Biological Psychiatry
AUSTRALIA

2022

Proceedings of the Biological Psychiatry Australia Scientific Meeting 2022

Welcome

The 12th Biological Psychiatry Australia Scientific Meeting

30 October – 1 November 2022

Dear Friends and Colleagues,

On behalf of the Local Organising Committee, we warmly welcome you to the 12th Annual Biological Psychiatry Australia 2022 (BPA2022) Scientific Meeting. This year marks our first in-person meeting since the beginning of the pandemic, and we are excited to meet again in person at Noah's on the Beach (Sunday evening, 30 October), and Newcastle City Hall (31 October – 1 November). We will also be using the Whova portal (Whova.com). You can use the app on a computer or mobile device to see the agenda, see all the session times, as well as connect with other attendees, either directly via their profiles or in Session Q&As.

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

Chair: Dr Lauren Harms

Stay connected with our Twitter accounts: @biolpsychaust @BPA_ECRN

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

All online material can be found at https://whova.com/portal/webapp/biolo_202210/

Contents

Acknowledgement of Country

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

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

BPA Equality and Diversity Statement

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

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

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

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

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

Society Profile

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

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

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

Executive Committee

President	Thomas Burne	Queensland Brain Institute
Vice-president	Andrea Gogos	Florey Institute of Neuroscience and Mental Health
Secretary	Tertia Purves-Tyson	Neuroscience Research Australia
Treasurer	Leigh Walker	Florey Institute of Neuroscience and Mental Health
ECRN rep	Cassandra Wannan	University of Melbourne
Webmaster	James Kesby	Queensland Brain Institute
Committee members		
	Sarah Cohen-Woods	Flinders University
	Yann Quidé	University of New South Wales
	Zoltan Sarnyai	James Cook University
	Lauren Harms	University of Newcastle
	Katrina Green	University of Wollongong

Isaac Schweitzer Lecture

2010	*not awarded*
2011	*not awarded*
2012	*not awarded*
2013	Michael Berk
2014	Paul Fitzgerald
2015	John McGrath
2016	Cyndi Shannon Weickert
2017	Patricia Michie
2018	Christos Pantelis
2019	Brian Dean
2020	Susan Rossell
2021	Anthony Hannan
2022	Jayashri Kulkarni

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

Organisers

Local Organising Committee

Chair: Lauren Harms

Michael Breakspear, Thomas Burne, Murray Cairns, Erin Campbell, Laura Greco, Behnaz Khavari, Dylan Kiltschewskij, Jayson Jeganathan, Lizzie Manning, Pat Michie, William Reay, Melissa Tadros, Juanita Todd

ECRN Committee

Position	Name	State	Site
Chair	Cassandra Wannan	VIC	University of Melbourne
Secretary	Abdalla Mohamed	QLD	University of the Sunshine Coast
Treasurer	Samara Brown	NSW	University of Wollongong
Social media	Laura Han	VIC	Orygen
	Luke Ney	QLD	Queensland University of Technology
QLD reps	Svetlina Vasileva	QLD	Queensland Brain Institute
	Athena Stein	QLD	University of Queensland
	Georgia Caruana	VIC	University of Melbourne
VIC reps	Bruna Panizzutti Parry	VIC	Deakin University
	Felicia Reed	VIC	Monash University
	Brandon Richards	NSW	Macquarie University
NSW reps	Jessica Chandra	NSW	NeuRA
	Joel Raymond	NSW	University of Sydney
SA rep	Elysia Sokolenko	SA	University of Adelaide

Scientific Advisory Committee

Robyn Brown, Tom Burne, Rose Chesworth, Kelly Clemens, Luca Cocchi, Sarah Cohen-Wood, Jennifer Cornish, Chris Dayas, Brian Dean, Chao Deng, Eske Derks, Ariel Dunn, Darryl Eyles, Claire Foldi, Andrew Gibbons, Andrea Gogos, Katrina Green, Melissa Green, Alex Guerin, Tony Hannan, Lauren Harms, Xu-Feng Huang, Tim Karl, Pat Michie, Kelly Newell, Jess Nithianantharajah, Claire O'Callaghan, Iain Perkes, Christina Perry, Tertia Purves-Tyson, Yann Quidé, Susan Rossell, Lianne Schmaal, Luba Sominsky, Suresh Sundram, Melissa Tadros, Adam Walker, Leigh Walker, Andrew Zalesky

Sponsors

We would like to thank all our Sponsors for their support.

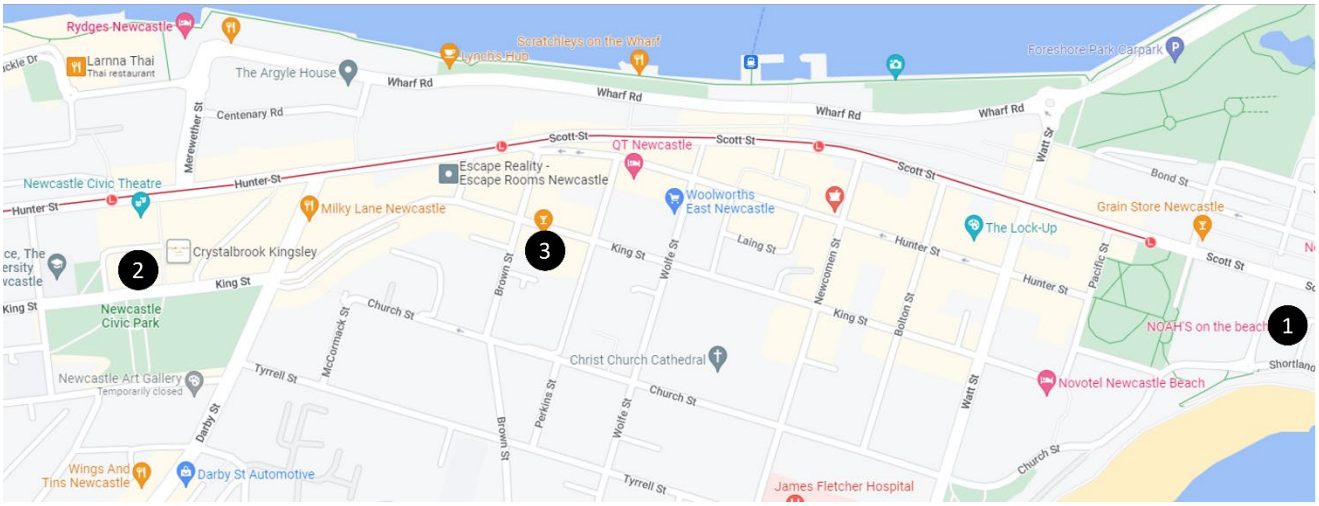
Brain Neuromodulation Research Program

Chief Scientist & Engineer

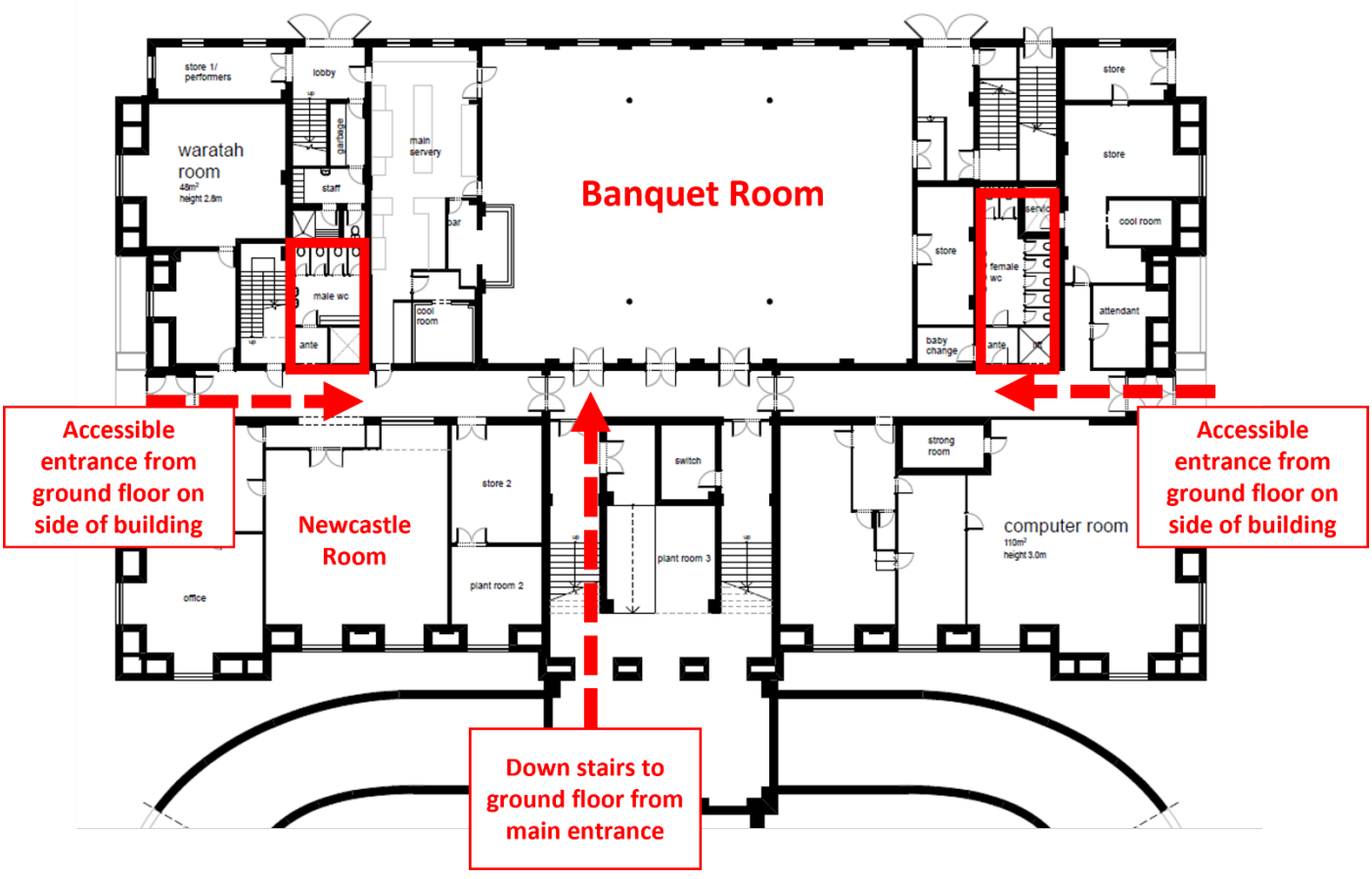
ant neuro
australia

Venue Information

1	Sunday 30 October, 5:30 PM – 8:30 PM	Noah's on the Beach	29 Zaara St, Newcastle East NSW 2300
2	Monday 31 October, 9:00 AM – 4:45 PM	Newcastle City Hall	290 King St, Newcastle NSW 2300
3	Monday 31 October, 6:00 PM – 10:00 PM	Babylon Newcastle	145 King St, Newcastle NSW 2300
2	Tuesday 1 November, 9:00 AM – 5:15 PM	Newcastle City Hall	290 King St, Newcastle NSW 2300



Map of Newcastle City Hall, Ground Floor



Program at a glance

Time (AEDT)	Sunday, 30 October Noah's on the Beach	Monday, 31 October Newcastle City Hall	Tuesday, 1 November Newcastle City Hall
8:00 AM			
9:00 AM		Conference Opening 10th Isaac Schweitzer Lecture: Prof Jayashri Kulkarni	13th Aubrey Lewis Lecture: Robyn Brown
10:00 AM		*Morning Tea*	*Morning Tea*
11:00 AM		Data Blitz #1 *Symposium.* Brain patterns in adolescence: modelling techniques and clinical applications	Data Blitz #3 *Symposium* . Neural Circuit Dysfunction in Psychiatric Disorders
12:00 PM		*Lunch*	*Lunch*
1:00 PM		Poster Presentations (MON posters)	Poster Presentations (TUE posters)
2:00 PM		ECRN Plenary Memorial for Prof Sally Andrews	Data Blitz #4 *Symposium* . Novel systems-level insights for neuropsychiatric symptoms
3:00 PM		Data Blitz #2	*Afternoon Tea, Melbourne Cup*
4:00 PM		*Afternoon Tea, ECRN Breakout Afternoon Tea (Newcastle Room)* Oral Presentations: Highest Ranked Abstracts	*Symposium.* Translational approaches for understanding the neurobiology of compulsions, compulsivity and habits in mental illness Annual General Meeting
5:00 PM			Award Presentation Conference Discussant
6:00 PM	Registration desk open, ECRN mentoring program introductions and meetings	*Social Event: Babylon Newcastle (Until 10pm)*	
7:00 PM	International Lecture: A/Prof Meaghan Creed		
8:00 PM	*Welcome reception*		

Presentation Guidelines

Lectures, Oral Presentations, Data Blitz

- Please bring your presentation on a USB drive to upload it in the morning on the day of your presentation OR email it to lauren.harms@newcastle.edu.au at least one day before your presentation
- We will aim to run all presentations from the same PC laptop, but a mac laptop will be available if needed
- You will not be able to connect your own computer to the AV system
- Be sure to run through the presentation after uploading with one of the LOC members to ensure the presentation is displaying properly
- A microphone will be available at the lectern, and a lapel microphone will also be available if preferred (though not for data blitz presentations)
- The chair will signal to you when you have one minute left, and when you are out of time

Posters

- Posters should be portrait orientation, no more than 90cm wide and 120cm long
- Poster boards will be numbered. Please hang your poster according to your number in the program. For example, poster MON_01 should be hung at poster board '1' on Monday
- Please hang your poster by 9:30 AM on the day in which it is to be presented, and remove at the end of the day
- Any posters left hanging at the end of the day on Monday or Tuesday will be taken down by the LOC

Scientific Program
Sunday, 30 October 2022 (Noah's on the Beach)

Registration desk opens
5:30 PM

ECRN Mentoring Program Meetings
5:30 PM – 6:30 PM

International Keynote Speaker
6:30 PM – 7:30 PM
Chair: Elizabeth Manning

Meaghan Creed
The role of non-canonical ventral pallidal neurons in reward-seeking behavior

Welcome Reception
7:30 PM – 8:30 PM

Monday, 31 October 2022 (Newcastle City Hall)

Opening Address
8:50 AM – 9:00 AM

Lauren Harms, Thomas Burne

10th Isaac Schweitzer Plenary Award
9:00 AM – 10:00 AM
Chair: Thomas Burne

Jayashri Kulkarni
Using Neurobiology to Innovate Women's Mental Health

Morning Tea
10:00 AM-10:30 AM

Data Blitz Session 1
10:30 AM – 11:00 AM
Chair: Lauren Harms

10:30 AM **Jessica Chandra**
Chronic antipsychotic treatment effects on cognition, neuroinflammation and trophic factors in the midbrain and hippocampus of healthy rats

10:36 AM **Wittaya Suwakulsiri**
Comprehensive analysis of snRNA sequencing in post-mortem brain tissues of people with treatment-resistant schizophrenia

10:42 AM **Noor S. Jarbou**
The Effect of Sertraline and Voluntary Exercise During Pregnancy on Depressive and Associated Behaviours as well as DNA Methylation in Rat Dams

10:48 AM **Isabella Breukelaar**
Neural connectome in adults with a history of child abuse

10:54 AM **Isobel A R Williams**
Can Sodium Butyrate be used to treat deficits associated with perinatal methadone exposure in female and male rat pups?

Symposium 1
11:00 AM-12:00 PM

Brain patterns in adolescence: modelling techniques and clinical applications
Chair/Discussant: Lianne Schmaal
Speakers: Laura Han, Gareth Ball, Niousha Dehestani

Lunch
12:00 PM – 1:45 AM

Monday, 31 October 2022 (Newcastle City Hall)

Poster Viewing - Session 1

12:30 PM – 1:45 PM

MON_01 **Anna Horton**
Investigating the effect of methamphetamine exposure and subsequent withdrawal on parvalbumin interneuron excitability in the prefrontal cortex

MON_02 **Brendan Gillespie**
Maternal immune activation -induced behavioural impairments in offspring are selectively altered by prophylactic maternal treatment with the BDNF-mimetic, 7,8-DHF

MON_03 **Bronwyn M Graham**
Dissociable roles of the basolateral amygdala in fear acquisition and extinction as a function of reproductive experience in female rats

MON_04 **Diana Sketriene**
Glutamatergic changes in dorsal striatum underlie compulsive-like eating in a rat model of binge eating

MON_05 **Georgia Watt**
Effects of chronic 100 mg/kg cannabidiol treatment in male double transgenic APPSwe/PS1ΔE9 (APPxPS1) mice

MON_06 **Jodie Ellen Pestana**
Motherhood alters menstrual cycle related changes in anxiety symptoms and circulating allopregnanolone: A translational approach in female rats and women

MON_07 **Jonathan Flintoff**
Repurposing antidiabetic drugs to treat cognitive impairment: Applications for schizophrenia?

MON_08 **Kade Huckstep**
Muscarinic acetylcholine receptors have distinct roles in alcohol consumption vs. seeking in the ventral subiculum of rats

MON_09 **Maria Kuznetsova**
Genetic and environmental modulation of small non-coding RNAs in a mouse model of affective disorders

MON_10 **Mia O'Shea**
Investigating the Role of Orexin in a Mouse Model of Female "Emotional" Stress-Induced Binge Eating

MON_11 **Byron Crimmins**
Basal Forebrain Cholinergic Signaling in the Basolateral Amygdala Promotes Strength and Durability of Fear Memories

MON_12 **Robine Marie Lili Michalscheck**
The effect of the anti-hypertensive drug clonidine on the acquisition and extinction of conditioned fear in rats.

MON_13 **Rose Chesworth**
Preclinical therapeutic utility of cannabidiol for cocaine use disorder

Monday, 31 October 2022 (Newcastle City Hall)

MON_14 **Sunil Srivastav**
EDiPs (Enhanced Dopamine in Prodromal schizophrenia) an animal of relevance to schizophrenia, displays increased phasic dopamine release possibly via upregulation of presynaptic release sites

MON_15 **Timothy Hill**
The nucleus accumbens shell is involved in the selection of nicotine dose

MON_16 **Yasmine Kostoglou**
Angiotensin receptor 1 blockade blocks cancer-induced memory impairment in mice

MON_17 **Asmahan Elgellaie**
Thyroid Axis Hormones: Relations with Cardiometabolic Disease Risk Indices in Major Depressive Disorder

MON_18 **Rita Hitching**
Virtual Reality To Facilitate Delivery of Evidence-Based Treatment For Insomnia.

MON_19 **Withdrawn**

MON_20 **Dylan J. Kiltschewskij**
Alteration of DNA Methylation Associated with Clinical Features of Schizophrenia and Genetic Risk

MON_21 **William Reay**
Evidence of a bidirectional genetic relationship between pneumonia susceptibility and mental health

MON_22 **Christine A. Leonards**
A distinct suppression subnetwork in the default mode network during cognitive tasks

MON_23 **Emiliana Tonini**
Structural and Functional Neural Correlates of Schizotypy: A Systematic Review

MON_24 **Georgia F. Caruana**
Relationships between white matter and cognition in bipolar disorder: a systematic review

MON_25 **Jessica R. Ramamurthy**
Resting-state electrocortical hemispheric asymmetry in schizotypy and depression

MON_26 **Sevil Ince**
Subcortical contributions to salience network functioning during negative emotional processing

MON_27 **Yoshito Saito**
Cortico-cognition Coupling in patients with recent-onset psychosis

MON_28 **Arnav Shesham**
Determining the role of midbrain hormone signalling in binge drinking

MON_29 **Chao Deng**
Epigenetic histone acetylation modulating prenatal Poly I:C induced long-term neuroinflammation in the prefrontal cortex of juvenile female rats

MON_30 **Natalie Matosin**
Effects of psychiatric disease and aging on FKBP5/1 expression are specific to cortical supragranular neurons

MON_31 **Meshwa Patel**
Circadian Clock Gene Expression in Animal Models of Genetic and Acquired Epilepsy

MON_32 **Sheida Shadani**
Neuroplastic effects of psilocybin in mice

MON_33 **K.H. Christopher Choy**
Human HKx31 influenza causes neurological changes reassembling schizophrenia in mice

MON_34 **Lauren Harms**
Loss of asymmetry of the descending vs ascending deviant MMN response in the alternating paradigm

MON_35 **Melissa A Tadros**
Sex- And Region- Specific Differences in Adult Microglia Following Systemic Neonatal Inflammation

MON_36 **Christina Perry**
Voluntary wheel running reduces incubation of craving for alcohol-associated cues.

MON_37 **Elizabeth E Manning**
Using optical recordings to investigate therapeutic mechanisms of selective serotonin reuptake inhibitors relevant to obsessive compulsive disorder

MON_38 **Elysha Ringin**
Associations of cardiovascular risk factors with cognition in bipolar disorder

MON_39 **Alexandra Gaillard**
Effects of cannabinoids on resting state functional brain connectivity: a systematic review

MON_40 **Isabel Chew**
Investigating the Role of pDMS Direct Spiny Projection Neurons in the Transition to Habits

MON_41 **Amber Curry**
Psychological stress alters cell density in the CA1 region of the hippocampus of severe psychiatric disorder cases

2nd Early Career Researcher Network Plenary Award

1:45 PM – 2:15 PM
Chairs: Cassandra Wannan, Kelly Newell

Luke Ney
Quantification of peripheral endocannabinoids: methods and applications to traumatic stress

Monday, 31 October 2022 (Newcastle City Hall)

Early Career Researcher Network Professional Development Awards
2:15 PM – 2:30 PM
Chair: Cassandra Wannan

Memorial for Prof Sally Andrews
2:30 PM – 2:45 PM
Pat Michie and Frini Karayanidis

Data Blitz Session 2
2:45 PM – 3:15 PM
Chair: William Reay

2:45 PM **Ariel L. Dunn**
Behavioural characterisation of a novel mouse model of a schizophrenia-relevant ARX gene mutation found in a person with schizophrenia

2:51 PM **Hayley North**
Transcriptomic analysis suggests inflammation in schizophrenia alters extracellular matrix and vasculature in the SEZ niche: implications for neurogenesis and neuronal migration

2:57 PM **Samara J. Brown**
Sex and suicide specific changes in the kynurenine pathway in the anterior cingulate cortex in major depressive disorder

3:03 PM **Laura K Milton**
FED up with conventional operant testing? Effects of psilocybin on reinforcement learning using novel operant home-cage devices

3:09 PM **Madilyn Coles**
Chronic 5 mg/kg Cannabidiol (CBD) Treatment Reverses Cognitive Deficits in APPswe/PS1ΔE9 Transgenic Female Mice

Afternoon Tea
3:15 PM – 4:00 PM

ECRN Afternoon Tea
Newcastle Room
3:15 PM – 4:00 PM

Monday, 31 October 2022 (Newcastle City Hall)

Oral Presentations: Highest-Ranked Abstracts

4:00 PM – 4:45 PM
Chair: Murray Cairns

4:00 PM **Laisa Umpierrez**
Cannabis extract and its combination with CBD is more effective than CBD alone to reduce methamphetamine relapse in rats.

4:15 PM **Suresh Sundram**
Plasma betacellulin levels differentiates treatment resistant schizophrenia from treatment responsive schizophrenia and other psychotic disorders

4:30 PM **Po-Han Kung**
Frontoamygdalar effective connectivity in youth depression and its association with treatment response

Social Function

Babylon Newcastle
6:00 PM – 10:00 PM

Tuesday, 1 November 2022 (Newcastle City Hall)

13th Aubrey Lewis Plenary Award
9:00 AM – 10:00 AM
Chair: Thomas Burne

Robyn Brown
Harnessing Addiction Neuroscience to Understand Overeating

Morning Tea
10:00 AM – 10:30 AM

Data Blitz Session 3
10:30 AM – 11:00 AM
Chair: Georgia Caruana

10:30 AM **Nicholas Everett**
KNX100: a novel clinical-stage molecule being developed for the treatment of stimulant use disorders

10:36 AM **Helen Clunas**
Effects of β-caryophyllene on inflammatory markers in the Wistar Kyoto rodent model of depression

10:42 AM **Megan Snelleksz**
Higher levels of AKT-interacting protein in the frontal pole from a sub-group of schizophrenia patients with markedly lower levels of muscarinic M1 receptors

10:48 AM **James Agathos**
Cognitively restructuring negative self and social beliefs differentially engages the posterior cingulate cortex

10:54 AM **Sebastien Naze**
Mechanisms and functional significance of imbalanced frontostriatal connectivity in OCD

Symposium 2
11:00 AM-12:00 PM

Neural Circuit Dysfunction in Psychiatric Disorders
Chairs/Discussants: Robin Cash, Lianne Schmaal, Luca Cocchi
Speakers: Ashlea Segal, Lianne Schmaal, Robin Cash, Bjorn Burgher

Lunch
12:00 PM – 1:30 PM

Poster Viewing - Session 2
12:30 PM – 1:30 PM

TUE_01 **Brandon Richards**
Investigating the properties and behavioural roles of RXFP3+ zona incerta/lateral hypothalamus neurons

Tuesday, 1 November 2022 (Newcastle City Hall)

TUE_02 **Brendan V. Navaneethan**
The Sex-Specific Effects of Raloxifene and Maternal Immune Activation on Dorsal Striatal Dopaminergic Transcripts in Adult Rat Offspring

TUE_03 **Delyse McCaffrey**
Cancer sensitizes microglia to stress, which may contribute to the high prevalence of anxiety in cancer patients

TUE_04 **Emily Jaehne**
Effects of early-life environmental enrichment in a rat model of the Brain-Derived Neurotrophic Factor (BDNF) Val66Met gene variant

TUE_05 **Jessica Leake**
Context modulates the consolidation of overlapping fear memories in the basolateral amygdala complex

TUE_06 **Teri Furlong**
A role for the lateral hypothalamus in habitual behaviour

TUE_07 **Kaixin Huang**
Testing the direct role of cognitive flexibility in activity-based anorexia using an automated experimenter-free touchscreen testing system

TUE_08 **Man Kumar Tamang**
The Developmental Vitamin D-Deficiency Rat Produces Autism-Relevant Behaviours and Gut Health-Associated Alterations

TUE_09 **Mia Langguth**
In vivo fibre photometry reveals increased neural activity in the lateral septum is associated with fleeing social contact in mice.

TUE_10 **Phoebe Mayne**
Sex differences in aversive and appetitive spatial memory tasks in mice

TUE_11 **Rhianne L Scicluna**
A novel clinical-stage treatment for the 'dark side' of addiction.

TUE_12 **Roisin A. Moloney**
Preterm Birth Causes Sex-Dependent Disruptions to Key Neurotransmitter Systems Within the Frontal Cortex of Guinea Pigs

TUE_13 **Sharvada Raju**
The role of Betacellulin in working memory performance

TUE_14 **Suzy Alexander**
Rapid assessment of cognition in rats and mice using the dynamic strategy shifting task (DSST)

TUE_15 **Xavier J. Maddern**
Sex differences in the role of cocaine- and amphetamine-regulated transcript in binge drinking

Tuesday, 1 November 2022 (Newcastle City Hall)

TUE_16 **Alexandre Guerin**
Novel pharmacotherapies for young people with methamphetamine use disorder: the MASKOT and CALM studies

TUE_17 **Jayson Jeganathan**
Sequential expression of dynamic facial patterns in melancholic depression

TUE_18 **Rachel Hill**
Maternal and infant outcomes following maternal exposure to SARS-CoV-2 during pregnancy in a Victorian cohort

TUE_19 **Shivani Vaidya**
Muscarinic receptor-targeted interventions in psychiatric disorders: A systematic review and meta-analysis

TUE_20 **Svetlina Vasileva**
Gut microbiome disturbances and treatment response in schizophrenia

TUE_21 **Withdrawn**

TUE_22 **Alec J. Jamieson**
Major depressive disorder associated alterations in the effective connectivity of the face processing network: a systematic review

TUE_23 **Elizabeth Haris**
Structural Covariance of Amygdala Subnuclei in PTSD show distinct patterns

TUE_24 **Withdrawn**

TUE_25 **Withdrawn**

TUE_26 **Yann Quidé**
Childhood trauma moderates schizotypy-related brain morphology: Analyses of 1,182 healthy individuals from the ENIGMA Schizotypy working group

TUE_27 **Yann Quidé**
Depressive symptoms moderate functional connectivity within the emotional brain in chronic pain

TUE_28 **Bruna Panizzutti**
Effects of antipsychotic drugs on energy metabolism

TUE_29 **Kyna Conn**
Defining the 'Scope' of psilocybin efficacy: Serotoninergic outcomes in activity-based anorexia

Tuesday, 1 November 2022 (Newcastle City Hall)

TUE_30 **Sophie R Debs**
Maternal immune activation and estrogen receptor modulation induce distinct changes in inflammatory-related gene expression in the substantia nigra of female and male offspring

TUE_31 **Xiaoying Cui**
Enhanced dopamine synthesis altered RNA methylation in dorsal striatum

TUE_32 **Dominic Kaul**
Human astrocyte cytoarchitecture and function are shaped by stress and associate with trans-psychiatric disorder diagnosis

TUE_33 **Carey Wilson**
The effects of exercise and environmental enrichment on behaviour and gastrointestinal function in a mouse model of obsessive-compulsive disorder (OCD)

TUE_34 **Bianca Jupp**
Stimulating toll-like receptor 4 reduces motor impulsivity in rats and is associated with reduced measures of astrocyte activation in the nucleus accumbens shell

TUE_35 **Nicholas J Burton**
Unpredictable chronic mild stress exposure increases motivational behaviour for reward

TUE_36 **Laura Stanton**
Studying chronic stress effects on hypothalamic corticotrophin releasing hormone (CRH) neuron activity using the unpredictable chronic mild stress (UCMS) model

TUE_37 **Aidan J Price**
Functional dissection of a novel pathway linking stress and action control systems: Hypothalamic corticotrophin releasing hormone (CRH) neuron projection to the globus pallidus externa (GPe)

TUE_38 **Natalie Wall**
Facial Processing Differences in Autistic and Neurotypical Children: An Event-Related Potential Study

TUE_39 **Athena Stein**
Using NODDI to characterise longitudinal changes in free water in children with chronic mild traumatic brain injury

TUE_40 **Behnaz Khavari**
Gene Expression and Its Regulatory Mechanisms are Widely Responsive to Oxidative Stress in Differentiating Neuroblastoma Cells: Significance for Psychiatric Diseases

TUE_41 **Naomi May**
Investigating the phenolic and antioxidant profile of plant-derived extracts: Potential novel therapeutics for brain health

Tuesday, 1 November 2022 (Newcastle City Hall)

Data Blitz Session 4
1:30 PM – 1:45 PM
Chair: Laura Han

1:30 PM **Eva Guerrero**
Changes in addiction-like eating behaviour towards palatable food after vertical sleeve gastrectomy in mice

1:40 PM **Rossana Rosa Porto**
Modulation of morphine reward by mGlu5 receptor is sex-specific and dose-dependent

Symposium 3
1:45 PM – 2:45 PM

Neural Circuit Dysfunction in Psychiatric Disorders
Chairs/Discussants: Claire O'Callaghan, Michael Breakspear
Speakers: Claire O'Callaghan, Ishan Walpola, Brandon Munn

Afternoon Tea
2:45 PM – 3:15 PM

Symposium 4
3:15 PM – 4:15 PM

Translational Approaches for Understanding the Neurobiology of Compulsions, Compulsivity and Habits in Mental Illness
Chairs/Discussants: Elizabeth Manning, Jess Nithianantharajah
Speakers: Poppy Watson, Karly Turner, Laura Bradfield, Iain Perkes

Annual General Meeting
4:15 PM – 4:45 PM
Chair: Thomas Burne

Award Presentation
4:45 PM – 5:00 PM
Chair: Thomas Burne

Conference Discussant
5:00 PM – 5:15 PM
Rachel Hill

Conference Close
5:15 PM
Lauren Harms

Invited Plenary Speakers

10th Isaac Schweitzer Plenary Lecture

Using Neurobiology to Innovate Women's Mental Health

Jayashri Kulkarni – Director, HER Centre Australia & Monash Alfred Psychiatry Research Centre (MAPrc)

Mental disorders represent the leading cause of disability and the highest burden of non-fatal illnesses for women in Australia 47% of women (3.5 million) have experienced mental illness at some time. COVID impacted women's mental health enormously, increasing the number of women with depression, anxiety, PTSD, Eating Disorders, and alcohol use disorder. Yet – the treatments offered for many of these conditions have not varied significantly over the past decades, leaving many women with suboptimal outcomes. In this talk, the role of gonadal hormones will be discussed as current and potential treatments for disorders such pre-menstrual depression, perinatal disorders, and postmenopausal depression. In addition, a bioaetiological model for the development of what is usually called "Borderline Personality Disorder" in women will be discussed. The role of early life trauma and its neurodevelopmental impacts will be discussed and how the application of better neurobiological understanding of this condition leads to new pathways for treatment. Overall, women's mental health has not received special attention or focus as a separate entity within mental health, with poor outcomes for many women. It is time for innovation in the diagnosis, understanding and treatment of women's mental ill health with a greater emphasis on neurobiological research.

2nd Early Career Researcher Network Plenary Award

Quantification of peripheral endocannabinoids: methods and applications to traumatic stress

Luke Ney – Queensland University of Technology

The endocannabinoid system is a profuse lipid signalling system that is a critical mediator of many other well-characterised biological systems, such as the glucocorticoid and catecholamine systems. Endocannabinoid signalling is therefore central the emerging theories of stress reactivity and recovery from traumatic experiences, and it is believed that treatment of trauma can involve modulation of the endocannabinoid system. However, the endocannabinoid system itself is incompletely characterised and little is known about endocannabinoids in the human peripheral nervous system. We developed novel mass spectrometry analyses for measuring endocannabinoids in human hair and saliva and used these methods to produce the world's first characterisation of endocannabinoids in these matrices. We also produced the world's first evidence of differential endocannabinoid signalling in participants with posttraumatic stress disorder who underwent a fear conditioning task and were able to associate these effects with cannabinoid genotypes in healthy participants. Our work also has begun to show potential associations between longitudinal endocannabinoid profiles in hair and memory-related processes in healthy participants, including fear conditioning and intrusive re-experiencing of trauma-related content. This body of work provides extensive new insights into how the endocannabinoid system can be measured in humans, as well as how these measurements can be used in clinical research across a broad spectrum of psychological processes.

Invited Plenary Speakers

13th Aubrey Lewis Plenary Award

Harnessing Addiction Neuroscience to Understand Overeating

Robyn Brown – University of Melbourne & Florey Institute for Neuroscience and Mental Health

With >2.8 million deaths/year attributable to overweight/obesity, it is now the 5th leading cause of global deaths and is rapidly surpassing smoking as the number one killer in the industrialized world. It is crucial, therefore, to understand why people overeat and why it is so difficult to resist the urge to eat “junk food” even in the absence of hunger. A growing body of research has identified striking similarities between attributes of addiction and overeating in obesity. This emerging evidence supports the hypothesis that the brain’s reward circuitry may be dysregulated in case of obesity. This seminar will explore the extent to which drug addiction and diet-induced obesity share coincident neural underpinnings including identifying endophenotypes underlying this behaviour. Furthermore, for women in particular, negative emotions such as stress, frustration, anxiety, and loneliness have been shown to strongly influence eating behaviour and bingeing episodes yet this area remains unexplored, primarily due to a lack of good animal models and a historical lack of focus on female subjects in scientific studies. Robyn will present a novel model of emotional stress-induced binge eating in mice recently developed in her laboratory and data which demonstrates a distinct thalamo-cortical circuit gates this behaviour.

Symposia Abstracts

Symposium 1. Brain patterns in adolescence: modelling techniques and clinical applications

Monday 31 October, 11am – 12pm

Adolescence is an important window for development, but also the period of peak onset of mental disorders, with disruptive and limiting consequences for a young person's potential. Mental disorders are increasingly conceptualised as disorders that may arise due to abnormal brain development. Therefore, it is critically important to characterise brain development, to identify and understand risk factors and indicators of mental disorders. A popular machine learning method to examine abnormal brain development is the "brain age paradigm". The basic modelling principle is to predict age from (sets of) brain features obtained from MRI, resulting in predicted brain age. By contrasting brain age to age, it can be studied whether individuals show younger or older appearing brains. Our symposium brings together 4 experts in developmental brain modelling to discuss important techniques and clinical applications targeted at adolescents. Our symposium will appeal to methodologists interested in using machine learning approaches to model brain patterns, as well as clinicians interested in gaining insight on abnormal brain development in disease. Our symposium is gender balanced and ethnically diverse, including representation from Asia, Europe, and Australasia, and represents multiple career stages, from PhD (Dehestani), to early- (Dr Han), and mid-career researchers (A/Prof Silk, Dr Ball, A/Prof Schmaal). Speakers are advocates for EMCRs and diversity in research, e.g. Dr Schmaal is a mentor in the University of Melbourne "Supporting Women in Science" scheme, Dr Han is guest editor for a journal promoting women in computational science and committee member of the BPA-ECRN.

Chairs and Discussants: Lianne Schmaal (Orygen)

Laura Han, University of Melbourne

Biography: Dr. Han's research is aimed at investigating quantifications of the biological age to better understand the complex interplay between mental health and ageing. She obtained her PhD at the Amsterdam University Medical Centre in 2021, where her work was focused on the development of machine learning models using biological data from large-scale population cohorts and global consortia, and the application of these models to (clinical) datasets to identify contributing factors to biological aging. She was awarded with a Rubicon grant from the Dutch NWO to continue this line of research at the University of Melbourne as a Postdoctoral Research Fellow. Here, she extends her work to young persons and evaluates whether abnormal age-related neurodevelopmental deviations predict functioning, disease severity, and treatment response. This ongoing work is a collaborative effort between, amongst others, researchers involved in the ENIGMA consortium.

Abstract: Previous studies have shown that adults with mood and anxiety disorders have brain patterns that correspond to those that are usually observed at older ages. Specifically, two of the largest mega-analyses in persons with depression show that they are estimated to be +1 year older than non-depressed peers based on whole-brain grey matter structural brain features. However, brain changes in adolescence (i.e., development) are markedly different from age-related brain changes in adulthood (i.e., ageing). This begs the question of whether a single metric of whole brain-based "brain age" does justice to the complex processes involved in brain development. In this talk, I will present methods that calculate individualised scores that signify precocious or delayed brain development. In particular, I will focus on the differences in interpretation of the brain age metric in young persons depending on whether it is an attempt to truthfully capture age-related brain patterns or to evaluate whether it has clinical relevance. Finally, I will present findings from the clinical application of brain age prediction models that investigate whether these scores predict functioning, disease severity, and treatment response.

Gareth Ball, Murdoch Children's Research Institute

Biography: Dr Gareth Ball is Senior Research Fellow at the Murdoch Children's Research Institute (MCRI) and Honorary Senior Fellow in the Department of Paediatrics at the University of Melbourne. Dr Ball received his PhD from Imperial College London in 2012. Following this, he was awarded a 3-year MRC Special Training Fellowship to study infant brain development at the Centre for the Developing Brain, King's College London. Dr Ball moved to Australia and joined the Developmental Imaging group at the Murdoch Children's Research Institute in Melbourne in 2016. He was recently awarded a 5-year Emerging Leadership (Level 1) Fellowship from the NHMRC to support his research program. Dr Ball's research sits at the interface of paediatrics, neuroscience and machine learning and focuses on the development and application of analysis methods to large clinical imaging datasets in order to understand the impacts and outcomes of early adverse events, including preterm birth, on typical brain development.

Abstract: Typical brain development follows a protracted trajectory throughout childhood and adolescence. Deviations from typical growth trajectories have been implicated in neurodevelopmental and psychiatric disorders. Recently, the use of machine learning algorithms to model age as a function of structural or functional brain properties has been used to examine advanced or delayed brain maturation in healthy and clinical populations. Termed 'brain age', this approach often relies on complex, nonlinear models that can be difficult to interpret. In this talk, I'll discuss the practical application of brain age models to understand typical brain development and introduce novel methods to identify cortical features that explain errors in brain age prediction on an individual level. I'll demonstrate that while brain age estimates based on cortical development are relatively robust and consistent across model types and preprocessing strategies, significant between-subject variation can exist in the features underlying brain age estimates.

Niousha Dehestani, Deakin University

Biography: Niousha Dehestani is a second year PhD student in cognitive neuroscience at Deakin university. Her research focuses on investigating the association of brain maturation, puberty development and psychopathologies by using normative modelling and machine learning approaches.

Abstract: Delayed and precocious pubertal timing have both been previously linked to the emergence and severity of psychopathology during adolescence. However, variability in the methods used to calculate pubertal timing may contribute to the inconsistencies in the literature. In terms of brain development, it also remains unclear whether abnormal brain trajectories parallel a change in pubertal timing, and whether either delayed or precocious development, or both, negatively impact psychopathology. Our understanding of the mechanisms that link pubertal timing to mental health problems via brain development thus remain largely unknown. To gain more insight in these mechanisms, I have developed robust and generalizable models for calculating timing of puberty and brain maturation, resulting in "brain age" and "puberty age" indices. Residuals from these models indicate individual differences in brain development and pubertal timing, respectively. I will present findings on whether "brain age" or "puberty age" may better capture associations with psychopathology, as well as discuss what feature-types might improve the sensitivity to detect these clinical associations.

Symposia Abstracts

Symposium 2. Neural Circuit Dysfunction in Psychiatric Disorders

Tuesday 1 Nov, 11am – 12pm

The importance of dysfunctional neural circuitry in psychiatric disorders is increasingly recognized. This symposium will focus on recent efforts to reliably delineate neural circuit dysfunction including disorder-specific and transdiagnostic features. We will illustrate the importance of interindividual variation in neural circuitry and the 'real-world' application of personalized brain stimulation to target and modulate aberrant brain circuits. Diversity statement: This symposium brings together a diverse team of speakers in terms of gender (50% female), career stage (2 ECRs and 2 midcareer researchers) and cultural and international perspectives (50% born overseas; A/Prof Lianne Schmaal is from The Netherlands; Dr Robin Cash was born in Germany, grew up in New Zealand and Australia and spent substantial time in Canada; Dr Bjorn Burger and Ashlea Segal are from urban and rural Australia). Our guest Chair Dr Luca Cocchi is from Switzerland. We have a broad range of expertise and experience across the speakers and chairs, including in neuroscience (LS, RC, BB, AS, LC), clinical psychiatry (BB), neuropsychology (LS, AS) and machine learning (LS, RC, AS, LC). The speakers are active in advocacy work for EMCRs and gender diversity in research through mentorship programs and committees.

Chairs and Discussants: Robin Cash (Melbourne University), Lianne Schmaal (Orygen and Melbourne University), Luca Cocchi (QIMR Berghofer Medical Research Institute, Brisbane)

Ashlea Segal, Turner Institute, Monash University

Biography: Ms Ashlea Segal is a PhD Candidate at Monash University specalising in neuroscience and psychiatry. Her research focuses on understanding individual-level brain changes associated with psychiatric disorders. This involves processing multiple large multimodal neuroimaging datasets—including structural, functional, and diffusion imaging—to model patient-specific brain changes across multiple macro topological brain scales.

Abstract: Talk title: Regional, circuit, and network heterogeneity of neural abnormalities in psychiatric disorders. Psychiatric disorders are characterized by individual heterogeneity in patterns of divergent brain structure, which raises questions about the mechanisms driving phenotypic similarities between patients assigned the same diagnosis. One possible explanation is that anatomically heterogeneous brain abnormalities are functionally connected to common brain circuits or networks across patients. In this talk, I will outline the importance of studying individual differences in brain abnormalities associated with psychiatric disorders. I will then introduce a novel framework combining normative modeling with elements of lesion network mapping to map the functional brain circuits and networks within which individual—level anatomical abnormalities are embedded. Next, I will present novel evidence derived from structural, functional, diffusion imaging across six major psychiatric disorders (attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive compulsive disorder, schizophrenia) which illustrates the importance of considering the circuit and network context of disorder-specific and disorder-general (transdiagnostic) pathophysiology. Namely, that the clinical expression of disease is not driven solely by sites of primary pathology, but also by the effect of this pathology on remote, connected systems.

Lianne Schmaal, Orygen & The University of Melbourne

Biography: Associate Professor Lianne Schmaal is an MRFF career development fellow and a Dame Kate Campbell fellow with the Centre for Youth Mental Health, The University of Melbourne and Orygen. She is

the head of the Mood and Anxiety Disorders Research Program at Orygen, which covers a broad spectrum of research ranging from identifying mechanisms underlying mood and anxiety disorders to trialling novel treatments. A key focus of Lianne's research program is on addressing the heterogeneity of the diagnosis and course of mood and anxiety disorders and suicidal thoughts and behaviours by integrating clinical, psychosocial, neurobiological and genetic data through computational modelling and machine learning methods. In addition, Lianne established and leads the two largest neuroimaging consortia on depression and suicidal behaviours worldwide, i.e. the ENIGMA Major Depressive Disorder (MDD) and the ENIGMA Suicidal Thoughts and Behaviours (STB) consortia. These international consortia pool neuroimaging, cognitive, psychosocial, genetic and clinical data from >35,000 people from >100 research institutes in 16 different countries worldwide.

Abstract: Talk title: Functional brain alterations in depression identified through large-scale data sharing A key objective in the field of translational psychiatry over the past few decades has been to identify brain biomarkers of mental disorders, to support the development of more effective interventions. However, various barriers have impeded the detection of clinically relevant neuroimaging markers and the translation of neuroimaging into clinical practice, including underpowered studies and a lack of reproducible findings. Large-scale data collection or pooling initiatives have been established to address the issue of small sample sizes. The Enhancing NeuroImaging Genetics through Meta-Analysis Major Depressive Disorder (ENIGMA MDD) consortium was established to boost statistical power to find brain abnormalities associated with depression. ENIGMA MDD pools data from >10,000 individuals from 49 research cohorts from 15 countries worldwide. In this talk, novel findings on functional brain alterations during rest (resting state fMRI) associated with depression will be presented. In addition, functional brain alterations that are unique to different stages of life and different stages of illness will be highlighted. Finally, findings in depression will be compared with functional brain alterations in other mental disorders, including post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD), derived from the ENIGMA PTSD and ENIGMA OCD consortia using the same harmonised processing and analytical protocols. The clinical and scientific implications of these insights will be discussed.

Robin Cash, Melbourne Neuropsych Centre & BiomedEngineering, University of Melbourne

Biography: Dr Robin Cash is an ARC-funded senior research fellow at the University of Melbourne specialising in brain stimulation and neuroimaging. After completing a PhD in Neuroscience at UWA, he trained with leading research teams across Germany, USA and Canada. He has focused on developing faster, personalised and more reliable brain stimulation therapeutics. An accelerated form of brain stimulation that he developed has been implemented in >10,000 patients in North America and his personalisation methodology is seeing rapid global uptake. He developed one of the first personalised TMS interventions (Cerebral Cortex, 2014) and performed some of the first work demonstrating the effects of TMS on brain connectivity (Neuroimage, 2017). His recent research focusses on understanding and harnessing the relation between brain network architecture and TMS clinical outcomes. His latest publications in this area have consistently ranked in the top 5% of international research outputs (Altmetric) and attracted the 2020 HBM Editors' Choice Award for 'most noteworthy and impactful manuscript'.

Abstract: Talk title: Targeting dysfunctional circuits using brain stimulation: personalization, generalizability and reproducibility Emerging research indicates that many psychiatric disorders are characterized by dysfunctional brain circuits rather than isolated brain regions. In this talk, I will introduce how this circuit-based framework has reshaped and improved the capacity to identify optimal brain stimulation targets for psychiatric disorders over the past 12 months. I will detail new findings on the importance of personalising brain sitmulation targets according to individual-specific brain network architecture and how this generalizes beyond the prefrontal cortex to other brain regions. Lastly, I will illustrate how a circuit based framework can help to reconcile neuroanatomically divergent findings in depression from the past 20 years of task-based

neuroimaging data comprising >100 experiments. By applying a connectivity-based analysis framework, statistically highly robust brain circuits could be delineated for the first time. These recapitulated clinically meaningful and independently derived models of depression circuitry. Moreover, in a cohort of individuals treated with noninvasive brain stimulation, therapeutic outcome was significantly dependent on how effectively this circuit was targeted on a personalized basis.

Bjorn Burgher, Queensland Neurostim Centre & QIMR Berghofer

Biography: Bjorn Burgher is an early career psychiatrist. He was the recipient of the Royal Australian and New Zealand College of Psychiatrist's Early Career Psychiatrist Award 2022. He is undertaking a PhD in computational psychiatry at QIMR Berghofer under the supervision of Prof. Michael Breakspear and Dr. Luca Cocchi. He obtained his clinical fellowship in 2018 and worked for Queensland Health as a consultant psychiatrist in the Early Psychosis. He is a founding member of the Australia Brain Foundation, a not-for-profit organisation that invests in translational brain disorder research. He is the director of the Queensland Neurostimulation Centre, the first clinical enterprise of the Australia Brain Foundation, translating computational methods into the clinical practice of personalised TMS for treatment resistant disorders.

Abstract: Talk title: Real world effectiveness of personalised TMS and biomarkers of clinical response Identifying predictors of clinical response to neurostimulation is critical to ensure judicious use of such a time and resource intensive therapy. Previous research has attempted to establish clinical, patient and biological predictors of TMS response, but was undermined by the variability of standard targeting practices. We have recently translated personalised TMS in the clinic using Cash et al.'s functional targeting methods. I will present summary data from our clinic, Queensland Neurostimulation Centre, after 12 months of operation to illustrate the realworld effectiveness of personalised TMS. Furthermore, I will explore the predictive power of three promising factors which could be deployed in the clinic; patient profile on underlying dimensions of depression, the link between stimulation site and symptom clusters, and cortical structure at the stimulation point.

Symposia Abstracts

Symposium 3. Novel systems-level insights for neuropsychiatric symptoms

Tuesday 1 Nov, 1:45 PM – 2:45 PM

Reconciling how the brain shapes cognition and behaviour at a systems level – across a variety of scales – remains a key challenge in neuroscience. This area holds promise for advancing our understanding of neuropsychiatric symptoms and for identifying new treatment options. Our symposium brings together new frameworks for a systems-level understanding of neuropsychiatric symptoms, drawing insights from cytoarchitecture, brain rhythms, large-scale functional neuroimaging and biophysical modelling. A shared focus across the talks will be the role of the ascending neuromodulatory system in shaping brain-wide dynamics. We will cover our empirical and theoretical work advancing new frameworks for: noradrenergic and serotonergic modulation of brain dynamics and behaviour; the hippocampal sharp-wave ripple as a driver of spontaneous thought; and von Economo neurons in interoception and awareness. We will demonstrate how failures in these processes underpin a variety of psychiatric symptoms – with the overarching theme that considering a systems-level approach to these symptoms can offer new insights into understanding and treating them. Representing gender diversity, the chair/nominee is a female ECR. We represent a range of career stages: 0-5 yrs post-PhD (Munn); 5-10 yrs post-PhD (O'Callaghan, Shine); senior researcher/psychiatrist (Breakspear); psychiatry trainee (Walpola); and a range of institutes: Sydney, Newcastle, South Eastern Sydney Local Health District /NeuRA. We also represent a unique mix of applied backgrounds: physics (Munn), clinical neuropsychology (O'Callaghan), medicine (Shine), and psychiatry (Breakspear, Walpola).

Chairs and Discussants: Claire O'Callaghan (University of Sydney), Michael Breakspear (University of Newcastle)

Mac Shine, University of Sydney

Biography: Mac is a systems neurobiologist working to understand the mechanisms of cognition and attention using functional brain imaging, both in health and disease. He has a particular interest in understanding how the different arms of the ascending arousal system flexibly modulate the cross-scale organisation of the brain to facilitate adaptive behaviour. He graduated from Medicine at The University of Sydney in 2007, obtained his PhD from The University of Sydney in 2013 and worked at Stanford University in California, USA, as an NHMRC CJ Martin fellow as a post-doctoral student. He currently runs an integrative neuroscience group at the University of Sydney where he is employed as a joint-Robinson/NHMRC/Bellberry fellow.

Abstract: Neuromodulatory arousal systems imbue the nervous system with the flexibility required for adaptive behaviour. These neuromodulatory systems – including serotonin, noradrenaline, dopamine and acetylcholine – play a crucial role in shaping behaviour and are among some of the key sites of pathology in neuropsychiatric disorders. Rich frameworks exist to explain how these systems shape behaviour. My talk will integrate these frameworks with novel hypotheses detailing how these systems shape large-scale neural dynamics. I will focus on the noradrenergic and serotonergic systems. Using evidence from our own empirical work and theoretical neurobiology, I will demonstrate how the noradrenergic locus coeruleus dynamically shapes the excitability and receptivity of neurons across the brain, to produce large-scale network changes and integration. A proposed framework for serotonin takes inspiration from the fact that over 95% of serotonin in the body is released in the gastrointestinal tract. Much in the way that serotonin-induced peristalsis facilitates the work of digestion, serotonergic influences over cognition can be reframed as performing the work of cognition. I will argue that the central serotonergic system allows the brain to arbitrate between different cognitive modes as a function of serotonergic tone: low activity facilitates cognitive automaticity,

whereas higher activity helps to identify flexible solutions to problems. These frameworks offer systems-level insights into how noradrenaline and serotonin shape adaptive behaviour, and, help explain why there are such pervasive links between pathology in these systems and psychiatric symptoms. References Wainstein…Shine. (2022). TiCS 26(6),527-538 Shine (2019) TiCS 23.7;572-583. Shine et al. (2018). Netw Neurosci 2.3;381-396

Claire O'Callaghan, University of Sydney

Biography: Claire O'Callaghan is a research fellow at the University of Sydney. She works across human cognitive and clinical neuroscience, exploring cognitive functions in the healthy brain and how they are affected in neuropsychiatric conditions. Her research combines neuropsychology, neuroimaging, mathematical modelling and psychopharmacology. Claire trained as a clinical neuropsychologist then completed her PhD at NeuRA/UNSW in 2015. She was awarded an NHMRC Neil Hamilton Fairley Early Career Fellowship in 2014, which took her to the University of Cambridge for a postdoc with Professor Trevor Robbins (2015-2019). She returned to the University of Sydney in 2019 and is currently supported by a Talented Researcher Fellowship from the Faculty of Medicine. Abstract: Mind-wandering, or spontaneous thought, has become a captivating topic for cognitive neuroscientists. Clinically, alterations in this process are a transdiagnostic feature of neuropsychiatric disorders. Indeed, this ability is impaired in a variety of psychiatric (i.e., schizophrenia, depression, ADHD) and neurodegenerative (i.e., Parkinson's, dementia) conditions. Mind-wandering is well described in terms of its phenomenology and the large-scale neural networks that support it. However, we know very little about what neurobiological mechanisms trigger a mind-wandering episode and sustain the mind-wandering brain state. My talk will focus on the role of ascending neuromodulatory systems in shaping mind-wandering. I will advance the hypothesis that the hippocampal sharp wave-ripple (SWR) is a compelling candidate for a brain state that can trigger mind-wandering episodes. The occurrence of the SWR is heavily dependent on hippocampal neuromodulatory tone – and I will describe how the interplay of neuromodulators may promote the hippocampal SWR and trigger mind-wandering episodes. I will cover human empirical work from ourselves (and others) demonstrating the role of impaired mind-wandering in neuropsychiatric disorders, and, I will outline the novel framework for neuromodulatory influences over the SWR, including our work testing this hypothesis in mouse data. The overarching goal of the talk will be to advance a novel systems-level hypothesis for mind-wandering, which also has critical implications for understanding and treating impairments in this process across neuropsychiatric conditions. References O'Callaghan et al. (2021). Philos Trans R Soc B: Biol Sci, 376(1817), 20190699 Walpola … O'Callaghan (2020). Cortex, 125(233-245) O'Callaghan C et al. (2019). PNAS, 116: 3316-3321

Ishan Walpola, South Eastern Sydney Local Health District, NeuRA

Biography: Ishan Walpola is a psychiatry trainee at South Eastern Sydney Local Health District. He is undertaking a research project at NeuRA investigating the von Economo Neuron in Schizophrenia. He has a particular interest in understanding the role of interoceptive neuropsychopharmacology in psychiatric conditions, including the negative symptoms of Schizophrenia.

Abstract: The mysterious von Economo Neuron (VEN) has many unique properties that have led to speculation that these large, spindleshaped cells – which have been identified in only a select number of species – may be involved in processes as complex and varied as intuition, social cognition, and self-awareness. In humans, VENs are prominently found only in layer Vb ventral subregions of the anterior insula and anterior cingulate cortex. Of interest to psychiatry, VEN abnormalities have been reported in behavioural variant frontotemporal dementia, addiction and schizophrenia. Much work remains to provide a neurobiologically grounded understanding of these cells and their role in neuropsychiatric illness. My talk will take the known neurotransmitter receptor expression profile of von Economo Neurons as a starting point to understand the cytoarchitecture of interoceptive neuropsychopharmacology both within and beyond the

cerebral cortex. Particular interest will be paid to the dendritic branching pattern of these morphologically distinct pyramidal-type neurons – likely projecting from cortical regions for autonomic control to the brainstem and spinal cord – in order to extrapolate how unique cellular structure can give rise to unique cellular function. I will review what is known about VEN pathology in Schizophrenia, and based on the above neurobiological considerations, discuss a role they might play in the negative symptoms of Schizophrenia. References Walpola et al. (2017). Neuropsychopharmacology, 42(11), 2152-2162.

Brandon Munn, University of Sydney

Biography: Brandon Munn a post-doctoral researcher at the University of Sydney. His work aims to understand the hidden order of complex systems through physics-inspired insights. He completed his PhD in the Complex Systems group at the University of Sydney's School of Physics in 2019. He is currently based within the University of Sydney's Brain and Mind Centre where he applies biophysical modelling techniques to human and preclinical data, to understand how cross-scale systems in the brain interact to produce cognition and behaviour. He has a particular interest in understanding how the ascending arousal system coordinates largescale brain patterns, with implications for how this may shape healthy adaptive behaviour and be affected in neuropsychiatric illness.

Abstract: Models of cognitive function typically focus on the cerebral cortex and overlook functional links to subcortical structures. Such corticocentric views fail to consider a role for the highly-conserved ascending arousal system and the computational capacities it provides the brain. Furthermore, cognition and behaviour do not arise from the modulation of individual neurons, but from the population dynamics of neural ensembles. Quantitative models that link microscale neuronal neuromodulation to systems-level brain function can address these issues, offering new insights into brain-behaviour relationships and providing new frameworks for integrating theoretical and experimental work. My talk will describe how such modelling approaches can advance the systems-level frameworks for neuropsychiatric symptoms that have been proposed in this symposium. I will draw on examples from our own empirical studies, including human neuroimaging work linking brain dynamics and conscious awareness with the noradrenergic system; and coarsegraining of neural dynamics from C elegans, zebrafish, mice and macaque that hint towards the hierarchical, modular organisation of the brain across phylogeny. Together, my talk will synthesise the frameworks presented in the symposium and I will propose modelling approaches as a viable strategy to test these ideas across scales and across species. I will further highlight avenues where these techniques could advance understanding and treatment of psychiatric symptoms. References Munn et al. Nature communications (2021) 12.1;1-9 Shine, Müller, Munn et al (2021) Nature neuroscience 24(6);765-776

Symposia Abstracts

Symposium 4. Translational approaches for understanding the neurobiology of compulsions, compulsivity and habits in mental illness

Tuesday 1 Nov, 3:15 PM – 4:15 PM

Disturbances in flexible, adaptive behaviour are a transdiagnostic feature of mental illnesses including addiction, obsessive compulsive disorder (OCD), and eating disorders. Behavioural inflexibility is often studied within the associative learning framework that contrasts goal-directed control with rigid stimulus-bound habitual behaviours. This framework is useful for cross-species translational research aimed at identifying behavioural elements and neural substrates t hat underly inflexible behaviour in mental illnesses, to help guide the development of novel targeted treatments. However this approach also has its limitations, particularly in the study of compulsive behaviours. Our symposium brings together experts from the fields of behavioural neuroscience, neuropsychology, and clinical psychiatry to discuss behavioural inflexibility in both humans and non-human animals. We will present empirical and theoretical work examining overlaps and distinctions between habits, compulsions, and compulsivity. The presentations will highlight novel preclinical paradigms aimed at identifying these behaviours, experiments identifying the putative aberrant neural circuitry that underlie them, and discuss links to transdiagnostic clinical disorders. This symposium features organizers and speakers from UNSW, UTS, University of Newcastle, Sydney Children's Hospital Network and the Florey, with a mix of genders and career stages: Level B (Watson, Turner, Manning), Level C (Bradfield, Perkes) and Level D (Nithianantharajah). Symposium speakers have diverse backgrounds and viewpoints on habits and compulsions and include two pre-clinical researchers, one experimental psychologist and one psychiatrist .

Chairs and Discussants: Lizzie Manning (Chair, University of Newcastle), Jess Nithianantharajah (Discussant, Florey Institute of Neuroscience and Mental Health)

Poppy Watson, School of Psychology, University of New South Wales

Biography: Dr. Poppy Watson received her PhD from the University of Amsterdam in 2016. She then worked in the Habit Lab (with Sanne de Wit) before moving to UNSW to work with Prof Mike Le Pelley. She is now an ARC Discovery Early Career Researcher Award (DECRA) research fellow with a focus on using basic science to better understand important societal and health issues. With expertise in translating experimental paradigms from the field of animal associative learning to humans, she has led work investigating how human decision-making is biased by exposure to rewarding outcomes such as high-calorie food or nicotine in both healthy and clinical populations. Poppy's recent work in this area has been supported by a pilot grant from the National Drug and Alcohol Research Centre (NDARC) at UNSW. Dr Watson has an outstanding track record relative to opportunity, having published 37 peer reviewed journal articles, with >1200 citations and a H index of 20.

Abstract: Habits are the subject of intense international research. Under the associative dual-process model the outcome devaluation paradigm has been used extensively to classify behaviours as being either goal-directed (sensitive to shifts in the value of associated outcomes) or habitual (triggered by stimuli without anticipation of consequences). This has proven to be a useful framework for studying the neurobiology of habit and relevance of habits in clinical psychopathology. However, in recent years issues have been raised about this rather narrow definition of habits in comparison to habitual behaviours experienced in the real world and observed in the clinic. Specifically, defining habits as the absence of goal-directed control, the very specific set-ups required to demonstrate habit experimentally, and the lack of direct evidence for habits as stimulus-response behaviours are viewed as problematic. I will address key critiques that have been raised

about habit research within the framework of the associative dual process model and discuss the implications for understanding disorders of compulsivity.

Karly Turner, Decision Neuroscience Lab, University of New South

Biography: Dr. Karly Turner received her PhD from the Queensland Brain Institute (UQ) in 2016. As a recipient of a NHMRC CJ Martin Early Career Fellowship she then moved to the UK to work with Professor Trevor Robbins at the University of Cambridge and now works in the Decision Neuroscience Lab at UNSW with Prof. Bernard Balleine. Her research is focused on dissecting the role of corticostriatal circuitry in decision-making and action control using translational tasks in rodents to improve our understanding of neuropsychiatric conditions. Dr Turner has 20 peer reviewed journal articles, including first-author publications in leading journals such as Journal of Neuroscience and Neuroscience and Biobehavioural Reviews, and her growing independent research is being supported by a UNSW Goldstar award and covid strategic support grant. In 2021 Karly received 1st Prize for Postdoc presentations in the Australian "Stay Connected Neuro" seminar series, and she has several competitive travel awards from organizations including the International Behavioural Neuroscience Society (IBNS), International Brain Research Organization (IBRO) and Federation of European Neuroscience Societies (FENS).

Abstract: Habits are defined as responses that are triggered automatically by stimuli and do not adapt when consequences change. Excessive habits have been linked to symptoms of inflexibility in a range of neuropsychiatric disorders, including those in addiction and OCD. However, habits have been challenging to study in the lab and there is limited preclinical evidence of specific stimuli triggering specific habitual behaviour. To facilitate the translational dissection of the psychological and neural underpinnings of habits we recently developed a novel paradigm to measure explicit and specific stimulus-response behaviours in rats. An innovative feature of this task is that it can dissociate impaired goal-directed control from habits, which is critical for understanding behaviour relevant to mental health disorders.

Laura Bradfield, University of Technology Sydney

Biography: Laura Bradfield completed her PhD in Neuroscience with Prof. Gavan McNally at the University of New South Wales (UNSW) in 2010. She spent the following 8 years as a Post-doctoral researcher for Prof. Bernard Balleine at University of Sydney and UNSW. During this time she published a number of high impact journal articles regarding the behavioural and brain mechanisms of decisionmaking in journals such as Neuron, Nature Neuroscience, and Current Biology. Bradfield started her own research group in 2018 during which she has battled through COVID-related disruptions to produce 20 publications, as well as being awarded an ARC discovery project as CIA and an NHMRC Ideas grant as sole CI. Bradfield is also a review editor at eLife and eNeuro. Her current research focuses on the behavioural and brain mechanisms of decision-making and action control, its modulation by context, and its dysfunction in disorders and degenerative diseases that feature compulsivity.

Abstract: Compulsivity is a trait that spans numerous mental health disorders and neurodegenerative diseases, from substance use disorder to Parkinson's disease. Neuroinflammation in brain regions such as the hippocampus and striatum is also commonly expressed in the brains of individuals who suffer compulsive-related diseases and disorders. However, the evidence linking compulsive action control with local neuroinflammation in these regions is correlative, and a direct, causal link is yet to be established. Several concurrent projects in our laboratory have employed rats and/or mice to investigate whether neuroinflammation in hippocampus and/or striatum is causal to impaired action control. Specifically, we have induced neuroinflammation by injecting the endotoxin lipopolysaccharide (LPS) into the dorsal hippocampus of mice, or into the dorsal or ventral striatum of rats, and tested the consequences of this for goal-directed action control and choice behaviours using a range of behavioural paradigms that involve rodents pressing

levers for food, including Pavlovian-instrumental transfer, outcome devaluation, and outcome-selective reinstatement. Neuroinflammation in the dorsal hippocampus and dorsal striatum appeared to facilitate performance on these tests, whereas neuroinflammation in the ventral striatum impair it. Together, these results suggest the precise pattern of neuroinflammation expressed in the brain of a compulsive individual will determine the level and type of dysfunctional action control they experience.

Iain Perkes, Psychiatry & Mental Health and Paediatrics & Children's Health, Faculty of Medicine and Health, University of New South Wales, Kensington, NSW, Australia

Biography: Iain Perkes is a physician-scientist whose research focusses on the transdiagnostic characterisation of behaviour and circuitry of disorders including OCD and Tourette syndrome using behavioural neuroscience and MR imaging. He is a Senior Lecturer at UNSW and the Sydney Children's Hospital Network (SCHN) where he established and leads the Mental Health Clinical Research Unit (MHCRU). Iain also leads the SCHN clinical research translation service for OCD as part of a national collaboration, OCD BOUNCE, which he co-founded with Professor Jessica Grisham and Professor Lara Farrell. He leads the Computational Psychiatry team in Professor Balleine's UNSW Decision Neuroscience Lab and is an Associate Editor for the Australian and New Zealand Journal of Psychiatry (Q1). Iain completed his medical degree at the University of Newcastle, Australia, in 2010. His intercalated research year was completed at Cambridge University's Neuroscience Critical Care Unit supervised by Professor David Menon and Professor Ian Baguley. He then trained as a psychiatrist at Royal Prince Alfred Hospital in Sydney before completing child and adolescent psychiatry training in SCHN. In 2017 Iain was awarded an NHMRC Medical Postgraduate Scholarship to investigate the pathophysiology of OCD supervised by Scientia Professor Bernard Balleine and Scientia Professor Philip Mitchell at UNSW, he continued clinical work in Dubbo during this time. His research is supported by national and international grants such the Tourette Association of America Young Investigator Award. Iain has been recognized with awards from the World Psychiatric Association (WPA) and International Association of Child and Adolescent Psychiatrists and Allied Professionals (IACAPAP).

Abstract: Goal-directed behaviour adapts to changes in the strength of outcome values and associations with causative actions. Controlled experiment paradigms entrain behaviour learnt to earn rewards, and impairment to goal-directed behaviour is then demonstrated by actions that persist despite reduction of reward salience. Cross-species experimentation has established the neural substrates of these elements as subregions of the caudate, putamen, orbitofrontal and prefrontal cortices. Neuropsychiatric conditions are associated with disruption to these same corticostriatal circuits. Moreover, a range of characteristic maladaptive repetitive behaviours including compulsions, drug-seeking, tics, and gambling characterise these clinical conditions and map to the concept of disturbance in decision-making. In context of the behavioural and anatomical overlap between these clinical conditions and decision neuroscience, cross-species tasks applied to investigate a range of mental disorders have shown impaired goal-directed behaviour in discrete cohorts of people diagnosed with schizophrenia, autism spectrum disorder, and obsessive-compulsive disorder. In parallel, impaired goal-directed behaviour has been interpreted by some as compulsions. I will present data from a transdiagnostic sample which show impaired behavioural sensitivity to outcome devaluation and Pavlovian-instrumental transfer across 20 diagnostic constructs including OCD, Tourette syndrome, gambling disorder, and alcohol use. These findings will be set against previously published and other recently acquired data to consider the interpretation of impaired goal-directed behaviour as synonymous with compulsions or compulsivity.

Oral Abstracts

Cannabis extract and its combination with CBD is more effective than CBD alone to reduce methamphetamine relapse in rats.

Presenting Author: Laisa Umpierrez

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Background
Methamphetamine (METH) use disorder is associated with severe health problems, and there are currently very few effective treatments available. Drug development initiatives are increasingly interested in the therapeutic potential of cannabinoids, such as Cannabidiol (CBD) for treatment of psychiatric disorders including METH addiction. Indeed, CBD reduces relapse to METH-seeking behaviour and METH-induced sensitization. This study aimed to examine whether a novel cannabis extract (GOO) and its combination with CBD reduces relapse to METH in rats as well as their effects on relapse to sucrose, a naturally reinforcing stimulus, and their rewarding properties.

Methods
To assess the therapeutic potential of GOO and/or CBD and their specificity to psychostimulant drug effects, male Sprague-Dawley rats underwent standard self-administration and reinstatement procedures for i) METH or ii) sucrose. Animals were trained to self-administer METH/sucrose via lever press, then this response was extinguished and subsequently reinstated by METH primed injection (1mg/kg;i.p.) or access to sucrose. 30 min prior to each reinstatement session, rats were administered intraperitoneally with Vehicle, CBD (80mg/kg), GOO, or CBD+GOO.Finally, to determine whether these cannabinoids have rewarding properties, rats were tested in the conditioned place preference (CPP) paradigm.

Results
All cannabinoid treatments reduced relapse to METH-seeking behaviour, but only the CBD+GOO treatment showed a significantly higher effect than CBD alone. None of the cannabinoid treatments affected relapse to sucrose-seeking, and there was no difference between treatment conditions on the baseline exploratory locomotor activity during the sucrose reinstatement sessions. Neither GOO, CBD nor their combination produced conditioned place preference, suggesting that these compounds are not intrinsically rewarding.

Conclusions
This is the first study to analyse the effect of a cannabis extract and its supplementation with CBD and provides evidence for the potential use of a novel alternative to treat METH use disorder. The combination of both treatments prevented METH relapse better than those provided by CBD alone, showing a synergistic effect to further reduce relapse. It also demonstrates that the effects of the cannabinoid treatments are specific to psychostimulant drug effects rather than to general reward mechanisms. Additionally, the lack of intrinsic rewarding properties suggests low abuse potential, hence increasing prospects that they are a viable intervention.

Oral Abstracts

Plasma betacellulin levels differentiates treatment resistant schizophrenia from treatment responsive schizophrenia and other psychotic disorders

Presenting Author: Suresh Sundram

Authors
Suresh Sundram - Monash University; Monash Health

Background
Symptom based diagnostic ambiguity plagues clinical and research endeavours to improve outcomes for people with psychotic disorders. Reliable pragmatic biomarkers to assist with diagnosis or treatment will provide substantive improvements to current care. From the clinical observation of response/non-response to conventional antipsychotic drugs (APD), we identified a potential molecular mechanism of action for the APD, clozapine, involving the epidermal growth factor (EGF) system that is effective in treatment non-responsive schizophrenia (TRS). Reasoning that signalling augmentation by clozapine may indicate a hypofunctioning system, we investigated peripheral levels of the EGF ligand, betacellulin, in a range of psychotic disorders and healthy controls.

Methods
Peripheral venous blood was collected and plasma assayed for betacellulin using commercial ELISA systems from three separate cohorts. Cohort 1 comprised patients with TRS who were assayed prior to and 26 weeks after commencing clozapine treatment and healthy controls; cohort 2 was a cross sectional sample of patients who were stably treated on clozapine >6 months; and cohort 3 was a cross sectional sample from multiple patient groups from the Survey of High Impact Psychosis (SHIP). Parametric and non-parametric statistics were used to compare between groups with post-hoc tests as appropriate.

Results
There was a highly significant main effect (p=0.0005) between healthy controls (median BTC 2385pg/ml, 95%CI 1652-2657; n=28), people with schizophrenia (1502pg/ml, 1332-1717; n=288), schizoaffective disorder (1981pg/ml, 1575-2901; n=71), mood disorders (2131pg/ml, 1780-2796; n=121) and other psychoses (2324pg/ml, 1693-2643; n=44) with schizophrenia significantly less than mood disorder. When schizophrenia was divided into TRS (clozapine treated) (1166pg/ml, 1005-1294; n=161) and non-TRS (2247pg/ml, 1729-2672; n=127) groups there was a highly significant overall effect (p<0.0001). Dunn's post-hoc multiple comparison tests showed the TRS group to be significantly less than healthy controls (p=0.006), non-TRS, schizoaffective and mood disorders (all p<0.0001) and other psychoses (p=0.001).

Conclusions
We used a reasoned clinical and bench-based approach to identify putative biomarkers to test in the clinic. Markedly decreased BTC levels in plasma samples from people with TRS compared to healthy controls, other diagnostic and non-TRS groups indicate its potential as a diagnostic and treatment biomarker. Moreover, inspection of the data indicates a minor proportion of each other patient group also demonstrated BTC values below the range of healthy controls. This suggests possible transdiagnostic alignment of pathological mechanisms and more importantly, a possible role for clozapine outside schizophrenia in these patients.

Oral Abstracts

Frontoamygdalar effective connectivity in youth depression and its association with treatment response

Presenting Author: Po-Han Kung

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Background
Altered frontoamygdalar function is hypothesised to underpin impaired emotion regulation in youth depression and an individual's capacity to benefit from first-line depression treatment. However, the precise frontoamygdalar mechanisms contributing to youth depression and prognosis remain inconclusive. This study aimed to characterise how cognitive reappraisal dynamically modulates frontoamygdalar effective connectivity in young people with depression, and to assess its utility in predicting individual response to a randomized clinical trial featuring cognitive behavioural therapy (CBT) plus fluoxetine or placebo.

Methods
One hundred seven unmedicated young people with moderate-to-severe depression and 94 healthy controls carried out a cognitive reappraisal task during functional magnetic resonance imaging (fMRI). After the task, 87 participants with depression were randomised and received 12 weeks of CBT, plus either fluoxetine or placebo. Dynamic causal modelling was used to investigate effective connectivity between the amygdala and prefrontal regions implicated in reappraisal: pre-supplementary motor area, ventrolateral (vlPFC), dorsolateral, and ventromedial (vmPFC) prefrontal cortices. We compared these baseline connectivity parameters in patients and controls, as well as treatment remitters and non-remitters assessed at a 12-week follow-up.

Results
Depressed participants showed weaker negative (disinhibitory) modulation of vlPFC-to-amygdala connectivity in relative to controls (expected value = 0.29 Hz, posterior probability = 1.00). Leave-one-out cross-validation demonstrated that this effect was sufficiently large to predict individual diagnostic status (r = .20, p = .003). Depression remission was associated with reduced excitatory modulation of vmPFC-to-amygdala connectivity (expected value = -0.56 Hz, posterior probability = 1.00), though this effect size did not predict individual remission (r = -.02, p = .561).

Conclusions
Youth depression is characterised by altered frontoamygdalar effective connectivity during reappraisal in circuits associated with attentional and semantic processing. Relatedly, modulation of vmPFC-to-amygdala connectivity during cognitive reappraisal, potentially reflecting an individual's capacity to reorient from internal to external states, is associated with response to treatment, though its predictive validity requires further validation.

Data Blitz Abstracts

Data Blitz Session 1

Chronic antipsychotic treatment effects on cognition, neuroinflammation and trophic factors in the midbrain and hippocampus of healthy rats

Presenting Author: Jessica Chandra

Authors
Jessica Chandra - Schizophrenia Research Laboratory, NeuRA
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Background
Elevated cytokines in brain regions associated with dopamine dysfunction, including the midbrain, characterises a high inflammatory biotype, seen in ~45% of people with schizophrenia. Antipsychotics may aid in dampening inflammation and increasing trophic support; however, cytokines positively correlate with lifetime antipsychotic exposure in the post-mortem human midbrain and so the neuroprotective role of antipsychotics remains unclear. This study aims to determine the effects of antipsychotics on markers of inflammation and neurotrophic support in the midbrain and hippocampus to test if long term antipsychotic treatment is associated with neuroinflammation, reduced trophic support and/or poorer cognition evident in people with schizophrenia.

Methods
Adult male Sprague-Dawley rats were treated daily with 1mg/kg of a typical (haloperidol) or atypical (risperidone) antipsychotic or vehicle, supplemented in cookie dough, for 7 months (n=16/group). Animals underwent a novel object recognition (NOR) task 6 months into treatment to assess for chronic treatment effects on cognition, indexed as a discrimination ratio between the time spent exploring a novel object compared to a familiar object. At 7 months, midbrain and hippocampal tissue were dissected and RNA was extracted for qPCR analysis of markers of inflammation (IL6, IL1B, IL1R1, GFAP, NfkB) and trophic factors/receptors (BDNF III, BDNF IV, TrkBTK+, TrkBTK-).

Results
Haloperidol impaired NOR performance [F(2,38)=4.71, p=0.002 (LSD p<0.05)]. Time spent exploring the novel object was negatively correlated with TrkBTK+ mRNA in the midbrain in the haloperidol treatment group (r= -0.5673, p=0.041), despite no group-wise effects on BDNF/TrkB in the midbrain. With risperidone treatment, IL1R1 mRNA in the midbrain was increased (37%) compared to controls (p=0.021) and BDNF III mRNA was reduced (35%) compared to haloperidol treatment (p=0.024). Gene expression levels of inflammatory mediators and trophic molecules in the hippocampus was not altered by either treatment nor did they correlate with NOR performance.

Conclusions
Chronic risperidone treatment may induce a specific inflammatory response in healthy rodents involving only the IL1-receptor, but not cytokines typically associated with neuroinflammation, which may compromise neuronal integrity alongside the putative reduction in trophic support. Whilst HAL-induced cognitive impediments are unrelated to hippocampal gene expression of inflammatory mediators or neuronal health factors, the association with midbrain TrkBTK+ mRNA implicates TrkBTK+-containing midbrain dopamine neurons in hippocampal-dependent behaviours. Overall, the subtle effects of long-term antipsychotics on neuroinflammation and trophic factors in the midbrain and hippocampus implies greater lifetime antipsychotic exposure in patients relates to disease-induced neuroinflammation, rather than prolonged treatment.

Data Blitz Abstracts

Data Blitz Session 1

Comprehensive analysis of snRNA sequencing in post-mortem brain tissues of people with treatment-resistant schizophrenia

Presenting Author: Wittaya Suwakulsiri

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Background
Schizophrenia is a chronic psychiatric disorder that affects 24 million people globally. Treatment outcomes vary substantially and are likely to depend upon different pathologies of schizophrenia. Understanding of different subtypes of schizophrenia is needed for better treatment outcomes. Our previous studies in human post-mortem brain tissue have identified low expression of EGF system ligand, betacellulin (BTC), in treatment-resistant schizophrenia (TRS). However, the molecular function of BTC in TRS is not understood. This study aimed to identify cell-specific molecular subtypes of TRS. We hypothesised distinct cell types would show altered molecular pathways that segregate TRS from treatment responsive schizophrenia and controls.

Methods
To better understand schizophrenia subtypes, we performed fluorescent activated nuclei sorting (FANS) and single nuclei (sn) RNA sequencing techniques. Nuclei were isolated separately from 15 human post-mortem brain tissues using centrifugation and filtration (5 for schizophrenia with normal expression of BTC, 5 for schizophrenia with low BTC expression and 5 for healthy controls). DAPI-positive nuclei were sorted and captured for snRNA sequencing using flow cytometry and microfluidic device from 10x Genomics. snRNA sequencing data were analysed using cellranger pipeline, Seurat and DESeq2 packages in R.

Results
We captured 159,143 nuclei in total (37,592 for schizophrenia with low BTC expression (lBTC), 60,476 for schizophrenia with normal BTC expression (nBTC) and 61,075 for healthy controls). Cell clustering analysis identified GABAergic, Glutamatergic, Dopaminergic neurons and their subtypes. Key finding is a differential gene expression analysis between 3 groups. Interestingly, gene expression in schizophrenia with nBTC group is largely dissimilar from schizophrenia with lBTC and healthy control groups with genes related to migration of neurons (TNC) and extracellular matrix modification such as ADAMs, TIMP2, suggesting the role of cell-extracellular communication in schizophrenia that is distinct from lBTC and control groups.

Conclusions
These exciting new snRNA data provide new understanding of different pathologies of schizophrenia at a single cell level. The data offer gene candidates for each brain cell type that may be used to differentiate TRS from treatment responsive schizophrenia. Findings from this study offer opportunities to identify novel targets for precise treatments of different schizophrenia subtypes for better treatment outcomes.

Data Blitz Abstracts

Data Blitz Session 1

The Effect of Sertraline and Voluntary Exercise During Pregnancy on Depressive and Associated Behaviours as well as DNA Methylation in Rat Dams

Presenting Author: Noor S. Jarbou

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Background
Sertraline is the frontline pharmacotherapy for the treatment of depression during pregnancy. However, there is little evidence regarding the effects of sertraline on maternal behaviour or the maternal brain. Furthermore, the efficacy of non-pharmacological approaches to treatment in pregnancy, such as exercise, are unclear. Therefore, the aim of this study was to examine the effects of sertraline and exercise during pregnancy on postnatal depressive-like and associated behaviours, in a rat model of depression. We also investigated the effects of these treatments on the maternal brain, focusing initially on DNA methylation, which regulates gene expression and has been implicated in depression.

Methods
Twenty-four female Wistar-Kyoto (WKY; model of depression) rats were divided into three groups: 1. WKY-Sertraline; 2. WKY-Exercise, 3. WKY-Vehicle; Six female Wistar rats were included as controls. Rats were treated with sertraline (10mg/kg) or vehicle (33% propylene glycol) twice/day, from gestational day (GD) 1 to postnatal day (PN) 14. The WKY-Exercise group were provided access to a running wheel during pregnancy for 3 hours/day from GD1-18. Dam and litter characteristics were measured. Dams underwent behavioural testing at 5-weeks postnatal to assess depressive-, anxiety- and cognitive-like behaviours. DNA methylation markers (Dnmt1 and Dnmt3a) were measured in the prefrontal cortex using RT-qPCR.

Results
The WKY-Sertraline group gained 39% less weight in their first pregnancy week compared to all other groups and produced smaller litters compared to Wistar controls (-43%) and WKY-Exercise (-38%). Maternal sertraline treatment did not significantly affect dam behavioural measures. The WKY-Exercise group however showed reduced anxiety-like behaviours, spending more time in the centre of the Open-Field-Test compared to WKY-Vehicle (132%), and more time in the open arms (620%) and less time in the closed arms (-22%) of the Elevated-Plus-Mase, compared to WKY-Vehicle. Furthermore, WKY-Exercise dams showed a 64% increase in Dnmt3a mRNA levels in the frontal cortex compared to WKY-Vehicle.

Conclusions
Voluntary exercise during pregnancy in the WKY rat model, reduced postnatal anxiety-like behaviour in the dam. This was accompanied by elevated Dnmt3a gene expression in the prefrontal cortex, suggesting this region may be sensitive to wider changes in gene expression following maternal exercise. In contrast, maternal sertraline did not impact these behaviours or markers. Maintaining sertraline treatment beyond PN14, may have resulted in broader effects on dam behaviour, which should be explored further. Our findings suggest a long-term beneficial effect of exercising during pregnancy and supports future studies examining the effects of exercise in antenatal depression in the human population.

Data Blitz Abstracts

Data Blitz Session 1

Neural connectome in adults with a history of child abuse

Presenting Author: Isabella Breukelaar

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Background
It is estimated that more than 10% of children experience sexual, physical or emotion abuse, and that the impact of abuse on brain connectivity may contribute to greater risk for and severity of psychiatric disorders. It is hypothesised that abuse during childhood triggers a cascade of physiological processes that impact brain structure and function. However, it is still unknown how extensive these changes are and how they relate to adult psychopathology. This study utilised whole-brain functional magnetic resonance imaging analyses to investigate the extent to which a history of childhood abuse impacts the adult brain across multiple psychiatric conditions.

Methods
127 adults who reported a history of childhood sexual, physical, and/or emotional abuse and 442 individuals with no experience of abuse completed a fMRI scan and underwent a psychiatric interview to determine diagnosis. For every individual, inter-regional intrinsic functional connectivity was estimated between 436 brain regions, comprising intra and inter-network connectivity of eight large-scale brain networks. Group-wise differences between those with and without a history of child abuse were investigated controlling for clinical diagnosis, age, sex, years of education and scan motion. For significant changes in connectivity associations with sex, diagnosis, symptom severity, age and type of abuse were investigated.

Results
Individuals with a history of abuse demonstrated an altered connectome signature of increased connectivity across 261 connections between 117 regions of the brain (pFWE<0.014). This pattern was primarily characterized by increased connectivity within somatomotor and attention networks, and between these networks and executive control, and default mode networks. Connectivity of this signature was independent of nature of abuse, current symptomatic state or clinical diagnosis, but connectivity differences were more prominent in healthy, depressive and anxiety groups than those with stress disorders. Additionally, significant differences were observed in connectivity for those that experienced abuse pre- and post-adolescence.

Conclusions
These findings suggest that the experience of child abuse leads to physiological changes in intrinsic connectivity, independent of psychopathology, in a way that may impact functioning of systems responsible for perceptual processing and attention. These findings also suggest unique neural manifestations of abuse depending on whether abuse occurs prior to adolescence or not and may imply different treatments are required for individuals with abuse-related psychiatric conditions dependent on abuse timing. A better understanding of how abuse changes the brain can further work to develop interventions, such as cognitive training, to prevent or minimise adverse outcomes of abuse in at-risk children.

Data Blitz Abstracts

Data Blitz Session 1

Can Sodium Butyrate be used to treat deficits associated with perinatal methadone exposure in female and male rat pups?

Presenting Author: Isobel A R Williams

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Background
The global opioid epidemic has dramatically increased the number of children with prenatal opioid exposure (POE). POE has a negative long-term impact on children's behaviour and cognition, increasing risk of mental illness. The underlying effects of POE are poorly understood, but are linked to a range of central nervous and enteric system issues such as neuroinflammation, impaired white matter development and gut dysbiosis. Sodium butyrate (NaB) is a short-chain fatty acid that is anti-inflammatory, pro-myelinating and enhances the gut microbiome. This study aimed to assess whether NaB could reverse the gut, brain and behavioral deficits associated with POE.

Methods
Pregnant rat dams were treated with methadone (9/mg/kg/day) and NaB (3% in drinking water), from gestational day ten until postnatal day 17. The offspring were then assessed for changes in physical development, behaviour and cognition during juvenile development (open field test, novel object/place recognition) and into adulthood (five choice serial reaction time task - 5CSRTT). Fecal samples were collected from dams and pups at four timepoints across the experiment and then processed using 16S ribosomal sequencing for gut bacteria diversity and abundance. The pup's serum and brain tissue were collected at two timepoints and used for analysis of inflammation.

Results
Across juvenile development methadone accelerated eye opening and weight gain, increased anxiety in the open-field test and in adulthood impaired attentional processing on the 5CSRTT. Perinatal treatment of dams with NaB and reversed these methadone-induced deficits in offspring – NaB significantly slowed abnormal weight gain and ameliorated attentional deficits in the 5CSRTT. Methadone alone decreased abundance of beneficial bacteria, and this was reversed was by NaB treatment. Methadone increased pups' levels of bacteria linked to obesity and inflammation, an effect ameliorated with concurrent NaB treatment, which additionally reduced bacteria associated with neuroinflammation and microbiome inflammation.

Conclusions
Perinatal exposure to methadone led to impairments in early development that persist into adulthood, particularly impacting anxiety-like behaviour and attention. Notably, this was associated with altered gut microbiome both in dams and their offspring. Treatment with NaB across the perinatal period reversed the majority of methadone-induced deficits, including accelerated weight gain and poor attention, and reversal of methadone-induced gut dysbiosis. Together these results highlight the link between gut integrity and cognition in animal models of POE. Furthermore, it indicates that early treatment with NaB could significantly improve the outcomes of children born with POE.

Data Blitz Abstracts

Data Blitz Session 2

Behavioural characterisation of a novel mouse model of a schizophrenia-relevant ARX gene mutation found in a person with schizophrenia

Presenting Author: Ariel Dunn

Authors
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Background
Schizophrenia is a devastating psychiatric disorder of unknown pathology and only symptomatic treatment options. Multiple genetic mutations associated with schizophrenia hold promise for development of new treatments. We identified one such novel association, the R264Q missense mutation in the ARX gene, which was found in a patient with schizophrenia. The ARX gene encodes a protein which plays a crucial role in neurodevelopmental processes and, thus, we hypothesise this mutation may alter behaviours relevant to schizophrenia. We tested this hypothesis using a mouse model of the Arx R264Q mutation that we developed using CRISPR-Cas-9 gene editing.

Methods
Male and female Arx R264Q mutant mice were characterised across multiple behavioural domains (N = 20-22/genotype) from postnatal day 70. Mice performed various tasks measuring anxious behaviours during the elevated plus maze (EPM), social interaction and recognition, as well as sensorimotor gating (prepulse inhibition, PPI) and locomotion both at baseline and following psychotomimetic drug administration (amphetamine, 5 mg/kg and MK-801, 0.5 and 1mg/kg). Simultaneous local field potential (LFP) recordings were taken during all tasks to assess gamma oscillations from the prefrontal cortex and hippocampus (N = 4/genotype).

Results
Arx mice had significantly reduced social interaction and social recognition compared to WT controls (p = <.0001 - .0047). This reduction was not due to motor deficits, as total distance travelled was comparable between Arx animals and WT controls. Moreover, no changes in exploration or ‘anxiety-like’ hiding were observed in the EPM, indicating a selective social deficit in Arx animals. Mutants also unexpectedly had significantly increased %PPI at baseline (p = .0396), which was reduced following high-dose MK801 (p = .0113; 1mg/kg), but not low dose MK801 (0.5mg/kg) or amphetamine (5mg/kg).

Conclusions
Our novel results show that the ARX gene is likely involved in social regulation and recognition, which was not mediated by general exploration or neophobia. Unexpectedly, the Arx R264Q mutation increased sensorimotor gating compared to controls. The Arx R264Q mouse may then represent a new model relating to social and sensory integration changes in schizophrenia. This may enable the targeted investigation of treatment options for people with schizophrenia and related disorders who show ARX gene variations. Simultaneous LFP recordings will provide further insight into the functional oscillatory changes caused by the mutation and the neurobiology of relevant behaviours to schizophrenia.

Data Blitz Abstracts

Data Blitz Session 2

Transcriptomic analysis suggests inflammation in schizophrenia alters extracellular matrix and vasculature in the SEZ niche: implications for neurogenesis and neuronal migration

Presenting Author: Hayley North

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Background
Compared to controls, people with schizophrenia have reduced markers of neurogenesis in the brain's largest niche for neurogenesis, the subependymal zone (SEZ). A subgroup of schizophrenia cases with elevated cytokines have exaggerated suppression of most neurogenesis and microglia markers and increased macrophage density. While studies show that macrophages can secrete factors that may impair neurogenesis, we do not know if the broad molecular changes are consistent with this possibility, or if other factors are key to inflammatory-related suppression of neurogenesis in schizophrenia. This research aimed to discover alterations across the whole transcriptome relating to SEZ inflammatory status within schizophrenia.

Methods
Deep total-RNA sequencing was performed on RNA extracted from post-mortem SEZ tissue of 27 schizophrenia cases previously designated into low inflammation (n=13) and high inflammation (n=14) subgroups based on cluster analysis of inflammation marker gene expression. Differentially expressed (DE) genes were identified using EdgeR software with a false discovery rate adjusted (FDR) p value < 0.05. The DE gene list was subsequently analysed using Ingenuity Pathway Analysis. Immunohistochemistry was conducted on 14µm thick SEZ sections from the same cohort.

Results
718 genes were DE in high compared to low inflammation schizophrenia (FDR p<0.05). The DE genes were most significantly over-represented in the pathway 'Hepatic Fibrosis/Hepatic Stellate-Cell Activation'. Genes in this pathway, which had predominantly increased expression in high inflammation schizophrenia, encoded proteins involved in extracellular matrix (ECM) stability (including ten collagens) and vascular remodelling including angiogenesis. Collagen-IV was primarily localised around blood vessels and in the SEZ hypocellular gap. The results suggest novel alterations to the ECM and changes to the SEZ vasculature, potentially facilitating immune cell transmigration, which together may dysregulate neurogenesis and neuronal migration.

Conclusions
This is the first discovery-driven comparison of the transcriptome between inflammatory subgroups in schizophrenia brain tissue. The findings of inflammation-dependent changes in the SEZ suggesting angiogenesis and ECM alterations have important implications for how inflammation contributes to heterogeneity in schizophrenia neuropathology; especially with regards to reduced neurogenesis. These molecular-level findings in human brain tissue may be a step towards developing more personalised treatment options for those with elevated inflammation in schizophrenia.

Data Blitz Abstracts

Data Blitz Session 2

Sex and suicide specific changes in the kynurenine pathway in the anterior cingulate cortex in major depressive disorder

Presenting Author: Samara J. Brown

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Background
Major depressive disorder (MDD) is a serious psychiatric disorder that in extreme cases can lead to suicide. Understanding the neurobiological changes fundamental to MDD is hindered by high levels of heterogeneity in the population, suggesting a need for characterisation of specific subgroups. Evidence suggests that alterations in the kynurenine pathway contribute to the aetiology of MDD. Activation of the kynurenine pathway leads to the formation of neuroactive metabolites, including kynurenic acid and quinolinic acid. These metabolites modulate glutamatergic transmission, which contributes to depression pathology. Currently, the status of the kynurenine pathway in the brain of MDD subjects is largely unknown.

Methods
Postmortem anterior cingulate cortex (ACC) was obtained from the National Institute of Health NeuroBioBank. Tissue samples came from individuals with MDD (n=44) that died by suicide or other causes, and matched nonpsychiatric controls (n=36). Gene expression levels of kynurenine pathway enzymes (kynurenic acid arm: KYAT1, KYAT2, KYAT3, KYAT4; quinolinic acid arm: KMO, KYNU, HAAO, QPRT) were investigated via RT-qPCR by high throughput Fluidigm. Metabolite levels of the kynurenine pathway (tryptophan, kynurenine, kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid) were measured using liquid chromatography-mass spectrometry.

Results
We report a significant increase in KYAT2 mRNA in MDD in those that did not die by suicide (p=0.016). MDD subjects that died via suicide had significantly decreased kynurenic acid and 3-hydroxykynurenine in comparison to controls

(p=0.004; p=0.040) and MDD subjects that did not die by suicide (p=0.016; p=0.034). Female MDD subjects had significantly decreased kynurenic acid and 3-hydroxykynurenine in comparison to female controls (p=0.036; p=0.039). Female MDD subjects showed a trend decrease in the kynurenic acid to quinolinic acid ratio compared to female controls (p=0.056). There were no diagnostic changes specifically in males.

Conclusions

Overall, we found sex and suicide-specific alterations in the kynurenine pathway in the ACC in MDD. This is the first molecular evidence in the brain of subgroup-specific changes in the kynurenine pathway in MDD, which not only suggests that treatments aimed at upregulation of the kynurenic acid arm in the brain may be favourable for female MDD sufferers but also might assist in managing suicidal behaviour. As the kynurenine pathway directly regulates glutamatergic receptor activity, these findings also highlight the possible differences in glutamatergic regulation

Data Blitz Abstracts

Data Blitz Session 2

FED up with conventional operant testing? Effects of psilocybin on reinforcement learning using novel operant home-cage devices

Presenting Author: Laura K Milton

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Background
Psilocybin is slated to be the biggest advance in the treatment of psychiatric disorders since Prozac was introduced to the market in the 1990s. The results from clinical trials are promising, however, surprisingly little is known about the mechanisms through which psilocybin acts to cause improvements in patient outcomes. We have previously shown that psilocybin improves cognitive flexibility in a standard deterministic reversal learning task using the Feeding Experimentation Device 3 (FED3) – an open source device that is placed into the home cage to minimise experimenter intervention, reduce stress and increase learning rates, without the need for food restriction.

Methods
Using the FED3 devices, we examined which aspects of reinforcement learning underlie the improvement seen in cognitive flexibility after psilocybin treatment. We first assayed flexible learning again using a within-session reversal task (n= 22) and then tested whether psilocybin improved extinction learning and reinstatement (n= 22), motivation, and economical choice (n= 25) in separate cohorts of female Sprague-Dawley rats. Rats received FED3 devices into their home cages for 3 hours each day, 1 hour after the onset of the dark cycle and were trained to make action-outcome associations at fixed ratios (FR) before treatment, with tests commencing the following day.

Results
FED3 devices facilitate rapid training of action-outcome associations (fixed ratio responding), – FR5 total pokes $\bar{x}$ = 380 at 99% accuracy. These studies extend our previous findings to show that psilocybin improves within-session reversal learning over time (p=.0396) but does not alter learning strategy (win-stay; p=.6494, lose-shift; p=.8268). Psilocybin did not improve the ability of animals to suppress a previously learned association during extinction training (p=.7581) or motivation to respond in a progressive ratio (PR) task (pellets p=.6704, active pokes p=.9863). Intriguingly, psilocybin improved economical choice using a “closed economy” modification of the PR (pellets p=.0112, active pokes p=.0416).

Conclusions
Cognitive inflexibility is characteristic of a range of disorders in which psilocybin is being trialled clinically, and flexible learning has recently been shown to improve after psilocybin treatment in patients with depression. However, in order to understand exactly how long-term effects on psychiatric outcomes might be mediated by the effects of psilocybin on cognitive flexibility, animal studies that pair cognitive tasks with manipulations and measurements of neuronal function are required. The present study provides a comprehensive basis from which to investigate, in detail, how effects of psilocybin on cognition are related to underlying changes in brain function.

Data Blitz Abstracts

Data Blitz Session 2

Chronic 5 mg/kg Cannabidiol (CBD) Treatment Reverses Cognitive Deficits in APPswe/PS1ΔE9 Transgenic Female Mice

Presenting Author: Madilyn Coles

Authors
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Background
Alzheimer's disease (AD) is a disabling neurodegenerative disease characterized by behavioural impairments and declining cognition. The need for novel therapeutics targeting aspects of AD beyond amyloid and neurotransmitter imbalance is demonstrated by the modest efficacy of currently available medications. Targeting the endocannabinoid system, affected in AD, could be a new approach. Cannabidiol (CBD) has anti-inflammatory, anti-oxidant and neuroprotective properties and in vitro and emerging in vivo evidence suggests that CBD possesses therapeutic-like properties for the treatment of AD. Cannabinoids have dose-dependent effects and the therapeutic potential of medium dose CBD for AD transgenic mice has not been assessed in detail.

Methods
We aimed to evaluate the potential of chronic treatment with 5 mg/kg bodyweight CBD to reverse the behavioural deficits of adult APPSwe/PS1ΔE9 mice. 12-month-old APPSwe/PS1ΔE9 transgenic female mice and their wild type-like littermates were treated (post-onset of AD-like symptoms) via daily intraperitoneal injection with 5 mg/kg bodyweight CBD (or vehicle) commencing three weeks prior to and continuing throughout assessment. Domains assessed included anxiety, exploration and locomotion, motor functions, cognition, and sensorimotor gating. Various ANOVAs and one sample t-test statistical analysis techniques were used, and significant differences were determined when p < .05.

Results
APPSwe/PS1ΔE9 mice exhibited a hyper-locomotive and anxiogenic-like phenotype but had wild type-like motor abilities. Importantly, vehicle-treated APPSwe/PS1ΔE9 mice were characterised by object recognition deficits and moderately delayed improvements to spatial learning, both of which were reversed by CBD treatment. AD transgenic mice took generally longer to complete the cheeseboard training (due to a lower locomotion speed). All mice displayed intact spatial memory and retrieval memory, but APPSwe/PS1ΔE9 mice showed reduced levels of perseverance in relation to spatial memory, regardless of treatment condition. Finally, impairments in sensorimotor gating of APPSwe/PS1ΔE9 mice were not affected by CBD.

Conclusions
Chronic administration of 5 mg/kg CBD may have therapeutic value for the treatment of particular behavioural impairments present in AD patients, including recognition impairments. Future research should consider the molecular mechanisms behind CBD's beneficial properties for AD transgenic mice, including changes to amyloid, tau, neuroinflammation, and the endocannabinoid system. Further investigations into sex-specific effects and the therapeutic potential of other phytocannabinoids for AD (including multi-cannabinoid regimes) would be of interest to the field.
This work was supported by the NHMRC Project Grants numbers APP1102012 and APP1141789. MC is supported by a PhD scholarship from Dementia Centre for Research Collaboration.

Data Blitz Abstracts

Data Blitz Session 3

KNX100: a novel clinical-stage molecule being developed for the treatment of stimulant use disorders

Presenting Author: Nicholas Everett

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Background
Despite rising rates of stimulant addiction globally, there are no approved pharmacotherapies. While psychosocial interventions are effective for some, they are inaccessible for many. Therefore, novel pharmacotherapies are urgently needed. KNX100 is a novel molecule discovered through a phenotypic screen for promotion of social behavior in rodents. KNX100 is orally bioavailable, with good plasma and brain half-life and a high brain free-concentration. KNX100 is currently being assessed in a Phase 1 clinical trial under an FDA IND for mitigation of opioid withdrawal symptoms. Here we explored whether KNX100 may also have utility as a novel therapeutic for stimulant use disorders.

Methods
We used a variety of rat, mouse, and non-human primate models of specific characteristics of human stimulant use disorder, in male and female subjects. Specifically, we train rats to self-administer intravenous methemphetamine, or rhesus macaques to self-administer intravenous cocaine, and test the effects of KNX100 on drug motivation and reinstatement of drug-seeking. We also used a recently developed rodent model of mutually exclusive choice between social and methamphetamine reward, and conducted locomotor sensitisation, reward/aversion, and reinforcement control experiments to ascertain the specificity of the effects of KNX100 on methamphetamine addiction-like symptoms.

Results
KNX100 dose-dependently reduced the breakpoint for methamphetamine in male rats, and for cocaine in female rhesus macaques. KNX100 dose-dependently reduced methamphetamine prime-induced reinstatement of methamphetamine seeking, and dose-dependently increased preference for social reward over methamphetamine. KNX100 slightly increased social rewards at the lowest dose, and at higher doses left social reward seeking intact while it inhibited methamphetamine intake. In rats, KNX100 inhibited sensitised methamphetamine-induced locomotor activity without impairing baseline locomotion. KNX100 has no apparent abuse liability, with rats failing to acquire self-administration of KNX100 and KNX100 inducing neither a conditioned place preference nor aversion in mice.

Conclusions
These data indicate that KNX100 decreased motivation to self-administer methamphetamine and cocaine, relapse-like drug seeking, drug reward preference, and methamphetamine-induced hyperlocomotion. KNX100 does not appear to be sedating, aversive, rewarding, reinforcing, or to have broad non-specific effects on motivated behaviour at any of the doses tested. Together, these data, and the fact that KNX100 is already in Phase 1 clinical trials, suggest KNX100 is a promising clinical candidate for methamphetamine and cocaine use disorders.

Data Blitz Abstracts

Data Blitz Session 3

Effects of β-caryophyllene on inflammatory markers in the Wistar Kyoto rodent model of depression

Presenting Author: Helen Clunas

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Background
Inflammation is implicated in the pathology of various psychiatric and mood disorders including depression. Previous studies show that β-caryophyllene (BCP), a bioactive terpene, can improve depressive, anxiety and cognitive behaviours in pre-clinical models. Whether these effects are linked to changes inflammatory pathways is unknown. The aim of this study was to examine the effects of chronic BCP treatment on peripheral inflammatory markers in males and females, using a rodent model of depression.

Methods
: Male and female Wistar-Kyoto (WKY) rats (model of depression) were administered BCP (50mg/kg, i.p.) or vehicle (control) for 3 weeks (n=12/sex/group). After chronic (21-days) treatment, rats were euthanised and blood was immediately collected by cardiac puncture. Cytokines were measured in the plasma fraction by multiplex assay using commercially available methods. BCP-treated WKY (WKY-BCP) rats were compared to WKY and Sprague-Dawley controls (SD-CTRL, n=12/sex, vehicle, non-depressed).

Results
In males, Il-1α and IL-6 were increased in the WKY vs SD (+68% and +76%, respectively, p0.05 WKY-BCP vs SD-CTRL). BCP also decreased MIP-1α (-83%, vs SD, p<0.05), which was not apparent in the WKY group (p<0.05 WKY-CTRL vs SD-CTRL). However, BCP exacerbated the increased TNFα in the WKY groups (+48%, p=0.06 and +63% p<0.01, WKY-CTRL and WKY-BCP vs SD, respectively). In females, BCP decreased IL-1β (-97%, p<0.05 vs SD-CTRL) with no changes in the WKY-CTRL group (vs SD-CTRL). 16 additional inflammatory markers were unaltered.

Conclusions
The WKY model showed sex-specific differences in select pro-inflammatory markers. BCP appeared to lower and restore levels of pro-inflammatory cytokines to control-like levels in the WKY model of depression; however, confounding results were observed in TNFα levels, as BCP further increased this cytokine compared to WKY CTRL. The results of the present study suggest that BCP treatment does have some anti-inflammatory effects. This could occur through cannabinoid CB2 receptor activation and downstream pathways that influence inflammation. Further investigation into the roles of these peripheral cytokines in depressive symptoms are justified.

Data Blitz Abstracts

Data Blitz Session 3

Higher levels of AKT-interacting protein in the frontal pole from a sub-group of schizophrenia patients with markedly lower levels of muscarinic M1 receptors

Presenting Author: Megan Snelleksz

Authors
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Background
We have shown AKT-interacting protein (AKTIP) RNA is lower (-23%) in the frontal pole from people with schizophrenia. It is now argued that studying subgroups within schizophrenia is fundamental to understanding its molecular pathology. Our laboratory has defined a subgroup, termed Muscarinic Receptor Deficit Schizophrenia (MRDS), defined by markedly lower levels of muscarinic M1 receptors (CHRM1) in a quarter of people with schizophrenia. We have also shown AKTIP RNA is higher (+57%) in the cortex of CHRM1 knockout mice. Hence, we seek to determine if AKTIP protein is altered only in the cortex from MRDS due to altered CHRM1 signaling.

Methods
This study uses autoradiography to measure CHRM1 binding in the frontal pole from people with schizophrenia and controls to first establish a cohort of 19 MRDS (15 male, 4 female), 19 non-MRDS (15 male, 4 female) and 19 controls (12 male, 7 female). Based on our gene expression studies in human frontal pole and mouse cortex, this study uses Western Blotting to determine if the lower levels of AKTIP RNA translates to lower levels of protein in the frontal pole from people with schizophrenia and if such changes were limited to those with MRDS due to altered CHRM1 signalling.

Results
This study found that CHRM1 binding is 90% lower in the frontal pole from MRDS, with no differences between non-MRDS and controls. This study also found higher levels (+43%) of AKTIP protein in the frontal pole from people with schizophrenia. However, when separating schizophrenia into 2 subgroups (MRDS and non-MRDS), this increase in AKTIP protein was specific to the MRDS group (+47%), with no differences between non-MRDS and controls.

Conclusions
Our findings suggest that AKTIP is altered in the cortex of patients with MRDS possibly due to altered CHRM1 signalling. Significantly, CHRM1 binding in the frontal pole from MRDS was profoundly lower than any other region previously studied. The cohort used in our previous transcriptomic study was predominantly patients who were non-MRDS and therefore the lower levels of AKTIP RNA in those subjects may be an attempt to normalize levels of that protein. As AKTIP is implicated in cell signalling and vesicle trafficking, our data suggests these important functions may be particularly affected in the MRDS subtype of schizophrenia.

Data Blitz Abstracts

Data Blitz Session 3

Cognitively restructuring negative self and social beliefs differentially engages the posterior cingulate cortex

Presenting Author: James Agathos

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Background
Negative self-beliefs are a core feature of psychopathology, encompassing both negative appraisals about oneself directly (i.e., self-judgment) and negative inferences of how the self is appraised by others (i.e., social-judgment). Cognitive restructuring methods which aim to challenge individuals' maladaptive self-beliefs are a core treatment mechanism of gold-standard psychotherapies. However, it is poorly understood what underlying neural mechanisms support the restructuring of these two kinds of negative self-beliefs.
Methods
in a novel paradigm, healthy control participants (n=78; 35 female, 41 male, 1 non-binary) used Socratic questioning techniques to restructure self-judgment and social-judgment negative self-belief statements during ultra-high resolution 7-Tesla functional magnetic resonance imaging. General linear model (GLM) analyses examined contrasts of challenging versus repeating statements, as well as comparing challenging of self- versus social-judgment beliefs. Analyses were corrected for multiple comparisons using threshold-free cluster-enhancement (TFCE), PFWE < .05. Subsequent psychophysiological interaction (PPI) analyses examined functional connectivity between regions involved in cognitive restructuring.
Results
Cognitive restructuring broadly elicited prominent activation in the default mode network (DMN), in conjunction with salience, reward and frontoparietal control networks. Restructuring of self- versus social-judgment statements was primarily distinguished by differential involvement of the posterior cingulate cortex (PCC), with comparatively greater activation in the ventral PCC/retrosplenial cortex during challenging of self-judgment statements, and in the dorsal PCC/precuneus while challenging social-judgment statements. During challenging relative to repeating of self-beliefs, both regions showed increased functional connectivity with the supplementary/pre-supplementary motor areas, while the dorsal PCC/precuneus displayed greater connectivity with salience/social cognition networks, including the anterior insula and dorsal anterior cingulate cortex.
Conclusions
Our findings highlight differential patterns of PCC engagement between the cognitive restructuring of self-judgment and social-judgment negative self-beliefs. During cognitive restructuring, we propose that the dorsal PCC in particular plays a role in modulating dynamic interactions between the DMN and frontoparietal/salience networks; thereby facilitating flexible switching between internal and external environments, allocation of attentional resources, and modification of self-representations that are coordinated by the PCC. Further work may examine how aberrant activation or interregional connectivity of these PCC subregions may inhibit cognitive restructuring success, or underpin psychiatric symptomatology.

Data Blitz Abstracts

Data Blitz Session 3

Mechanisms and functional significance of imbalanced frontostriatal connectivity in OCD

Presenting Author: Sebastien Naze

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Background
The diagnosis of obsessive-compulsive disorder (OCD) has been associated with changes in frontostriatal resting-state connectivity. However, replication of prior findings is lacking and the functional and mechanistic understanding of these effects is incomplete.

Methods
Following clinical and neuropsychological assessments, participants with a diagnosis of OCD (n=52) and matched healthy controls (n=45) underwent resting-state functional, structural, and diffusion neuroimaging.
We assess changes in the activity of discrete frontostriatal systems in OCD, use computational modelling to infer mechanisms of cortico-striatal and striato-cortical neural couplings, and diffusion MRI to assess anatomical connectivity.

Results
OCD participants showed greater functional connectivity (T=4.3, pFWE=0.01) between the nucleus accumbens (NAcc) and the orbitofrontal cortex (OFC), but lower functional connectivity between the dorsal putamen (dPut) and lateral prefrontal cortex (lPFC) (T=3.8, pFWE=0.04) relative to controls. Computational modelling suggest that NAcc-OFC connectivity changes reflect an increased influence of NAcc over OFC activity and reduced OFC influence over NAcc activity (posterior probability, Pp>0.66). Conversely, dPut showed reduced modulation over lPFC activity (Pp>0.95). These functional deregulations emerged on top of a generally intact anatomical substrate.

Conclusions
We provide out-of-sample replication of distinct changes in ventro-anterior and dorso-posterior frontostriatal connectivity in OCD, and advance the understanding of the neural underpinnings of these abnormal patterns of brain connectivity. These findings motivate the development of targeted therapies normalising distinct frontostriatal dynamics in OCD.

Data Blitz Abstracts

Data Blitz Session 4

Changes in addiction-like eating behaviour towards palatable food after vertical sleeve gastrectomy in mice

Presenting Author: Eva Guerrero

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Background
People with obesity often display high levels of disordered eating including compulsive or addictive eating, which can hinder weight-loss outcomes. Bariatric surgery is currently the most effective weight loss treatment for obesity, which results in reduced appetite and improved glycaemic regulation due to pronounced changes in the gut-brain axis. Emerging evidence suggests neuroendocrine alterations after bariatric surgery may also impact disordered eating via changes in reward-related food intake. As such, the aim of this study was to investigate the effect of bariatric surgery on addiction-like behaviour towards highly palatable food in a mouse model of vertical sleeve gastrectomy (VSG).

Methods
C57BL/6 mice (n=74) were fed a high-fat diet for at least 10 weeks before undergoing VSG or sham surgery. The operant self-administration paradigm was then used to assessed three addiction-like behaviours: 1) high motivation to obtain the substance; modelled using progressive ratio schedule, 2) loss of control over seeking the substance modelled by persistence of lever pressing during periods of reward unavailability; and 3) relapse behaviour modelled by the reinstatement paradigm. Another cohort of mice received stereotaxic injections of dopamine sensor (pAAV-hSyn-GRAB_DA1h) and fibre optic implant into the nucleus accumbens for fibre photometry l recordings during operant testing.

Results
Compared to sham mice, VSG mice showed reduced motivation to work for a palatable food reward, reduced lever pressing during periods of reward unavailability (suggestive of decreased impulsive action/increased control over food-seeking behaviour) and reduced relapse-like behaviour. There was no difference between VSG and sham mice in terms of their learning of the instrumental task or their extinction timecourse, suggesting no impact of VSG on learning. Further, preference and baseline fixed ratio responding for the palatable food reward (Ensure®) was unchanged in VSG mice suggesting the rewarding value of Ensure® was not impacted by VSG. Fibre photometry experiments are ongoing.

Conclusions
Collectively these data suggest that the changes in the gut-brain axis following bariatric surgery have the capacity to ameliorate addictive eating symptoms displayed by people with obesity. Fibre photometry data presented will provide insight into the possible role of dopamine in this effect.

Data Blitz Abstract

Data Blitz Session 4

Modulation of morphine reward by mGlu5 receptor is sex-specific and dose-dependent

Presenting Author: Rossana Rosa Porto

Authors
Rossana Rosa Porto - Western Sydney University
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Tim Karl - Western Sydney University
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Background
Globally, opioid addiction causes significant health, social and economic costs. Men report a higher lifetime use of opioids; however, women are more likely to relapse during abstinence. Current treatments are limited and do not address biological processes involved in addiction. The metabotropic glutamate 5 receptor (mGlu5) receptor is a potential target for treating addiction. Mice with a genetic deletion (i.e. knockout, KO) of mGlu5 exhibit addiction-like behaviour for psychostimulants and ethanol, but their response to opioids has yet to be examined. Assessing opioid addiction-like behaviour in these mice will determine if mGlu5 could be a treatment target for opioid abuse.

Methods
We measured opioid reward using morphine on conditioned place preference (CPP) in mGlu5 KO mice. Male and female mGlu5 KO and WT mice were conditioned to associate 5 or 10 mg/kg morphine with a distinct environment over 4 consecutive days. Following conditioning, preference for the morphine-paired environment was assessed weekly for 4 weeks during morphine abstinence, to test memory persistence, which is an indicator of drug craving and risk of relapse. Locomotor data was also collected during all conditioning and test sessions and assessed for morphine-induced locomotion and locomotor sensitisation.

Results
All male and female mice acquired morphine CPP for 5 and 10 mg/kg morphine. With dose of 5 mg/kg, male WT mice displayed a persistent preference during abstinence while male mGlu5 KO did not. In contrast, female mGlu5 KO mice showed a higher preference on all test days compared to WT females. There were no sex differences in preference for 10 mg/kg morphine. Both 5 and 10 mg/kg morphine induced hyperlocomotion in WT-like mice, while only mGlu5 KO females showed hyperlocomotion after 10 mg/kg morphine administration.

Conclusions
There were opposing effects of genotype in each sex for persistence of morphine preference. These results suggest that male mGlu5 KOs are less susceptible to morphine reward than WTs, while female mGlu5 KOs have higher persistence scores than respective controls. mGlu5 KO mice, regardless of sex, are less sensitive to morphine-induced locomotion than WTs, suggesting that morphine reward and locomotion are mediated by different pathways. Sex seems to play an important role on how mGlu5 modulates addiction-relevant pathology. Future investigations should identify potential mechanisms for the impact of sex on mGlu5 mediation of morphine on reward and locomotor activity.

Poster Abstracts

Poster Session 1: Monday

MON_01 Investigating the effect of methamphetamine exposure and subsequent withdrawal on parvalbumin interneuron excitability in the prefrontal cortex

Presenting Author: Anna Horton

Authors:
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Prof Andrew Lawrence - The Florey Institute of Neuroscience & Mental Health
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Background
Methamphetamine (METH) is a highly addictive psychostimulant that can lead to serious drug dependence and addiction. The transition to drug addiction involves changes within the prefrontal cortex (PFC), which sends excitatory glutamatergic signals from pyramidal neurons to the nucleus accumbens (NAc). Impairment in this pathway is a critical feature underlying relapse vulnerability. The strength and timing of output signals from the PFC are modulated by a number of different types of inhibitory GABAergic interneurons. This project investigates whether a subset of these interneurons expressing parvalbumin (PV) are altered following METH exposure.

Methods
To investigate the effect of repeated non-contingent METH injections on the intrinsic properties of PV interneurons, PV-reporter mice either received experimenter administered vehicle (saline, 0.9% w/v, 10mL/kg, i.p) or METH (2mg/kg, i.p) injections before being placed in locomotor cells to measure locomotor activity for 60min. This was repeated daily for 10 days. 24h after the last administration mice were culled and in vitro whole-cell electrophysiological recordings were made from PV interneurons (labelled with td tomato) to determine whether METH has an effect on the electrophysiological properties of PV interneurons.

Results
METH administration induces locomotor hyperactivity in male and female mice compared to saline controls (****p < 0.0001), with female METH mice moving significantly more than male METH mice (*p < 0.05), however no alterations in intrinsic cell or action potential properties were observed. Further functional data analysis is currently being performed on firing frequency data.

Conclusions
It is important to investigate if alterations in GABAergic signalling within the PFC may contribute to corticostriatal dysregulation in addiction. Preliminary data indicates that repeated METH administration and 24hr withdrawal does not result in alterations in the electrophysiological properties of PV interneurons. Literature suggests that PV output and excitability may vary across intoxication/withdrawal states, so future studies aim to elucidate the activity of PV interneurons in vivo across different addiction states.

Poster Abstracts

Poster Session 1: Monday

MON_02 Maternal immune activation -induced behavioural impairments in offspring are selectively altered by prophylactic maternal treatment with the BDNF-mimetic, 7,8-DHF

Presenting Author: Brendan Gillespie

Authors:
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Background
Infections during pregnancy increase the risk for the offspring developing autism or schizophrenia later in life, and there are no interventions to mitigate this risk. Brain derived neurotrophic factor (BDNF) is altered in the fetal rodent brain following maternal immune activation (MIA); plays an important role in brain development; and reduced expression is associated with autism and schizophrenia, thus BDNF may be a promising target for early intervention strategies. BDNF mimetic 7,8-didydroxyflavone (7,8-DHF) crosses the blood brain barrier and activates the BDNF receptor TrkB. We investigated if maternal supplementation with 7-8 DHF in mice prevents MIA-induced behavioural deficits in offspring.

Methods
C57BL/6 mice were time mated and given plain water or water supplemented with 7-8 DHF (0.015mg/g/day) between gestational day(GD) 9 and birth. On GD17, dams were injected with poly-I:C (20mg/kg IP) or saline. Male and female offspring (8-12/group) were tested in a battery of behavioural assessments relevant to schizophrenia and autism in adulthood. These tests included the open field test and elevated plus maze tests for anxiety, a spontaneous alternation task for working memory, a baited Y-maze paradigm to test cognitive flexibility, sociability tests, and pre-pulse inhibition (PPI) to assess sensorimotor gating.

Results
Similar to previously published studies, offspring exposed to poly-I:C exhibited reduced sociability ($p=0.024$), and a trend towards increased anxiety-like behaviour in the open field test ($p=0.08$) but not elevated plus maze. Exposure to poly-I:C was also associated with learning disruptions during the acquisition phase of the baited y maze in female ($p=0.03$) but not male offspring, and a trend towards an increase in the acoustic startle response in both sexes ($p=0.065$). Maternal treatment with 7-8 DHF did not recover MIA induced sociability deficits or anxiety-like behaviour. However, 7-8 DHF increased PPI ($p=0.02$).

Conclusions
To our knowledge, this is the first study investigating the potential benefit of 7-8 DHF as a prophylactic pregnancy supplement. While 7,8-DHF was not able to recover sociability or anxiety phenotypes, its effects on PPI and locomotion are of significant interest. Indeed, previous studies treating MIA exposed mice with 7-8 DHF in adolescence or adulthood, showed no effect on PPI, suggesting that early maternal treatment may be key. Our data warrant further investigation using a novel, more bioavailable, 7,8-DHF derivative, R13 with promising translational application.

Poster Abstracts

Poster Session 1: Monday

MON_03 Dissociable roles of the basolateral amygdala in fear acquisition and extinction as a function of reproductive experience in female rats

Presenting Author: Bronwyn M Graham

Authors:
Kelly A Kershaw - School of Psychology UNSW
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Background
Fear extinction is an evolutionarily conserved mechanism of fear regulation that occurs when a threatening cue is repeatedly presented in the absence of danger, causing a reduction in fear responses elicited by the cue. In female rats and humans, reproductive experience (i.e., pregnancy) alters the behavioural, hormonal and molecular substrates of fear extinction. E.g., following pregnancy, fear extinction in female rats and humans is no longer modulated by the sex hormone estradiol. Here, we assessed whether reproductive experience also modifies the involvement of a central component of the neural circuitry of fear extinction, the basolateral complex of the amygdala (BLA).

Methods
Nulliparous (virgin) and primiparous (one prior pregnancy; pups weaned one month before behavioural testing) female Sprague Dawley rats received intracranial surgery to implant bilateral cannulas into the BLA. Rats received fear conditioning (5 x white noise conditioned stimulus; CS, paired with 0.4mA footshock), extinction training (30 x CS presentations; no footshock), and an extinction retention test (15 x CS presentations; no footshock) over three consecutive days. Across different experiments, muscimol (a GABA receptor agonist; temporarily inactivates the BLA) or vehicle was infused into the BLA prior to fear conditioning, or prior to or immediately after extinction training.

Results
Temporary inactivation of the BLA prior to fear conditioning impaired the acquisition and consolidation of fear conditioning in both nulliparous and primiparous rats. In nulliparous rats, temporary inactivation of the BLA prior to extinction training suppressed freezing during extinction training, and impaired extinction retention the following day, indexed by high CS-elicited freezing during the retention test. Surprisingly, temporary inactivation of the BLA prior to, or after, extinction training did not impair extinction retention in primiparous rats, indexed by low CS-elicited freezing during the retention test, despite suppressing freezing during extinction training.

Conclusions
The BLA is a central component of the neural circuitry of fear acquisition and its extinction in virgin female rats, consistent with the dominant model of these processes based on research in males. However, after pregnancy, there is a fundamental shift in this neural circuitry, such that female rats no longer depend on the BLA to extinguish fear, despite requiring the BLA to acquire fear. Fear extinction forms the basis of exposure therapy for anxiety disorders. To improve exposure therapy efficacy, we may need to target different mechanisms in females dependent on their reproductive history.

Poster Abstracts

Poster Session 1: Monday

MON_04 Glutamatergic changes in dorsal striatum underlie compulsive-like eating in a rat model of binge eating

Presenting Author: Diana Sketriene

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Background
Intermittent limited access to highly palatable food has been associated with the development of binge-like eating behaviour. Binge eating is characterized by the compulsive engagement in excessive eating and mirrors compulsive drug-seeking observed in substance use disorder. In the latter case, drug consumption continues despite known negative consequences and is associated with glutamatergic dysfunction in the striatum. The present study investigated if ten weeks of intermittent limited access to a high-fat high-sugar diet could result in similar compulsive-like behaviour towards highly palatable food and changes in the brain akin to those observed in substance use disorder.

Methods
Adult male Sprague-Dawley rats were given either extended daily access (24h) or limited intermittent access to highly palatable diet (1h/day, Mon/Wed/Fri) and compared to a control group that only had access to a standard rodent chow. Compulsive-like behaviour was assessed in a conditioned suppression test where an aversive signal was associated with a mild foot shock. The standardized scores for five main behaviours were used to calculate a global “addiction score”. Aggressive behaviour was measured in the bottle-brush test. Western blots analysis were done in a separate cohort of animals.

Results
Rats that received time-limited intermittent access to the high-fat high-sugar diet developed binge-like eating during these access periods over the 10 week protocol . They also showed compulsive-like eating as measured by the conditioned suppression task. These rats also showed increased aggressive behaviour in the bottle-brush test. Furthermore, the intermittent access group was enriched with rats with the highest addiction score. Western blots analysis revealed that rats with intermittent access to ‘junk food’ showed increased expression of GluN2B and GluA1 glutamate receptor subunits in the dorsal striatum.

Conclusions
Collectively these data suggest that occasional access to junk food can cause an addiction-like pathology both in terms of compulsive behaviour towards food and associated neuroadaptations in the brain. The intermittent nature of access seems to be driving these changes as the same was not observed in rats with continuous access to junk food. These findings support the concept of addiction-like glutamatergic dysfunction underlying disordered overeating behaviour and the theory that individuals with history of bingeing are in the highest risk group for developing compulsive-like behaviour.

Poster Abstracts

Poster Session 1: Monday

MON_05 Effects of chronic 100 mg/kg cannabidiol treatment in male double transgenic APPSwe/PS1ΔE9 (APPxPS1) mice

Presenting Author: Georgia Watt

Authors:
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Background
Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive decline and the accumulation of amyloid-β (Aβ), tau hyperphosphorylation, neurodegeneration and neuroinflammation in the brain. There are currently no treatments which stop or prevent the disease progression, highlighting the need for novel therapeutics. Cannabidiol (CBD) has demonstrated antioxidant, anti-inflammatory and neuroprotective properties. Importantly, studies have found that chronic CBD treatment (20 mg/kg and 50 mg/kg) reverses social recognition memory deficits of APPxPS1 transgenic mice, however, no pronounced effects on AD-relevant brain pathology were detected.

Methods
Therefore, this study investigated male APPxPS1 mice in the early symptomatic phase (7.5 months) treated with 100 mg/kg CBD via daily intraperitoneal injections for 6 weeks. Mice were treated for 3 weeks prior to the start of behavioural testing. Mice were then assessed for anxiety, two forms of recognition memory and social behaviours including territorial aggression. Neuropathological analyses for a number of AD-relevant markers were also conducted using ELISA and western blot.

Results
Vehicle-treated APPxPS1 transgenic males demonstrated reduced wrestling behaviour and increased socio-positive behaviours as well was impaired social recognition memory. The deficits in recognition memory were restored by CBD. APPxPS1 mice also exhibited reduced hippocampal levels of TNF-α and IL-1β and elevated cortical levels of BDNF regardless of treatment condition. CBD increased proBDNF levels in WT controls. Aβ42, PPARγ and IBA1 protein levels were not affected by genotype or CBD treatment.

Conclusions
This study demonstrates that high dose CBD restores social recognition memory, thus emphasising the clinical relevance of CBD in AD. The mechanisms involved in CBD's therapeutic effects still require further investigation.

Poster Abstracts

Poster Session 1: Monday

MON_06 Motherhood alters menstrual cycle related changes in anxiety symptoms and circulating allopregnanolone: A translational approach in female rats and women

Presenting Author: Jodie Ellen Pestana

Authors:
Jodie Ellen Pestana - University of New South Wales
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Background
Fluctuations in sex hormones, estradiol and progesterone, across the estrous/menstrual cycle in female rats and women are associated with changes in anxiety, which could contribute to the maintenance of anxiety disorders. Pregnancy causes long-term changes in sex hormonal fluctuations, such as a reduction in circulating estradiol, yet extant research on cyclic-related changes in anxiety has focused on reproductively inexperienced females. Therefore, we employed a cross-species approach to assess whether the impact of estrous/menstrual cycle on anxiety differs pre-versus post-motherhood. We also examined whether circulating allopregnanolone levels (an anxiolytic neurosteroid) differs across the estrous cycle pre-versus post-motherhood.

Methods
Naturally cycling virgin rats (n=14) and mother rats (n=18) were tested twice on the elevated plus maze to measure anxiety-like behaviour; during metestrus (low sex hormones), and proestrus (high sex hormones). In addition, a human community sample of naturally cycling non-mothers (n=35) and mothers (n=28) completed the Patient Health Questionnaire-4 at three timepoints; during the early-follicular phase (low sex hormones), ovulation (high sex hormones), and mid-luteal phase (high sex hormones). Finally, experimentally naïve virgin (n=37) and mother rats (n=36) were euthanised at multiple timepoints to measure plasma allopregnanolone; during proestrus (9am, 2pm, 6pm), estrus (9am), or metestrus (2pm).

Results
Replicating past research, virgin rats showed higher anxiety-like behaviour during metestrus compared to proestrus (ps.05). Conceptually consistent findings were observed in humans. Replicating past research in humans, non-mothers reported higher anxiety and depression during the early-follicular phase compared to other menstrual phases (ps.05). Finally, circulating levels of allopregnanolone were reduced during proestrus in mother rats compared to virgin rats, and mother rats showed a more gradual decline following the peak in allopregnanolone (ps <.05).

Conclusions
Changes in anxiety coincident with cycling hormones is an evolutionarily conserved feature of the estrous/menstrual cycle in rats and women, which may be mitigated following reproductive experience in both species. Given that allopregnanolone fluctuations are thought to underlie menstrual-related effects on anxiety, reductions in circulating allopregnanolone in reproductively experienced females may be one mechanism that mitigates estrous/menstrual effects on anxiety. These findings highlight the importance of not only considering menstrual cycle, but also reproductive status, in studies on anxiety in females.

Poster Abstracts

Poster Session 1: Monday

MON_07 Repurposing antidiabetic drugs to treat cognitive impairment: Applications for schizophrenia?

Presenting Author: Jonathan Flintoff

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Background
Cognitive impairment is a disabling feature of schizophrenia that remains untreated by current medications. Individuals with schizophrenia also experience an increased incidence of metabolic dysfunction alongside cognitive impairment. Currently, glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as liraglutide are used to improve glucose homeostasis in individuals with type 2 diabetes. However, altered insulin signalling may be a common pathophysiological mechanism leading to cognitive impairment in neuropsychiatric disorders. In the current study, we developed a novel flexibility task to examine the effect of the GLP-1RA liraglutide on strategy shifting in a subchronic ketamine model of schizophrenia.

Methods
Firstly, the dynamic strategy shifting task (DSST) was developed to assess cognitive flexibility in male Sprague-Dawley rats. The DSST integrated automated shifts between a cue-light task, fixed location task, visual continuous detection task, and an auditory continuous detection task. After completing training, rats were administered 30 mg/kg ketamine to disrupt strategy-shifting, or saline via intraperitoneal injection over 10 days. After a drug washout of 14 days, rats were administered either 0.4 mg/kg liraglutide or saline, 1 hour before testing on the DSST (n=4 per group). Finally, an intraperitoneal glucose tolerance test was conducted to confirm the effects of liraglutide.

Results
Open field testing indicated ketamine administration significantly increased locomotion on day 10 of injections. No effect of ketamine on the number of trials to criterion was indicated at any stage of the DSST. However, there was a significant increase in the number of incorrect trials made in the rats treated with subchronic ketamine and acute liraglutide during the visual continuous detection task. Furthermore, these rats showed an increase in the number of perseverative errors on the fixed location task. Glucose tolerance testing confirmed liraglutide significantly improved glucose tolerance two weeks post-testing.

Conclusions
This study indicates that acute liraglutide administration does not improve strategy-shifting performance during the DSST. Furthermore, subchronic ketamine does not consistently impair strategy-shifting performance as shown in attentional set-shifting tasks. Interestingly, rats given liraglutide and ketamine showed a perseverative strategy and were unable to shift away from the response required in the cue-light task when tested on the fixed location task. This study confirms the antidiabetic actions of liraglutide even in an acute dosing strategy. However, future studies are needed to investigate whether liraglutide may improve cognitive flexibility in other dosing schedules and models of cognitive impairment relevant to schizophrenia.

Poster Abstracts

Poster Session 1: Monday

MON_08 Muscarinic acetylcholine receptors have distinct roles in alcohol consumption vs. seeking in the ventral subiculum of rats

Presenting Author: Kade Huckstep

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Background
Alcohol Use Disorder is a chronic condition with limited and ineffective therapeutic options despite its large personal and socioeconomic burdens. We have recently shown muscarinic acetylcholine receptors (mAChRs) mediate alcohol consumption and seeking in rats, in part via the striatum; however, involvement of muscarinic signalling in other brain regions involved remains unexplored. The ventral subiculum (vSub) is a strong candidate as it modulates alcohol-seeking via its projection to the nucleus accumbens shell (AcbSh), and densely expresses both M4 and M5 mAChRs. Therefore, we sought to determine the role of vSub M4 and M5 mAChRs in alcohol consumption and seeking.

Methods
In male Indiana alcohol-preferring (iP) rats, a combination of retrograde tracing and RNAscope was used to examine Chrm4 (M4) and Chrm5 (M5) localisation and determine what proportion of vSub cells projecting to the AcbSh express Chrm4 and/or Chrm5. Expression levels of vSub Chrm4 and Chrm5 following long-term alcohol consumption and 14 days abstinence was examined using qPCR. Using the subtype-selective allosteric modulators VU0467154 (M4 PAM) and ML375 (M5 NAM) microinjected directly into the vSub, we examined the functional role of vSub M4 and M5 mAChRs in alcohol consumption, context-induced reinstatement of alcohol seeking, locomotor activity, and food/water consumption.

Results
Chrm4 and Chrm5 were expressed throughout the vSub, including on neurons projecting to the AcbSh. 70% of vSub to AcbSh neurons expressed Chrm4, while 18% expressed Chrm5. Long-term alcohol exposure and abstinence dysregulated the expression of vSub mAChR genes, with Chrm4 significantly downregulated following abstinence from long-term alcohol, while Chrm5 was upregulated following long-term alcohol consumption. Consistent with this, positive allosteric modulation of vSub M4 mAChRs reduced context-induced alcohol-seeking, but not motivation for alcohol self-administration. Conversely, vSub M5 mAChR negative allosteric modulation reduced initial motivation for alcohol self-administration but not context-induced alcohol-seeking. Neither influenced locomotor activity, nor food/water consumption.

Conclusions
Collectively, these data highlight mAChR dysregulation in the vSub following long-term alcohol consumption and abstinence, and that pharmacologically counteracting these alcohol-induced changes can reduce alcohol consumption or seeking behaviours. Further, our data demonstrate that, functionally, vSub M4 and M5 mAChRs are differentially involved, and this is consistent with both the time of dysregulation (following access or abstinence), and the proportion of vSub to AcbSh neurons expressing each mAChR subtype. Allosteric modulation of mAChRs may be a promising future target for pharmacotherapeutic development targeting alcohol use disorder.

Poster Abstracts

Poster Session 1: Monday

MON_09 Genetic and environmental modulation of small non-coding RNAs in a mouse model of affective disorders

Presenting Author: Maria Kuznetsova

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Background
Depression is a devastating condition and the leading cause of disability worldwide. It is caused by complex interactions between genetic and environmental factors. Gene-environment interactions may include epigenetic shifts in miRNA expression, whose potential role in mood disorders is only beginning to be recognized. miRNA expression may be altered after exercise and stress, as well as in various psychiatric disorders, including depression. We aimed to find differentially expressed miRNAs in wild type mice and in a mouse model of affective disorders under different environments and modulate these DE miRNAs to alleviate depressive-like behaviour in mice by mimicking gene-environment interaction.

Methods
We used serotonin transporter knockout (5-HTT KO) mice, which display depressive-like behaviours and other features of relevance to depression. 5-HTT KO and wild-type mice at 8 weeks of age were randomly assigned to either standard housing, exercise, or corticosterone treatment groups for 4 weeks. Hippocampal tissues were collected for miRNA-seq, which was analysed using bioinformatic approaches. For the second part of the study, mimics or inhibitors of DE miRNAs from the first part were injected directly in the brain with ICV injection. Anxiety and depressive-like behaviour was analysed in several tests including LDB, EPM, SPT and FST.

Results
We described miRNA expression profiles in the hippocampal tissues of a genetic mouse model of depression after exercise and stress, in comparison to wild-type (WT) littermate control mice. Our miRNA sequencing revealed differentially expressed (DE) miRNAs in 5-HTT KO mice compared to WT in standard-housing conditions, and after exercise and stress in both genotypes. Next, we used miRNA mimics and inhibitors to alleviate depression-like behaviour through changing of miRNA expression. Significant antidepressant behavioural effects were detected 24 and 72 hours after the mimic/inhibitor injection in WT mice. In addition, we detected significant effects in anxiety-related behavioural tests.

Conclusions
Our observations suggest that dysregulation of miRNAs may play a role in the pathogenesis of anxiety and depression, and their levels may be rescued with exercise, while stress can potentially cause the same effects as observed in genetic model of anxiety and depression. Furthermore, our study uncovered novel miRNAs first described to be altered in 5-HTT KO, as well as confirmed previous findings in other animal models, and highlighted the potential of these miRNAs as therapeutic targets. Following further validation and future intervention studies, we hope to determine whether these miRNAs could be pursued as candidate targets for novel therapies.

Poster Abstracts

Poster Session 1: Monday

MON_10 Investigating the Role of Orexin in a Mouse Model of Female "Emotional" Stress-Induced Binge Eating

Presenting Author: Mia O'Shea

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Background
It is well established that stress and negative affect (e.g. sadness, anger) trigger overeating. This form of maladaptive eating behaviour, commonly referred to as "emotional eating", is particularly common in women, and is associated with binge eating disorder and bulimia. The neural mechanisms that underpin this form of dysregulated eating are yet to be elucidated but likely implicate neuronal substrates involved in both homeostatic and hedonic feeding. Orexin represents a distinct population of lateral hypothalamic neurons, that have been previously implicated in reward, stress and feeding. Thus, we aim to investigate the role of orexin in female stress-induced binge eating.

Methods
To do so, a mouse model was employed that used a mild, psychological stressor and intermittent access to highly palatable food to induce binge eating in test mice. Mice exposed to the frustrative stressor and food reward consumed significantly more than control mice exposed to the food reward only. Immunohistochemistry for the neuronal activity marker Fos was used to assess the recruitment of lateral hypothalamic neurons, including orexin during this behaviour.

Results
Statistical analysis of cell counts has revealed significant activation in neurons throughout the lateral hypothalamus of stress-induced binge eating mice (p < .05). Early analysis of orexin data is indicative of a trend toward significant neuronal activation; however, full quantification of orexin data is ongoing. We hypothesize that orexin neurons will be significantly activated as a result of stress-induced binge eating as compared to control.

Conclusions
Our preliminary evidence indicates a significant role for neurons of the lateral hypothalamus in female stress-induced binge eating, and a potential role for the orexin system. Investigation into the extent of orexin's involvement remains ongoing. When completed, the results of this study will provide insight into the neurobiological processes underlying stress-driven binge eating.

Poster Abstracts

Poster Session 1: Monday

MON_11 Basal Forebrain Cholinergic Signaling in the Basolateral Amygdala Promotes Strength and Durability of Fear Memories

Presenting Author: Byron Crimmins

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Background
The basolateral amygdala (BLA) is critical for the acquisition and inhibition of fear memories. Within the BLA, cumulating evidence points to the importance of local cholinergic inputs. These inputs predominantly originate from two sub-territories of the basal forebrain: the nucleus basalis of Meynert (NBM) and the horizontal diagonal band of Broca (HDB). Recent work has shown that silencing the NBM-BLA cholinergic pathway during fear conditioning enhanced fear inhibition. The opposite was found when the same pathway was stimulated. Although evidence suggests that this signalling regulates fear memories, the breadth of this regulation and its underlying mechanisms remain unknown.

Methods
The present experiments sought to examine how basal forebrain cholinergic signalling in the BLA regulates the formation, extinction, and renewal of fear memories. We used optogenetics in transgenic rats to silence the NBM-BLA or HDB-BLA cholinergic pathways during fear conditioning or extinction. We assessed the long-term consequences of silencing these pathways during a post-extinction test and two retrieval tests. One test was conducted in the extinction context and the other in the conditioning context. The latter allowed us to examine the capacity of the fear memory to renew.

Results
NBM-BLA silencing during fear conditioning had no effect during fear conditioning or extinction the following day. However, it produced lower freezing during a post-extinction test and it abolished fear renewal.
Notably, NBM-BLA silencing during a weaker fear conditioning protocol revealed a reduction in freezing during extinction.
HDB-BLA silencing during fear conditioning had no effect during fear conditioning, extinction, a post-extinction test, and did not abolish fear renewal
NBM-BLA silencing during extinction reduced freezing during extinction and a post-extinction test but did not abolish fear renewal.
HDB-BLA silencing during extinction reduced freezing during extinction, a post-extinction test, and abolished fear renewal.

Conclusions
Cholinergic projections from the NBM and HDB to the BLA appear to regulate the strength and durability of fear memories. This control may be implemented by the NBM cholinergic projections during fear memory formation and supported by HDB cholinergic projections during extinction. Removing either form of cholinergic control produced a fear memory that lost its fear-eliciting capacity faster across extinction and that was unable to trigger fear again despite context shifts. Furthermore, the abolition of fear renewal suggests that these cholinergic BLA inputs may underly the protective mechanisms that protect fear memories and enable their restoration following extinction.

Poster Abstracts

Poster Session 1: Monday

MON_12 The effect of the anti-hypertensive drug clonidine on the acquisition and extinction of conditioned fear in rats.

Presenting Author: Robine Marie Lili Michalscheck

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Background
PTSD is a psychological disorder 12% of Australians experience in their lifetime. Exposure-based treatments for PTSD (i.e., cue exposure) are intended to reduce the ability of feared cues to activate trauma memories and undermine a patient's quality of life. However, treatment outcomes of cue exposure tend to be transient, and PTSD symptoms (i.e., panic, fear and avoidance triggered by trauma-associated cues) return. Using an animal model to mimic aspects of PTSD, the present series of four experiments examined the use of the anti-hypertensive drug clonidine as an enhancing adjunct to exposure-based treatments.

Methods
Experiment 1 examined the effect of clonidine on the acquisition of PTSD-like fears by conditioning rats to fear an initially innocuous stimulus (a sound) paired with danger (foot shock) under a systemic injection of clonidine/vehicle. On each of two days, rats were injected with clonidine (0.01; 0.05 or 0.1mg/kg) or vehicle 5 min before a single trial of fear conditioning to a sound. One day later, rats were tested drug-free to assess the ability of the sound to elicit fear (measured by freezing). Clonidine impaired the acquisition of fear to the tone in a dose-dependent manner.

Results
Experiments 2-4 examined the effect of combining clonidine and cue exposure by exposing rats to a fear-eliciting sound in the absence of danger (no foot shock; i.e., extinction of conditioned fear) under a systemic injection of clonidine/vehicle. On each of two days, rats received a single trial of fear conditioning to a sound. On each of the subsequent four days, rats received clonidine or vehicle 5 min before receiving four trials of cue exposure to the sound alone (no foot shock). One day later, rats were tested drug-free to assess the ability of the sound to activate the fear memory.

Conclusions
Experiment 2 showed that clonidine enhances the extinction of conditioned fear in a dose-dependent manner and that this clonidine effect persists several weeks after receiving the clonidine + cue exposure treatment. Experiment 3 showed that the extinction-enhancing effect of clonidine is equally evident when it is injected before or after each cue exposure session. Experiment 4 showed that the clonidine effect is also evident when each cue exposure session involves just a single trial. Taken together, these findings indicate that combining clonidine and cue exposure enhances the effectiveness of exposure-based treatments by stripping trauma memories of their distressing, emotional components.

Poster Abstracts

Poster Session 1: Monday

MON_13 Preclinical therapeutic utility of cannabidiol for cocaine use disorder

Presenting Author: Rose Chesworth

Authors:
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Background
Cocaine use disorder is a global health problem for which there are no approved pharmacotherapies. In the past few years, our laboratory has examined the potential of the non-intoxicating cannabinoid compound, cannabidiol (CBD), for the treatment of cocaine use disorder, as CBD modulates several neurotransmitter systems relevant to cocaine use e.g. cannabinoid, dopaminergic, serotonergic receptor systems. Here we present recent data on the impact of CBD on several substance abuse relevant domains e.g. cocaine self-administration, extinction of cocaine seeking, abstinence from cocaine, as well as impacts of chronic CBD on endocannabinoid and serotonergic protein levels.

Methods
We examined effects of CBD (10 mg/kg) on extinction and abstinence behaviour using cocaine conditioned place preference (CPP) in C57BL/6J mice. CBD was administered daily prior to extinction sessions or during 3 weeks of abstinence. Protein markers for cannabinoid receptor 1 (CB1), fatty acid amide hydrolyse (FAAH), the enzyme which breaks down the endogenous cannabinoid anandamide, and serotonin receptor 1A (5-HT1A) in substance abuse-relevant brain regions (hippocampus, prefrontal cortex, striatum) were analysed after abstinence. In a separate experiment, we assessed the impact of CBD (20 mg/kg) on cocaine self-administration and motivation for cocaine using intravenous self-administration in C57BL/6J mice.

Results
CBD did not facilitate extinction of cocaine CPP. Surprisingly, CBD administered in abstinence increased the preference for a cocaine-paired environment, and this may be linked to effects of CBD on consolidation of new memories. 3 weeks of CBD treatment increased CB1 receptor levels in the hippocampus, and there was a trend for reduced hippocampal FAAH levels. There were no changes to CB1 or FAAH in the prefrontal cortex or striatum, and no change to 5-HT1A levels following chronic CBD. We also found a reduction in cocaine self-administration under CBD treatment but no effect of CBD on motivation for cocaine.

Conclusions
Our findings demonstrate therapeutic utility of CBD for cocaine use disorder, and highlight specific memory processes that can be targeted with CBD. For example, CBD may help to reduce cocaine consumption and impair consolidation of cocaine-relevant memory, but may not reduce cocaine-associated memory via extinction. Our findings of elevated CB1 protein levels are consistent with fear literature showing impaired consolidation of fear memory by CBD is dependent on hippocampal CB1, and extend this mechanism to the substance abuse domain.

Poster Abstracts

Poster Session 1: Monday

MON_14 EDiPs (Enhanced Dopamine in Prodromal schizophrenia) an animal of relevance to schizophrenia, displays increased phasic dopamine release possibly via upregulation of presynaptic release sites

Presenting Author: Sunil Srivastav

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Background
Clinical studies in patients with schizophrenia using PET (Positron Emission Tomography) have shown a progressive increase in dopamine (DA) synthesis capacity in the dorsal striatum (DS) from the prodromal stage to first psychotic episode. Based on this important finding, our lab has developed a novel animal model (EDiPs) which replicates this. Our aim in this study is to explore if increased DA synthesis capacity leads to increased DA release

Methods
Unilateral EDiPs rats were produced by delivering viral construct containing genetic material for rate limiting enzymes in DA synthesis; TH (Tyrosine Hydroxylase) and GCH1 (Guanosine triphosphate Cyclo-Hydrolase 1) to one substantia nigra and control construct (without TH) to the other nigra. To observe the effect of EDiPs on phasic dopamine, FSCV (fast scan cyclic voltammetry) was used to assess the phasic nature of DA release in the dorsal striatum in response to electrical stimulation of medial forebrain bundle (MFB). We correlated our findings with quantitative immunohistochemical analysis of presynaptic protein density within TH axons of the striatum using Imaris software

Results
On stimulation of MFB bilaterally evoked or (phasic) DA release was measured in dorsal striatum of both hemispheres. We observed a significant elevation of phasic DA in the dorsal striatum of ipsilateral hemisphere who's nigra had received the active EDiPs construct compared to its matched control. Immunohistochemical analysis showed that, in dorsal striatum of active EDiPs hemisphere, there was an increase in number of TH surfaces, suggesting more TH positive axons. EDiPs increased the presynaptic marker Bassoon, within TH axons specifically within the dorsal but not the ventral striatum consistent with the increased phasic release of DA in this region.

Conclusions
We suggest the increased DA synthesis capacity seen in prodromal patients with schizophrenia who transition to clinical disease may also have alterations in evoked DA release dynamics possibly due to an increase in presynaptic release sites. These findings may help to explain the role increasing dorsal striatal DA plays in transition to disease.

Poster Abstracts

Poster Session 1: Monday

MON_15 The nucleus accumbens shell is involved in the selection of nicotine dose

Presenting Author: Timothy Hill

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Background
The increasing use of electronic smoking devices (ESD), and its link to later smoking dependence, has renewed interest in the brain's control of nicotine intake. The nucleus accumbens shell (AcbSh) is recruited during nicotine reward and reinforcement, as well as during behavioural selection. AcbSh activity also tracks food reward-size which could suggest that the AcbSh biases nicotine use towards using higher doses, with greater frequency. However, no study has investigated if AcbSh activity tracks nicotine reward-size nor if it predicts greater or more frequent nicotine use. We therefore investigated the association between AcbSh activity and nicotine reward-size.

Methods
We used intravenous nicotine self-administration in combination with in-vivo fibre photometry to capture calcium sensor (GCaMP7f) activity in the medial AcbSh of rats (n=9) throughout behavioural testing. To assess the neural response to non-contingent nicotine rats received three sessions of subcutaneous nicotine (saline, 0.1mg/kg and 0.3mg/kg) and one session with four intravenous infusions (saline, low: 15ug/kg, medium: 30ug/kg, and high: 60ug/kg). Rats then acquired self-administration for nicotine (30ug/kg/infusion) before training to choose between self-administering the low, medium, and high doses of intravenous nicotine. Finally, rats underwent an instrumental session, identical to the day prior, except nicotine infusions were withheld.

Results
Recordings of activity in response to experimenter-administered nicotine indicated that the AcbSh activity peaked higher after high-dose nicotine compared to medium or low-dose nicotine. Further, AcbSh response to infusion alone sessions predicted the AcbSh response to doses chosen during three-choice self-administration. Increased post-infusion AcbSh activity predicted a shorter latency to next nose-poke, whereas decreased post-infusion activity predicted an increased likelihood of subsequently choosing a higher nicotine dose. AcbSh activity increased after nose-pokes during the cue-only sessions, with a similar pattern to post-infusion AcbSh activity.

Conclusions
Results suggest that the AcbSh tracks nicotine reward-size, with a higher dose predicting greater neuronal activity. Likewise, AcbSh activity may reflect the expected reward, as much as the reward size itself. The AcbSh therefore distinguishes between nicotine dose, suggesting a potential role in decision-making processes during nicotine-use. Implications for neural pathway models engaged during nicotine-use are discussed.

Poster Abstracts

Poster Session 1: Monday

MON_16 Angiotensin receptor 1 blockade blocks cancer-induced memory impairment in mice

Presenting Author: Yasmine Kostoglou

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Background
70% of cancer patients self-report cognitive deficits and 40% show measurable impairment on neuropsychological assessment, yet no treatment exists for cancer-related cognitive impairment (CRCI). Recent clinical evidence implicates the renin-angiotensin system (RAS) in the pathophysiology of CRCI, however whether the RAS plays a causal role in CRCI remains unknown. In the brain, angiotensin receptor (ATR)1 signalling is associated with cognitive impairment, whereas ATR2 signalling promotes brain health and cognition. Using a mouse model of breast cancer, we investigated if a peripheral tumour impacts brain RAS gene expression and memory impairment, and if the ATR1 antagonist, candesartan, reduces tumour-induced memory impairment.
Methods
To determine the impact of cancer and candesartan on memory and brain RAS gene expression, 48 female Balb/c mice bearing 4T1.2 mammary tumours or non-tumour bearing mice were treated with candesartan (3mg/kg, IP) or vehicle, and assessed for short-term memory using the Y-Maze test and long-term memory using the novel object/novel place recognition task. Because RAS activation can enhance blood-brain barrier (BBB) leakiness, we injected mice intravenously with fluorescein prior to euthanasia and measured the amount of blood-to-brain fluorescein diffusion into the hippocampus and prefrontal cortex post-mortem. Brain region-specific changes in RAS gene expression were quantified using qRT-PCR.
Results
Mammary tumours induced short-term but not long-term memory impairment, which was prevented by treatment with candesartan (p < 0.05). Tumours reduced hippocampal expression of ATR1 (p < 0.05) and ATR2 (p = 0.07). Candesartan increased cortical angiotensin-converting enzyme (ACE) expression, which produces the ligand for ATRs, and significantly enhanced cortical BBB integrity (p < 0.05). Candesartan had no effect on cancer progression, sickness responses or behaviour, supporting its safety for use in cancer patients.
Conclusions
For the first time, we demonstrate that the RAS plays a causal role in CRCI. We show that a solid peripheral tumour is sufficient to induce changes in brain RAS gene expression and memory impairment, which is blocked by ATR1 antagonists. Antagonism of the AT1R and increased production capacity of angiotensin II may improve cognition by shifting angiotensin signalling toward the pro-cognitive AT2R pathway. Another possibility is that reducing BBB permeability is sufficient to block cancer-induced memory impairment. The findings suggest that candesartan may be a safe and effective treatment for cancer-induced memory impairment, supporting its advancement to clinical trials.

Poster Abstracts

Poster Session 1: Monday

MON_17 Thyroid Axis Hormones: Relations with Cardiometabolic Disease Risk Indices in Major Depressive Disorder

Presenting Author: Asmahan Elgellaie

Authors:
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Dr Susan Thomas - Senior lecturer
Dr Jessica Bartschi - Research fellow
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Background
Thyroid axis hormones are related to both major depressive disorder (MDD) and cardiometabolic disease (CMD) risk indices. Thyroid functioning is linked to MDD as they affect function and development of regions associated with MDD. Hyperthyroidism can cause anxiety while hypothyroidism can cause depressed mood. Thyroid hormones also have roles in metabolic rate, body weight and heart rate regulations, which are all implicated with CMD risk. Therefore, it is important to examine whether the thyroid axis hormones, triiodothyronine (T3) and thyroxine (T4) and thyroid stimulating hormone (TSH), are associated with MDD and specific measures of CMD risk since this is under-researched.

Methods
Plasma of 120 participants (n=60 meeting DSM 5 criteria for MDD and n=60 healthy controls; age and sex matched) were analysed to assess T3, T4, TSH levels. For all participants, CMD risk indices of BMI, waist circumference, blood pressure, heart rate and usual physical activity levels were assessed. Anxiety, depression and stress severity were measured using the Depression Anxiety Stress Scale (DASS). Two-way ANOVAs were used to test between-group differences. Pearson's correlations were used to determine relationships between variables.

Results
Participants' age range was 18 to 63 years (26 ± 8). Those with MDD had higher depression, anxiety and stress scores, higher BMI, waist circumference and heart rate, fewer active hours, more inactive hours than control participants. Plasma T3, T4 and TSH concentrations did not differ between groups, and the only significant correlation with the thyroid hormones was T3 with systolic and diastolic blood pressure and with plasma glucose.

Conclusions
Multiple health indices indicated that the MDD group was at higher risk of CMD. The results of non-significant group effect for the thyroid axis hormones and the lack of significant correlations between these and any psychometrics suggest that thyroid hormones are not associated with MDD. The correlation of T3 with glucose and blood pressure warrants further investigation. Overall, although the participants with MDD had significantly higher risk indices for CMD, these were not related to thyroid axis hormones in the current study.

Poster Abstracts

Poster Session 1: Monday

MON_18 Virtual Reality To Facilitate Delivery of Evidence-Based Treatment For Insomnia.

Presenting Author: Rita Hitching

Authors:
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Background
In Australia and elsewhere, insomnia is associated with substantial societal burden. Epidemiological data consistently demonstrates high prevalence rates with population-based studies exhorting its impact and inextricable link to physical and psychiatric morbidity.
Insomnia is a complex disorder associated with hyperarousal and predicated/perpetuated by genetic, socioeconomic, neurological, cognitive, behavioural, and environmental factors. Insomnia has a bidirectional and modulating relationship in the onset, continuation, and relapse of all mood and anxiety disorders.
The shortcomings of current treatment approaches warrant the exploration of alternative treatment delivery modalities.

Methods
Virtual reality has shown efficacy in the treatment of disorders commonly comorbid with insomnia - pain, anxiety, depression, and PTSD. The usefulness of VR for the treatment of insomnia may be beneficial and needs warrants investigation.
Objective: To explore therapeutic uses of virtual reality for insomnia; determine what characteristics of insomnia virtual reality is able to target, and discuss clinical integration of virtual reality with existing therapies for insomnia;

Results
Discuss preliminary results on the ability of virtual reality to capture focused attention and generate a distraction-free immersive and calming virtual environment to facilitate the adoption of insomnia treatment.
Summarise forthcoming on the feasibility, efficacy, and scalability of virtual reality to deliver insomnia treatment.
Present a proposed randomised clinical trial into self-guided virtual reality relaxation and mindfulness to prior to bedtime to target pre-sleep hyperarousal in insomnia.
Discuss the process of collecting treatment response indices and recommend analytical approaches to develop a predictive treatment response model.

Conclusions
Insomnia is a '…global epidemic…' associated with substantial economic and healthcare burden, plus morbidity, and mortality. Current insomnia treatments are limited and new approaches are urgently needed. Virtual reality has been effective at treating comorbid psychiatric disorders since the mid-to-late 1990s. Emerging evidence suggests virtual reality shows potential in the treatment of insomnia. A treatment response model aided by machine learning and a revision to treatment guidelines is proposed to facilitate clinical adoption. Improvements to the treatment of insomnia may concurrently contribute to reductions in the prevalence of associated physical illnesses and to the risk of psychiatric disorders.

Poster Abstracts

Poster Session 1: Monday

MON_20 Alteration of DNA Methylation Associated with Clinical Features of Schizophrenia and Genetic Risk

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Background
Schizophrenia is a complex and devastating neuropsychiatric disorder that arises from genetic and environmental factors, both of which may be associated with DNA methylation. Although recent epigenome-wide association studies (EWAS) have identified disruption of DNA methylation in schizophrenia, clinical dimensions of the disorder that account for a large proportion of phenotypic heterogeneity remain relatively underexplored. In the current study, we sought to characterise epigenetic dysregulation associated with specific clinical features of schizophrenia to explore molecular dimensions of phenotypic variability in the disorder and examine the interrelationship with common variant genetic risk.

Methods
Epigenome-wide profiles of DNA methylation were quantified in a cohort of 381 individuals with schizophrenia from the deeply phenotyped Australian Schizophrenia Research Bank. Epigenetic alterations were examined for five traits, including cognitive status, age of onset, treatment resistance, Global Assessment of Function scores and genetic risk for schizophrenia indexed by polygenic risk scores. To examine interplay between DNA methylation and genetic variation, methylation quantitative trait loci (mQTLs) were mapped for 315 individuals with matched genotype data using linear models. Epigenetic risk scores for schizophrenia and treatment resistance were also constructed for each individual using EWAS from an independent cohort.

Results
EWAS revealed 662 differentially methylated probes across all traits at a discovery threshold of P < 6.72x10–5, with many residing in close proximity to genes previously associated with schizophrenia. We further examined how schizophrenia polygenic risk may influence changes in methylation associated with the other four phenotypic features, which revealed an additional 432 probes. Interestingly, mQTL signals within the cohort exhibited evidence for correlation with EWAS effect size estimates, whilst negative correlation was observed amongst EWAS and methylation-associated gene expression. Finally, epigenetic risk scores for treatment resistance strikingly explained approximately 6% of phenotypic variance amongst clozapine-treated individuals.

Conclusions
These findings collectively provide novel evidence suggesting several clinical features of schizophrenia are associated with alteration of DNA methylation, which may contribute to inter-individual phenotypic variation in those with this disorder. Strikingly, our results also indicate that schizophrenia-associated common genetic variants may contribute to changes in methylation related to the clinical features. While validation in large, independent cohorts is required to ascertain these findings, our study nonetheless presents

important molecular insights into clinical dimensions of schizophrenia to further dissect phenotypic heterogeneity in the disorder and improve understanding of the molecular landscape for development of personalised intervention strategies.

Poster Abstracts

Poster Session 1: Monday

MON_21 Evidence of a bidirectional genetic relationship between pneumonia susceptibility and mental health

Presenting Author: William Reay

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Background
Pneumonia remains one of the leading causes of death worldwide and has a complex underlying pathophysiology. Epidemiological data suggests pneumonia is a risk factor for subsequent mental health challenges, as well as elevated likelihood of developing pneumonia after a mental health diagnosis. However, correlation is difficult to separate from causality in this context. As a result, we believe that improving our understanding of the genetic architecture of pneumonia susceptibility can assist to refine how pneumonia is related to other phenotypes like mental health that already have well-characterised genetic data available.

Methods
We performed the largest genetic study of lifetime pneumonia susceptibility to date (N = 391,044) by meta-analysing participants collected by 23andMe Inc. with Finnish hospital registry data. The proportion of genetic overlap (genetic correlation) was calculated between pneumonia and 674 different medical/self-reported phenotypes collected by the UK Biobank in a hypothesis-free scan. We followed up findings related to mental health phenotypes with genetic studies of nine clinically ascertained psychiatric disorders provided by the Psychiatric Genomics Consortium. Latent Causal Variable models were then constructed to evaluate whether there was any evidence for a causal relationship between mental health and pneumonia.

Results
After multiple-testing correction, there were 318 phenotypes that exhibited non-zero genetic correlation with pneumonia susceptibility. Interestingly, these traits included robust relationships with several mental health phenotypes, including depression, neuroticism, anxiety, and self-harm. We further demonstrated that the genetic overlap between pneumonia and mental health was consistent using clinically ascertained mental health diagnoses. Local analysis within the major histocompatibility complex (MHC) region of the genome, a key determinant of immune function, revealed a particularly strong overlap between pneumonia and mental health in this region. Latent Causal Variable models suggested a bidirectional relationship between susceptibility to pneumonia and mental health conditions.

Conclusions
Pneumonia susceptibility displays notable genetic correlation with mental health conditions, suggesting the existence of shared underlying biology. Further work is now required to characterise the systems that underly this shared biology, with this study suggesting that the MHC region, including factors like human leukocyte antigen type status, may be an important mediator of this relationship.

Poster Abstracts

Poster Session 1: Monday

MON_22 A distinct suppression subnetwork in the default mode network during cognitive tasks

Presenting Author: Christine A. Leonards

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Background
Suppression of the brain's default mode network (DMN) during externally-directed cognitive tasks has been consistently observed in neuroimaging studies. This suppression effect is thought to reflect an active tuning down of self-related mental processes to facilitate efficient task performance. While initially considered a unitary "task-negative" network, emerging insights suggest the DMN is a complex system comprised of subnetworks that show functional heterogeneity. However, few studies have investigated task-related modulation of DMN suppression across multiple cognitive tasks within the same participants.

Methods
In this study, 85 healthy 15- to 25-year-olds completed three distinct functional magnetic resonance imaging (fMRI) cognitive tasks: two relating to emotional processing and one to language processing. All tasks were designed to map activity suppression from a resting baseline.

Results
We found a distinct suppression subnetwork apparent across the three tasks that partially encompassed DMN regions but also extended beyond the network. Specifically, common suppression was observed in the medial prefrontal cortex, dorsal-to-mid cingulate cortex extending to the precuneus, and posterior insular and surrounding cortex. We further found that the magnitude of suppression of these common regions was correlated within individuals across tasks.

Conclusions
Our results indicate that task-related suppression during externally-directed cognitive tasks reflects a distinct suppression signature that is not limited to the DMN but extends to regions involved in broader aspects of self-awareness and cognitive control. Further, consistent intra-individual suppression suggests this may be a stable feature of brain function. Our findings demonstrate that DMN suppression plays a critical role in optimising goal-directed behaviour and extends our understanding of the neural mechanisms underlying efficient cognitive function. These findings have important implications for understanding psychopathology as disruptions to these processes may underlie common cognitive disturbances present in several psychiatric disorders.

Poster Abstracts

Poster Session 1: Monday

MON_23 Structural and Functional Neural Correlates of Schizotypy: A Systematic Review

Presenting Author: Emiliana Tonini

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Background
Schizotypy refers to a multidimensional construct that spans a range of cognitive, behavioural, and personality features, representing liability to psychosis on a continuum between health and illness. Schizotypy has been associated with functional and structural brain alterations as potential intermediate phenotypes on the developmental path to psychosis.

Methods
We scanned the literature between February 2019 and August 1st, 2020 using PubMed, Medline, APA PsycINFO, and ProQuest. We identified eligible articles conducted on participants assessed with psychometric schizotypy across the health-illness spectrum and reporting a direct statistic between schizotypy and a structural, task-related, or functional magnetic resonance imaging brain measure. Articles not peer-reviewed and not written in English were excluded.

Results
We systematically reviewed 84 studies that determined the changes in gray matter, brain activation, and connectivity associated with schizotypy in both healthy and clinical cohorts. Morphological and functional changes in the default and the frontoparietal networks, specifically frontal and temporal cortices, were most frequently associated with schizotypy. Yet, we were unable to identify consistent patterns of morphological or functional brain aberrations associated with schizotypy, due to methodological differences between studies in the conceptualisation and measurement of schizotypy.

Conclusions
Efforts towards greater methodological concordance in future neuroimaing research of schizotypy are needed to improve the identification of brain-based endophenotypes for schizophrenia.

Poster Abstracts

Poster Session 1: Monday

MON_24 Relationships between white matter and cognition in bipolar disorder: a systematic review

Presenting Author: Georgia F. Caruana

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Background
Cognitive dysfunction is becoming increasingly established as a core feature of bipolar disorder (BD), however, the neural substrates underpinning this dysfunction remain unclear. Converging neuroimaging evidence has proposed alterations in white matter as being related to cognitive outcomes BD, yet to date, no single body of work has aggregated these findings. This systematic review sought to address this, by providing a comprehensive summary of relationships between white matter micro/macrostructure and cognition in BD.

Methods
This systematic review was conducted in line with PRISMA protocols. An initial search of PubMed, Scopus, and Web of Science databases identified 2689 records, published from inception until April 2022. Two reviewers appraised articles in line with eligibility criteria which included; study of adult BD participants, use of neuroimaging to directly measure white matter, and objective assessment of cognition via the use of a validated task. A total of 33 reports met these criteria and were reviewed.

Results
All 33 exploring white matter-cognition relationships to date were cross-sectional, with replicated evidence of significant relationships between cognition and either microstructure or macrostructure minimal. A limited number of microstructural studies using diffusion tensor imaging broadly observed that complex attention and executive functioning were positively correlated with fractional anisotropy, and negatively correlated with mean diffusivity, in regions associated with the corpus callosum. The majority of microstructural findings were, however, unable to detect or replicate such associations. Further, no major macrostructural morphologies, including white matter volume, hyperintensities, or thickness, were robustly linked to cognition.

Conclusions
Collectively, this review highlights that whilst key regions such as the corpus callosum are significantly associated with some domains of cognition, white matter abnormalities do not show a strong direct relationship with cognition in BD. It is recommended that future research takes a multi-modal neuroimaging approach, with consideration of clinical and cognitive factors specific to the BD illness course, to more comprehensively examine any such structure-function associations.

Poster Abstracts

Poster Session 1: Monday

MON_25 Resting-state electrocortical hemispheric asymmetry in schizotypy and depression

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Background
Schizotypy is a cluster of subclinical psychotic traits representing an intermediary between healthy and psychotic disorder populations, consistent with a dimensional approach to the psychosis spectrum. Asymmetrical patterns of spontaneous electrocortical activity at rest is associated with cognitive deficits and affective dysregulation characteristic of psychosis. This study aims to determine whether these patterns of asymmetrical electrocortical activity extend to schizotypy, and explores their interaction with comorbid depressive symptomology.

Methods
Spontaneous electroencephalographic (EEG) data for 51 participants was recorded via 34 scalp electrodes for three minutes under eyes-open, resting conditions. EEG data was subjected to a Fast Fourier Transform (Hanning window, 10%) and mean power was quantified for theta (4-8Hz), beta (13-30Hz), and gamma (30-45Hz) bands. Electrodes were collapsed into sagittal (frontal, central, parietal) and lateral (left, right) planes, excluding central line and frontoparietal electrodes; collapsed power values were natural log transformed. Hemispheric asymmetry was calculated for each sagittal plane as the difference in hemispheric power (right minus left).

Results
Schizotypy subgroups included participants with high (N=10) and low (N=11) Schizotypy Personality Questionnaire (SPQ) total scores approximately one standard deviation above and below the sample mean, respectively. Repeated measures ANOVAs (between-subjects: 2-groups; within-subjects: 2-lateral, 3-sagittal planes) did not identify patterns of asymmetry related to schizotypy, yet revealed higher global theta power in high versus low schizotypy (p=.011). Secondary analyses across the entire sample (N=51) revealed no associations between hemispheric asymmetry and SPQ subscale scores (all p>.18), nor any mediatory effects of depression, measured using the Beck Depression Inventory, on the relationship between hemispheric asymmetry and SPQ total score (all p>.33).

Conclusions
Our findings did not support patterns of hemispheric asymmetry reported across the psychosis spectrum, suggesting intact neural networks at rest in schizotypy. Findings of globally augmented theta power in high schizotypy may index compensatory resource reallocation in preparation of cognitive processing, and may underpin an increased liability for psychosis proneness. While low-range depressive symptoms did not support associations with hemispheric asymmetry, further studies should analyse samples with increased symptom severity. Future investigations of spontaneous brain activity as an indicator of psychosis vulnerability should examine the role of schizotypy trait severity on theta power and determine their significance to cognitive performance.

Poster Abstracts

Poster Session 1: Monday

MON_26 Subcortical contributions to salience network functioning during negative emotional processing

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Background
The salience network (SN) is responsible for detecting salient information, and subsequently reorganizing attentional resources and autonomic processes for adaptive cognitive and homeostatic responses. Negative emotional events elicit greater engagement of the SN due to their salience for survival, incorporating bottom-up signals from key subcortical brain regions such as the amygdala and periaqueductal gray (PAG). However, there has been limited examination of these dynamic interactions, therefore the precise nature of these relationships remains unclear.
Methods
Using ultra-high field 7-Tesla functional magnetic resonance imaging, we had thirty-seven healthy participants (17 females, Mage = 24.3) complete an emotional oddball paradigm that was designed to elicit a salient negative emotional response with the presentation of random, task-irrelevant negative emotional images. Dynamic causal modelling (DCM) was deployed to examine how negative emotional salience modulated the interactions between the subcortical and core SN regions,- the amygdala and PAG, and the anterior insula (aINS) and dorsal anterior cingulate (dACC), respectively.
Results
We found that negative emotional salience was associated with robust activation in the SN, spanning the amygdala, PAG, aINS, and dACC. Results from the DCM revealed that during the processing of negative emotional salience, there was an excitatory influence from the amygdala to the aINS, dACC, and PAG, while the PAG had an inhibitory influence on the amygdala, aINS, and dACC activity.
Conclusions
Our findings suggest that the amygdala may facilitate the processing of negative emotional stimuli in the SN to enable access to attentional resources, while the PAG may primarily modulate sympathetic-parasympathetic arousal mediated by the SN via inhibition. The latter is possibly initiated by amygdala input to the PAG and may be involved in optimizing bottom-up sensory processing of negative emotional stimuli. Overall, our results provide the first direct evidence that the amygdala and PAG may enhance processing of salient negative emotional stimuli by modulating distinct functions of the SN.

Poster Abstracts

Poster Session 1: Monday

MON_27 Cortico-cognition Coupling in patients with recent-onset psychosis

Presenting Author: Yoshito Saito

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Background
Cognitive impairment is frequently observed in recent-onset psychosis (ROP), does not improve with standard treatment, and is a key predictor of functional outcomes. Widespread cortical thickness reductions are observed in ROP, but their relationship to cognitive impairment is unclear. This study aimed to investigate multivariate cortico-cognition patterns in individuals with ROP using multiblock partial least squares correlation analyses (MB-PLS-C).

Methods
T1-weighted MRI scans and cognitive assessments were used from 75 nonaffective ROP patients (age 21.7±3.3) and 75 matched healthy controls (age 21.5±3.0) from the Human Connectome Project for Early psychosis and the Lifespan Human Connectome Project Development datasets. We performed MB-PLS-C analyses using volumes from 68 brain regions (Desikan-Killiany atlas) and five variables from the NIH Toolbox Cognitive Battery to identify multivariate patterns of cortico-cognitive coupling.

Results
MB-PLS-C revealed two significant latent variables (LVs), explaining 87.5% of the sum-of-squares variance between cortical volume and cognition: LV1 (explaining 78.6% of variance) described a shared, widespread structure-cognitive pattern relevant to both ROP and HCs. LV2 (explaining 9.0% variance) comprised a differential cortico-cognitive pattern including parietal and temporal lobes as well as cognitive tasks for attention, working memory, episodic memory, and flexible cognition. These patterns were consistent with our previous MB-PLS-C study on patients with treatment-resistant schizophrenia.

Conclusions
We identified a specific cortico-cognition pattern in early psychosis using MB-PLS-C. The differential between-group pattern indicates a potential signature of brain alterations contributing to multidomain cognitive dysfunction in the early stages of schizophrenia.

Poster Abstracts

Poster Session 1: Monday

MON_28 Determining the role of midbrain hormone signalling in binge drinking

Presenting Author: Arnav Shesham

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Background
Binge drinking is mediated by a complex construct of circuitry including the centrally projecting Edinger Westphal nucleus (EWcp). The EWcp expresses several neuropeptides and receptors implicated in arousal, motivation and alcohol consumption, including the ghrelin receptor (Growth-Hormone-Secretagogue-Receptor-1a, GHSR1a). Despite the dense expression, the distribution of GHSR in the EW and its specific roles in regulating binge drinking are unclear. Here we aimed to explore the expression patterns and influence of EWcp-GHSR on binge drinking. We hypothesised that EWcp-GHSR will be co-expressed across distinct populations of CART/VGLUT2 cells and GHSR will regulating binge alcohol consumption.

Methods
Using RNAscope, EWcp CART, VGLUT2 and GHSR mRNA were analysed in C57BL6J male and female mice. To examine binge drinking, mice were trained to binge drink alcohol in a 2hour restricted access paradigm, following this GHSR was knocked down using a short-hairpin-RNA (shRNA) targeted against GHSR in C57BL6J wildtype mice or scramble control virus, after recovery mice were retrained for binge drinking and tested in an extended 4 hour test. Finally, CART-cre female mice and VGLUT2-cre mice underwent the same paradigm but were used for targeted delivery of a cre-dependent GHSR-ShRNA or scram-ShRNA virus in the EW.

Results
RNAscope mRNA expression analysis showed 86-92% of CART cells and 33-40% of VGLUT2 cells expressed GHSR, with no sex differences in expression observed. Knockdown of GHSR in EWcp exhibited reduced binge drinking in female C57BL6J wildtype, but not male mice. Specific knockdown of GHSR in EWcp CART, but not VGLUT2 cells, of female mice displayed lowered levels of binge drinking.

Conclusions
Overall, our results highlight a novel role for GHSR in the EWcp to regulate binge drinking in a sex dependent manner. Further our data suggest this may be driven by actions specifically on CART-expressing, not vGlut2 cells in this region. This effect does not appear to be driven by differences in GHSR expression between the sexes. The signalling pathways involving these peptides and sex differences in CART-cre vs VGLUT2-cre mice require future examination.

Poster Abstracts

Poster Session 1: Monday

MON_29 Epigenetic histone acetylation modulating prenatal Poly I:C induced long-term neuroinflammation in the prefrontal cortex of juvenile female rats

Presenting Author: Chao Deng

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Background
Epigenetic modulation plays a key role in the process of neurodevelopment. However, it is not well-understood how it is involved in the pathology of neurodevelopment disorders induced by maternal immune activation (MIA). This study explored the modulation of histone acetylation in both neuroinflammation and neurotransmission using a juvenile MIA rat model constructed by prenatal polyriboinosinic-polyribocytidylic acid (Poly I:C) exposure.

Methods
Timed pregnant Sprague–Dawley rats were treated with 5 mg/kg Poly I:C or saline (control) on gestation day 15. Female offspring from these treated pregnant rats were sacrificed on postnatal day 60. The prefrontal cortex was collected for RT-qPCR and Western blot assays. ChIP-qPCR was used to evaluate the enrichment of H3ace or H4ace binding on the promoter region of target genes of both the NF-kB/NLRP3 pathway and neurotransmitter receptors.

Results
Prenatal Poly I:C exposure led to the global changes of histone acetylation on H3 (H3ace) and H4 (H3ace) in the prefrontal cortex. This study revealed enhancement of both H3ace and H4ace binding on the promoter region of Rela (a subunit of nuclear factor kappa-B (NF-κB)), as well as positive correlations between Rela and genes encoding histone acetyltransferases (HATs), CREB-binding protein (CBP) and E1A-associated protein p300 (EP300). A positive correlation between Nlrp3 (Nod-Like-Receptor family Pyrin domain containing 3) and gene encoding histone deacetylase 6 (HDAC6), an important independent factor in inflammation, was also observed.

Conclusions
These findings were consistent with the increased expression of both Rela and Nlrp3 reported previously, which demonstrated that epigenetic modulation contributes to NF-κB/NLRP3 mediated neuroinflammation and neurotransmission deficiency induced by prenatal Poly I:C exposure. This occurred through enhancing the histone acetylation of H3 and H4 on the promoter of Rela which was recruited by EP300 and CBP, or through HDAC6-mediated NLRP3 activation.

Poster Abstracts

Poster Session 1: Monday

MON_30 Effects of psychiatric disease and aging on FKBP5/1 expression are specific to cortical supragranular neurons

Presenting Author: Natalie Matosin

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Background
Deducing genes capable of classifying biologically-distinct psychiatric subtypes, and their targets for treatment, is a priority approach for the field of psychiatry. FKBP5 is a gene with decades of evidence indicating its pathogenic role in a subset of psychiatric patients, with high potential to be leveraged as a therapeutic target for these individuals. While it is widely reported that FKBP5/FKBP51 protein (FKBP5/1) expression is impacted by psychiatric disease state, risk genotype and age, in which cell-types and sub-anatomical brain areas FKBP5/1 is specifically affected is not known. This knowledge is critical to propel FKBP5/1-targeted treatment development.

Methods
We performed an extensive, large-scale postmortem study (n=1024, 6 cohorts) of FKBP5/1 examining dorsolateral prefrontal/orbitofrontal cortex (BA9, BA11, BA24) samples derived from subjects that lived with schizophrenia, major depression or bipolar disorder. With an extensive battery of RNA (bulk RNA sequencing, single-nucleus RNA sequencing, microarray, qPCR, RNAscope) and protein (immunoblot, immunohistochemistry) analysis approaches, we thoroughly investigated the effects of disease-state, aging and genotype on cortical FKBP5/1 expression.

Results
Our results demonstrate that FKBP5/1 cortical expression was strikingly increased (+17-40%) in individuals with schizophrenia or depression (+24%) vs controls. We also observed a strong effect of age with heightened FKBP5/1 expression in older psychiatric subjects versus older controls (e.g. mRNA: R=0.664, P(FDR)=5.6E-06). Further examination of the cell-type specificity of these findings with single nucleus RNA sequencing (snRNAseq) and targeted RNAscope/immunohistochemistry demonstrated that the disease- and aging-effects on FKBP5/1 expression are specific to supragranular neurons in cortical layer 3, with +25-32% increase specifically in supragranular layer 2-3 excitatory neurons in both schizophrenia and depression.

Conclusions
Our results provide a new contribution to the field, indicating that effects of psychiatric disease-state and age converge on supragranular neurons of the superficial cortical layers, thus pinpointing a clear cellular target for future drug development.

Poster Abstracts

Poster Session 1: Monday

MON_31 Circadian Clock Gene Expression in Animal Models of Genetic and Acquired Epilepsy

Presenting Author: Meshwa Patel

Authors:
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Background
Epilepsy is the fourth most common neurological disorder worldwide with more than 20 anti-seizure medications (ASMs) failing to manage seizures that impact several bodily functions, including circadian rhythms. These rhythms are powerful internal clock systems responsible for homeostasis and proper synchronization through core clock genes. The hypothalamus houses the master central clock while peripheral tissues like the heart, liver, small intestine (SI) and stomach are each equipped with their own separate peripheral clocks. Understanding how the clock gene expression is altered during epilepsy can provide a better understanding of the pathophysiology and provide possible diagnostic interventions to reduce seizure activity.

Methods
Adult male rats were kept in a 12:12 light dark cycle. Brain (hypothalamus and hippocampus) and peripheral organ (liver and SI) tissues were collected from the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model of absence epilepsy and the post-status epilepticus (SE) model of temporal lobe epilepsy every three hours throughout the day to determine clock gene expression. Quantitative Real Time polymerase chain reaction was performed to quantify mRNA expression of the core circadian clock genes PER1, CRY1, CLOCK and BMAL1 against housekeeping genes CYCA and YWHAZ to generate relative expression profiles. Results were analysed via a two-way ANOVA.

Results
Housing the central clock, which is functionally redundant to change, no significant differences were noted in the hypothalamus of both GAERS and SE cohorts. The hippocampus is a more susceptible part of the brain and therefore resulted in the overexpression of genes in the GAERS and SE rats. However, the liver and SI tissues were reported to either over or under express the clock genes further validating the notion that the peripheral clock is more susceptible to change as a result of epilepsy compared to the central clock.

Conclusions
Nonetheless, further analysis of these clock gene expression is required, especially during the active night period to thoroughly understand how their expression is altered. This study only focused on male rats and therefore cannot comment on any gender differences. Future studies would also need to explore the differences noted amongst male and females generalise any findings.

Poster Abstracts

Poster Session 1: Monday

MON_32 Neuroplastic effects of psilocybin in mice

Presenting Author: Sheida Shadani

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Background
There is growing interest in the potential for psychedelics to treat a range of mental health outcomes. Both human and animal studies have shown the subjective effects of psilocybin are dependent on binding to the serotonin 2A (5-HT2A) receptor, which is abundantly expressed in the prefrontal cortex (PFC). Studies in mice have recently revealed that a single dose of psilocybin increases outgrowth of dendritic spines in the PFC, which persist for at least 1 month after treatment. However, the neurochemical mechanisms through which psilocybin acts following stimulation of the 5-HT2AR to cause long-term structural changes in the brain remain unknown.
Methods
In order to identify these potential mechanisms, we first conducted a fiber photometry study, in which we examined the effects of psilocybin on dopamine release in the ventral striatum of mice (n=4 psilocybin, n=4 saline). Fluorescence emitted by a constitutive dopamine sensor (GRAB-DA, AAV9-hSyn-DA4.3) was measured in response to eating a peanut butter chip, both acutely as well as 24h and 7 days after psilocybin treatment. We also investigated the effects of psilocybin on expression of brain-derived neurotrophic factor (BDNF) and TrkB in the PFC and striatum 24h or 7 days (n=16 psilocybin, n=14 saline) after treatment using western blotting.
Results
Dopamine (DA) release in the ventral striatum did not change in response to eating a highly palatable peanut butter chip either acutely under psilocybin, 24h or 7 days post-administration (AUC; F=1.025, p=.383). Intriguingly, DA release immediately prior to eating the peanut butter chip was enhanced 24h after psilocybin administration (AUC; F=13.59, p<.001), suggesting that psilocybin encoded a strong learning signal that facilitated reward anticipation the following day. Assessment of how psilocybin alters protein levels of BDNF and TrkB at 24h and 7 days post-administration are currently ongoing, and these results will be presented at the conference.
Conclusions
Other work from our laboratory has shown that psilocybin improves reinforcement learning across a number of different tasks, and the results of these studies suggest that increased dopamine release in response to rewards might underpin improvements in learning. The effects of psilocybin on the expression of BDNF will provide key information about how this molecule may be involved in the structural outgrowth of dendrites in mice and long-term psychological improvements in human clinical trials. Future studies will examine the temporal profile of DA release following psilocybin treatment and whether neurochemical changes are directly related to improvements in learning.

Poster Abstracts

Poster Session 1: Monday

MON_33 Human HKx31 influenza causes neurological changes reassembling schizophrenia in mice

Presenting Author: K.H. Christopher Choy

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Background
The developmental hypothesis of schizophrenia postulates that early insult predisposes the disease. Early insult includes maternal infection which can increase the risk of schizophrenia supported by the epidemiological studies. Here, we determine the effect of human influenza during prenatal ages to the neurological function later in life in the offspring in mice.

Methods
Pregnant C57Bl/6 mouse dams were inoculated with HKx31 influenza (H3N2) or PBS as a control treatment via intranasal administration at E12. A battery of behavioural tests was then conducted when the offspring were 11-14 weeks old for the neurological functions. These included prepulse inhibition (PPI) of acoustic startle, measure of gating mechanism; amphetamine (2.5mg/kg, i.p.) induced locomotor activity, measure of responsiveness to dopaminergic stimulant; and Y-maze alternation, measure of spatial working memory

Results
The infected offspring (n = 9 – 14/treatment/gender) showed a robust disruption of PPI (P < 0.001, PBS: 38.06 ± 2.37% vs. x31: 19.27 ± 2.74%), pronounced effect of drug-induced hyperactivity in the open-field (P = 0.002, PBS: 438.15 metre vs. x31: 600.20 metre), and decrease of alternation in Y-maze (P = 0.0321, PBS: 63.60% vs. x31: 57.27%). The hippocampus weight was also found to be decreased by the influenza (P = 0.0261, PBS: 39.00mg vs. x31: 36.23mg), without any change of the total brain weight (P = 0.4385, PBS: 464.7mg vs. x31: 461.4mg).

Conclusions
This study showed long-lasting deleterious effects of maternal influenza infection on the adult offspring. Prenatal infection led to the deficit of gating mechanism, dopaminergic hypersensitivity, deficit of working memory and reduced size of hippocampus, which reassembles aspects of schizophrenia in mice. This maternal immune activation preclinical model using influenza virus can potentially provide a better translational tool for future antipsychotic drug discovery research.

Poster Abstracts

Poster Session 1: Monday

MON_34 Loss of asymmetry of the descending vs ascending deviant MMN response in the alternating paradigm

Presenting Author: Lauren Harms

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Background
Mismatch negativity (MMN), an enhanced response to unexpected deviant stimuli compared to expected standard stimuli, has recently gained strong interest from both preclinical and clinical researchers due to the findings of reduced MMN amplitude in schizophrenia. An enhanced understanding of the factors that influence MMN amplitude could lead to a better understanding of neural mechanisms underpinning the changes in schizophrenia. Human studies have demonstrated a first-impression/primacy bias in auditory processing, where the MMN amplitude to two tones shows differential patterns of modulation over the course changing sound sequences, based on their relative probabilities when first encountered at sequence onset.

Methods
Using a multi-time scale sequence paradigm, we investigated if rat mismatch responses (MMRs) are sensitive to the contextual information at the sequence onset similar to human MMN. Stainless steel screw electrodes were implanted on the caudal and rostral surface of the rat skull. MMRs were studied in awake, freely moving male and female Wistar rats using wireless telemetry. The multi-time scale sequence paradigm comprised of four sequences that were presented with 1 min silence breaks in between.

Results
We found no sensitivity to primacy bias in rats, however, we did find that the alternating paradigm removed the frequency asymmetry in low vs high deviant responses, similar to a previous finding by Shiramatsu & Takahashi, 2018.

Conclusions
Our results suggest that the context of the auditory stimulation influences the process of automatic change detection in the rat auditory system.

Poster Abstracts

Poster Session 1: Monday

MON_35 Sex- And Region- Specific Differences in Adult Microglia Following Systemic Neonatal Inflammation

Presenting Author: Melissa A Tadros

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Background
Microglia are key immune mediators of the central nervous system (CNS) and provide supportive and protective functions to brainstem neuronal networks. However, when an insult occurs, microglia can become activated, thus proliferating, changing their morphology and inducing an inflammatory state within the CNS. It is unknown whether or not insults during critical perinatal periods alter the normal development of microglia, causing long-term alterations in their activity. We aimed to determine how an early life peripheral inflammatory event affected two autonomic centres in the brainstem, the nucleus tractus solitarii (NTS) and the dorsal motor nucleus of the vagus (DMV), in adulthood.

Methods
Wistar rat pups were given an intraperitoneal injection of either lipopolysaccharide or saline at postnatal days (P) 3 and 5. Animals were sacrificed in adulthood (P90), with brainstems dissected and processed for immunofluorescence to identify microglia. The two autonomic regions, NTS and DMV, were isolated and run through a custom MATLAB script for microglia tracing.

Results
In the DMV, results showed sex-specific differences in the number of microglia following LPS exposure, and also between male and female saline groups, indicating baseline differences between the sexes. Morphologically there were also baseline sex differences observed in the number of primary branches and soma area of saline-treated males and females. In the NTS, there were no significant differences, although, the significance seen in the DMV was conserved as a trend across cell number, primary branches and soma area in the NTS. There were significant baseline sex differences in both number of primary branches and soma area.

Conclusions
In conclusion, a number of sex-specific differences were observed in control groups, suggesting male and female microglia differ in their baseline activation levels. Moreover, after neonatal inflammation, microglia remained primed well into adulthood and this could have wide reaching implications on autonomic neuronal networks.

Poster Abstracts

Poster Session 1: Monday

MON_36 Voluntary wheel running reduces incubation of craving for alcohol-associated cues.

Presenting Author: Christina Perry

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Background
Incubation of craving is the time dependent increase in craving elicited by drug-associated cues. This is a well-documented phenomenon in clinical populations, and can be modelled in rodents by measuring drug-seeking in response to drug-associated cues. Although the mechanisms incubation of craving has been reasonably well-studied for cocaine and methamphetamine, there is very little literature examining the effect for alcohol. This is despite incubation of craving being a robust effect in people seeking treatment for alcohol use disorder and may contribute to high relapse rates.

Methods
Rats were trained to lever press for an alcohol solution paired with a discrete cue light. Once stable self-administration was acquired, the response was extinguished by withholding delivery of alcohol and alcohol-associated cues. The extinguished response was reinstated by reintroducing the cue (without further alcohol reinforcement) either one or 29 days after final extinction session. Of those rats that underwent delayed reinstatement, half were given daily four-hour access to running wheels; the remainder were handled only. All rats were perfused transcardially 90 minutes after reinstatement, and neural correlates assessed by quantifying c-fos immunoreactivity in key regions of the reward circuitry.

Results
We found that 28 days of abstinence resulted in a significant increase in cue-induced reinstatement, but not where rats were permitted to run in the intervening period. All regions quantified showed a robust increase in fos expression except for the insula cortex. Furthermore, in most regions assessed (medial prefrontal cortex, orbitofrontal cortex, dorsal and ventral striatum, paraventricular thalamus, and basolateral amygdala), exercise reduced fos recruitment along with behavioural reinstatement. On the other hand, in the central amygdala and lateral hypothalamus fos immunoreactivity was not different between abstinence only and abstinence with exercise conditions.

Conclusions
These results confirm that incubation of craving occurs for alcohol-associated cues across a 28 day period. As with incubation of craving for psychostimulants, this effect is associated with augmented recruitment of the cotico-striatal-amygdala circuitry. Importantly exercise reversed both the increased responding and the increase recruitment of this circuitry across abstinence, suggesting that it rescues neuroadaptations that occur across abstinence, although effects in central amygdala and lateral hypothalamus were more enduring. These findings suggest that exercise may be an effective means of reducing relapse propensity following intervention for alcohol use disorder.

Poster Abstracts

Poster Session 1: Monday

MON_37 Using optical recordings to investigate therapeutic mechanisms of selective serotonin reuptake inhibitors relevant to obsessive compulsive disorder

Presenting Author: Elizabeth E Manning

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Background
Selective serotonin reuptake inhibitors (SSRIs) are the first line pharmacotherapy for obsessive compulsive disorder (OCD). Although antidepressant mechanisms of SSRIs are well established, therapeutic mechanisms in OCD remain poorly understood. Several lines of evidence suggest that SSRI actions in OCD differ to those in depression, including the need to use relatively high doses for OCD, and different effects of tryptophan depletion, which tests the involvement of elevated serotonin levels in SSRI effects. SSRIs reduce striatal dopamine, and precise regulation of striatal dopamine is important for flexible decision making and is implicated in transdiagnostic compulsive behaviour.

Methods
Our ongoing work aims to test whether SSRI reduction of striatal dopamine is involved in their therapeutic effects in OCD. This study aimed to establish in vivo optical recordings of striatal dopamine across SSRI treatment to facilitate this research. 5 male C57/BL6 mice underwent stereotaxic surgery to express the fluorescence dopamine indicator DLight in the central striatum. Following recovery from surgery and habituation to handling, mice were recorded at baseline and throughout treatment with the SSRI fluoxetine (18mg/kg in the drinking water).

Results
Mouse behaviour was recoded from below, and test sessions consisted of 20 minutes baseline recording, followed by introduction of palatable food (Reece's peanut butter drop) and 5 minutes post-palatable food recording. Studies are ongoing, and dopamine signals associated with palatable food approach from baseline and 1 and 3 weeks SSRI treatment will be presented.

Conclusions
These studies establish in vivo optical imaging for examining dopamine signalling changes associated with SSRI treatment. Completion of these studies will test the effect of 5HT2C receptor antagonist after 5 weeks SSRI treatment, which is expected to reverse SSRI effects on dopamine. Future studies will examine dopamine dynamics in preclinical models of OCD during SSRI treatment, to determine whether SSRI associated dopamine signalling changes occur during improvement of OCD-relevant behaviours.

Poster Abstracts

Poster Session 1: Monday

MON_38 Associations of cardiovascular risk factors with cognition in bipolar disorder

Presenting Author: Elysha Ringin

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Background
Cardiovascular risk factors (CVRFs) are disproportionately prevalent in bipolar disorder (BD) and are associated with cognitive impairment. Despite this, the extent to which CVRFs are associated with cognitive impairment in BD remains unknown. This study aimed to quantify associations of an array of CVRFs with cognitive impairment in BD and to determine whether these associations differed during mid and later life.

Methods
Data were available for 996 BD participants aged 40 – 70. Age, sex, socio-economic status, smoking status, type 2 diabetes (T2D), usual walking pace, handgrip strength, passive sedentary behaviour, mentally active sedentary behaviour, C-reactive protein, system immune-inflammation index, and a cardio-metabolic risk score were selected as the CVRFs of interest. Multivariable regression models were built to quantify associations of the CVRFs with global cognition. A sub-sample of participants was then categorised into either mid (< 50 years) or later life (≥ 60 years), and the model was re-run in each group.

Results
Age was the strongest statistical predictor of cognitive impairment in BD, followed by handgrip strength, usual walking pace, socio-economic status, mentally active sedentary behaviour, smoking status, and T2D status. Associations of CVRFs with cognition differed between the age groups, such that socio-economic status, handgrip strength, usual walking pace, and C-reactive protein were associated with cognition in those below 50, whereas mentally active sedentary behaviour, age, and socio-economic status were associated with cognition in those above 60.

Conclusions
Several CVRFs may act as useful indicators of cognitive impairment in BD. How these risk factors interact with cognition may depend on age. Future research should investigate the mechanisms by which these associations exist, and explore whether interventions aiming to reduce these CVRFs may help to reduce cognitive impairment in BD.

Poster Abstracts

Poster Session 1: Monday

MON_39 Effects of cannabinoids on resting state functional brain connectivity: a systematic review

Presenting Author: Alexandra Gaillard

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Background
Cannabinoid-based products are widely used globally and are becoming increasingly accessible, potent, and diversified. Over the past decade, the concentration of cannabis' main psychoactive compound ∆9-tetrahydrocannabinol (THC) in cannabis products has doubled. This is concerning as THC binds to brain cannabinoid receptors that are densely innervated in selected cortical regions implicated in cognitive processes that are altered with cannabinoid intoxication, as well as mental health symptoms. The brain pathways underlying cannabinoid intoxication are yet to be uncovered. This review aimed to investigate the brain functional changes that occur during acute cannabinoid intoxication using resting state functional connectivity (rsFC) MRI.

Methods
Functional neuroimaging evidence of connectivity during acute cannabinoid administration was systematically reviewed. Studies that investigated those of any age who were psychiatrically and neurologically healthy, and free of regular substance use were included. Specific attention was paid to the influence of cannabinoids and their administration (type, dosage, routes of administration) on the putative rsFC phenotype of cannabinoid intoxication. The associations between the level of rsFC alteration and self-reported intoxication or cognitive performance was also overviewed. 13 studies were included with 318 participants and mean age of 25 years. All studies but one contrasted rsFC between intoxication with cannabinoids versus placebo.

Results
All but two of the 13 studies reported altered connectivity following cannabinoid administration. Overall, 130 distinct region-pairs were reported to have altered rsFC during one of the following contrasts: THC vs placebo (94 pairs), cannabis plant matter vs placebo (23 pairs), CBD vs placebo (11 pairs), and THC vs CBD (2 pairs). The most consistent finding was lower connectivity during THC vs placebo between the NAcc, postcentral gyrus, supramarginal gyrus, insula, and other frontal regions. Alterations in these regions were positively correlated with self-reported intoxication and a greater number of attentional lapses.

Conclusions
The emerging evidence shows that acute cannabinoid administration causes changes in resting state functional connectivity in distinct brain pathways and as a function of the type of cannabinoid administered. Notably that intoxication with THC and cannabis plant matter lowers resting state functional connectivity between striatal and parieto-insular pathways implicated in cognitive processes altered during cannabinoid intoxication (reward processing, disinhibition, sensorimotor function). Interestingly, resting state fMRI evidence has shown that THC and CBD affect neurobiological pathways implicated in prominent neuroscientific theories of addiction. More robust and large-scale studies are required to further uncover brain functional changes.

Poster Abstracts

Poster Session 1: Monday

MON_40 Investigating the Role of pDMS Direct Spiny Projection Neurons in the Transition to Habits

Presenting Author: Isabel Chew

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Background

Action selection is governed by goal-directed and habit control systems. While the goal-directed system allows performance of actions aligned with one's current motivations, the habit system allows us to gain efficiency through automaticity. In psychiatric disorders including addiction there is evidence that these systems become imbalanced, which contributes to disturbances in flexible behaviour. The posterior dorsomedial striatum (pDMS) is essential for goal directed actions, and specific contributions of the two output populations are beginning to emerge. However, the changes in pDMS output populations associated with cocaine exposure and inflexible behaviour have not been explored in vivo.

Methods
Neural activity was measured in direct pathway spiny projection neurons (dSPNs) in pDMS using fiber photometry in D1-Cre rats. Rats were injected with cocaine (30mg/kg) or saline for 6 days prior to behavioural testing. Goal directed behaviour was examined using outcome devaluation procedure following standard and extended training within subjects, followed by extinction training.

Results
Both groups showed goal-directed behaviour in early training as expected. In late training, half the rats in both groups showed habitual behaviour. Although there was no difference between groups on outcome-devaluation, the cocaine group was significantly impaired on extinction day 1 compared to the saline group. Preliminary analysis shows overall neural differences between groups during early training associated with lever presses and a sharp decay of activity in cocaine animals relative to saline animals during non-devalued sessions (assessed using area under the curve measure, trend for interaction).

Conclusions
We have shown a significant difference in neural firing surrounding a lever press during the outcome devaluation test as well as a significant behavioural difference on extinction day 1 between groups. We will next examine the neural signatures that are occuring during these extinction sessions. By characterising and comparing the neural population activity of the dSPNs across these sessions, we hope to gain an increased understanding of their role in habit and learning associated with addiction.

Poster Abstracts

Poster Session 1: Monday

MON_41 Psychological stress alters cell density in the CA1 region of the hippocampus of severe psychiatric disorder cases

Presenting Author: Amber Curry

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Background
The hippocampus is a brain area involved in how stress contributes to the development of psychiatric disorders, including depression, schizophrenia and bipolar disorder. Structural magnetic resonance imaging studies (sMRI) suggest that the hippocampus is atrophied in these individuals. However, the underlying cellular pathology is unknown. The aim of this study was to begin to understand the impact of stress on the cellular architecture of the hippocampus in individuals with psychiatric disorders.

Methods
Postmortem brain tissues were acquired from the NSW Brain Tissue Resource Centre. The cohort consisted of trans-diagnostic psychiatric disorder cases with varying significant stress exposures at specific timepoints in their lives (childhood, adulthood, no stress) and matched controls (n=8/group). As our samples were derived from blocks previously stained with the Golgi-Cox method, we optimised and implemented a method for clearing the Golgi-Cox stain before processing the sections with Nissl. We then determined potential alterations of cell density in the CA1 region of the hippocampus according to stress exposure and psychiatric disorder status.

Results
Cell density in the CA1 region was 34% higher in psychiatric disorder cases with childhood
stress compared to cases with no significant life stress ($p=0.0397$), and 27% higher compared to cases characterised by stress experienced in adulthood ($p=0.0241$). There were no differences in cell density between any of the psychiatric disorder groups compared to the control group.

Conclusions
The preliminary data suggests that significant levels of stress exposure in childhood may be associated with increased CA1 cell density. The data is so far inconclusive. Increased cell density may suggest an increase in cell numbers, or it may suggest that volumetric changes in the hippocampus (observed in sMRI studies) are underpinned by other changes to the neuropil, causing more condensed cell numbers. Our ongoing single cell sequencing studies (droplet-based and spatially resolved) will help us to further understand this and overall how the hippocampus cytoarchitecture is impacted by stress in psychiatric disorders.

Poster Abstracts

Poster Session 2: Tuesday

TUE_01 Investigating the properties and behavioural roles of RXFP3+ zona incerta/lateral hypothalamus neurons

Presenting Author: Brandon Richards

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Background
The relaxin-3/RXFP3 neuropeptide-receptor system primarily regulates behavioural arousal via widespread ascending relaxin-3 projections from the pontine nucleus incertus. We recently identified a dense population of RXFP3+ cells in the zona incerta (ZI) and the adjacent lateral hypothalamus (LH) of unknown function. Thus, we examined the neurochemical identity and efferent connectivity of RXFP3+ LH/ZI cells to establish their potential roles. From this, we determined that these cells are likely involved in context-dependent fear expression and behavioural arousal.

Methods
RXFP3-Cre mice were used to investigate RXFP3+ LH/ZI neurons. A Cre-dependent anterograde tracer was injected in the LH/ZI to define RXFP3+ efferents. Fluorescent immunohistochemistry for select neurochemical markers was performed for cell phenotyping. The excitatory DREADD, hM3D(Gq), was used to chemogenetically activate cells during behaviour. One day after auditory fear conditioning, cells were activated during extinction in the conditioning context or a novel context, and context-dependent fear expression was assessed. Locomotor effects were examined by activating these cells during an open-field test. Cells were activated two hours before perfusion, and immunohistochemical Fos analysis was performed to assess brain-wide activity.

Results
RXFP3+ LH/ZI cells were not a subset of orexin, melanin-concentrating hormone, or cocaine and amphetamine-regulated transcript expressing cells but putatively synapsed with LH orexin neurons and ZI A13 cells. Strong efferents were observed across the hypothalamus, periaqueductal gray, nucleus reuniens, and lateral habenula. Activating these cells during conditioned fear extinction decreased conditioned stimulus-evoked freezing in a novel context only and induced transient jumping in a subset of mice irrespective of context. During open-field testing, activating these cells increased locomotor activity, rearing, and centre zone duration. Chemogenetically activating these cells increased Fos expression in arousal- and defensive behaviour-related areas.

Conclusions
Our study provides an initial account of the connectivity and function of RXFP3+ LH/ZI cells, implicating the population in context-dependent fear expression and arousal. Additional studies are necessary to determine if increased locomotion and jumping upon ensemble activation reflects heightened stress necessary to engage in defensive behaviour, or an increased exploratory drive, as anterograde tracing and Fos patterns suggest both possibilities. Furthermore, different subpopulations of RXFP3+ cells may have contributed to the context-dependent freezing reduction versus enhanced behavioural arousal observed upon activation of RXFP3+ LH/ZI cells, given the neurochemical heterogeneity of both nuclei, which warrants further investigation.

Poster Abstracts

Poster Session 2: Tuesday

TUE_02 The Sex-Specific Effects of Raloxifene and Maternal Immune Activation on Dorsal Striatal Dopaminergic Transcripts in Adult Rat Offspring

Presenting Author: Brendan V. Navaneethan

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Background
Hyperdopaminergia in the dorsal striatum (dSTR) contributes to psychosis in schizophrenia. Psychosis is sometimes ameliorated by adjunctive treatment with the selective oestrogen receptor modulator, raloxifene, as demonstrated in clinical trials of post-menopausal women with schizophrenia. Maternal immune activation (MIA) via polyinosinic:polycytidylic acid [Poly(I:C)] injection of dams leads to dopamine dysregulation in offspring, including striatal hyperdopaminergia. This makes MIA offspring a suitable model to investigate the molecular mechanisms through which raloxifene may exert neuroprotective effects in schizophrenia. We used MIA in rats to examine the effect of raloxifene on dopaminergic transcripts in the dSTR of male and female adult offspring.
Methods
Wistar rat dams were injected via tail vein with saline (n=11) or 4mg/kg high molecular weight Poly(I:C) (n=10) on GD19. Offspring received daily raloxifene (5mg/kg, cookie dough) or placebo from PND58 to 84, with 4 treatment groups per sex [n=10-12; saline/placebo, saline/raloxifene, poly(I:C)/placebo, poly(I:C)/raloxifene]. Offspring were euthanised (PND83-84), dSTR tissue dissected, RNA extracted, and cDNA prepared for RT-qPCR. Expression of dopaminergic transcripts (receptors: DRD1, DRD2 short and long, metabolising enzymes: COMT, MAOA, MAOB) was determined via normalisation to the geomean of housekeeper transcripts (GUSB and HPRT1, delta-delta CT method). Data was analysed with 2-way ANOVAs (males and females separately).
Results
In female offspring, MIA decreased MAOB mRNA (p<0.05), whilst raloxifene increased MAOA mRNA at a trend level (p=0.063). Raloxifene treatment increased COMT mRNA levels in female offspring (p<0.01) and decreased COMT mRNA in male offspring (p=0.056). MIA increased DRD1 mRNA in male offspring (p<0.05), but neither MIA nor raloxifene altered DRD2 short or long mRNA levels in males and females. However, interaction effects were observed in male DRD2 short (p<0.01) and DRD2 long (p=0.061) mRNAs. This was driven by increased DRD2 short and DRD2 long mRNAs in the male poly(I:C)/raloxifene group compared to the control/raloxifene group (p<0.01 and p<0.05 respectively).
Conclusions
MIA and raloxifene had opposing effects on dopamine-metabolising transcripts in female offspring, with metabolising potential being reduced by MIA and increased by raloxifene. Interestingly, raloxifene had opposite effects on COMT transcripts in males and females. The effects of MIA alone and combined interactions of MIA and raloxifene on DRD1 and DRD2 expression in males only highlight sex-specific effects on dopamine receptor transcripts. Future studies will determine whether MIA and raloxifene influence dopamine transporter and tyrosine hydroxylase protein expression in the dSTR. These results highlight the importance of considering sex-specific effects when exploring novel therapeutics for schizophrenia that target dopaminergic transcripts.

Poster Abstracts

Poster Session 2: Tuesday

TUE_03 Cancer sensitizes microglia to stress, which may contribute to the high prevalence of anxiety in cancer patients

Presenting Author: Delyse McCaffrey

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Background
Anxiety is 3-times more prevalent in patients with chronic inflammatory conditions, such as cancer, compared to the general population. This may be attributable to the impact of both the stress of living with cancer and cancer-induced inflammation on the brain. Glial cells respond to stress and inflammation and are implicated in neurobiological changes associated with psychiatric comorbidities in other neurodegenerative diseases. Therefore, to disambiguate the role of cancer versus stress, we examined anxiety-like behaviour and glial activation in tumour and non-tumour bearing mice exposed to restraint stress (vs no stress) using a mouse model of metastatic breast cancer.
Methods
40 female BALB/c mice bearing 4T1.2 mammary tumours (vs no tumour) underwent 2 h of restraint stress (vs handling) starting 2 days after tumour cell injection for seven consecutive days, and were assessed on a battery of anxiety-related behavioural tests. After CO2 euthanasia, spleens and primary tumours were dissected before perfusion with PBS and paraformaldehyde. Brains were sectioned coronally and stained for Iba1 (soma area, immunoreactive material), GFAP (immunoreactive material) and ΔFosB (density). Immunoreactive sections were imaged and changes in morphology indicating glial activation were quantified in stress-relevant neurocircuitry.
Results
Restraint stress activated the paraventricular nucleus indicated by ΔFosB staining (p<0.0001) and increased plasma corticosterone (p<0.01) in control mice. However, restraint stress did not increase plasma corticosterone in tumour-bearing mice despite activating the paraventricular nucleus. Cancer and restraint stress independently activated microglia in subcortical brain regions (p<0.05). However, combining cancer and stress reduced microglial activation in the dentate gyrus (p<0.05). Cancer but not stress reduced cortical astrocyte reactivity (p<0.05). Restraint stress and cancer each induced anxiety-like behaviour which correlated with microglial activation (p<0.05). Unexpectedly, the combination of cancer and restraint stress increased time in the light zone (p<0.05).
Conclusions
The findings demonstrate that tumours prime microglia in brain regions targeted by chronic stress and change how they respond. Although combining cancer and stress did not augment microglial activation, they may synergise to induce dystrophic microglia in the dentate gyrus. This potentially contributed to stress neurocircuitry dysregulation and aberrant behavioural changes, emphasised by the absence of a stress-induced corticosterone response despite activation of the paraventricular nucleus. Cancer reduced astrocyte reactivity in the cortex, suggesting that the impact of cancer on glia are cell and brain-region specific. Glia-specific interventions may therefore be required to treat stress-and-anxiety disorders in cancer patients.

Poster Abstracts

Poster Session 2: Tuesday

TUE_04 Effects of early-life environmental enrichment in a rat model of the Brain-Derived Neurotrophic Factor (BDNF) Val66Met gene variant

Presenting Author: Emily Jaehne

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Background
The Val66Met polymorphism is a common variant of the BDNF gene which reduces activity-dependent release, and which has been suggested as a risk factor for affective disorders, particularly by interacting with early-life stress and other environmental factors. A potential protective factor against affective disorders is environmental enrichment. However, little is known about differential effects of early-life environmental enrichment on affective behavioural phenotypes in BDNF Val66Met genotypes. Here we used a novel rat model of the BDNF Val66Met gene variant (Val68Met) to study this interaction.

Methods
Following conception, pregnant Val68Met rat dams were moved from standard housing (double level IVC cages, standard crinkle nest enrichment) to either a high or low enrichment environment. High enrichment environments consisted of IVC cages with regularly rotated additional wooden, cardboard and plastic toys, while low enrichment environments were smaller open top cages with only standard crinkle nest. Dams remained in their assigned cages until pups were born and weaned at 3 weeks of age. Pups were weaned into standard housing until adulthood when behavioural testing was conducted, including elevated plus maze, open field, fear conditioning and forced swim test (n=7-12/group).

Results
The body weight of rats reared in high enrichment was shown to be higher than those in low enrichment at weaning ($p=0.0058$), however there was no longer a significant difference in adulthood. Behavioural testing showed that rats reared in high enrichment displayed decreased time in the open arm of the elevated plus maze ($p=0.0042$) and the centre of the open field ($p=0.032$) compared to low enrichment, indicating an increase in anxiety-like behaviour. There was no significant effect of enrichment on fear conditioning or forced swim test behaviour. There was no effect of Val68Met genotype on any of these measures.

Conclusions
Despite the expectation that enriched environments would reduce anxiety, our results suggest early-life enrichment actually increased this behaviour during adulthood. There was no influence of the Val66Met genotype on these behaviours or the effect of environmental enrichment.

Poster Abstracts

Poster Session 2: Tuesday

TUE_05 Context modulates the consolidation of overlapping fear memories in the basolateral amygdala complex

Presenting Author: Jessica Leake

Authors:
Jessica Leake - UNSW
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Background
Studies investigating the biological basis of fear memories typically use protocols involving a single fearful event. In reality, traumatic experiences often occur more than once and this has implications for how memories are processed in the brain. Within the basolateral amygdala, protein synthesis is required for forming an initial fear memory, but not a second, overlapping, fear memory. This suggests that changes induced by the first event are capable of supporting learning about related sources of danger. Here, we examined whether the timing and location of the events regulates the requirement for protein synthesis in consolidating a second fear memory.

Methods
Rats were trained in a two-stage fear conditioning protocol. In stage one, rats received pairings of a novel stimulus (e.g., tone) and shock, forming an initial fear memory. In stage two, rats received light-tone-shock sequences, forming a second fear memory involving the light. Immediately after stage 2 training, they received an intra-amygdala infusion of the protein synthesis inhibitor cycloheximide. Finally, they were tested for fear to the light and tone. The experiments differed with respect to the timing (2 days vs 2 weeks) and location (same vs. different context) of the second conditioning experience.

Results
Our experiments showed that both a context shift and a time delay reinstated the requirement for protein synthesis in the basolateral amygdala in the consolidation of a second fear memory. Interestingly, further experiments showed that the effect of shifting location and time on the requirement for protein synthesis could be reversed by reminding animals of their prior experience.

Conclusions
These results are taken to imply that the physical and temporal context mediates how discrete fear memories are retrieved and stored in the brain. These findings indicate that protein synthesis is not universally required for fear learning and suggests that contextual information regulates how fearful memories are linked across experience.

Poster Abstracts

Poster Session 2: Tuesday

TUE_06 A role for the lateral hypothalamus in habitual behaviour

Presenting Author: Teri Furlong

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Background
Selecting actions appropriate to current circumstances is necessary for adaptive behaviour. Such behaviour is known to be dependent on two distinct neurocircuits which regulate either goal-directed or habitual actions. These two neurocircuits centre on different parts of the striatum, and also differ in their associated limbic inputs from prefrontal cortex and amygdala. Imbalances in the functioning of these neurocircuits is recognised to underlie symptoms of psychiatric conditions, including poor decision-making abilities, reduced cognitive control, behavioural inflexibility, altered motivation, addiction, and compulsions. The aim of this study was to implicate the lateral hypothalamus in action selection.

Methods
The lateral hypothalamus of adult male rats was stereotaxically targeted using short hairpin RNAs (shRNA) or vehicle for control. Compared to control, shRNA was shown to reduce the expression of at least two neuropeptides within the lateral hypothalamus (orexin and melanin-concentrating hormone) using immunohistochemical procedures. Control and shRNA treated rats were trained to press a lever for a food outcome. Sensitivity to devaluation of the food outcome was used to test for goal-directed actions after moderate instrumental training (3 sessions) and to test for habitual actions after extended instrumental training (a further 6 sessions).

Results
shRNA targeted at the lateral hypothalamus did not alter goal-directed actions following moderate instrumental training (significant main effect of devaluation only; $F(1,25) = 28.5$, p<0.001), however, habitual actions did not develop following extended training (significant interaction between treatment group and devaluation; $F(1,22) = 6.4$, p<0.02). That is, control rats developed the expected habitual behaviour where lever-response rates were insensitive to outcome value when tested, whilst the shRNA groups reduced rates of responding on the lever under devalued conditioned and hence remained goal-directed. Non-selective effects on motivation, arousal and motor behaviour resulting from targeting the lateral hypothalamus were also ruled out.

Conclusions
For the first time, we demonstrate that the lateral hypothalamus promotes habitual behaviour in rats, and thus extend the neurocircuits known to regulate habitual actions. Habitual actions are adaptive as they reduce cognitive load and allow for learned, efficient, automated behaviour. Dysfunction of the lateral hypothalamus is associated with several psychiatric conditions, including drug addiction, post-traumatic stress disorder, and Parkinson's disease. Hence, the lateral hypothalamus may contribute to reduced decision-making and cognitive abilities seen in these conditions, as well as to disordered habit learning that has been demonstrated for schizophrenia and obsessive-compulsive disorder.

Poster Abstracts

Poster Session 2: Tuesday

TUE_07 Testing the direct role of cognitive flexibility in activity-based anorexia using an automated experimenter-free touchscreen testing system

Presenting Author: Kaixin Huang

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Background
Anorexia nervosa (AN) has the highest mortality rate of all psychiatric disorders, yet there is no effective medicinal treatment, due to a limited understanding of the biological causes. Deficits in cognitive flexibility are reported both in patients with AN and rats exposed to the activity-based anorexia (ABA) paradigm, however, whether cognitive inflexibility predisposes humans (or rodents) to develop anorectic behaviour remains unknown. Due to the extended training time required to examine cognitive flexibility in rats, and the requirement for ABA to be conducted in young animals, it has been impossible to answer this question in our laboratory… until now.

Methods
Using a fully-automated and experimenter-free touchscreen testing system, the PhenoSys, we can assay cognitive flexibility in rats 10 times faster than conventional methods, allowing us to examine the direct role of cognitive flexibility in susceptibility to ABA. Here, female Sprague-Dawley rats (n=36; 6 weeks-old) underwent a touchscreen-based visual reversal learning task prior to commencement of ABA conditions, which consisted of unlimited access to a running wheel paired with time-limited access to food (90min/day). We also determined whether exposure to ABA conditions altered cognitive performance on the same task in a separate cohort of rats (n=24) after body weight recovery.

Results
Contrary to prediction, rats that went on to be resistant to weight loss in ABA were more inflexible in the reversal learning task, requiring more sessions to reach performance criteria than rats that went on to be susceptible to ABA ($F_{1,20}=5.52$, $p=.0292$). Exposure to ABA conditions impaired reversal learning without effects on discrimination learning, whereby >50% of animals exposed to ABA were unable to effectively learn the reversal task after 20 consecutive sessions. Moreover, those ABA-exposed animals that were able to learn the reversal task required more sessions of training than animals naive to ABA conditions ($F_{1,20}=18.8$, $p=.0492$).

Conclusions
These studies revealed that experience with ABA impairs cognitive flexibility, even after body weight recovery, which mirrors deficits seen in patients recovered from AN. Intriguingly, rats that went on to be susceptible to ABA demonstrated increased flexibility in reversal learning that did not translate to more adaptive wheel running. Future studies will differentiate specific aspects of flexibility involved in both reversal learning and body weight maintenance in ABA, including the transition from goal-directed to habitual behaviour with respect to running wheel activity. Moreover, the role of metabolic adaptation/flexibility in ABA will be elucidated, with techniques such as whole-body calorimetry.

Poster Abstracts

Poster Session 2: Tuesday

TUE_08 The Developmental Vitamin D-Deficiency Rat Produces Autism-Relevant Behaviours and Gut Health-Associated Alterations

Presenting Author: Man Kumar Tamang

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Background
Developmental Vitamin D (DVD)-deficiency is an epidemiologically established risk factor for autism. Emerging studies also highlight the involvement of gut microbiome/gut physiology in autism. Our lab was the first to develop the animal model of DVD-deficiency in a rat to study the effect of vitamin D-deficiency on brain function and behaviour. The current study aims to examine a broad range of autism-relevant behavioural phenotypes and impacts on gut health/physiology induced by DVD-deficiency.

Methods
DVD-deficiency was induced by placing four-week-old outbred female Sprague-Dawley rats on standard casein AIN93G rodent chow without any added vitamin D (0 IU Cholecalciferol) for six weeks. Then, the females are mated, with the resulting pregnant dams remaining on DVD-deficient diets throughout pregnancy and until weaning postnatal day 21 (P21). Offspring remain on the same diet until behavioural testing, P35. Maternal behaviour was assessed from P2-P6, pup USVs and pup retrieval were measured at P7 and P9. Social behaviour on adolescent offspring were assessed at P35 and all gut experiments were conducted using the samples collected from the adolescent animals.

Results
DVD-deficient rat dams exhibited altered postnatal maternal care. DVD-deficient pups at P9 showed increased ultrasonic vocalizations and in adolescence (P35), decreased social behaviour and increased repetitive self-grooming behaviour. There were significant impacts of DVD-deficiency on offspring gut health as demonstrated by altered microbiome composition, decreased villi length, and increased ileal propionate levels.

Conclusions
Overall, our animal model of this epidemiologically validated risk exposure for autism shows an expanded range of autism-related behavioural phenotypes and now alterations in gut microbiome that correlate with social behaviour. This model remains informative for studying autism-relevant brain and gut mechanisms.

Poster Abstracts

Poster Session 2: Tuesday

TUE_09 In vivo fibre photometry reveals increased neural activity in the lateral septum is associated with fleeing social contact in mice.

Presenting Author: Mia Langguth

Authors:
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Background
Social avoidance is a core feature of numerous disorders. Recent evidence indicates neurons in the lateral septum (LS) play a key role in modulating social avoidance in mice. However, the specific social avoidance behaviours mediated by the LS in this context have yet to be characterised. Our aim, therefore, was to examine the relationship between LS dynamics and specific social approach and avoidance behaviours with high temporal precision using fibre photometry.

Methods
C57BL/6 mice underwent surgery to infuse a fluorescent calcium sensor and implant a fibre optic cannula within the LS. 2 weeks post-surgery mice were socially isolated for one week and then presented with a series of novel social stimulus (caged novel mice) for 3 min each with a 3 min ITI (SFC-). One week later, the same mice were socially fear conditioned and the next day were again presented with a series of social stimuli (SFC+). Using fibre photometry and frame-locked video recordings, we correlated LS dynamics during exposure to SFC- and SFC+ social stimuli with specific behaviours.

Results
Peaks in LS activity immediately preceded instances of the mouse rapidly fleeing the social stimulus. These peaks were observed when mice were unconditioned and when they were socially fear conditioned. However, peaks were most pronounced on the first social stimulus exposure during the SFC+ test, and showed a reduction over successive social stimulus exposures, alongside the extinction of social fear. No other clear association between LS activity and specific behaviours was identified.

Conclusions
These findings suggest that neuronal firing in the LS may promote social avoidance by driving social fleeing behaviour.

Poster Abstracts

Poster Session 2: Tuesday

TUE_10 Sex differences in aversive and appetitive spatial memory tasks in mice

Presenting Author: Phoebe Mayne

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Background
Across 10 fields of biological research including neuroscience, single-sex studies wherein only male mice are used, outnumber those using both sexes 5.5 to 1. This sex bias has been highlighted as a potential factor contributing to poor translation and reproducibility of biological experiments. In behavioural neuroscience, studies using mice have revealed sex effects on various cognitive tasks, yet male subjects continue to be favoured. The aim of this study was to test female and male mice on aversive and appetitive spatial tasks and examine the expression of perineuronal nets (PNNs) and parvalbumin interneurons (PV) in regions correlated with spatial memory.

Methods
Adult female and male BALB/c mice underwent the aversive Active Place Avoidance (APA) task or the appetitive Trial-Unique Nonmatching-to-Location (TUNL) touchscreen task. For APA, mice learnt to avoid foot-shocks in a certain spatial location. Measures included latency to entry and number of shocks. For TUNL, mice were trained to respond for a strawberry milk reward, and then assessed on separation and delay manipulations. Three outcomes were measured: percentage of incorrect, reminder and correct responses. Mouse brains were collected for immunohistochemistry to assess the number and intensity of PNNs and PV in the hippocampus and granular and agranular retrosplenial cortex (RSC).

Results
Female and male mice in the APA cohort learnt to avoid the foot-shock and no differences were observed on key measures of the task nor in the number and intensity of PNNs and PV. In the separation manipulation of TUNL, there was a main effect of Outcome and Separation but no main effect for Sex. In the delay manipulation, there was a main effect of Outcome, Delay and Sex, with females receiving more incorrect and reminder trials and less correct trials compared to males. Furthermore, females exhibited higher intensity for PNNs and PV in the agranular RSC, compared to males.

Conclusions
These data show that female and male mice perform similarly on spatial learning tasks. However, females and males may differ in how they retain spatial information on an appetitive task. Given the sex differences in PNNs and PV in the agranular RSC, a region postulated to support spatial encoding and retrieval, and directly connected to the hippocampus, it is possible that neural processes involved with time-sensitive spatial information may be processed differently in female and male mice. Male mice have been the default research subject; however, these data emphasise the importance of including both sexes of mice in future studies.

Poster Abstracts

Poster Session 2: Tuesday

TUE_11 A novel clinical-stage treatment for the 'dark side' of addiction.

Presenting Author: Rhianne L Scicluna

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Background
The 'dark side' of addiction is the negative affective component of opioid withdrawal that drives drug seeking through negative reinforcement. It's characterised by an acute phase, representing the first hurdle to recovery and a protracted phase, which is a significant barrier to long-term recovery. There is only one non-opioid treatment for acute withdrawal, associated with limited efficacy and serious side effects and no treatment for protracted withdrawal. KNX100 is a novel phase-I molecule that reduces acute naloxone-precipitated oxycodone withdrawal in mice. Here, we examined the efficacy of KNX100 for the negative affective symptoms of acute withdrawal and protracted abstinence.

Methods
Rats were trained to self-administer oxycodone for 44-48 days through a surgically implanted intravenous catheter. Each infusion was accompanied by a light+tone. Prior to oxycodone administration, rats were tested for their baseline aggressive and defensive behaviour and were assed for wet dog shakes. To elicit spontaneous withdrawal, rats underwent a 24-hour withdrawal period and were tested twice again using the same tests, treated once with vehicle and once with KNX100. Rats underwent a 15-day protracted abstinence period and were tested for cue-induced reinstatement on day 2 and 15, with rats receiving KNX100 or vehicle prior to testing on day 15.

Results
We showed that KNX100 treatment significantly reduced withdrawal-induced aggressive behaviour and defensive behaviour, but not wet dog shakes, in male and female rats, indicating that KNX100 ameliorates the negative affective aspects of the acute opioid withdrawal syndrome. We showed that KNX100 potently inhibited cue-induced reinstatement of drug seeking 15 days into abstinence, indicating that KNX100 may alleviate the negative psychological state that emerges during protracted abstinence, which contributes to relapse.

Conclusions
Taken together, these data suggest that KNX100 may be a viable therapeutic for alleviating the negative affective aspects of acute withdrawal and reducing relapse during protracted abstinence. These data, along with the lack of currently available pharmacotherapies, motivate a focus on the 'dark side' of addiction for phase II efficacy trials.

Poster Abstracts

Poster Session 2: Tuesday

TUE_12 Preterm Birth Causes Sex-Dependent Disruptions to Key Neurotransmitter Systems Within the Frontal Cortex of Guinea Pigs

Presenting Author: Roisin A. Moloney

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Background
Preterm birth is associated with a significantly increased risk of neurobehavioral disorders, in particular attention deficit hyperactivity disorder (ADHD) and anxiety. Key neurotransmitter dysregulation is implicated in these disorders, with disruptions occurring to the dopaminergic system, as well as the inhibitory GABAergic and excitatory glutamatergic balance. Preterm birth results in the premature exposure to the harsh ex-utero environment, as well as removal from the placentally derived inhibitory neurosteroids that are critical to the developing brain. We propose that these disturbances may cause disruptions to key neurotransmitters, which could be a mechanism underpinning the development of such disorders following preterm birth.

Methods
Dunkin Hartley time-mated guinea pig dams were allocated to fetal collection (preterm fetal; GA62, or term fetal; GA68), preterm induction of labour (preterm neonate; corrected postnatal day 1, or preterm juvenile; corrected postnatal day 40), or spontaneous term labour (term neonate; 24hrs old, or term juvenile; postnatal day 40). Relative mRNA expression of key neurotransmitter receptors in the frontal cortex were quantified by RT-PCR. Protein analysis is underway.

Results
Dopamine receptor 1 (DRD1) mRNA expression was reduced in preterm male fetuses, neonates and juveniles compared to term-born ($p=0.01$, $p=0.02$, and $p=0.01$). A developmental increase of dopamine receptor DRD2 was observed in preterm females between fetal to neonatal age ($p=0.02$). GABAA receptor α6 subunit (GABRA6) expression was increased in preterm male and female neonates compared to term-born ($p=0.02$, $p=0.03$). GABAA receptor α4 subunit (GABRA4) expression was reduced in preterm male and female juveniles compared to term-born ($p=0.02$, $p=0.03$). Male and female preterm neonates had increased glutamate NMDA receptor subunit 3A (GRIN3A) expression compared to term-born ($p=0.01$ and $p=0.03$).

Conclusions
This study showed that preterm birth has altered receptors of the dopaminergic, GABAergic, and glutamatergic pathways in a sex dependent manner, which could contribute to the development of neurobehavioral disorders such as ADHD and anxiety following preterm birth.

Poster Abstracts

Poster Session 2: Tuesday

TUE_13 The role of Betacellulin in working memory performance

Presenting Author: Sharvada Raju

Authors:
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A/Prof Rachel Hill - Monash University
Prof Suresh Sundram - Monash University

Background
The epidermal growth factor system is altered and associated with cognitive deficits in schizophrenia. Our laboratory showed that a ligand from this system called betacellulin (BTC) was reduced in the serum and dorsal-lateral prefrontal cortex of patients with schizophrenia and that low BTC expression was associated with severe cognitive symptoms. To further probe the role of the BTC ligand in the specific cognitive domain of working memory, we aimed to assess working memory in a BTC knock down mouse model using a translatable and sensitive touchscreen cognitive testing platform. We hypothesised that BTC KO mice will show disrupted working memory.

Methods
BTC knockdown and wildtype mice (n=5-7/group) underwent food restriction to 90% of their body weight from PND 70 and commenced touchscreen training for the Trial Unique Non-Matching to Location Task (TUNL). For this task in phase one, a lit square will appear and disappear, followed by a delay period. In phase two, two lit squares consisting of the familiar lit square and a novel lit square will appear. The mice must correctly distinguish the novel lit square. The task difficulty is increased by a long delay period and decreased separation between the novel square and familiar square.

Results
A significant genotype x sex interaction was found for number of correction trials required in the initial phases of testing ($p = 0.04$). Here, female but not male KO mice required more correction trials than WT littermate controls. In addition, there was a significant effect of sex for time taken to complete the task during the training phases. Here female WT and KO mice took significantly longer than males (p<0.05). Once all mice had learned the task there were no group differences in performance.

Conclusions
Although there were no group differences in overall working memory performance once the mice hard learned the task, female KO mice required more correction trials in order to learn the task. This may suggest that the BTC ligand may be involved in the learning rather than working memory performance. Overall the data provides further understanding of the contribution of EGF pathways to more specific cognitive domains disrupted in schizophrenia.

Poster Abstracts

Poster Session 2: Tuesday

TUE_14 Rapid assessment of cognition in rats and mice using the dynamic strategy shifting task (DSST)

Presenting Author: Suzy Alexander

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Background
The translational validity of rodent tests of cognition has become a critical issue in the pursuit of more effective medications and has been a key consideration in the selection of preclinical cognitive tasks. We have developed an operant-based cognitive task to mirror elements of the human measures of cognitive flexibility with the purpose of creating a translational measure of cognition in rats, mice and humans. The aim was to have a task that could rapidly assess cognitive flexibility across different spatial and non-spatial rules, and in response to visual or auditory cues in both rats and mice.

Methods
We used adult male Sprague-Daley rats (n=12) and C57BL6/J mice (n=12). Training was conducted in operant chambers (Med Associates). Animals were food restricted, trained to collect a reward (Rats:45mg pellet; Mice:0.02ml milk), initiate trials with a nosepoke, and respond to a left or right retractable lever. They were then exposed to a series of discriminations (visual, spatial, non-spatial light or tone). Finally, they were tested using each of these rules separated by a reversal phase. The rule was dynamically altered within a session after 6 consecutive correct responses. The key measures were the number of sessions and trials to criteria.

Results
There was a significant (p100 trials to acquire. However, mice took significantly longer than rats to learn the non-spatial auditory rule. A few rats completed training, exposure and testing in as little as 10 sessions, whereas the fastest mice took 20 sessions.

Conclusions
The DSST is a fully automated test of cognitive flexibility. Here we show that the DSST can be completed in as little as 10 sessions, with an average of 20 sessions in rats and 28 sessions in mice. The DSST involves instrumental learning, decision making, spatial and non-spatial rule learning, modality shift from visual cue to a tone, as well as reversals of each rule. These data show that rats and mice perform at similar levels on cognitive flexibility and the DSST provides a complex cognitive testing protocol accessible to researchers needing a high throughput task to assess cognitive flexibility.

Poster Abstracts

Poster Session 2: Tuesday

TUE_15 Sex differences in the role of cocaine- and amphetamine-regulated transcript in binge drinking

Presenting Author: Xavier J. Maddern

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Background
Binge drinking is a problematic form of risky alcohol consumption that can lead to a variety of short- and long-term health consequences. Despite the prevalence of binge drinking, the neural mechanisms involved, and potential sex differences that may exist remain elusive. The neuropeptide cocaine- and amphetamine-regulated transcript (CART) has previously been implicated in reward, feeding, stress, and alcohol seeking behaviours, but has yet to be examined in the context of binge drinking. Therefore, this study investigated potential sex differences in the role of CART in binge drinking.

Methods
Male and female CART-KO or WT littermates (Exp 1-4) and C57BL6J (Exp 5) mice underwent three 2-hour binge drinking sessions per week, where the water bottle was replaced by a bottle containing 10% v/v ethanol. After each 2-hour training period, the water bottle was returned in place of the ethanol bottle. Each session commenced 3-hours into the dark-phase, with the ethanol bottle being weighed before and after to determine alcohol intake. Following at least 10 training sessions, mice completed a 4-hour test session, where the ethanol bottle was weighed each hour during the test session.

Results
Male CART-KO mice increased, whilst female CART-KO mice decreased, alcohol intake compared to wildtype littermates (Exp 1). Female CART-KO mice also displayed heightened sensitivity to bitter tastes (quinine) compared to wildtype mice; enhancing palatability of alcohol/quinine via sucrose supplementation returned intake to wildtype levels (Exp 2-3). In female CART-KO mice, ovariectomy had no effect on alcohol intake compared to SHAM surgery (Exp 4). Therefore, to examine the role of CART signalling in key gustatory loci, we neutralised CART signalling in the parabrachial nucleus (PBN) which increased binge drinking in male and female mice (Exp 5).

Conclusions
Here we report sexual dimorphism in the role of CART in binge drinking. The reduced binge drinking phenotype observed in female CART-KO mice appeared to not be driven by circulating sex steroids, but rather bitter taste perception, as this phenotype was rescued by enhancing palatability. Neutralisation of CART signalling in the PBN, a key taste processing node, increased binge drinking in male and female mice, with the effect being more pronounced in males. Future experiments will assess the role of CART signalling in other key gustatory regions of the brain and elucidate the neural circuits underpinning these behaviours.

Poster Abstracts

Poster Session 2: Tuesday

TUE_16 Novel pharmacotherapies for young people with methamphetamine use disorder: the MASKOT and CALM studies

Presenting Author: Alexandre Guerin

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Background
Methamphetamine use disorder is a is a chronic, relapsing condition with adverse health and psychosocial consequences. Methamphetamine use commonly starts in adolescence or early adulthood, adversely impacting developmental trajectory. New treatment approaches for young people are required. The aim of these two open-label studies is to assess candidate pharmacotherapies for safety and tolerability in young people (15–25-year-old) with methamphetamine use disorder who wish to reduce their use. The MASKOT study (MethAmphetamine use in young people: Sub-anaesthetic ketamine open-label trial) will test sub-cutaneous ketamine, and the CALM study (Cannabidiol – A novel pharmacotherapy for Lowering Methamphetamine use) will test oral cannabidiol.

Methods
In the MASKOT study, participants (N=20) receive two doses of sub-cutaneous ketamine one week apart (initial dose 0.75mg/kg), with follow-up at weeks 2, 3, 4, and 6. Primary endpoints are safety (change in past month ketamine use, and liver function tests at week 2) and tolerability (number of participants withdrawing due to adverse medication effects). In the CALM study cannabidiol, participants (N=12) complete 8 weeks of oral cannabidiol (800-1000mg/day), with follow-up at weeks 4, 8, and 12. Primary endpoints are safety (liver function tests at weeks 4 and 8) and tolerability (number of participants withdrawing due to adverse medication effects).

Results
To date two participants (n=2) have completed the MASKOT study. There were no changes in liver function at week 2, and no changes in past month use of ketamine at follow-up for either participant. Both participants competed the full protocol, and no serious adverse events were reported. One participant (n=1) reduced their methamphetamine use at follow-up compared to baseline, the other participant (n=1) did not. The CALM study will commence recruitment in mid-2022. Both studies will be completed by the end of 2023.

Conclusions
These studies will provide feasibility and tolerability data on two novel candidate pharmacotherapies in young people with methamphetamine use disorder. These data will be used for subsequent fully power randomized controlled trials funding applications. These studies will provide the empirical basis for larger investigations, with the potential to lead to the first efficacious medications for methamphetamine use disorder.

Poster Abstracts

Poster Session 2: Tuesday

TUE_17 Sequential expression of dynamic facial patterns in melancholic depression

Presenting Author: Jayson Jeganathan

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Background
Facial affect is expressed dynamically – a giggle, grimace, or agitated frown. However, the characterization of human affect has relied almost exclusively on static images. This approach is unable to capture the nuances of human communication or support assessment of affective disorders. Using the latest in machine vision and systems modelling, we study dynamic facial expressions of people viewing emotionally salient film clips.

Methods
Facial video recordings were acquired from participants with melancholic depression and healthy controls who watched emotionally valenced video clips. The continuous wavelet transform was used to extract the time frequency representation of facial responses – capturing oscillatory facial dynamics such as laughing. A hidden Markov model was fitted to find latent facial states.

Results
We find that the apparent complexity of dynamic facial expressions can be captured by a small number of simple spatiotemporal “atoms” - composites of independent facial actions, each expressed with a unique spectral fingerprint. Sequential expression of these states is common across individuals viewing the same film stimuli but varies in those with melancholic depression. Depressed participants had ambiguous facial expressions and anomalous patterns of switching between affective states.

Conclusions
This approach provides a platform for translational research, capturing dynamic facial expressions under naturalistic conditions and enabling new quantitative tools for the study of melancholic depression and other psychiatric disorders.

Poster Abstracts

Poster Session 2: Tuesday

TUE_18 Maternal and infant outcomes following maternal exposure to SARS-CoV-2 during pregnancy in a Victorian cohort

Presenting Author: Rachel Hill

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Background
Historically, it is well documented that severe infections during pregnancy increase the risk for offspring to later develop neurodevelopmental disorders such as Autism and Schizophrenia. The effects of in utero exposure to SARS-CoV-2 on infant neurodevelopment is unknown, but we hypothesis that severe maternal infection with SARS-CoV-2 will increase risk for the offspring. The aim of this study is to prospectively monitor children exposed in utero to SARS-CoV-2 in a series of longitudinal neurodevelopmental assessments from birth to 15 years of age with a secondary aim to determine if early biological or clinical signs of neurodevelopmental impairments can be detected.

Methods
Women infected with SARS-CoV-2 during pregnancy as well as matched controls of women who gave birth in the same month of delivery, are of similar age and socio-demographic profile, but who were not exposed to SARS-CoV-2 were recruited from Monash Health (N=96), Victoria. Demographic information (e.g. educational status, medical conditions, pregnancy complications, vaccination status) were collected from the mother. Biospecimens and clinical data are collected from the participants at multiple time points from birth through to 15 years of age using standardised sample collection and neurological and behavioural scales. We present here the birth time point data.

Results
Mothers and infants are divided into 3 groups; control, mild SARS-CoV-2 infection (limitation of activities) and severe SARS-CoV-2 infection (hospitalised). Mothers who suffered severe SARS-CoV-2 infection showed significantly higher scores on the Edinburgh postnatal depression scale compared to controls ($p=0.02$). Maternal attachment scores were unchanged across the groups. APGAR scores were lower in severe SARS-CoV-2 exposed infants compared to controls ($p=0.08$). Hammersmith neonatal and infant neurological assessment scores were unchanged across groups, as were length, weight and head circumference. Parent-completed questionnaires showed that severe SARS-CoV-2 exposed infants had lower adaptive behaviour scores compared to controls ($p=0.03$).

Conclusions
Overall the data show that both mothers and infants belonging to the severe SARS-CoV-2 exposed group are faring worse, particularly within specific adaptive behaviour domains for the infants. Follow up assessments at 1-5 years will inform as to whether these initial group differences are early signs of more severe neurodevelopmental outcomes. While group numbers are still building, this study will establish if in utero exposure to SARS-CoV-2 is a major risk factor for infant neurodevelopmental disorders. Clinical data as well as ongoing biospecimen collection and analysis will provide insight into early biomarkers of infants at risk with significant societal implications.

Poster Abstracts

Poster Session 2: Tuesday

TUE_19 Muscarinic receptor-targeted interventions in psychiatric disorders: A systematic review and meta-analysis

Presenting Author: Shivani Vaidya

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Background
For decades, treatment of psychoses, mood disorders and anxiety have been confounded by limited efficacy to one symptomatic domain and high rates of treatment resistance. Robust preclinical and clinical evidence has highlighted cholinergic signalling disruption in several psychiatric conditions and examined strategies to combat acetylcholine imbalance, including acetylcholinesterase inhibitors and nicotinic receptor-targeted intervention. However, the effectiveness of these compounds is often curtailed by on-target side effects. Results from post-mortem studies showed that muscarinic receptors have also been implicated in pathophysiology; therefore, we conducted a systematic review to investigate the therapeutic efficacy of muscarinic receptor-targeted interventions in adults with psychiatric disorders.

Methods
A narrative synthesis approach was utilised for the systematic review to describe findings from incorporated randomised controlled trials. Where three or more studies with a similar intervention were available, we calculated effect sizes from standardised mean differences and performed a meta-analysis using a random-effects model. Cochrane risk of bias assessment tool (ROB-2) was used to calculate the risk of bias, and sensitivity analysis was performed to identify potential publication bias. To assess certainty in meta-analysis effect estimates, evidence was judged using the grading of recommendation assessment, development, and evaluation (GRADE) system.

Results
Overall, twenty-seven studies met the criteria for inclusion in the review, examining mood disorders, primary psychotic disorders, and generalised anxiety disorders. Despite limited studies with diverse interventions, we found higher therapeutic efficacy of xanomeline (M1/M4 agonist) in primary psychotic disorders and scopolamine (muscarinic antagonist) in a combined cohort of major depressive (MDD) and bipolar (BP) disorders. However, results from GRADE analysis suggest “very low” certainty in the evidence for scopolamine’s antidepressant effect. No conclusive findings could be drawn for anxiety disorders as only two clinical trials were available, and neither examined the same compound.

Conclusions
While the results are not yet definitive, findings on muscarinic receptor-targeted interventions in several mental disorders are promising in efficacy and safety, specifically in treating schizophrenia and mood disorders such as MDD and BP. Critical limitations of these studies include low power, high heterogeneity in the patient population and lack of active comparators. Further, adequately powered prospective studies with more subtype-selective interventions are required to determine the clinical effectiveness of muscarinic-receptor targeted interventions.

Poster Abstracts

Poster Session 2: Tuesday

TUE_20 Gut microbiome disturbances and treatment response in schizophrenia

Presenting Author: Svetlina Vasileva

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Background
One third of people with schizophrenia don't respond to first-line treatment with atypical antipsychotics. These treatment resistant patients are prescribed clozapine, the most effective medication for decreasing psychotic symptoms and hospital bed days. However, 60% of people have an inadequate response to clozapine and many frequently experience side effects. Recently, researchers have identified differences in the microbiome composition of individuals with schizophrenia. The aim of this research was to confirm the gut microbiome is associated with schizophrenia diagnosis, and to further investigate if the gut microbiome is associated with clozapine use, response to clozapine, and medication-related side-effects.

Methods
We collected stool from 97 participants (25 non-psychiatric controls, 24 patients with schizophrenia taking first-line atypical antipsychotics, 26 patients with treatment resistant schizophrenia responding to clozapine, 22 patients with treatment resistant schizophrenia not responding to clozapine). Samples were sequenced through shotgun metagenomics with a depth of 3Gbp per sample. OmicS-data-based Complex trait Analysis (OSCA) was used to investigate the association of common and rare bacterial species with schizophrenia diagnosis, clozapine use, response to clozapine and medication-related side effects. Bacterial richness, alpha diversity, and beta diversity measures were compared between groups. Bacterial abundance between groups was investigated through ANCOM analysis.

Results
After adjusting for age, sex, BMI, stool type, diet and physical activity, OSCA revealed significant associations between schizophrenia diagnosis and common bacterial species (32% variance, SE=0.14, p=1.62E-04), clozapine use and common species (24% variance, SE=0.18, p=9.83E-03) and clozapine use and rare species (81% variance, SE=0.19, p=2.29E-05). There was no evidence for association of microbiome composition with response to clozapine, or side effects, including metabolic syndrome or constipation. Schizophrenia patients had decreased richness and significantly different beta diversity, but no difference in alpha diversity compared to controls. Clozapine responders had decreased richness compared to clozapine non-responders, but no other differences.

Conclusions
Our study confirms that people with schizophrenia have a different microbiome compared to non-psychiatric controls. In addition, amongst people with schizophrenia, those with treatment resistant schizophrenia have a different microbiome composition compared to those not taking clozapine. Therefore, our findings strongly suggest that clozapine use may influence the presence of rare microbial species. Longitudinal studies in patients prior to and post clozapine treatment are needed to disentangle whether those gut microbiome differences pre-exist in treatment resistant individuals or are in fact due to clozapine exposure.

Poster Abstracts

Poster Session 2: Tuesday

TUE_22 Major depressive disorder associated alterations in the effective connectivity of the face processing network: a systematic review

Presenting Author: Alec J. Jamieson

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Background
Major depressive disorder (MDD) is marked by altered processing of emotional stimuli, including facial expressions. Recent neuroimaging research has investigated how these stimuli alter the directional interactions between brain regions, however, due to methodological heterogeneity the reliability of these findings remains unclear.

Methods
To address this, we systematically searched five databases: PsycINFO, EMBASE, PubMed, Scopus, and Web of Science, using a preregistered protocol (PROSPERO CRD42021271586). Of the 649 studies screened, 16 examined effective connectivity in MDD during the processing of emotional expressions.

Results
Overall, MDD patients demonstrated (1) reduced excitatory or increased inhibitory connectivity from the dorsolateral prefrontal cortex to amygdala during the processing of negatively valenced expressions, and (2) increased inhibitory connectivity from the ventromedial prefrontal cortex to amygdala during the processing of happy facial expressions.

Conclusions
Consistencies observed across neuroimaging modalities warrant further investigation to determine the specificity of these effects. Future research examining a wider range of emotional expressions, longitudinal changes in effective connectivity, and effects of different treatments are necessary steps in clarifying the findings of this review.

Poster Abstracts

Poster Session 2: Tuesday

TUE_23 Structural Covariance of Amygdala Subnuclei in PTSD show distinct patterns

Presenting Author: Elizabeth Haris

Authors:
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Background
Psychiatric disorders, such as post-traumatic stress disorder (PTSD), are increasingly being understood as brain circuit disorders. While neuroimaging has identified the amygdala as implicated in PTSD, the individual contributions of its subnuclei remain unclear. To address this gap, graph theory was used to quantify brain network topology in PTSD, delineating the amygdala into three distinct subregions: superficial, basolateral, and centromedial nuclei.

Methods
Structural T1-weighted SPGR MRI scans from 67 adults with PTSD and 71 healthy controls were analysed. Anatomical networks for both groups, based on grey matter volume covariance between 98 brain regions, were calculated. Using graph theory, we computed characteristics of network topology between groups. To explore differences between subnuclei, specific covariance patterns of amygdala subregions within-groups were also examined.

Results
Between-group differences did not survive FDR-corrections for multiple comparisons. Within-group differences for healthy controls revealed unique structural covariance between basolateral nuclei and hippocampi, and between the left superficial nucleus and right parahippocampal gyrus, relative to centromedial nuclei. Within-group differences for PTSD also showed unique covariance for basolateral and superficial nuclei when compared to centromedial nuclei. Specifically, covariance was greater between bilateral basolateral/superficial nuclei and the midcingulate cortex and bilateral superior frontal/temporal gyri. Additionally, basolateral nuclei showed higher covariance with the left cerebellum, bilateral medial temporal gyri, left frontal pole, and right rostral anterior cingulate cortex.

Conclusions
Differential grey matter volume covariance of amygdala subnuclei in HC appears to involve brain areas associated with memory processing, while in PTSD it appears to involve brain areas associated with social decision making, social cognition, and approach-avoidance learning and behaviour. These results demonstrate a delineation between the contribution of distinct amygdala nuclei to PTSD pathophysiology specifically underlying dysregulated fear/safety learning and responsivity, and possibly affecting the typical functioning of memory systems that can be seen in HC. This study provides a novel contribution to the current literature by delineating the differential roles of amygdala subnuclei in PTSD.

Poster Abstracts

Poster Session 2: Tuesday

TUE_26 Childhood trauma moderates schizotypy-related brain morphology: Analyses of 1,182 healthy individuals from the ENIGMA Schizotypy working group

Presenting Author: Yann Quidé

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Background
Schizotypy represents an index of psychosis-proneness in the general population that is associated with childhood trauma exposure. Both schizotypy and childhood trauma are associated with overlapping morphological brain alterations and it is possible that trauma exposure moderates the extent of brain morphological changes associated with schizotypy. This study aimed to disentangle the individual and interactive effects of these two risk factors for psychosis on brain morphology. In addition to observe effects specific to schizotypy and childhood trauma, we hypothesised that additive effects of schizotypy and trauma would be evident on cortical thickness of stress-sensitive regions (e.g., insula, middle frontal gyrus).
Methods
A total of 1,182 healthy adults, pooled from nine sites worldwide, contributing from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Schizotypy working group, completed the Schizotypal Personality Questionnaire Brief version (SPQ-B), the Childhood Trauma Questionnaire (CTQ), and underwent a T1-weighted brain scan from which regional indices of cortical thickness were determined. A series of multiple linear regressions determined the direct associations between the severity of schizotypy and childhood trauma reported, as well as their interactive effects, on individual region-of-interest (age, sex, mean cortical thickness as covariates; model p<7.35e-4). Significant associations with the interaction term were followed up with moderation analyses.
Results
Changes in cortical thickness in four regions-of-interest were significantly associated with the interaction term: increasing levels of schizotypy were associated with thicker left caudal anterior cingulate gyrus, right middle temporal gyrus and insula, and thinner left caudal middle frontal gyrus, in people exposed to higher (but not low or average) levels of childhood trauma. This was in the context of direct associations with schizotypy (thicker bilateral medial orbitofrontal gyri, right rostral anterior cingulate gyrus, left temporal pole, left insula, thinner left paracentral lobule) and childhood trauma (thinner left postcentral, superior parietal and fusiform gyri, thicker left caudal middle frontal gyrus).
Conclusions
Despite some limitations (e.g., cross-sectional design of the study, use of retrospective self-reports), this study provides evidence for a moderating role of childhood trauma exposure in the relationship between schizotypy and brain morphology (thickness of middle temporal, insula, caudal anterior cingulate gyrus and caudal middle frontal gyrus) in a large cohort of healthy adults. Future large-scale multimodal imaging (morphological and functional) studies are needed to better understand the functional implications of changes in brain morphology associated with risk for psychosis in the general population, their developmental timing, and their implications for risk of other mental disorders beyond the schizophrenia spectrum.

Poster Abstracts

Poster Session 2: Tuesday

TUE_27 Depressive symptoms moderate functional connectivity within the emotional brain in chronic pain

Presenting Author: Yann Quidé

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Background
Depressive symptoms are often comorbid to chronic pain, with these two conditions sharing aberrant emotion processing and regulation, and brain networks. Although aberrant top-down regulation from the medial prefrontal cortex (mPFC) over the amygdala is reported in both conditions, the relationship between depressive symptoms and chronic pain and their effects on emotional brain function is unclear. This study aims to disentangle the impact of chronic pain and depressive symptoms on amygdala-mPFC functional connectivity. We hypothesised that increasing levels of depressive symptoms would be associated with weaker amygdala-mPFC connectivity in healthy participants, and with stronger connectivity in people with chronic pain.

Methods
Twenty-six individuals with diagnosed chronic pain disorders (referred to as the Pain group) and 32 healthy controls (HC) underwent resting-state functional magnetic resonance imaging and completed the Beck Depressive Inventory (BDI). Whole-brain seed-based functional connectivity maps were used in multiple linear regressions to determine the main effects of group, depressive symptoms (BDI total score), and their interaction on functional connectivity of three seed regions (separately, the left and right amygdalae, mPFC) with the rest of the brain, accounting for age and sex. In case of significant interaction, moderation analyses were conducted. Corrections for multiple testing were applied as appropriate.

Results
The group-by-depressive symptoms interaction was significantly associated with changes in connectivity between the right amygdala and the mPFC (pFWEc=0.008). Moderation analysis indicated that, compared to the HC group, the Pain group showed weaker right amygdala-mPFC connectivity at lower levels of depressive symptoms (p=0.019), and stronger connectivity at higher levels of depressive symptoms (p=0.002). In addition, the strength of connectivity decreased in the HC (p=0.005) and increased in the Pain group (p=0.012) as the severity of depressive symptoms increased. There were no significant effects of group, depressive symptoms, or interaction on left amygdala and mPFC seeds connectivity.

Conclusions
Severity of depressive symptoms moderates resting-state functional connectivity between regions critical for emotional recognition (amygdala), and regulation (mPFC) in people with chronic pain and healthy controls. These results may have implications for the choice of treatment for chronic pain, independently of chronic pain disorder diagnosis, in the context of reported depressive symptoms. Future studies should consider testing the efficacy of repetitive transcranial magnetic stimulation (rTMS) of the mPFC in people with chronic pain. Targeting the mPFC may ameliorate both affective and physical suffering of people with chronic pain.

Poster Abstracts

Poster Session 2: Tuesday

TUE_28 Effects of antipsychotic drugs on energy metabolism

Presenting Author: Bruna Panizzutti

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Background
There is some evidence of mitochondrial dysfunction in schizophrenia. However, it remains unclear whether this dysfunction is associated with the pathophysiology of schizophrenia or results from treatment with antipsychotic drugs. Most studies of antipsychotic effects on “mitochondrial function” are based on indirect measures (gene or protein expression, ion flux or mitochondrial membrane potential) and have been conducted in non-neuronal models such as peripheral blood mononuclear cells, cultured hepatocytes or lymphoblastoid cells. To investigate the effects of antipsychotic drugs currently used to treat schizophrenia, i.e., amisulpride, aripiprazole, clozapine and risperidone; on energy metabolism in cultured human NT2-N neuronal-like cells.

Methods
NT2-N cells were cultured and treated with amisulpride (10μM), aripiprazole (0.1μM), clozapine (10μM) and risperidone (0.10μM) or vehicle for 24 hours. Gene expression, metabolites and mitochondrial bioenergetic profile were measured.

Results
In NT2-N cells, risperidone decreased the expression of genes involved in the OXPHOS and glycolysis pathways, accompanied by a reduction in basal mitochondrial respiration. Aripiprazole caused a significant dose-dependent reduction in all aspects of mitochondrial function (i.e., basal respiration, ATP production, proton leak, maximal respiration, spare respiratory capacity and coupling efficiency). Amisulpride and aripiprazole increased levels of metabolites in the TCA cycle.

Conclusions
Overall, we have shown that antipsychotics target processes associated with mitochondrial dysfunction. Risperidone, aripiprazole and amisulpride affect a range of cellular bioenergetic processes that could impact their efficacy in patients with schizophrenia and contribute to drugs side effects.

Poster Abstracts

Poster Session 2: Tuesday

TUE_29 Defining the 'Scope' of psilocybin efficacy: Serotoninergic outcomes in activity-based anorexia

Presenting Author: Kyna Conn

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Background
Psilocybin is currently being trialled for a range of psychiatric conditions, including anorexia nervosa (AN). The preliminary results are promising, but not all individuals respond to psilocybin with clinically significant outcomes. Similarly, we have shown that improvements in body weight maintenance in the activity-based anorexia (ABA) rat model are driven by subpopulations of "responders". Psilocybin binds to multiple receptors; however, the subjective effects are mediated though signalling at the serotonin (5-HT) 2A receptor. Patients with AN show changes in cortical 5-HT2A and 5-HT1A receptor binding, therefore, it is plausible that psilocybin differentially effects "responders" based on 5-HT receptor expression.

Methods
Female Sprague-Dawley rats were treated with saline (n=6) or 1.5 mg/kg psilocybin (n=6) and underwent exposure to ABA conditions the following day. Age-matched rats naïve to ABA were used as controls (saline; n=2; psilocybin n=3). Fixed brains were collected either at body weight loss criterion (ABA) or 7 days after treatment (control) and specific changes in expression of 5-HT1A and 5-HT2A receptor subtypes were examined in the medial prefrontal cortex (mPFC) using RNAscope. Deconvoluted fluorescence micrographs were processed using an automated Cell Profiler pipeline, to determine the effects of exposure to ABA conditions and/or treatment with psilocybin on receptor expression.

Results
Experience with ABA altered the overall proportion of 5-HT expression within discrete mPFC regions, infralimbic and prelimbic. ABA significantly reduced the proportion of all cells (unique and co-labelled) that express 5-HT1A (p<.001) and 5-HT2A (p<.01) across the mPFC and its subregions, in comparison to controls. The same effect of ABA was also observed for the mean number of labelling per cell, for both subtypes (p<.001 and p<.05, respectively). Likewise, ABA specifically reduced the proportion of unique 5-HT2A cells (p<.001), yet in contrast, increased the proportion of unique 5-HT1A cells (p<.05). No significant effects of psilocybin were observed on 5-HT expression.

Conclusions
The decreased 5-HT2A yet increased 5-HT1A expression following ABA exposure recapitulates receptor binding studies in AN. This highly translational finding provides support for using the ABA model to probe the effects of psilocybin relevant to AN. While psilocybin did not alter 5-HT receptor expression in this study, the delay between treatment and tissue collection, which was necessary to incorporate ABA exposure, may have prevented detection of changes at this level. Combined, these results highlight specific serotonergic outcomes that may mediate pathological weight loss in ABA, and inform a refined administration schedule for investigating therapeutic effects of psilocybin for AN.

Poster Abstracts

Poster Session 2: Tuesday

TUE_30 Maternal immune activation and estrogen receptor modulation induce distinct changes in inflammatory-related gene expression in the substantia nigra of female and male offspring

Presenting Author: Sophie R Debs

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Background
Maternal immune activation (MIA) recapitulates aspects of schizophrenia pathophysiology in adult offspring, including dopamine dysregulation, behavioural abnormalities, and midbrain neuroinflammatory changes comparable to those observed in individuals with schizophrenia. The selective estrogen receptor modulator, raloxifene, improves cognition and symptom severity in women and men with schizophrenia. The mechanism through which raloxifene exerts these effects is unclear, though may relate to its ability to modulate neuroinflammation. In this study, we examined how raloxifene alters inflammatory-related gene expression in the substantia nigra (SN) in female and male adult rat offspring exposed to the viral mimetic polyinosinic:polycytidylic acid [Poly(I:C)] in utero.

Methods
MIA was induced in Wistar rat dams on gestational day 19 with high molecular weight Poly(I:C) via tail vein injection [4mg/kg, saline/poly(I:C) n=11/10]. Raloxifene (5mg/kg) was administered to offspring daily (cookies) from postnatal day (PND)58-85. The cohort consisted of four groups per sex, including: vehicle/placebo, vehicle/raloxifene, MIA/placebo, MIA/raloxifene (n=23-30 per group per sex). Half of these animals completed behavioural tests. Offspring were euthanised (PND83-85), SN was dissected, and cDNA was prepared. Pro-inflammatory cytokine (IL-1a, IL-1β, IL-12a, IL-18, and TNF), cytokine receptor (IL-17RA), and immune cell (CD68, CD64, CD163 and CD45) mRNAs were then measured using RT-qPCR.

Results
IL-6 and IL-17RA mRNAs were reduced in the SN of female MIA offspring (both p<0.05), whereas IL-18 mRNA was increased in the SN of male MIA offspring (p=0.006). TNF mRNA was reduced in the SN of male MIA offspring only (p<0.05). Raloxifene-treated female MIA offspring displayed reduced IL-12a mRNA (p<0.05) in the SN. In contrast, mRNA levels of the immune cell markers CD68, CD64, CD163, or CD45 mRNAs were unchanged in the SN of female and male offspring.

Conclusions
MIA elicits sex-specific alterations in pro-inflammatory cytokine transcripts in the midbrain of adult offspring. Besides elevated IL-18 in male MIA offspring, we observed an overall suppression of pro-inflammatory cytokines in female and male MIA offspring, though these transcriptional changes were more pronounced in females. Raloxifene suppressed pro-inflammatory cytokines in MIA-exposed female offspring only, suggesting that immunomodulatory effects in the midbrain may be sex- and pathway-specific. MIA-induced inflammation did not result in immune cell marker transcriptional changes. Further work will determine whether changes are identified following stratification of offspring into “high” and “low” inflammatory subgroups based on multiple cytokine mRNA levels.

Poster Abstracts

Poster Session 2: Tuesday

TUE_31 Enhanced dopamine synthesis altered RNA methylation in dorsal striatum

Presenting Author: Xiaoying Cui

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Background
The EDiPS model (Enhanced Dopamine in Prodromal Schizophrenia) reiterates the key discovery regarding the development of schizophrenia, that patients experience increased dopamine synthesis and release in the dorsal striatum. Structural alterations exhibited by EDiPS model, include increased dopamine release sites and synapse numbers. Understanding the mechanism underlying these synaptic adaptations is critical to develop effective prophylactic interventions. As one plausible basis for these alterations, we investigated RNA methylation, a post-transcriptional modulation that is essential for brain plasticity and adaption to external challenges. We will determine whether increased dopamine synthesis capacity induces RNA hypermethylation, thereby enhancing dopaminergic transmission in EDiPS model.

Methods
To generate EDiPS animals, we injected a construct coding for tyrosine hydroxylase and GTP cyclohydrolase 1 into the pars compacta of juvenile P35 rats. These enzymes are transported to dorsal striatum, where they increase dopamine synthesis. Six weeks following construct delivery, we collected the dorsal striatum, extracted RNA and performed methylated RNA(N6-methyladenosine, m6A) immunoprecipitation (meRIP) sequencing. Western blot was conducted to assess the expression of RNA modifiers that regulate RNA methylation and thus affect RNA splicing and translation. RNA modifiers include methyltransferases Mettl3 and Mettl14, demethylase FTO, m6A readers that facilitate m6A-modified RNA translation, YT521-B homology domain family (YTHDF) proteins.

Results
RIP-sequencing results showed that 80% of mRNAs in the EDiPS dorsal striatum are significantly hypermethylated (95 out of 119 mRNAs differentially modified). The majority of these m6As are localised in coding regions that are known to promote translation. KEGG pathway analysis reveals that altered m6A RNAs are enriched in synaptic vesicle cycling, glutamate, dopamine synapses and long-term potentiation. Consistent with enhanced RNA methylation, there was increased expression of Mettl14 and YTHDF1 in EDiPS dorsal striatum. We also detected increased protein production of the hypermethylated RNAs, including phospholipase C β1, a gene linked to schizophrenia, suggesting RNA methylation promotes translation.

Conclusions
Hyper-dopaminergia in the dorsal striatum is a robust marker that provides a highly plausible neurochemical prophylactic target. The EDiPS model provides the opportunity to examine a possible interaction between this clinical finding and potentially crucial changes to the epitranscriptome. We have provided the first evidence that increased dopamine synthesis capacity in the dorsal striatum enhances RNA methylation and subsequently promotes protein translation, which in turn regulates synaptic structure and plasticity. Further exploration of this finding will not only provide etiological insight, but also help to identify novel treatment targets for schizophrenia.

Poster Abstracts

Poster Session 2: Tuesday

TUE_32 Human astrocyte cytoarchitecture and function are shaped by stress and associate with trans-psychiatric disorder diagnosis

Presenting Author: Dominic Kaul

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Background
Severe stress is the leading trans-diagnostic environmental risk factor for the development of psychiatric disorders such as depression and schizophrenia. However, we have limited understanding of what underlies this association in humans. Astrocytes, an abundant non-neuronal cell type, are key regulators of synaptic transmission. Rodent studies demonstrate that stress impairs astrocytic capacity to clear neurotransmitters from the extracellular space and associates with the development of psychiatric-like symptoms. However, these cells are poorly evolutionarily conserved and psychopathology in humans is complex, necessitating human-relevant evidence to translate these findings.

Methods
We curated a unique human postmortem brain cohort of psychiatric disorder cases with well-characterised timings of periods of severe stress associated with onset of psychopathology. Coronal sections from the orbitofrontal section were processed using fresh-frozen fluorescent immunohistochemistry (FF-IHC) to evaluate the cytoarchitecture (density, distribution, morphology) of astrocytes positive for the glutamate and GABA transporters (EAAT2 and GAT3, respectively). Human-relevant functional probing was conducted using a transcription factor-driven astrocyte (iAst) model from human embryonic stem cells. iAsts were exposed to 100nM dexamethasone (synthetic cortisol analogue) for 1-7 days and their capacity to clear glutamate and GABA from media were evaluated.

Results
FF-IHC demonstrated that the density of astrocytes expressing EAAT2 are increased in psychiatric cases with severe life stress in childhood in orbitofrontal cortex, across all layers of the grey matter (P=0.01-0.02). Area coverage of EAAT2+ cells similarly increased 15-25% from controls (Padj=0.0001-0.006). Area coverage of GABA transporter (GAT3)+ cells also increased across the grey matter 6-11%, most distinctly in cases with severe stress (Padj=0.0001-0.01). Further, iAsts exposed to dexamethasone demonstrated a significant reduction in their capacity to clear glutamate from solution in as little as 3 days exposure (P=0.04), however, returned to non-significant levels by 7 days exposure.

Conclusions
These findings provide evidence that stress has human-specific impacts on astrocytes, and that the duration and timing of stress are both central to understanding the persistent consequences of the stress. These findings also demonstrate that cases of psychiatric disorders associated with severe stress earlier in life are also biologically distinguishable from cases without profound stress, strengthening the notion that stress is a key biological consideration in human cases of psychiatric disorders.

Poster Abstracts

Poster Session 2: Tuesday

TUE_33 The effects of exercise and environmental enrichment on behaviour and gastrointestinal function in a mouse model of obsessive-compulsive disorder (OCD)

Presenting Author: Carey Wilson

Authors:
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Background
Obsessive-compulsive disorder (OCD) is characterised by obsessions (i.e., intrusive thoughts) and compulsions (i.e., repetitive actions or mental rituals). OCD is frequently refractory to treatment and can have a profoundly deleterious effect on quality of life. While exercise and environmental enrichment have been shown to produce beneficial behavioural and molecular effects in the context of psychiatric disorders such as depression, this remains to be studied in preclinical models of OCD. Gastrointestinal function has also not yet been assessed at the preclinical level, despite reports of gastrointestinal disease occurring in OCD.

Methods
We used the SAPAP3 knockout (KO) mouse model of OCD, which displays an anxiety-like and over-grooming phenotype. At 8 weeks of age, SAPAP3 KO mice were exposed to exercise or environmental enrichment (versus control standard housing) for 4 weeks, followed by behavioural testing and assessment of gastrointestinal function.

Results
SAPAP3 KO mice spent more time grooming than wild-type (WT) controls, an effect that was more pronounced in male KO mice. They also had a more ritualistic approach to grooming, showed increased anxiety-like behaviour, decreased locomotion, and exhibited gut dysfunction. This phenotype was not lessened following either environmental intervention, and paradoxically we found that exercise worsened grooming behaviour generally.

Conclusions
Our study is the first to assess grooming microstructure and gut function in SAPAP3 KO mice, and is also the first to report a sexually dimorphic effect of grooming in SAPAP3 KO mice at 8-12 weeks of age. In addition, we found no beneficial effects of exercise or environmental enrichment in this model, and unexpectedly revealed an overall deleterious effect of exercise on some outcome measures.

Poster Abstracts

Poster Session 2: Tuesday

TUE_34 Stimulating toll-like receptor 4 reduces motor impulsivity in rats and is associated with reduced measures of astrocyte activation in the nucleus accumbens shell

Presenting Author: Bianca Jupp

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Background
A growing body of evidence has implicated alterations in peripheral inflammatory markers in individuals demonstrating high levels of impulsive behaviour, however it is currently unclear whether similar neuroinflammatory alterations are observed within the central nervous system or indeed if the innate immune system contributes to the expression of this behaviour. This study aimed to establish whether trait impulsivity in rats, as assessed by the five-choice serial reaction time task (5CSRTT), is associated with altered measures of neuroinflammation, and to examine the effect of stimulating this process on impulsive behaviour on this task via systemic activation of toll-like receptor 4 (TLR4).

Methods
Male rats were trained on the 5CSRTT and divided into high (HI) or low (LI) impulsive groups based upon their level of premature responding. Rats were treated with the detoxified TLR4 agonist, monophosphoryl A (MPLA; 50mg/kg, 100mg/kg, i.p.), or vehicle using a cross-over design, 24 hours prior to behavioural testing to examine the effect of stimulating inflammation on impulsive behaviour. Gene expression analysis of neuroinflammatory related transcripts were performed in key regions involved in the expression of this trait following MPLA (50 mg/kg, n=5) or vehicle (n=4) treatment, and a separate group of naïve HI and LI rats (n=6/group).

Results
TLR4 activation significantly reduced premature responding, only in HI rats, at both doses tested (50mg, p=0.005; 100mg, p=0.028), while having no effect on any other task measure. Naïve HI rats were found to have broadly elevated expression of pro-inflammatory transcripts within the nucleus accumbens shell when compared to LI animals, with post hoc analysis revealing this was driven by an effect on glial fibrillary acidic protein (GFAP, p<0.01). Further, MPLA treatment was found to reduce GFAP transcript expression in this region compared to vehicle treated animals (p=0.005). No other differences in inflammatory transcripts were observed.

Conclusions
Together these results suggest that mildly stimulating TLR4 is sufficient to reduce impulsivity in highly impulsive animals and that astrocyte function specifically within the nucleus accumbens shell may contribute to the expression of this behaviour.

Poster Abstracts

Poster Session 2: Tuesday

TUE_35 Unpredictable chronic mild stress exposure increases motivational behaviour for reward

Presenting Author: Nicholas J Burton

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Background
Chronic stress is a leading risk factor for developing numerous neuropsychiatric disorders. Motivational dysfunction is one of the fundamental elements across these disorders, serving as a point of vulnerability to disrupt the pursuit of natural positive reinforcement. Hurdles to improve treatment efficacy remain, due in part to our incomplete understanding of how chronic stress exposure influences and shapes motivational behaviour. Here, we aim to investigate alterations in motivational behaviour for reward using an unpredictable chronic mild stress (UCMS) protocol to induce depression-like behaviour in mice coupled with an operant behavioural task.

Methods
C57/BL6 (N=12) were exposed to UCMS for 8 weeks, prior to behavioural validation assays relevant to depression and anxiety. Mice were food-restricted for the initial stages of an operant training protocol before engaging in a progressive ratio (PR) operant task without food-restriction for 3 days, to evaluate motivation for a natural reward.

Results
UCMS mice had a significantly ($p=0.0082$) higher PR breakpoint (mean=34) compared with healthy controls (mean=24). Sex differences in motivational behaviour were also observed. A three-way ANOVA showed a significant main effect of sex ($p=0.0044$), and a significant interaction effect of treatment and sex ($p=0.039$).

Conclusions
Our preliminary findings suggest that exposure to chronic stress increases motivational behaviour for rewards. We were also able to capture sex-dependent changes, with UCMS exposure significantly increasing motivation only in males. This framework is expected to provide valuable insight to guide development of new treatment strategies and elucidate comorbidities (addiction vulnerability) following chronic stress. Future studies aim to leverage computational modelling to explore potential divergence in learning rates under environmental uncertainty. Additionally, we aim to characterise alterations in striatal activity using calcium imaging miniature microscopes to examine neural changes following chronic stress in circuits involved in flexible reward related behaviours.

Poster Abstracts

Poster Session 2: Tuesday

TUE_36 Studying chronic stress effects on hypothalamic corticotrophin releasing hormone (CRH) neuron activity using the unpredictable chronic mild stress (UCMS) model

Presenting Author: Laura Stanton

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Background
Chronic stress is a leading risk factor for depression, and yet the mechanisms through which stress contributed to depression symptoms are poorly understood. Hypothalamic (paraventricular nucleus; PVN) corticotrophin releasing hormone (CRH) neurons control the stress hormone axis, which has been proposed to mediate the association between stress and depression symptoms, however recent data highlights non-endocrine roles of these neurons in controlling behaviour. Chronic stress increases the excitability of PVN-CRH neurons, but changes in their activity associated with stress and depression related behaviours are unknown.

Methods
The current studies aim to test whether UCMS produces hyperexcitability of hypothalamic CRH neurons in vivo. UCMS was established in reverse light cycle. In experiment 1, C57/BL6 mice were exposed to UCMS for 8 weeks before testing in acute paradigms relevant to depression and anxiety to validate the procedure. In experiment 2, transgenic mice expressing a fluorescent neural activity marker in CRH neurons (CRH:GCaMP6f) were implanted with fibre optic probes to record neural activity in PVN-CRH neurons. They were subsequently recorded at baseline and every 2 weeks during UCMS during an acute stress exposure.

Results
Preliminary data shows that UCMS does not alter hypothalamic CRH neuron activity during the early period of UCMS exposure (2 weeks), although 4-week data will also be presented.

Conclusions
This framework is expected to provide new insight on the contribution of changes in PVN-CRH neuronal activity to depression related behaviours following chronic stress.

Poster Abstracts

Poster Session 2: Tuesday

TUE_37 Functional dissection of a novel pathway linking stress and action control systems: Hypothalamic corticotrophin releasing hormone (CRH) neuron projection to the globus pallidus externa (GPe)

Presenting Author: Aidan J Price

Authors:
Aidan J Price, Nicholas Burton, Christopher Dayas, Elizabeth E Manning -

Background
Stress exacerbates the symptoms of neuropsychiatric disorders associated with repetitive behaviours, including Tourette Syndrome (TS) and obsessive compulsive disorder (OCD). In TS, stress interferes with the ability to suppress repetitive behaviours (or tics), suggesting that stress may directly influence action control circuitry. Recently, a novel circuit was identified linking hypothalamic stress sensitive neurons and the basal ganglia indirect pathway, which is involved in suppression of actions, however the functional role of this circuit is unknown.

Methods
: To examine this circuit, cell and pathway specific optogenetic activation and inhibition were performed during baseline and stress sessions. Transgenic mice expressing cre-recombinase in corticotrophin releasing hormone (CRH) neurons were used (n=24), and the circuit connecting these neurons in the paraventricular nucleus (PVN) of the hypothalamus to the globus pallidus externa (GPe) in the indirect pathway was examined using retrograde targeted expression of the excitatory opsin ChR2, and terminal inhibition using the newly developed inhibitory opsin eOPN3.

Results
Preliminary findings suggest that inhibition of this PVN-CRH->GPe pathway suppresses repetitive behavioural responses to stress (grooming).

Conclusions
This work may identify new pathways through which stress impacts neuropsychiatric symptoms in disorders including TS and OCD, and may help guide the development of new treatment strategies that enhance control over symptoms when patients are exposed to stress. The basal ganglia indirect pathways is also involved in decision making, and thus future research should explore a potential role of this pathway on stress incudes changes in decision making.

Poster Abstracts

Poster Session 2: Tuesday

TUE_38 Facial Processing Differences in Autistic and Neurotypical Children: An Event-Related Potential Study

Presenting Author: Natalie Wall

Authors:
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Background
Autism is a neurodevelopmental condition that has an approximate global prevalence rate of one in 100; with an early diagnostic indicator being difficulties with understanding facial expressions. In neurotypical people, understanding facial expressions becomes quicker over time, whereas for autistic people this process is slower. These differences between groups have been linked to facial processing in the brain which can be measured by the N170; an event related potential that occurs when an individual views a face. The following study used event related potential recordings to further examine these differences before and after implementing a novel facial expression intervention.

Methods
It was hypothesised that by improving facial feature encoding, this will increase the face-specific N170 event-related potential and along with improving social communication skills. Non-autistic and autistic children between six and twelve years old were invited to participate. Both groups of children viewed 60 colour images of facial expressions (happy, angry, neutral) and objects (cars, trees and houses) while they were participating in the EEG recording. Autistic children were given an iPad with the intervention for two weeks. Parents completed the Social Communication Questionnaire at the time of recording.

Results
There were 15 autistic and 20 non-autistic children who participated in the study. There was no age difference between groups or on the full-scale IQ. A difference between groups was found on the social communication questionnaire both pre and post intervention, but there was no difference within the autistic group from pre to post. The EEG recording showed differences in the facial feature processing between groups, with autistic people interpreting faces more like objects. However, there was not a significant difference from pre- to post-intervention for the autistic group.

Conclusions
The study results provide further evidence that there is a difference in the way autistic people process faces when compared to non-autistic people. Although early intervention may support skill building in this area, the present novel intervention is not indicative of being beneficial in its current form. Further conversation with the autistic community is needed to determine how to best design intervention in a way that is engaging and supportive.

Poster Abstracts

Poster Session 2: Tuesday

TUE_39 Using NODDI to characterise longitudinal changes in free water in children with chronic mild traumatic brain injury

Presenting Author: Athena Stein

Authors:
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Background
By 10 years, 16% of children sustain at least one brain injury requiring medical attention, where approximately 25-30% have long-term cognitive problems. Following mild traumatic brain injury (mTBI), diffuse axonal injury (DAI) causes chronic neuroinflammation, creating movement of cerebrospinal fluid (CSF) into the extracellular space and leading to free water (FW) accumulation in white matter (WM) tracts. Diffusion tensor imaging (DTI) is unable to differentiate brain tissue diffusion from CSF-FW diffusion. A newly-developed DTI technique, FW elimination (FWE), separates CSF FW contamination from brain tissue diffusion using the NODDI model, providing a detailed insight into microstructural WM pathology.

Methods
Using NODDI free water elimination, we explored whole-brain and tract specific (uncinate (UF) and inferior fronto-occipital fasciculi (IFO)) FW changes in children with persistent symptoms after mTBI and those with clinical recovery by one and two-months post-mTBI compared to healthy controls (HCs). Voxel-wise two-sample t-tests were conducted as permutation tests of general linear model statistics to compare whole-brain and tract-specific diffusion across groups. All results were corrected at pFDR<0.05.

Results
Whole-brain diffusion was significantly increased in symptomatic participants compared to HCs at both one and two-months post-injury. Both left and right IFO and UF tract-specific diffusion was significantly higher in symptomatic and asymptomatic mTBI children compared to HCs. A linear trend was evident, where diffusion was highest in symptomatic participants and progressively decreased to healthy controls, who displayed the lowest diffusion in the UF and IFO white matter tracts (corrected at pFDR<0.05).

Conclusions
These results indicate that children who are symptomatic at one and two months post-mTBI display increased white matter diffusion compared to healthy children. In addition, diffusion appears to decrease, or ‘normalise’ in IFO and UF tracts as children clinically recover from mTBI. Therefore, compared to conventional DTI, NODDI may provide more specific insights into microstructural damage in pediatric mTBI, and diffusion in the IFO and UF tracts may predict mTBI patient clinical outcomes at one and two months post-injury.

Poster Abstracts

Poster Session 2: Tuesday

TUE_40 Gene Expression and Its Regulatory Mechanisms are Widely Responsive to Oxidative Stress in Differentiating Neuroblastoma Cells: Significance for Psychiatric Diseases

Presenting Author: Behnaz Khavari

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Background
Oxidative stress (OS), defined as the increased levels of reactive oxygen species, is well-linked to a variety of malignancies and neurodegenerative diseases, but its relationship with neurodevelopmental or psychiatric disorders and the underlying molecular mechanisms remains ambiguous, especially in terms of prenatal exposures. Here we hypothesised that OS, arising from environmental risk factors associated with neurodevelopmental disorders, will alter the transcriptional landscape of differentiated neurons.

Methods
We treated the neuroblastoma SH-SY5Y cells with 10 μM of hydrogen peroxide (H_2O_2) before the initiation or during the neuronal differentiation process and examined changes in the expression of genes and microRNAs (miRNAs) in differentiated neurons by RNA-sequencing and bioinformatics analyses. The Pearson's correlation coefficient was calculated to suggest the subset of genes whose expression was negatively regulated by differentially expressed miRNAs. The enrichment of dysregulated miRNAs in psychiatric disorders was examined using Fisher's exact test.

Results
Although the resultant cells showed typical features of differentiated neurons, their transcriptomes were substantially different from H_2O_2-untreated cells, such that around 4000 genes and 300 miRNAs were differentially expressed. Gene-set enrichment analysis revealed that many of the dysregulated genes were localised to the synapse, and involved in neurogenesis, neuronal differentiation, and synaptic signalling, plus the schizophrenia-associated signalling pathways, PI3K-Akt and retinoic acid signalling. The stress-responsive miRNAs were significantly enriched in psychiatric diseases, with 20% previously reported as dysregulated in patients' tissues. The expression of a subset of genes was regulated by some well-studied psychiatric-associated miRNAs, including miR-137, miR-181b, and miR-17-5p.

Conclusions
We suggest that even non-cytotoxic levels of oxidative stress have the potential to widely affect the transcriptome in a critical early stage of neurodevelopment and might mediate some of the biological impact of prenatal environmental risk factors associated with later life mental illness, such as maternal smoking and alcohol consumption.

Poster Abstracts

Poster Session 2: Tuesday

TUE_41 Investigating the phenolic and antioxidant profile of plant-derived extracts: Potential novel therapeutics for brain health

Presenting Author: Naomi May

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Background
Excessive levels of inflammation, oxidative stress and neurotoxins in the brain are associated with poor brain health, cognitive dysfunction, and a higher risk of neurodegenerative and psychiatric disorders. Therefore, novel therapeutics that address these parameters may hold promise as a preventative or adjunct therapy for brain disorders with common underlying inflammatory and oxidative stress neuropathologies. Evidence suggests that phenolic compounds, including flavonoids and anthocyanins, have antioxidant, anti-inflammatory and neuroprotective effects. This study aimed to investigate the phenolic profile and antioxidant capacity of key candidate fruit and herb extracts.

Methods
Whole plant (WP) (Piper nigrum (black pepper), Salvia officinalis (sage), Sambucus nigra (elderberry), Melissa officinalis (lemon balm), Syzygium aromaticum (clove)) and complementary medicine (CM) counterparts were extracted (acidified methanol). Total phenolic content (TPC) (modified colorimetric Folin-Ciocalteu method (765nm)), flavonoid subgroups: flavanols and flavones (aluminium chloride (425nm)) and flavan-3-ols (sodium nitrate (510nm)), and monomeric anthocyanin content (MAC) (pH differential method (520nm, 700nm)), and antioxidant capacity (oxygen radical absorbance capacity (ORAC) assay (540nm)) were analysed. Levels were compared to the Queen garnet plum (QGP), which is known to be high in dietary phenolics and antioxidant capacity.

Results
Clove (CM,WP) and elderberry (WP) had the highest TPC (11140.71, 8875.00, and 1296.43, respectively, vs 485.29mgGAE/100gFW), flavanols and flavones were highest in clove (CM) elderberry, and sage (WP) (604.20, 262.90, and 159.08, vs 60.43mgQTCE/100gFW). Clove (CM,WP), and lemon balm (CM), were rich in flavan-3-ols (548.64, 441.19, and 562.45, vs 54.56 mgCAE/100gFW), MAC was highest in QGP (WP) and elderberry (CM,WP) (197.06, 99.80, and 24.98mgC3GE/100gFW). Black pepper (WP,CM) and clove (WP,CM) exerted the highest antioxidant capacity (3315.98, 435.03, 344.89 and 455.93, vs 150.72µmol Trolox equiv/gFW). Total phenolic content and flavanols/flavones levels positively correlated to ORAC (r=0.65 and 0.59,p<0.05).

Conclusions
The data have identified high phenolic content and strong antioxidant capacity of several plant extracts. Levels were higher than the Queen Garnet Plum, which is a known dietary source of phenolics, flavonoids and anthocyanins with strong anti-oxidant and anti-inflammatory properties. Therefore, substances with higher levels that the QGP are interesting candidates for further research into potential novel therapeutics for brain illness that manifest inflammation and oxidative stress.

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

BPA 2023 will be held in Far North Queensland

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