecipitation followed by sequencing (MeRIP-seq) on EDiPS striatal tissue to identify dopamine-responsive RNA methylation (m6A) changes.

Results
In human schizophrenia caudate samples, we detected significant alterations in RNA splicing patterns, with differential exon usage in transcripts enriched for postsynaptic dopaminergic, GABAergic, and glutamatergic signalling pathways. These alternative splicing events may reflect underlying changes in RNA modification. In the EDiPS model, MeRIP-seq revealed elevated m6A methylation in transcripts involved in similar synaptic pathways, supporting the hypothesis that dopamine drives the regulation of RNA methylation. Furthermore, several of the genes altered in EDiPS overlapped with those showing splicing variation in schizophrenia samples, suggesting a convergent mechanism linking dopamine dysregulation with epitranscriptomic remodelling.

Conclusions
This is the first study to generate a direct RNA sequencing dataset from postmortem caudate tissue in schizophrenia, offering novel insights into native transcriptome alterations in the disorder. The convergence between human and EDiPS model data strengthens the hypothesis that dopamine dysregulation contributes to altered RNA modification, which may influence synaptic gene expression and splicing outcomes. Our findings suggest that RNA methylation may play a causal role in disease pathogenesis. Furthermore, this work highlights the utility of translational models, such as EDiPS, in linking molecular alterations to schizophrenia-relevant neurobiology, paving the way for RNA-targeted interventions.

P_61b Circular RNA biomarker for depression diagnosis

Presenting Author: Yao Honghong

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Background
How we develop our IVD test for depression diagnosis. Dr. Yao Honghong first began researching Circular RNA in the United States in 2008. Later, in 2016, she led a research team at Southeast University in Nanjing to advance studies on Circular RNA technology. By 2019, her team conducted experiments on mice with depression, screening over 20,000 genes to identify four highly expressed Circular RNA biomarkers associated with the condition. This was no small feat—the team progressively narrowed down candidates from 20,000 to 3,000, then to 1,000, then 200, and finally to the four key genes, a process that took nearly three years. Following this breakthrough, the team obtained gene sequence data through next-generation sequencing (NGS) and developed specific primers, ultimately completing the development of an RT-PCR detection kit for depression. The clinical trials for the "Major Depressive Disorder (MDD) CircRNA RT-PCR Detection Kit"(Clinical Trial 467 cases) are being led by Dr. Yao Honghong from Southeast University's School of Medicine from March 2023 to June 2024. Collaborating institutions include: Zhongda Hospital Affiliated to Southeast University, Huzhou Third People's Hospital, and Huaian Third People's Hospital.

Methods
The test is the standard qPCR process. Then 4CT values of 4 Circular RNA genes will be input in software to calculate the score.

Results
Accuracy 99.5%, specificity 100%.

Conclusions
CircRNA-based IVD test: Objective & measurable: CircRNAs are stable, detectable in blood, and correlate with depression. Early detection: Could identify at-risk patients before severe symptoms manifest. Personalized treatment: predict treatment response (e.g., SSRIs, SNRIs, TMS, ECT). Reduces stigma: A "lab test" makes depression feel more like a medical condition, improving patient acceptance.

P_45b Do complex affect dynamics improve predictive power for psychological and behavioral outcomes?

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Background
Ecological momentary assessment (EMA) is increasingly used to track fluctuations in affect and their links to mental health. While many methods exist to quantify affect dynamics, recent multi-study analyses suggest that simple metrics like the mean (M) and standard deviation (SD) explain most variance in outcomes such as depression, borderline symptoms, and life satisfaction, questioning the value of more complex approaches. To inform future research, it is crucial to assess the utility of these measures. This study evaluates the associations between various EMA-derived affect dynamics and a wide range of mental health outcomes within a single cohort.

Methods
314 adults (97 male; 18–45 years) completed 28 days of EMA, providing daily PANAS-10 ratings and measures of stress, sleep, and alcohol use. We computed 22 affect dynamics measures, including 16 established metrics (e.g., M, SD, MSSD, AR, ICC, Gini) and six from dynamic network analysis (e.g., flexibility, promiscuity). Predictive performance was tested using 10-fold cross-validated linear models on 117 outcomes from five psychometric scales and EMA-based behavioral data. Each complex measure was compared against baseline models using only the mean or mean + SD of positive affect (PA) and negative affect (NA) to assess added predictive value.

Results
Across all 117 outcomes, no complex affect dynamics measures improved the cross-validated R^2 by more than 5.3 % beyond the M and SD of PA and NA.

Conclusions
Elaborate measures of affect dynamics, as indexed by the PANAS-10, offer minimal incremental explanatory power in predicting psychopathology beyond basic summary statistics of daily affect. These findings question the added value of increasingly complex affect dynamics constructs for predicting standard psychological and behavioral outcomes.

P_39b Molecular Modulation of Cognitive Flexibility: Investigating the Role of Protein Kinase C in Instrumental Reversal Learning

Presenting Author: Yuting (Heather) Chen

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Background
Instrumental reversal learning is a form of cognitive flexibility in which behaviours are adjusted according to changes in response-outcome contingencies, allowing efficient decision-making in a constantly changing environment. Previous studies highlight the importance of projections from the parafascicular thalamus (Pf) to cholinergic interneurons (CINs) in the dorsomedial striatum for reversal learning in rodents. Here, we investigated the molecular regulation of the Pf-CIN pathway, focusing on the role of protein kinase C (PKC) in modulating CIN function during reversal learning.

Methods
Mice and rats were first trained to press one of two levers to obtain distinct outcomes (Action 1 → Outcome 1, Action 2 → Outcome 2), then either continued training on the same contingencies or were trained on reversed contingencies (Action 1 → Outcome 2, Action 2 → Outcome 1). Animals were culled either on day 1 (early phase of learning) or day 5 (late phase of learning) of reversal/continued initial training.

Results
We observed that striatal PKCα expression was primarily restricted to CINs in both mice and rats. Notably, animals in the early phase of reversal learning showed increased PKCα localization to the cytoplasmic membrane compared to animals that underwent continued initial training, an effect absent in the late learning phase.

Conclusions
As membrane translocation of PKC indicates its activation, these findings suggest that PKCα activation is specifically associated with the early phase of reversal learning. This implies a potential role for PKCα in modulating CIN activity to support the flexible updating of action–outcome associations.

P_26b Acute Activation of Serotonergic Neurons in the Dorsal Raphe Nucleus Following Subanaesthetic Ketamine

Presenting Author: Zoe J. Phelan

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Background
Ketamine has been shown to produce rapid and sustained antidepressant effects in people with treatment-resistant depression and preclinical models after a single, subanaesthetic dose. While the mechanisms that underlie these effects are not fully understood, activation of serotonergic systems, particularly, serotonergic neurons in the dorsal raphe nucleus (DR) have been implicated. Importantly, the DR is composed of anatomically and functionally distinct subpopulations of serotonergic neurons. These are characterised by differences in their anatomy, connectivity and function. This research aims to identify a unique population of serotonergic neurons in the DR that are involved in the antidepressant effects of ketamine.

Methods
Ninety minutes after administration of ketamine (10 mg/kg) or 0.9% saline, male and female BALB/c mice were transcardially perfused to measure the acute effects of ketamine. Brain tissue was collected and prepared for immunohistochemical staining for c-Fos and tryptophan hydroxylase 2 (TPH2) to measure activation of serotonergic neurons in the DR. Three rostrocaudal levels of the DR (4.42 mm, -4.78 mm and -5.14 mm bregma) were analysed and counted. This included the dorsal part (DRD), the ventral part (DRV), the ventrolateral part (DRVL), the interfascicular part (DRI) and the caudal part (DRC) of the DR.

Results
Ketamine had differential effects on serotonergic neurons depending on sex and DR region. In male mice, ketamine decreased activation of serotonergic neurons in the midrostrocaudal DRVL subregion, but it was without effect in female mice. Although not statistically significant ($p = 0.06$), ketamine increased activation of serotonergic neurons in the DRI, a region that has been associated with antidepressant effects in male and female mice.

Conclusions
Ketamine may exert its antidepressant effects through changes in DR neuronal signalling, and this research suggests that subpopulations of serotonergic neurons in the DRVL and the DRI could be involved. Sex differences observed in the activation of serotonergic neurons in the DRVL suggest that the mechanisms underlying the effects of ketamine may differ for males and females. This research further supports the role of functionally distinct subpopulations of serotonergic neurons in the DR that are involved in the antidepressant actions of ketamine.

Late Breaking Abstracts

P_62a Midbrain ghrelin receptor signalling regulates binge drinking in a sex specific manner

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Background
Risky drinking rates are rising, particularly in women, yet the consideration of sex as a biological variable has only recently gained traction. The centrally projecting Edinger-Westphal (EWcp) nucleus has emerged as a key regulator of alcohol consumption, while the neurochemical contributors and potential sex differences in its role remain unclear. Therefore, here we aimed to address this gap in the literature through exploring the role of ghrelin signalling in the EWcp in binge drinking mice, and how that role differs between the sexes.

Methods
Firstly, we assessed sex differences in activation of EWcp^peptidergic cells through immunohistochemistry staining of CART and Fos in alcohol-consuming and naive mice of both sexes. To assess the functional role of EWcp^peptidergic cells, we used a cre-dependent DREADD approach to functionally inhibit these cells during a binge drinking test session, as well by using Ghsr-shRNA to knockdown receptor expression in the EW. We assessed the effect of peripherally circulating hormones by performing both ovariectomy/sham surgeries plus receptor knockdown and comparing alcohol intake. We further explored Ghsr involvement through intra-cranial delivery of an inverse agonist and antagonist into the EWcp.

Results
We found that EWcp peptidergic cells reduce binge drinking specifically in female mice. We showed this effect is mediated by the ghrelin receptor (GHSR), with EWcp peptidergic inhibition blocking ghrelin-induced drinking ($p = 0.0209$) and Ghsr knockdown in EWcp peptidergic, but not EWcp glutamatergic or ventral tegmental area cells, reducing binge drinking in females ($p = 0.0281$), independent of circulating sex hormones. Female mice showed higher EWcp Ghsr expression, and EWcp peptidergic neurons were more sensitive to ghrelin ($p = 0.0438$). Moreover, intra-EWcp delivery of GHSR inverse agonist and antagonist reduced binge drinking, suggesting direct actions of ghrelin.

Conclusions
These findings highlight a neurobiological mechanism that underlies the relationship between ghrelin and alcohol consumption. We identify the EWcp as a locus where ghrelin/GHSR1a signalling at peptidergic cells mediates excessive alcohol consumption specifically in female mice. Collectively, our data build upon a growing literature suggesting sex differences in ghrelin/GHSR1a actions in the brain and elucidate mechanisms underpinning sex differences in excessive alcohol consumption.

Late-Breaking Abstracts

P_67a Uncovering Microbiota-Mediated Benefits of Exercise in a Schizophrenia Mouse Model

Presenting Author: Carolina Gubert

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Matilda Doran, *The Florey Institute of Neuroscience and Mental Health*
Michelle Wheeler, *The Florey Institute of Neuroscience and Mental Health*
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Background
Current treatments for schizophrenia are often ineffective and limited by side effects, leaving one-third of patients untreated and many symptomatic. Exercise has consistently been shown to alleviate positive, negative, and cognitive symptoms in schizophrenia and to improve gut and microbiota health, both of which are disturbed in patients. However, schizophrenia symptoms commonly hinder adherence to regular exercise. Given the increasing evidence linking gut microbiota modulation to symptom improvement, identifying exercise-related pathways that benefit the brain and gut may provide new therapeutic opportunities. Exercise mimetics targeting gut microbiota function are therefore emerging as promising interventions for schizophrenia management.

Methods
We employed the metabotropic glutamate receptor 5 knockout (mGlu5 KO) mouse model of schizophrenia, which exhibits behavioural and gut microbial disturbances resembling those observed in humans. Male and female mGlu5 KO and wild-type mice underwent an exercise intervention to determine whether physical activity could modulate the gut microbiota and rescue schizophrenia-relevant phenotypes. We comprehensively assessed parameters across multiple domains, including locomotor activity, cognition, metabolism, gastrointestinal health and function, and exercise performance. Gut microbial composition and diversity were evaluated using 16S rRNA sequencing. These measures enabled us to identify behavioural and physiological correlates of exercise-induced gut–brain modulation.

Results
The mGlu5 KO mice demonstrated multiple schizophrenia-relevant abnormalities, including hyperactivity, impaired metabolic regulation, gastrointestinal dysfunction, and reduced exercise performance compared to wild-type controls. Exercise effectively normalised hyperactivity and improved gut health and function in mGlu5 KO mice. Preliminary microbiome analyses suggest that exercise partially restored microbial diversity and altered key taxa associated with metabolic and cognitive outcomes. The differential exercise performance observed in mGlu5 KO mice may reflect metabolic or motivational deficits. Together, these findings highlight a complex interplay between exercise capacity, gut health, and schizophrenia-like behaviours, and suggest potential microbiota-mediated mechanisms underlying exercise benefits.

Conclusions
Our findings corroborate the presence of gut and metabolic dysfunction in the mGlu5 KO model of schizophrenia and provide the first evidence of reduced exercise performance in this model. Importantly, exercise improved behavioural and gut outcomes, indicating that restoring microbiota–gut–brain axis function may contribute to its therapeutic effects. These results suggest that negative symptoms and motivational deficits in schizophrenia could be linked to gut microbiota alterations. Future studies should characterise microbiota-derived metabolites and signalling pathways mediating the beneficial effects of exercise, to identify candidate exercise mimetics capable of improving brain and gut function in schizophrenia patients.

P_65b Sustained Cross-Network Integration Following Low-To-Moderate Psilocybin Doses

Presenting Author: Dr Chiranth Bhagavan

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Background
Psilocybin is a classic psychedelic that exerts widespread effects on brain activity and is associated with encouraging treatment outcomes in neuropsychiatric disorders. Neuroscientific studies of psilocybin have provided intriguing insights into these effects and proposed treatment mechanisms. Of these studies, resting-state functional magnetic resonance imaging (rs-fMRI) has been the most common neuroimaging technique. Common findings include reduced functional connectivity (FC) within the default mode network (DMN) and increased FC between the DMN and other networks during the acute drug effects. However, little is known about the persisting effects on brain connectivity and whether these changes are sustained at low-to-moderate doses.

Methods
This rs-fMRI study was conducted as part of a wider dose-finding pilot study investigating the impact of low-to-moderate psilocybin doses on motor function in healthy participants. 10 participants received three psilocybin doses, ranging from 5mg to 20mg, in a randomised order, and were blinded to the order of dosing (mean dose = 14.5mg). Participants were administered a series of movement tasks at baseline and at three time-points during the acute drug effects at each dose. Rs-fMRI scans were completed at baseline and one week following a subsequent dose. Changes in within- and between-network resting-state functional connectivity (FC) were investigated.

Results
After correcting for multiple comparisons, significant increases in between-network FC were seen for the (1) visual network (VN) with the frontoparietal control network (FPCN), (2) VN with the DMN, (3) somatomotor network with the salience network (SN), (4) dorsal attention network (DAN) with the SN, (5) DAN with the FPCN, and (6) DAN with the DMN. No significant within-network changes were identified.

Conclusions
The numerous cross-network connections following psilocybin emphasise its widespread effects and transdiagnostic treatment potential. The lasting changes at one week post-dose support theoretical frameworks of psilocybin leveraging a persisting window of neuroplasticity and the application of therapeutic interventions post-dose. These findings at low-to-moderate doses expand the potential feasibility and tolerability of psilocybin treatment to other individuals and clinical cohorts. Studies with larger sample sizes and advanced analysis methods examining dynamic aspects of brain activity are required to further characterise these lasting effects and corresponding therapeutic mechanisms at low-to-moderate doses.

Late-Breaking Abstracts

P_61a Childhood maltreatment and limbic substructure volumes using ultra-high field imaging

Presenting Author: Hana McMahon

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Background
Childhood maltreatment (CM) is a transdiagnostic risk factor for adult psychopathology (e.g. depression, PTSD) and is linked volumetric alterations in key limbic regions, including the hippocampus and amygdala (Hakamata et al., 2022; Teicher et al., 2016). As prior MRI technology lacked sufficient resolution, the amygdala and hippocampus have been typically analysed as single units. However, emerging high-resolution research show differential amygdala nuclei and hippocampal subfield changes in stress-related disorders (Haris et al., 2023; Liu et al., 2023; Zhang et al., 2021). No study to date has examined these substructure-level patterns in a transdiagnostic sample of individuals with and without CM.

Methods
Participants included 123 adults with a history of CM (abuse or neglect ≤ 18 years; mean age 26.4 years, 86% female) and 141 adults with no history of CM (mean age 24.3 years, 57% female) who completed T1-weighted MP2RAGE anatomical scans using a 7-Tesla MRI Scanner. FreeSurfer (Fischl, 2012) was used to parcellate 9 bilateral amygdala subnuclei and 21 bilateral hippocampal subregions. Group effects were analysed via ANCOVA (CM vs no CM) controlling for age, sex, and total brain volume; FDR-corrected across regions. A secondary model added PTSD (PCL-5) and depression/anxiety severity (DASS-21) as covariates. Post-hoc Tukey tests determined direction.

Results
In the base model, CM was associated with larger volumes in six left-hemispheric nuclei (medial, basal, accessory-basal, central, cortical, cortico-amygdaloid transition; FDR-$p \leq 0.05$), while no hippocampal subfields survived FDR. After adding current symptomology (PCL and DASS), CM was associated with larger volumes across all bilateral amygdala nuclei, all left-hemispheric hippocampal subfields, and the majority of right-hemispheric hippocampal subfields (FDR-$p \leq 0.05$).

Conclusions
CM is associated with widespread enlargement of hippocampal and amygdala substructures independent of age, sex, intracranial volume, and current PTSD/mood symptoms. Importantly, these effects became clearer after adjusting for symptom scores, indicating that current symptoms obscure CM-related differences. Together, these results suggest that CM alters trajectories of limbic structural development.

P_66a Effects of Maternal Immune Activation and Raloxifene on Dopamine-Related Behaviour and Substantia Nigra Gene Expression in Adolescent Male and Female Rats

Presenting Author: Jasmine Campbell

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Background
Maternal infection during pregnancy increases risk of schizophrenia in progeny. The most common age for diagnosis of schizophrenia is late adolescence/early adulthood. Estrogen may protect against dopamine dysfunction and contribute to sex differences in schizophrenia, which is more common in men. The selective estrogen receptor modulator raloxifene shows therapeutic benefit for some patients, but underlying brain mechanisms remain unclear. Nigrostriatal hyperdopaminergia can contribute to psychotic symptoms. We tested the effect of chronic raloxifene commencing in early adolescence on dopamine-related behaviours and substantia nigra (SN) gene expression in adolescent male and female rats following a prenatal immune insult.

Methods
Maternal immune activation (MIA) in pregnant dams (n=17) was induced via tail vein injection with 3-4mg/kg HMW-poly(I:C) on gestational day 15. Controls received equivalent saline. MIA was confirmed by sickness behaviour and weight loss. Between postnatal days (PND) 30-57, offspring received daily 5mg/kg oral raloxifene or placebo. Prepulse inhibition (PPI) was assayed on PND46-48 and amphetamine-induced locomotion on PND50-53. Rats were euthanised on PND58-59 and SN dissected. Dopamine metabolic enzyme, catechol-o-methyltransferase (Comt) and dopamine D2 receptor short (Drd2s) gene expression in SN were measured by RT-qPCR. Analysis was with 2-way (behaviour, sexes separate) and 3-way ANOVA (MIA, treatment, sex).

Results
MIA dams lost weight ($F(1, 15)=18.241$, p=<0.001) and exhibited more sickness behaviours ($F(1, 15)=6.221$, $p=0.025$) compared with controls. MIA decreased PPI in females only (100ms ISI, 78dB, $F(1, 80)=5.384$, $p=0.023$). In males, raloxifene increased PPI in MIA offspring (50ms ISI, 78dB, $F(1, 59)=4.102$, $p=0.047$). In females, in the third 30-minute period after amphetamine, MIA increased amphetamine-induced locomotion ($F(1, 80=4.482$, $p=0.037$). In males, in the first 30-minute period after amphetamine, raloxifene increased amphetamine-induced locomotion for controls ($F(1, 59)=6.334$, $p=0.015$). MIA increased relative Comt ($F(1, 85)=8.916$, $p=0.004$) and Drd2s ($F(1, 83)=4.493$, $p=0.037$) mRNA levels in SN of both sexes.

Conclusions
We identified a bidirectional effect of raloxifene on sensorimotor gating (PPI) deficits in males which suggests a benefit for the dysregulated dopamine system and a detriment to the healthy dopamine system. Our data suggests the timing of MIA-induced behavioural abnormalities during adolescence may differ in males and females and sex differences in the effects of raloxifene on dopamine-relevant behaviours exist. Increased Comt and Drd2s mRNAs in the SN of young adult offspring exposed to MIA may be compensatory mechanisms to reduce excessive dopamine transmission. This work contributes to understanding the sex-specific development of dopamine dysregulation and the actions of raloxifene.

P_67b The Behavioural Effect of Oxytocin Treatment During Adolescence on Male and Female Offspring Exposed to Maternal Immune Activation

Presenting Author: Mara Jkorkozian

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Background
Schizophrenia is a complex neuropsychiatric disorder characterised by cognitive impairments, positive symptoms, and negative symptoms. Current treatments are insufficient in addressing all three symptoms and are not universally effective. Oxytocin has shown promise as a treatment for symptoms of schizophrenia; however, the evidence is mixed. This study employs a reverse translational approach, using the rat maternal immune activation (MIA) model of dopamine dysregulation, to determine the impact of oxytocin administration during adolescence on behavioural outcomes related to schizophrenia. The study aims to identify novel sex differences in the effects of oxytocin on behaviours relevant to specific symptom domains of schizophrenia.

Methods
Pregnant Wistar dams received tail vein injections of 4 mg/kg high molecular weight (HMW)-poly(I:C)(n=7) or saline (n=5) on GD15, yielding 16/42 male/female MIA and 24/31 male/female control offspring. During post-natal days (PND) 30-39, offspring received daily intraperitoneal injections of saline or oxytocin (1mg/kg for 4 days; 0.6mg/kg for 6 days). Behavioural testing throughout adolescence and young adulthood (PND40-71) included the attention set-shifting task (ASST), sucrose preference, novel object and social recognition, and amphetamine-induced locomotion (1mg/kg females; 1.5 mg/kg males). Results were analysed using 3-way (MIA, sex, treatment) or 2-way ANOVA (sexes separately for amphetamine-induced locomotion), followed by Bonferroni comparisons.

Results
The results of amphetamine-induced locomotion ($F(4, 70)=4.62$; $p=0.0023$) showed MIA males had greater locomotor activity when compared to controls ($t=4.61$, $p<0.001$). A similar effect was seen between MIA and control females ($t=3.08$, $p=0.012$). Oxytocin treatment during adolescence reduced amphetamine-induced locomotor activity for MIA males compared to placebo-treated MIA males ($t=-3.05$; $p=0.018$). There was no impact of oxytocin treatment during adolescence on amphetamine-induced behaviours in the female groups ($t=-0.23$, $p=1$). ASST, novel object and social recognition are under analysis. There were no significant differences between groups in the sucrose preference test (all $F(3,109)= 1.85$; $p=0.071$).

Conclusions
Male and female MIA offspring showed significantly increased amphetamine-induced locomotor activity in young-adulthood compared to controls. This indicates amphetamine hypersensitivity, commonly associated with dopamine dysregulation following MIA and relevant to psychosis in schizophrenia. Oxytocin administration reduced the enhanced amphetamine-induced activity in MIA males only. This suggests oxytocin's mechanism differs by sex and may help to explain variability in clinical efficacy of oxytocin treatment. Neither MIA nor oxytocin altered anhedonia-related behaviour. These results highlight the importance of considering sex differences when investigating novel treatment options for symptoms of schizophrenia. Future studies will explore brain molecular mechanisms underlying oxytocin-induced behavioural changes.

Late-Breaking Abstracts

P_64a Comparing food addiction phenotypes in animal models of obesity and binge eating

Presenting Author: Michael D Kendig

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Background
Excessive consumption of high-fat, high-sugar foods is implicated in the pathogenesis of obesity, binge-eating disorder and 'food addiction', estimated to affect one in five young Australians. Food addiction comprises a range of harmful eating behaviours derived from aspects of substance use disorder, including escalation of intake over time, high motivation for food reward, and compulsive consumption that continues despite adverse consequences. However, the relative prevalence of food addiction behaviours in obesity versus binge eating remains unclear. This study tested measures of escalation, motivation and compulsion for a high-fat high-sugar food in animal models of diet-induced obesity and binge-eating.

Methods
Over a seven-week diet intervention, three groups of young adult female Sprague-Dawley rats (n = 12) were fed chow and water only (Control) or chow and water supplemented with continuous or restricted (1h/day, 3x/wk) access to sweetened condensed milk (SCM). Addiction-like behaviour was quantified by assessing (1) escalation of SCM intake over time; (2) motivation for SCM in progressive ratio tests; and (3) compulsive intake of SCM when adulterated with quinine and during a modified novelty-suppressed feeding test.

Results
Across the diet intervention, percent weight gain was greater in the Continuous group than the Control group, with intermediate weight gain in the Restricted group. Only the Restricted group exhibited 'binge-like' escalation of SCM intake and compulsive consumption of SCM in both the quinine adulteration test and the novelty suppressed feeding test, relative to Continuous and Control groups. However, motivation for SCM did not differ between groups, as assessed by progressive ratio breakpoints.

Conclusions
A preclinical model of binge eating (Restricted group) more closely recapitulated the phenotype of food addiction than diet-induced obesity (Continuous group). Despite the absence of changes in motivation for SCM, the pattern of access to high-fat, high-sugar foods appears the key predictor of addiction-like behaviour.

Late-Breaking Abstracts

P_65a Development and validation of a methylation profile score for the cortisol response to stress

Presenting Author: Sarah Cohen-Woods

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Background
Stress can have a significant impact on mental and physical health. The pathways between stress and health are not fully understood, although emerging evidence indicates a possible role for lasting changes in the cortisol response to stress, potentially mediated by DNA methylation. To date, studies investigating the relationship between DNA methylation and the cortisol response to stress have yielded broadly inconsistent results. Machine learning methods have not yet been explored in this field, but they may yield new insight.

Methods
We developed a new methylation profile score (MPS) for the cortisol response to stress by comparing four probe selection methods and six machine learning algorithms. Three models were ensembled to optimise the MPS. Models were trained using whole blood Illumina Infinium HumanMethylation 450K BeadChip (450K) data (N=85, mean age=34, 49% female), predicting the salivary cortisol response to the Trier Social Stress Test (TSST). Follow-up analyses were performed using two independent data sets, one with salivary methylation and TSST cortisol response data (N=55, mean age=20, 51% female), and the other with whole blood 450K data (N=422, mean age=42, 71% female).

Results
The novel MPS, which included 1087 probes, was associated with the cortisol response in independent data (β = 0.29, p = .032). The relationship was attenuated substantially after adjusting for mCigarette, a previously-developed smoking MPS (β = 0.18, p = .197). In a different independent dataset, the MPS was associated with cumulative life stress before and after adjusting for age, sex, ancestry, mCigarette, and cell composition (β = 0.13, p = .020). Associations were not affected after removing two probes that overlapped with mCigarette. Nominally significant KEGG terms for the MPS included pancreatic secretion and regulation of actin cytoskeleton.

Conclusions
We have developed and validated a new MPS for the cortisol response to stress which is also associated with cumulative life stress in independent data. It is not yet possible to disentangle causality in relation to smoking, which is associated with both DNA methylation and stress. Results are consistent with previous work indicating that actin-binding proteins may be influenced by stress and impact neuroplasticity, providing a plausible pathway from stress to mental health. Additional research is needed to investigate how the MPS relates to stress, smoking, cortisol, and health, providing new insight into the complex interplay between these factors.

P_66b Identifying a synaptic deficit subtype of schizophrenia using in vivo PET imaging

Presenting Author: Sidhant Chopra

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Background
Synaptic loss has emerged as a fundamental pathophysiological mechanism in schizophrenia, presenting a promising target for novel disease-modifying treatments. While several synaptogenic compounds are entering clinical trials, their effective implementation requires identifying which patients may benefit most and when intervention would be most effective. He hypothesis that there a subset of patients will fall into a synaptic deficit subgroup (SDS), with prominent synaptic loss, who are potentially more likely to benefit from emerging medications.

Methods
We leveraged a recently established databank comprising the largest sample of in vivo synaptic density PET scans in the world (N=155; aged 18–55), including 31 patients with schizophrenia. These scans used the [11C]UCB-J radiotracer which selectively binds to synaptic vesicle protein 2A (SV2A), a well-validated marker of synaptic density. Importantly, scanning of all participants was done using the same procedure on the same scanner. This exceptionally rare circumstance, especially for large PET datasets, mitigates the severe confounds associated with using multi-site dataset aggregations. We use multiple statical tests to examine whether distinct synaptic density subgroups of patients were detachable.

Results
While healthy controls exhibit a normal distribution of mean synaptic density, patients exhibit a bimodal distribution with a subset of patients showing synaptic deficits . This bimodality was especially prominent with examining mean synaptic density of the bilateral prefrontal cortex as well as bilateral hippocampus. Gaussian Mixture Modelling showed the schizophrenia group was better characterised by a two-component model with nearly equal proportions (51.3% and 48.7%), while controls fit a single-component model (BIC: 3.77). The bimodality was strongly confirmed by Hartigan's dip test (D = 0.097; p=0.009).

Conclusions
Our analyses of the world’s largest in vivo synaptic density PET dataset have revealed a distinct subgroup of schizophrenia patients with marked synaptic loss—a synaptic deficit subgroup (SDS). This robust finding, supported by multiple statistical approaches, aligns with post-mortem evidence of reduced synaptic protein expression in a subset of individuals with schizophrenia. Future research will examine whether a SDS is present at illness onset or emerges later in the disease course, and whether these patients will respond between to next generation synaptogenic treatments.

Late-Breaking Abstracts

P_59a Validating a Translational Approach to Assess Deficits in Motivation in Rodent Models to Enable Novel Drug Discovery

Presenting Author: Sue He

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Background
Schizophrenia is a complex psychiatric disorder characterized by positive (e.g., psychosis, delusions, hallucinations), negative (e.g., reduced affect and motivation), and cognitive symptoms. While current treatments primarily target positive symptoms, effective therapies for negative and cognitive impairments remain lacking, despite these domains being key predictors of functional outcomes and quality of life. A critical step toward addressing this gap is the development of reliable preclinical assays to measure motivational and cognitive deficits. The rodent touchscreen platform has begun to bridge the translational gap. In this study, we evaluated an adapted, scalable approach to measure motivation and systematically screen therapeutic candidates.

Methods
Male and female C57BL/6 mice were trained on a progressive ratio touchscreen-based task and subsequently tested using an adapted protocol to assess pharmacological interventions over several weeks. We evaluated the effects of amphetamine, clozapine, and haloperidol on motivational outcome measures.

Results
We confirmed our testing approach was able to detect both increases and decreases in motivational responding, supporting its utility towards drug discovery screening for pharmacological effects on motivation.

Conclusions
This work contributes to the refinement of objective methods for measuring motivational processing in rodents that model negative symptoms of schizophrenia. Our approach supports future efforts to develop and translate novel therapeutic candidates targeting this critical and unmet symptom domain.

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, Newcastle
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)
2022	12th meeting at Newcastle City Hall, Newcastle
2023	13th meeting at Pullman Palm Cove Sea Temple Resort & Spa, Cairns, Queensland
2024	14th meeting at Mercure, Sydney
2025	15th meeting at the Florey Institute, Melbourne

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