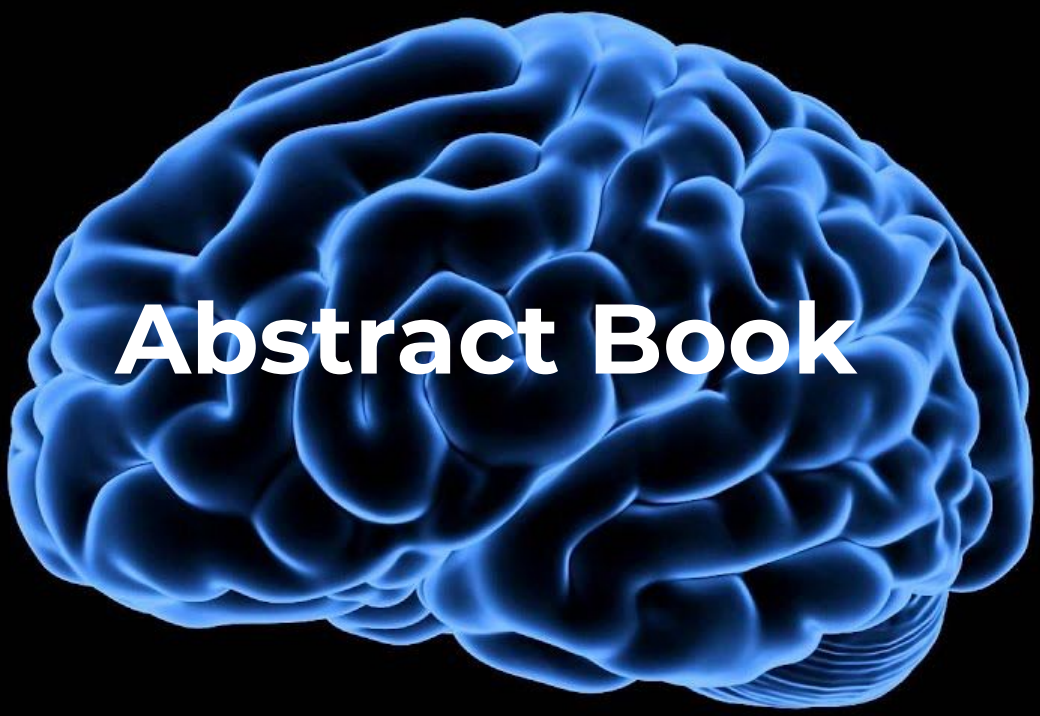
Biological Psychiatry
AUSTRALIA

10th Annual Scientific Meeting



Abstract Book

Oct 19 - 21
2020

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Biological Psychiatry AUSTRALIA

NeuRA
Discover. Conquer. Cure.

BPA presents:

We're all in this together

A discussion of barriers and opportunities for collaboration between basic scientists and clinicians (2-3 pm Tues 20.10.20)

Team Discovery

A/Prof Jess Nithianantharajah
Florey Institute, VIC

Prof Chris Dayas
U Newcastle, NSW

Moderator

Prof Jayashri Kulkarni
Monash, VIC

Team Clinical/Psychiatry

A/Prof Jackie Curtis
NSW Health, NSW

Prof James Scott
QIMR Berghofer, QLD

BPA presents:

Trivia Night Social Evening

With virtual host Jeeves Verma

From 8pm Monday 19.10.20

Acknowledgement of Country

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

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

Welcome

On behalf of the Local Organising Committee, we warmly welcome you to the first virtual Biological Psychiatry Australia (BPA) Conference hosted from Neuroscience Research Australia (NeuRA) in Sydney!

We would like to thank all members of the Scientific Review Panel, especially Rose Chesworth for chairing the panel. It was a mammoth task with 13 Symposia and over 150 Individual Abstracts. Thanks to Adam Walker for organising Poster and Session Judges and Moderators, as well as everyone who agreed on taking on these roles. Thanks to Amelia Brown, Priscila Almeida Costa and Sarasa Mohammadi for putting together the Abstract Book. Thanks to Kelly Clemens and Adith Mohan for organising the Panel Discussion. Thanks to Hannah Savage (Chair of the BPA Early Career Researcher Network) for organising the ECRN Session. Thanks to the BPA-ECRN for organising the BPA2020 mentorship program. Thanks to everyone on the BPA LOC for the multitude of tasks required to put this conference together. We would also like to thank and acknowledge the financial support of our gold sponsor, Janssen, and the invaluable IT support provided by NeuRA.

Finally, we would like to thank you all for attending and contributing to this year's meeting, and hope you will enjoy the quality and diversity of the research presented at BPA.

Physically Distant but Scientifically Connected

Kind regards,

Tertia and Yann
Co-Chairs, Local Organising Committee
BPA 2020 Conference

Local Organising Committee

Co-Chairs: Dr Tertia Purves-Tyson and Dr Yann Quidé

Dr Adam Walker
Ms Amelia Brown
Dr Rose Chesworth
Ms Priscila Almeida Costa
A/Prof Thomas Burne (BPA President)
Dr Christina Perry (BPA Treasurer)
Dr Samantha Owens
Dr Sarasa Mohammadi
Dr Adith Mohan
Dr Kelly Clemens

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.

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1. Symposia

Stratifying the links between genes, environment and symptoms: targeted molecular and translational approaches to understand psychiatric subtypes

Chairs
Dr Natalie Matosin
Dr Zoltan Sarnyai

Discussant
A/Prof. Tom Burne

Overall Abstract

Diagnosing psychiatric disorders is still dependant on clinical observations with current diagnostic criteria only separating disorders at the syndromic level. Treatment strategies are usually decided by clinical observation in combination with a degree of trial-and-error. Understanding the biological mechanisms that contribute to disease origin and course may enable patient subtyping for optimised treatment selection and improved clinical care. This symposium will discuss research that answers this global call for molecular psychiatry approaches that reclassify psychiatric diagnoses based on a biological framework, rather than on symptomatology alone. **Dr Matosin** will focus on genetic contributions to psychiatric subtypes, exploring the hypothesis that the FKBP5 gene could function as a transdiagnostic risk marker for psychiatric disorders. **A/Prof. Nithianantharajah** will focus on cognitive dysfunction across psychiatric disorders, and how we could trans-diagnostically deconstruct symptoms by examining the synaptic basis. Prof. Sarnyai will present evidence that there is a role of the environment, and how high levels of “wear and tear” (allostatic load) on the brain and body could have utility for psychiatric subtyping. Lastly, **Prof. Dean** will present evidence of a cortical muscarinic receptor schizophrenia subtype, and potential biological pathways which could be targeted for the treatment of cognitive deficits. This symposium will discuss new possibilities for how we better understand patient clusters based on combinations of genes, environment and/or symptoms, and how this mechanistic knowledge can be leveraged to initiate novel ways to classify patient sub-populations that might benefit from specific treatment strategies.

Stratifying the links between genes, environment and symptoms: targeted molecular and translational approaches to understand psychiatric subtypes

Exploring the hypothesised FKBP5 psychiatric subtype with evidence from the human brain

Dr. Natalie Matosin, Illawarra Health and Medical Research Institute

Abstract: Severe psychiatric disorders – including depression, bipolar disorder and schizophrenia – share genetic and environmental risk factors that may cause overlapping biological features across disorders. FKBP5 is an allosteric co-chaperone of the glucocorticoid receptor that is highly responsive to stress, and physiologically important for propagating and extinguishing the stress response. Genetic and epigenetic dual disinhibition of FKBP5 can increase psychiatric risk by causing overexpression of FKBP5 throughout the brain and body, leading to dysfunction of the stress response and other critical cellular pathways including cell division, cell migration and cell fate. To better understand this process, we examined FKBP5 in the human brain, where psychiatric symptoms manifest and pharmacological interventions predominately exert therapeutic effects. In this talk, I will present our results from the largest and most comprehensive postmortem study examining FKBP5 to date. We studied tissues from the dorsolateral prefrontal cortex (DLPFC; Brodmann Area 9, BA9) of 681 individuals with psychiatric disorders and controls. We report (i) the FKBP5 gene expression (gex), protein and DNA methylation (DNAm) life-course trajectories; (ii) the age-related changes in FKBP5 that are moderated by psychiatric disease status and/or FKBP5 risk genotype; and (iii) the FKBP5 cell-type specificity and thus cell-type contributions to the heightened FKBP5 gex phenotype. Our results show convergence of FKBP5 gene and protein expression with age, which may be related to changes in DNAm and genotype contributing to the process by which FKBP5 raises risk to psychiatric disorders in a subset of psychiatric patients.

Biography: Dr Natalie Matosin PhD is an NHMRC CJ Martin Research Fellow and Group Leader at the Illawarra Health and Medical Institute and Molecular Horizons (UOW) with a joint appointment at the Max Planck Institute of Psychiatry. She was awarded her PhD in Molecular Psychiatry from UOW in 2015, and subsequently undertook early postdoctoral training at UNSW. In 2016, Matosin was recruited to the Max Planck Institute of Psychiatry in Munich for advanced postdoctoral training, and was awarded internationally competitive fellowships to make this move. Matosin relocated back to IHMRI and Molecular Horizons (UOW) in 2018. Matosin's research group now focus on understanding the contribution of stress to the development of psychiatric disorders, combining cutting-edge targeted and genome-wide molecular and genetic approaches with advanced histology techniques and postmortem brain tissues. Matosin is the recent recipient of the 2020 Rebecca L Cooper Memorial and Brain Sciences Awards, and currently serves on the Editorial Board of PLOS One.

Stratifying the links between genes, environment and symptoms: targeted molecular and translational approaches to understand psychiatric subtypes

Stress and allostatic load in psychiatry: using AL biomarkers to delineate psychiatric patients

Prof. Zoltan Sarnyai, James Cook University

Abstract: Chronic stress is a well-recognised contributor to the pathophysiology of psychiatric disorders. It activates and perturbs multiple pathways, including hormonal, immune/inflammatory and metabolic, to exert a variety of effects on different organ systems in the body and on the brain. It is likely that these systemic processes have both direct and indirect effects on brain function and contribute to psychopathology. This multi-system dysregulation has been captured in the concept of Allostatic Load (AL) that is defined as the increasing "wear and tear" on the body and the brain. Recent studies have shown that AL, e.g. the deleterious multi-system dysregulation, is increased in a number of psychiatric disorders. This talk will summarise the recent advances in this emerging field by drawing examples from studies on Indigenous Australians exposed to considerable stress and trauma as well as from clinical populations with psychiatric disorders, such as schizophrenia, major depression and bipolar disorder. The talk will highlight the potential of using the AL concept, and the AL biomarkers, to early diagnosis, staging and stratification within an etiologically relevant conceptual framework.

Biography: Professor Zoltán Sarnyai, M.D., Ph.D. is Professor and Head of the Laboratory of Psychiatric Neuroscience at James Cook University. He was previously University Lecturer in the Department of Pharmacology, University of Cambridge and a Fellow of Pembroke College, Cambridge where he was Director of Studies for Medicine. He trained at the Department of Psychiatry at Harvard Medical School and at The Rockefeller University. He was appointed as Lady Davis Visiting Professor at Technion-Israel Institute of Technology for 6 months in 2019 to investigate the neuro-metabolic aspects of schizophrenia. He conducts research on major psychiatric disorders and studies the contribution of systemic factor such as stress, energy metabolism, gut microbiota and immune activation to brain health. He has over a hundred publications (H index 35). He was awarded the Curt Richter Prize by the International Society of Psychoneuroendocrinology; the DuPont-Warren Award by the Department of Psychiatry, Harvard Medical School; and the Brain Research Foundation (formerly NARSAD) Young Investigator Award. He currently serves on the Executive Committee of the Biological Psychiatry Australia and of the International Society for Nutritional Psychiatry Research. He is Associate Editor for *Nutritional Neuroscience* and for *Frontiers in Neuroscience*, and member of the editorial board of the journals *Stress* and *International Journal of Environmental Research and Public Health*.

Stratifying the links between genes, environment and symptoms: targeted molecular and translational approaches to understand psychiatric subtypes

Synaptic basis of transdiagnostic cognitive makers in mental disorders

A/Prof. Jess Nithianantharajah, Florey Institute of Neuroscience and Mental Health

Abstract: One size never fits all. In psychiatry, a challenge for understanding mental illnesses lies in their heterogeneity and comorbidity. Towards this, we need to tackle a major knowledge gap – elucidating the molecular and neurobiological basis of distinct cognitive symptoms that can be both selectively or collectively disrupted between individuals diagnosed with the same mental illness, and shared across different mental disorders. In the clinical space, there is a growing need for transdiagnostic measures of cognitive domains and constructs. Aligning this, there is a critical need for preclinical behavioural approaches in rodents to enable analysis of homologous cognitive constructs. I will discuss our recent work addressing this, dissecting cognitive constructs in mouse models carrying mutations in synapse genes implicated in neurodevelopmental disorders. Specifically, undertaking a detailed behavioural dissection exploiting a battery of novel and established rodent touchscreen-based cognitive tests in mice with mutations in the neuroligin postsynaptic cell-adhesion gene family, we demonstrate the regulation of distinct cognitive constructs such as learning and motivational processing can be dissociated. Importantly, we showcase analysis of response latencies and examine their differential contribution to decision-making and learning, capturing different response epochs during behavioural responding analogous to processing speed and reaction times in human tasks. Our team is developing the approaches and platforms necessary to enhance how we measure complex cognitive constructs in preclinical rodent models, thus enabling deeper understandings into the synaptic and biological basis of transdiagnostic measures of cognitive function and dysfunction in mental illness.

Biography: Associate Professor Jess Nithianantharajah heads the Synapse Biology and Cognition laboratory at the Florey Institute of Neuroscience and Mental Health, University of Melbourne. She completed her doctorate in behavioural neuroscience at the University of Melbourne and commenced postdoctoral training at the Howard Florey Institute investigating gene-environment interactions on neural plasticity. She was recruited to the Wellcome Trust Sanger Institute, Cambridge UK and held a joint appointment at the Department of Experimental Psychology, University of Cambridge UK working on the development of the rodent touchscreen cognitive tests. She then relocated to the University of Edinburgh before returning to The Florey Institute as an independent group leader. Her research interests lie in understanding the role of synaptic genes in cognition and disease.

Stratifying the links between genes, environment and symptoms: targeted molecular and translational approaches to understand psychiatric subtypes

Studying a sub-group within the syndrome of schizophrenia: The frontal pole and cognition

Prof. Brian Dean, Florey Institute of Neuroscience and Mental Health

Abstract: It is argued that studying more biologically homogeneous sub-groups within the syndrome of schizophrenia is critical to understanding its aetiology1. We previously showed that ~25% of patients with schizophrenia can be separated into a subgroup due to a loss of cortical muscarinic M1 receptors (CHRM1)2 and this sub-group have unique changes in gene expression in the dorsolateral prefrontal cortex (DLPFC)3, indicating a sub-group specific cortical aetiology. At the level of the syndrome we showed a log fold greater change in number of genes with altered expression in the frontal pole (FP) compared to the DLPFC4. Our unpublished data shows that 202 genes with changed levels of expression in the cortex of CHRM1-/- have changed levels of expression in FP in schizophrenia. These data suggest there is dysregulation in CHRM1 controlled gene expression in our study with a Sz cohort, of which 25% of patients were from our sub-group. Finally, 6 of the 202 genes are listed as being associated with cognitive ability in the Cognition GWAS. Hence, in this presentation it will be argued that identifying changes in gene expression in the FP in our sub-group of patients with schizophrenia will reveal biochemical pathways involved in the cognitive deficits experience by the sub-group.

Biography: Professor Brian Dean is Head of The Molecular Psychiatry Laboratory and Deputy Director of the Victorian Brain Bank at the Florey. Brian completed his studies for a Doctoral Degree at the University of Melbourne during which he began his studies on understanding which cellular biochemical pathways are affected by the pathophysiology of schizophrenia. A key component of this mission has been to identify changes in the molecular cytoarchitecture of postmortem CNS from subjects with schizophrenia and to understand how these changes are impacting on brain function. Brian has published significant bodies of work contributing to current understanding of the role of muscarinic receptors, serotonin receptors and cytokine-regulated pathways in the aetiology and treatment of schizophrenia and has recently focussed on how changes in cortical gene expression could contribute to the pathophysiology of schizophrenia. Brian is a Fellow of the Royal Society of Biology and has been recognised as an outstanding basic scientists in the field of schizophrenia research by SIRS and the ACNP. Brian has presented the BPA Schweitzer Lecture, Melbourne University Beattie Smith Lecture and the ASPR Lilly Oration. Brian was the Founder and Inaugural President of Biological Psychiatry Australia and has served as President of the Melbourne Chapter of the Society of Neuroscience, Treasurer of the CINP and ANS and Secretary of the Asian College of Schizophrenia Research. Brian is a Director and the Chairman of the SAC of the Rebecca Cooper Medical Research Foundation which has a particular focus on funding early career researchers investigating brain disorders.

Are we there yet? The push to develop improved behavioural and animal models to advance translational research in neuropsychiatry

Chair
Dr James Kesby

Discussant
Prof. Tim Karl

Overall Abstract

There is a growing awareness that translational research - from preclinical research in animal models to the patient and back again - is critical for improving our understanding and treatment of mental health disorders. With pharmaceutical companies retreating from psychiatric research due to a lack of effective drug development, one main cause remains the discrepancy between positive outcomes of candidate preclinical drugs and apparent lack of efficacy in humans. Now more than ever, new approaches are required to drive innovation in neuropsychiatry research. This symposium will showcase national early- to mid-career researchers focussed on advancing cross-species translation in the mental health space. **Dr Kesby** will discuss how the basic-to-clinical pipeline needs better integration to accelerate bidirectional research and how we can capitalise on established tasks to study psychosis in a new light. **Dr Harms** will focus on how similar electrical brain signatures in rodents and humans can assess key aspects of cognition. **Dr Clemens** will discuss her recent research looking at how rats, similar to humans, adapt nicotine intake to suit their current and future access. **Dr Turner** will focus on the relationship between impulsive actions and habits, revealing a link between impulse control and associative learning. To conclude, **Prof. Tim Karl**, who has strong expertise in preclinical modelling of brain disorders will lead an interactive discussion on the current state of translational research in neuropsychiatry and priorities for moving forward.

Are we there yet? The push to develop improved behavioural and animal models to advance translational research in neuropsychiatry

Dr. James Kesby, University of Queensland

Abstract: Our knowledge of the neurobiology of schizophrenia has advanced considerably, nevertheless drug development is almost at a standstill. The most effective antipsychotic treatment currently available to clinicians, clozapine, was discovered over 60 years ago. This is in part because there exists a large disparity between the tests we use for 'psychotic symptoms' in animal models and the clinical evidence of the underlying neurobiology in people with schizophrenia. Therefore, the best avenue for using animal models may be to identify outcomes that are sensitive to the underlying neurobiology observed in schizophrenia and psychosis. Given recent clinical data and the action/effectiveness of antipsychotics, our primary downstream region of interest is the associative striatum with a particular focus on dopamine signalling. To assess associative striatal function we are using translational tests of goal-directed action and serial reversal learning in both humans and rodents. Animal studies using these tasks include dopamine-based pharmacology and studies using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). I will show comparative data between human and rodents demonstrating similar levels of performance, and importantly, impaired cognitive performance induced by increased dopamine signalling (i.e., psychosis). These results suggest a more direct link between cognition and psychosis in schizophrenia and provide a potential avenue for targeted translational studies. Ultimately, we need better behavioural tests for positive symptoms in animal models so that more efficacious therapies can be developed.

Biography: Dr. James Kesby's research has focused on the dopamine system and its role in addiction, depression, cognition and psychosis. He received his PhD at UQ in 2010 working on how developmental risk factors tor schizophrenia alter brain neurochemistry. He then moved to the USA to work with Professor Athina Markou at the University of California San Diego. His work focused on the cognitive outcomes of combined methamphetamine dependence and HIV disease in mice and humans. In 2016, he returned to Australia (with Darryl Eyles at the Queensland Brain Institute) with an Advance Queensland Fellowship in collaboration with Associate Professor James Scott (consultant Psychiatrist at the Royal Brisbane and Women's Hospital). This work combines human and mouse studies in order to establish a translational platform looking at better ways to model psychosis in animal models.

Are we there yet? The push to develop improved behavioural and animal models to advance translational research in neuropsychiatry

Dr. Lauren Harms, University of Newcastle

Abstract: Reduction in the size of mismatch negativity (MMN), an auditory prediction error signal, is one of the most highly replicated neurophysiological findings in schizophrenia. The ability of MMN to be elicited without the subject attending to stimuli makes it an excellent candidate for back-translation into animal models. To offer new, and potentially more translatable outcome measure options for preclinical schizophrenia research, we have been focused on developing a rodent model of MMN. It has been demonstrated that rat brains are certainly capable of generating a human-like prediction error signal, both by surface-level and local field potential recordings. The next step for the field, however, is to find an animal model system in which these responses are reduced, similar to what is seen in schizophrenia. Acute administration of a NMDA receptor antagonist, MK-801, was examined for its impact on MMN in male and female Wistar rats. We found that MK-801 dose-dependently reduced MMN, similar to what is seen in human schizophrenia and in healthy human controls given NMDA antagonists. In addition, in mid-range doses (0.3mg/kg for males and 0.1mg/kg for females), MK-801 disrupted the relationship between rat MMN size and the stimulus characteristics, with high-probability (low salience) stimuli producing equal MMN responses to low-probability (high salience) stimuli, an effect which is also seen in schizophrenia. These findings indicate that schizophrenia-like neurophysiological disruptions can be induced and observed in rats, opening up new opportunities for preclinical models of schizophrenia.

Biography: Dr. Lauren Harms received her PhD in 2012 from the Queensland Brain Institute at The University of Queensland. In 2012, she began a postdoctoral position at the University of Newcastle's School of Psychology, where her research focused on developing and evaluating new risk factor-based animal models of schizophrenia and developing a rodent EEG system with which neurophysiological biomarkers of schizophrenia can be assessed. In 2018, she joined the School of Biomedical Sciences and Pharmacy at the University of Newcastle with an academic appointment. Her research focuses on exploring neurophysiological biomarkers for schizophrenia in rodent models, with the ultimate aim of developing highly predictive outcome measures for preclinical schizophrenia research.

Are we there yet? The push to develop improved behavioural and animal models to advance translational research in neuropsychiatry

Dr Kelly Clemens, University of New South Wales

Abstract: People adapt to restrictions on when and where they can smoke by adjust their smoking patterns. We have developed an animal model of restricted access to nicotine where rats can freely choose between 3 different infusion doses. With progressive restriction on access to nicotine (from free access, to access every 5 min), rats develop a clear preference for high dose nicotine. In a second experiment, rats were trained to choose between 3 different doses of nicotine based on a signal of future restricted access. Under these conditions, rats were able to regulate their current dose selection in anticipation of a future absence of nicotine. Together these results indicate that rats, like people, modify their behaviour to both compensate and anticipate a restricted access period.

Biography: Dr Kelly Clemens is a UNSW Scientia Fellow in the School of Psychology at UNSW. Her laboratory studies the behavioural and epigenetic factors that are associated with the development, maintenance and relapse of drug-seeking. Her research falls into two broad themes: first, how cues in the environment can sustain drug-seeking, with a particular focus on how nicotine can produce aberrant learning about these associations. The second is focused on the intersection between behavioural neuroscience and molecular biology, including the possibility that epigenetic modifications may be responsible for the maintenance of drug memories across periods of abstinence.

Are we there yet? The push to develop improved behavioural and animal models to advance translational research in neuropsychiatry

Dr. Karly Turner, University of New South Wales

Abstract: Impulsive actions and habits both occur without forethought of the consequences and are often triggered by internal or external stimuli. However, the link between impulsive behaviour and habit formation has not been directly examined. To determine if impulsive actions are associated with habit formation we combined a differential reinforcement of low rates of responding (DRL) task to measure impulsive action with a devaluation test to determine propensity to develop habits. We found that rats with low impulsivity did not alter responding when sated on a non-specific food but did reduce premature responses when the reward was devalued. In contrast, high impulsive rats improved efficiency on both devalued and valued sessions, without sensitivity to outcome-specific satiety. These results suggest that low impulsive rats were able to think through their actions to consider the outcome and respond appropriately, however high impulsive rats do not. High impulsive rats did reduce their impulsive responses when motivation was reduced but failed to show outcome-specific updating. If we can understand the associative learning mechanisms that underlie impulse control disorders, then novel therapeutic strategies can be developed.

Biography: Dr. Karly Turner received her PhD from the Queensland Brain Institute (UQ) in 2016. During her PhD, Dr. Turner developed a translational task to examine how psychostimulants improve attentional deficits. 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

Sex hormones and Psychiatric Disorders

Chair
Dr Andrea Gogos

Discussant
Prof. Maarten van den Buuse

Overall Abstract

The aim of this symposium is to drive the message forward that sex steroid hormones play a major role in the psychopathology of psychiatric disorders. This diverse symposium includes four speakers (3 female and 1 male), ranging from PhD student to Professor, with two national (two different states) and two international (two different countries) speakers. These speakers will present data from human, animal and molecular studies. Marked sex differences are evident in schizophrenia, post-traumatic stress disorder (PTSD) and depression. Increasing evidence suggests that sex hormones, such as estrogen, may be responsible for these sex differences. With many journals publishing special issues on sex differences in the last couple years, this is an important topic and timely presentation. We hope that this symposium will reinforce that researchers need to consider and use both males and females in their studies.

A/Prof Christina Dalla (Greece) will present data on sex differences in animal models of depression, stress response and antidepressant activity. PhD student and clinical psychologist, **Ken Hsu** (Tasmania), will present a meta-analysis of emotional memory studies that examine the impact of sex hormones, highlighting the role of estradiol and progesterone in anxiety and PTSD. Recently submitted PhD student, **Dr Samantha Owens** (Sydney) will present data on raloxifene-mediated gene expression changes in rats, aiming to identify its therapeutic potential for schizophrenia. **Prof Liisa Galea** (Canada) will present data from two animal models of postpartum depression to show that heterogeneity of models is advantageous in demonstrating different subtypes of depression.

Sex hormones and Psychiatric Disorders

Sex differences in neuropsychopharmacology: the antidepressant paradigm

A/Prof Christina Dalla, Dep. of Pharmacology, Medical School, National & Kapodistrian University of Athens; Vice-President of the Mediterranean Neuroscience Society

Abstract: Neuropsychiatric disorders are overall more prevalent in women than in men and sex differences exist in their pathophysiology and treatment. However, most preclinical studies typically use male subjects, an issue that is gaining attention, as new guidelines require the consideration of female subjects in neuroscience and neuropsychopharmacology. Especially, in the field of neuropsychopharmacology, there are substantial sex differences in pharmacokinetics and pharmacodynamics of several psychotropic drugs. In this respect, our group has thoroughly studied sex differences in models of depression, stress response and antidepressant activity. Furthermore, we have investigated the behavioral and neurochemical effects of estrogen depletion by aromatase inhibition in both male and female rats. Recently, we have observed that in the search of new antidepressants, based on the hypothalamus-pituitary adrenal (HPA) axis, compounds preclinically studied in males were tested in clinical trials that recruited more, if not exclusively, women than men and did not control for potential sex differences (1). We suggest that this mismatch between preclinical and clinical studies has contributed to the failure of discovering new antidepressants based on the HPA axis. Moreover, our studies suggest that corticosterone levels do not predict depressive-like behavior in female rats, as they do in males (2). Overall, these findings highlight the importance of studying sex differences in preclinical neuropsychopharmacological research.

Biography: A/Prof Christina Dalla received her first diploma from the Pharmacy School of the National and Kapodistrian University of Athens in 2000 and continued her studies in Neuropsychopharmacology, Behavioral Neuroendocrinology and Neurosciences in Athens, in Belgium and at Rutgers University of New Jersey, U.S.A. with two Marie Curie Fellowships from the European Union. Dr. Dalla has more than 60 research papers, 10 invited chapters in international and Greek books, over 3180 citations and more than 100 abstracts and talks at international and national conferences. She has participated and leads several research grants with European and Greek collaborators from the academia and the industry. She has received numerous awards and distinctions, such as the “L’Oreal-Unesco” for Greek Women in Science and the ECNP fellowship award in 2015. The same year, she joined the European College of Neuropsychopharmacology (ECNP) Preclinical Data Network Forum and she is currently a member of the ECNP Educational Committee. Dr. Dalla is also teaching at the Medical School of the National and Kapodistrian University of Athens since 2008 and in more than 10 master programs. She has served as President of the Hellenic Society for Neurosciences and currently she serves as Vice President and President-elect of the Mediterranean Neuroscience Society and as Treasurer of the Institute of Stress Biology and Medicine. Finally, she is participating in the organization of Greek and International scientific meetings, as well as in public activities for brain awareness, as member of the DANA initiative for the brain and the Erasmus+ program Share4Brain.

Sex hormones and Psychiatric Disorders

Gonadal steroid hormones and emotional memory: A meta-analysis

Ken CMK Hsu, School of Psychology, University of Tasmania

Abstract: Stress hormones have been reliably associated with emotional memory consolidation, yet there has been comparatively little investigation of the impact of gonadal steroid hormones (oestradiol, progesterone, testosterone) on emotional memory. Emerging evidence suggests an influence of gonadal hormones on emotional memory, but findings are inconsistent. This study presents a meta-analysis of emotional memory studies that examine the impact of gonadal steroid hormones. Meta-regression analyses were conducted to examine the impact of hormonal level (oestradiol, progesterone) on intentional recall, intrusive memories, recognition memory, and extinction recall. 28 studies were included in the meta-analysis– 11 intentional recall, 4 recognition memory, 6 intrusive memory and 7 extinction recall. For intentional recall, increased progesterone levels were significantly associated with recall of negative stimuli, and this was particularly evident under stressful conditions. Oestradiol was also associated with increased recall of negative stimuli under stress but not under non-stress conditions. There was no significant association of hormone level with recognition memory or intrusive memories, however, there was significant heterogeneity in this data. Finally, low levels of oestradiol and progesterone were associated with greater fear recovery (impaired fear extinction recall) in fear conditioning and extinction recall studies. In summary, findings suggest that increased oestradiol and progesterone are associated with increased recall of negative affective stimuli, particularly under stressful conditions, and low levels of oestradiol and progesterone are associated with enhanced fear recovery (poor extinction recall).

Biography: Ken Chia Ming Hsu is a PhD candidate in the School of Psychology, University of Tasmania and a clinical psychologist. His research is investigating the impact of both gonadal steroid and stress hormones on varying indices of emotional memory in healthy controls and patients with Posttraumatic Stress Disorder, and his research is employing both meta-analytic techniques and experimental memory and hormonal research. He has six publications to date in his candidature.

Sex hormones and Psychiatric Disorders

Dopamine-, inflammatory-, and sex steroid-related gene expression is modulated by raloxifene in multiple regions in the male rat brain

Dr Samantha Owens, Schizophrenia Research Laboratory, NeuRA

Abstract: The selective estrogen receptor modulator raloxifene has been shown to enhance cognition and alleviate psychotic symptoms in some people with schizophrenia; however, the molecular changes underlying these effects are unknown. Both dopaminergic dysregulation and neuroinflammation are implicated in schizophrenia pathophysiology and may influence neurocognitive and psychotic symptoms. Sex steroid hormones can influence both dopamine neurotransmission and inflammation suggesting raloxifene may act via these pathways to elicit beneficial effects in schizophrenia. We investigated the extent to which raloxifene alters sex steroid-, dopaminergic-, and inflammatory-related gene expression in five key dopaminergic brain regions in normal adult male rats [prefrontal cortex (PFC), dorsal striatum (DS), ventral striatum (VS), substantia nigra (SN), and ventral tegmental area (VTA)]. Raloxifene decreased estrogen receptor mRNA in the VS [$t(21)=2.6$, $p=0.02$] and increased dopamine-related mRNAs in midbrain regions and VS [$t(21\text{-}25)>2.1$, $p<0.05$]. Raloxifene-treated animals exhibited increased IL-1 in all five brain regions [$t(9.8\text{-}25)>3.2$, $p<0.05$] and decreased TNF mRNAs in midbrain and striatum [$t(22\text{-}24>2.9$, $p<0.05)$]. IL-6 mRNA was significantly increased by raloxifene in all regions except VTA [$t(21\text{-}24>3.5$, $p<0.05$]. Our findings suggest raloxifene may influence dopaminergic-related behaviours by altering dopamine reception and breakdown in multiple brain regions, particularly in the dopaminergic cell bodies. Additionally, we provide evidence that raloxifene may also act to modulate neuroinflammation in dopaminergic regions implicated in schizophrenia, although the behavioural and neurobiological correlates of these neuroinflammatory changes are still to be determined.

Biography: Samantha Owens is a postdoctoral researcher at the Schizophrenia Research Laboratory, Neuroscience Research Australia. She completed her PhD at the University of New South Wales in 2020 under the supervision of Prof. Cyndi Shannon Weickert and Dr. Tertia Purves-Tyson. She completed a Bachelor of Science (Advanced) at the University of New South Wales in 2012 and was awarded the FC Courtice Prize for the best performance in a Physiology major. She completed her honours project at the Schizophrenia Research Laboratory where she examined sex steroid modulation of dopamine signalling molecules in the nigrostriatal pathway of adolescent rats. Her PhD project involved post-mortem, animal, and clinical studies to examine both sex steroid and dopaminergic pathways and their potential contribution to the pathophysiology of schizophrenia. She is first author on three publications from her PhD, has attended several domestic and international conferences, and was awarded a BPA poster prize in 2017. Her current project involves using RNA sequencing to examine inflammatory biotypes in a large post-mortem midbrain cohort of people with schizophrenia.

Sex hormones and Psychiatric Disorders

Embracing the heterogeneity of animal models of depression: the special case for postpartum depression

Prof. Liisa A.M. Galea, Djavad Mowafaghian Centre for Brain Health, Dept of Psychology, University of British Columbia

Abstract: Most animal models of depression have used males, but women are more than twice as likely to develop depression, particularly during the reproductive years. Pregnancy and postpartum are associated with an increased risk to develop neuropsychiatric disorders, such as perinatal depression (PND). The timing onset of PND influences severity of symptoms and has implications for etiology, treatment implications and efficacy. Women can develop depression during gestation (early or late) or during the postpartum (early or late). We developed two animal models of postpartum depression that show manifestations of depressive endophenotypes either early or later in the postpartum, to examine different physiological (hormonal) factors that may contribute to depression during these two time periods and to determine treatment efficacy. In these models, we see symptoms of depressive-like behaviours either early after parturition mimicking depression seen during the early postpartum or later after parturition mimicking depression occurring in the late postpartum after a normal pregnancy. I compare postpartum models to other models of PND that use gestational stress to initiate depression during pregnancy. Together these studies show that fluctuations in steroid hormones increase vulnerability to develop a depressive-like phenotype and that efficacy of pharmacological antidepressants depends on timing of treatment and the model. The aim of my talk will be to show that heterogeneity of animal models of PND are advantageous in demonstrating different subtypes of depression. I will highlight that researchers need to consider females in animal models of depression to gain a full understanding of the etiology and treatment of depression.

Biography: Liisa Galea is a Professor in the Department of Psychology and Djavad Mowafaghian Centre for Brain Health, Director of the Graduate Program in Neuroscience, Lead of Women's Health Research Cluster, and a Scientific Advisor at Women's Health Research Institute at the University of British Columbia. Her research goal is to improve brain health for women and men by examining the influence of sex and sex hormones on normal and diseased brain states such as depression and Alzheimer's disease. Dr. Galea obtained her Ph.D. in Neuroscience from Western University and was a postdoctoral fellow at the Rockefeller University. Dr. Galea is a Distinguished University Scholar, is a twice winner of the NSERC (Natural Sciences and Engineering Research Council of Canada)-Discovery Accelerator Supplement, received the Michael Smith Senior Scholar Award, Cattell Sabbatical Award, and the Vancouver YWCA Women of Distinction award. She was recognized as a Fellow at International Behavioral Neuroscience Society (IBNS). She has over 160 scientific papers in peer-reviewed journals. Dr. Galea is the chief editor of FiN (Frontiers in Neuroendocrinology IF: 9.059), an editor of eNeuro, and serves/served on the editorial boards of Endocrinology, Hormones and Behavior, and Neuroscience. Dr. Galea served on peer review panels for National Institute of Health (US), Canadian Institutes for Health Research (CIHR), Wellcome Trust (UK) and NSERC. She has secured over $7M as PI. She is a President-Elect of the Organization for the Study of Sex Differences (OSSD), and serves on numerous committees (advocacy, EDI) and advisory boards (e.g. Institute for Gender and Health CIHR).

Recent advances in personalised brain stimulation for modulating neurocircuitry in psychiatric disorders

Chair/Discussant
A/Prof. Andrew Zalesky

Overall Abstract

Repetitive transcranial magnetic stimulation (rTMS) has gained increasing interest for its capacity to directly target and modulate aberrant neurocircuitry in treatment resistant psychiatric disorders, especially depression. Brain stimulation targets have been informed and guided by neuroimaging since its clinical inception. It has become increasingly clear that the prefrontal cortex is particularly heterogenous across individuals and that response rates depend on precisely where rTMS is administered. Concurrently, rTMS has become increasingly conceptualized as a network therapy – although stimulation is typically applied to a single brain region, its effects are mediated via distributed networks. Advances in mapping brain networks now allow us to identify the connections underpinning treatment effects and establish an optimal TMS target. We illustrate evidence, derived from rodent and human studies, for lasting effects of TMS on brain networks and how these are understood to mediate treatment response. We discuss new opportunities to personalize TMS interventions using neuroimaging and computational modeling, and by applying an improved basic understanding of mechanisms, aiming to optimize treatment to suit particular individuals and clinical subgroups. We demonstrate that it is now possible to robustly and precisely pinpoint personalised connectivity-based cortical stimulation targets and that clinical response is significantly better when patients are treated closer to their personalized connectivity-based cortical target. Our speakers will present different approaches in neuroimaging and discuss the relative merits to facilitate the development of targeted interventions for psychiatric disorders. Attendees will also be provided with practical advice for translation of these methods into basic research and clinical practice.

Recent advances in personalised brain stimulation for modulating neurocircuitry in psychiatric disorders

Overview of personalized brain stimulation therapies for psychiatric disorders

A/Prof. Andrew Zalesky, School of Medicine and Engineering, University of Melbourne

Abstract: Mounting evidence suggests that personalization of neural stimulation therapies such as transcranial magnetic stimulation (TMS) and Deep Brain Stimulation (DBS) can improve efficacy and treatment outcomes. I will introduce some of the key neuroimaging modalities that enable treatment personalization. Neuroimaging can be used to identify individualized circuit-based targets that account for inter-individual variation in brain morphology, connectivity and network architecture. I will specifically focus on personalization based on structural and functional connectivity derived from functional and diffusion-weighted MRI, respectively, and briefly consider alternative neuroimaging modalities that can be used to optimize and personalize neural stimulation therapies. I will show how whole-brain circuit maps can be derived from these modalities and how these maps can be utilized to identify optimal stimulation targets as well as optimize other parameters of a stimulation protocol. This talk will provide the necessary background for the subsequent talks that will focus on specific clinical studies on personalization of neural stimulation therapies in psychiatry.

Biography: Andrew Zalesky is Principal Fellow at the University of Melbourne, Australia. He holds a joint appointment in Medicine and Engineering. After completing his PhD in Electrical Engineering at the University of Melbourne in 2007, he applied his modeling expertise to investigate neural connectivity in psychiatric illness. He leads multidisciplinary research team positioned at the interface of psychiatry and engineering. He developed the network-based statistic, one of the most widely used methods for performing statistical inference on brain networks. His contributions to neuropsychiatry include mapping of the schizophrenia connectome and development of methods to analyze neuroimaging data. He co-authored Fundamentals of Brain Network Analysis, one of the best-selling Elsevier neuroscience titles published in 2016. His 2010 nodes paper has become a classic in the field of imaging connectomics. He is ranked in the top-1% of researchers worldwide in his field according to citations. Associate Professor Zalesky was awarded the 2016 Aubery Lewis Award and the 2014 Young Tall Poppy Science Award.

Recent advances in personalised brain stimulation for modulating neurocircuitry in psychiatric disorders

Neuroimaging-guided transcranial magnetic stimulation in Obsessive-Compulsive Disorders

A/Prof. Luca Cocchi, QIMR Berghofer Medical Research Institute

Abstract: Brain functions are supported by the neural activity of specialised brain regions as well as macroscopic brain networks. The neural mechanisms that link changes in neural activity in specialised regions, with the emergence of large-scale brain network dynamics remain largely unknown. This knowledge is essential to understand how information flows across brain regions, as well as guide new brain stimulation interventions aiming to restore brain networks dysfunctions supporting psychiatric illnesses. In this talk, I will start by describing the results of empirical and computational studies that have aimed to unfold the neural principles that underpin the emergence of distinct patterns of functional brain network activity following local deregulations. I will then present how knowledge gathered from these fundamental studies have been translated to a clinical trial aiming to restore known whole-brain networks pathology in obsessive-compulsive disorders (OCD). The final part of the talk is going to present new emerging avenues to link neuroimaging and clinical data to further personalise brain stimulation interventions in psychiatric illnesses including OCD.

Biography: Dr Luca Cocchi obtained his PhD in Neuroscience at the University of Lausanne and Geneva (Switzerland) in 2007. Following postdoctoral training in mental health research institutes including the Melbourne Neuropsychiatry Centre (The University of Melbourne) and the Queensland Brain Institute (University of Queensland), Dr Cocchi started a position at the QIMR Berghofer Medical Research Institute in March 2016. He is currently head of the clinical brain network team at QIMR Berghofer Institute. Dr Cocchi is internationally recognised for his work on brain imaging in health and disease. He has applied novel image analysis to identify functional and anatomical brain connectivity underpinning symptoms of schizophrenia, depression, ADHD, autism, and obsessive-compulsive disorders (OCD). His work is having a major influence on the conceptualization of healthy and pathological brain functions as resulting from complex neural dynamics emerging on top of anatomical brain connectivity. With the goal of progressing evidence-based psychiatric therapies, Dr Cocchi recently investigated the impact that local brain stimulation techniques such as Transcranial Magnetic Stimulation (TMS) has on the activity of whole-brain neural networks. Results from these investigations have motivated two ongoing clinical trials assessing the use of TMS as a viable tool to restore brain network activity and reduce symptoms of OCD.

Recent advances in personalised brain stimulation for modulating neurocircuitry in psychiatric disorders

Toward state-of-the-art personalised brain stimulation: precision, feasibility and relation to clinical outcome

Dr Robin Cash, School of Medicine and Engineering, The University of Melbourne

Abstract: Mounting evidence suggests that antidepressant response to rTMS depends on functional connectivity with the subgenual cingulate cortex (SGC) at the precise stimulation site. Critically, SGC functional connectivity shows considerable interindividual variation across the spatial extent of the dorsolateral prefrontal cortex, indicating that connectivity-based target personalisation might be necessary to improve treatment outcomes. However, recent work suggested that the intraindividual reproducibility of optimal targets is limited to 3.5cm (Ning et al., 2018). To bridge this translational gap, we developed novel methodology with which reproducible personalised connectivity-based cortical stimulation targets can be pinpointed with millimetre accuracy, validated across functional MRI scans acquired in 1000 healthy adults. Critically, better clinical outcome was associated with closer proximity to these personalised targets in a retrospective analysis of 26 individuals with treatment resistant depression who received rTMS using conventional rudimentary targeting methodology. Moreover, personalised targets were heritable, suggesting that connectivity-guided rTMS personalisation is stable over time and under genetic control. These data indicate that connectivity-based personalisation of rTMS can be achieved with current MRI technology and potentially improve treatment response. Various lines of research add further evidence that personalised rTMS has the potential to be clinically transformative in the treatment of psychiatric disorders.

Biography: Dr Robin Cash obtained his PhD in Neuroscience at the University of Western Australia. He completed international training in Germany, USA and Canada and Australia. He is now an ARC funded senior research fellow at the Melbourne Neuropsychiatry Centre. He has performed basic and clinical research utilizing TMS, EEG, MEG, DBS, TES and fMRI. He developed one of the first personalised TMS interventions (Cerebral Cortex, 2014), as well as a rapid 3-minute rTMS paradigm, which elicits equivalent clinical benefits compared to conventional 25 minute rTMS in individuals with depression (Brain Stimulation, 2017, 2019). His work has helped to highlight the effects of rTMS across distributed brain networks (Neuroimage, 2017) and the role of brain connectivity in mediating antidepressant response to TMS (Biol Psych, 2019, 2020, JAMA Psych 2020). He has developed novel methodology for connectivity-guided TMS personalisation, which he now aims to implement clinically to improve treatment outcomes. He has recently authored invited reviews for Biological Psychiatry and the Oxford Handbook of Transcranial Stimulation.

Recent advances in personalised brain stimulation for modulating neurocircuitry in psychiatric disorders

Combined rTMS/MRI studies in animal models to study lasting effects of rTMS

Bhedita J Seewoo, School of Biological Sciences, The University of Western Australia

Abstract: There is increasing concern surrounding the interindividual variability in response to rTMS. I will discuss the importance of investigating the underlying mechanisms of rTMS in preclinical animal studies to understand these sources of variability and how they may be overcome to develop tailored treatments for specific individuals and neuropsychiatric disorders. A key challenge is to align the different experimental approaches used in human (non-invasive: MRI, PET, TMS and behavioural) and preclinical studies (invasive: cellular and molecular outcomes). Our research uses low-intensity (LI) rTMS to preserve focality of stimulation in the small rodent brain and applies multimodal MRI methods to link our understanding of cellular and molecular mechanisms to brain changes that are clinically relevant. We have recently shown that a single session of LI-rTMS in healthy rats has frequency-specific effects on functional connectivity that are similar to those described in humans following rTMS. When delivered daily for 2 weeks, 1 Hz LI-rTMS had subtler but opposite and longer-lasting effects on functional connectivity and neurometabolite levels than 10 Hz stimulation. We have also validated the chronic restraint stress (CRS) model of depression in rats using MRI measures: CRS induced similar functional connectivity, neurometabolite and hippocampal volume changes as found in humans with depression. We are currently investigating the long-term effects of LI-rTMS in rats following CRS using behavioural measures, invasive methods and MRI. These correlational measures may suggest how to improve personalised rTMS treatment protocols and outcomes.

Biography: Bhedita Seewoo is a fourth year international PhD candidate in Neuroscience at The University of Western Australia. The title of her doctoral thesis is “In-vivo MRI study of the effects of low-intensity rTMS on brain activity, chemistry and structure in rodents.” Upon completion of a Bachelor’s degree in Biomedical Science at Murdoch University (Australia) in 2015, she was awarded the university medal for being among the top seven graduating students across all disciplines. In 2016, she completed her Honours project entitled “Resting state fMRI study of brain activation using rTMS in rats” with an upper first-class outcome, following which she was awarded a Forrest Research Foundation Scholarship funded by the philanthropic donation of Andrew and Nicola Forrest. Bhedita’s research focuses on the use of in-vivo MRI to examine the effects of low-intensity rTMS on brain activity, chemistry, and structure in rodent models to inform protocol development for human studies.

Current research in neurodevelopment and neurodevelopmental disorders

Chair
Dr Anne Masi

Discussant
Dr Adam Lawther

Overall Abstract

Neurodevelopmental disorders are highly heterogeneous conditions that result from multiple biological and environmental events occurring in early life. This symposium will address current research and findings across a spectrum of neurodevelopmental disorders from basic mechanisms to clinical translation. The talks will cover recent preclinical research investigating the role of gene-environment interactions and oxidative stress (**Dr Adam Walker**); post-mortem brain assessment of changes in the immune system's complement pathway across typical neurodevelopmental stages (**Ms Rachel Sager**); and clinical studies, translational approaches and the need to stratify from a clinician researcher's perspective (**Prof. Valsamma Eapen**).

In addition to covering basic, translational and clinical studies, speakers of all career stages will contribute to this symposium. Prof. Valsamma Eapen is an established child and adolescent psychiatrist, and Dr Adam Walker is an early-mid career researcher and Group Leader. Ms Rachel Sager is a USA-based PhD student. **Dr Anne Masi** (clinical and biobank focused) and **Dr Adam Lawther** (animal model focused) will co-serve as chairs and discussants for the symposium. Both are early career postdoctoral researchers and Dr Anne Masi will set the stage for the symposium by conveying her lived experience as a parent of a child with complex needs.

Current research in neurodevelopment and neurodevelopmental disorders

Prof. Valsamma Eapen, University of New South Wales

Abstract: Autism Spectrum Disorder (ASD) is a heterogeneous condition with varying aetiology and clinical presentations. The prevalence estimates range from 1 in 160 (World Health Organisation 2017)1 to 1 in 54 (Centre for Disease Control 2020) with an estimated annual cost of $9.7 billion to the Australian economy. The variability in the signs and symptoms of ASD, along with the considerable behavioural overlap with other neurodevelopmental conditions often leads to significant diagnostic challenges. This presentation will cover the overlap in clinical symptoms and the unique differentiations between ASD and the common comorbidities such as Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD) and Tourette Syndrome. Genetic, neuroimaging and clinical phenomenological studies will be examined to provide a framework for understanding the converging and yet distinct neuropathological processes involved in the pathogenesis of these conditions. Neuroanatomical substrates involved in translating genetic vulnerability to varying clinical phenotypes mediated by disruption in neuronal development and circuitry formation will be discussed. Understanding the convergence and divergence in the genesis of different clinical symptom constellations and clinical conditions has implications for the assessment and management of ASD and associated co-morbidities. Further, stratifying ASD into homogeneous subgroups can aid personalised care.

Biography: Professor Valsamma Eapen is Chair of Infant, Child and Adolescent psychiatry at UNSW Sydney; Head of the Academic Unit of Child Psychiatry at Liverpool Hospital; Stream Leader for ELDoH Clinical Academic Group, Sydney Partnership for Health Education Research and Enterprise (SPHERE); and Director of BestSTART Child Health Academic Unit South West Sydney. As a clinician researcher, she has consistently demonstrated the ability to translate research findings into clinical practice and policy applications, including developing service delivery frameworks for early identification of developmental disorders. Her specific areas of research interest include neurodevelopmental disorders such as autism (Director of Early Years Program at the Autism Co-operative Research Centre) and Tourette Syndrome (Medical and Publicity Liaison Officer for Tourette Syndrome Association Australia). Through a Department of Social Services funded study across six states in Australia, she is leading a program to build evidence base on early intervention in autism in Australia. Further, she was part of a four member Executive Committee for the development of the National Autism Diagnostic Guideline and member of the reference group for the independent assessment pilot for functional evaluation in Autism commissioned by the NDIS. Her research has focused on the prevalence and correlates of developmental disorders in pre-school children, genetic and phenotypic characteristics of neuro-developmental disorders including genetic and environmental contribution to the occurrence of child mental health problems as well as subgrouping and stratification of neurodevelopmental disorders for precision care.

Current research in neurodevelopment and neurodevelopmental disorders

Rachel Sager, SUNY Upstate Medical University, Syracuse NY, USA

Abstract: Despite their traditional roles in fighting disease, immune system components play critical roles in neurodevelopment. Prenatally, the complement pathway is implicated in progenitor cell proliferation and neuronal migration. Work in the postnatal mouse has identified a role for complement in synaptic elimination, and potential involvement in neurodevelopment. However, the developmental trajectory of complement expression in the human brain has not been characterised. Given that complement increases during periods of active synaptic engulfment in rodents, we hypothesized that complement expression would increase during postnatal development in humans, particularly during adolescence. Through assessment of human post-mortem prefrontal cortices in infants, children and adolescents that presented with no evidence of neurodevelopmental disorders, we observed that activating complement factors (C1QB and C3) peak in early neurodevelopment, are highest in toddlers, and decline in teenagers. Complement protein C4 was highest between ages 1 and 5 whereas C3 protein levels are unchanged with age. mRNA expression of the microglial complement receptor subunit CD11b steadily increased across infancy and peaked in toddlers. Complement inhibitors (CD46 and CD55) increased early in life, but failed to decrease like complement activators. These data suggest that activation of complement in the human prefrontal cortex occurs between 1 and 5 years old. We do not find evidence of induction of complement factors during adolescence and instead find increased or sustained expression of complement inhibitor mRNA at maturation. Dysregulation of these typical patterns of complement may predispose the brain to neurodevelopmental disorders such as autism or schizophrenia.

Biography: Rachel Sager obtained her BA in Biological Science in 2011 from Mount Holyoke College in South Hadley, Massachusetts, and is currently in her final year of a Neuroscience PhD at the SUNY Upstate Medical University in Syracuse, USA. Her current research is focused on the role of immune signalling in healthy brain development using post-mortem brain tissue. The human post-mortem work which she will be presenting at this symposium is currently under review in the Journal of Neurochemistry.

Current research in neurodevelopment and neurodevelopmental disorders

Dr Adam Walker, Neuroscience Research Australia

Abstract: Deleterious deletions within the IMMP2L gene have increased frequency in autism spectrum disorder (ASD) and Gilles de la Tourette syndrome (GTS), and to a lesser extent in attention deficit hyperactivity disorder (ADHD) and intellectual disability. Moreover, the knockout of IMMP2L expression has been associated with increased oxidative stress, which has been associated with a range of neurodevelopmental disorders, including ASD and GTS. However, it is uncertain whether oxidative stress has a causal association with these behavioural disorders. Here, we use the first viable knockdown mouse model for IMMP2L deficiency to explore the impact of IMMP2L on a broad range of behavioural domains with and without the antioxidant mitoquinone (MitoQ). MitoQ targets mitochondria-induced oxidative stress by selectively accumulating in the mitochondria and inhibiting the accumulation of reactive oxygen species. IMMP2L knockdown exacerbated dexamphetamine-induced hyperlocomotion and increased repetitive grooming behaviours, which were unaffected by MitoQ. These findings indicate that while IMMP2L deficiency in mice corresponds with ASD- and GTS - relevant behaviours, targeting mitochondria-derived oxidative stress using MitoQ following weaning is not a tractable intervention to modulate these behaviours. These findings suggest that individuals suffering from IMMP2L-mediated neurodevelopmental disorders may not benefit from treatments that target mitochondrial-induced oxidative stress.

Biography: Dr Adam Walker is a Senior Lecturer in the School of Psychiatry at UNSW and leads the Laboratory of ImmunoPsychiatry at Neuroscience Research Australia. He completed his PhD at the University of Newcastle in 2011 and completed postdoctoral fellowships at the University of Illinois – Urbana-Champaign and The University of Texas MD Anderson Cancer Center. He returned to Australia in 2015 and joined Monash University as a National Breast Cancer Foundation Research Fellow, investigating the mechanisms underlying cognitive and psychiatric side-effects of cancer and its treatment. At NeuRA, Adam's team investigates the mechanisms responsible for inflammation-associated psychiatric and neurodevelopmental disorders, as well as when symptoms of depression and cognitive impairment occur in patients with chronic inflammatory illness such as cancer. Using preclinical mouse models of inflammation, he has pioneered discovery of available drugs that may be repurposed to prevent and treat inflammationinduced depression (ketamine, leucine) and cancer-associated cognitive impairment (aspirin). As a member of the steering committee for the ELDoH Clinical Academic Group, Sydney Partnership for Health Education Research and Enterprise (SPHERE), Adam is using preclinical models and biomarker assessments of children with ASD to identify novel targets for intervention to improve the lives of children with neurodevelopmental disorders.

Cross talk between the brain and body - preclinical insights into the role of inflammation

Chair
Dr Kyoko Hasebe

Discussant
Dr Chiara Bortolasci

Overall Abstract

There is mounting evidence for bi-directional relationships between inflammation and psychiatric disorders. We are now moving toward mechanistic models that describe how peripheral and central factors interact at molecular and cellular levels to impact mental state and psychiatric health. This symposium showcases recent findings by ECRs across three institutions investigating relevant animal models to explore potential mechanisms underpinning how the brain and body interact in the context of mental health.

Dr Suzanne Hosie (RMIT) will discuss novel findings on the crosstalk between inflammation and the enteric nervous system alongside effects on the central nervous system, mood and autism-like behaviour using the Nlgn3 transgenic mouse model. Dr Hosie's research provides new insights into our current understanding of the disorder by characterising the involvement of alterations in gut microbiota and microglial populations.

Dr Sarah-Jane Leigh (UNSW Sydney) will discuss interactions between cafeteria diets and cognition and characterise roles of central and peripheral inflammation and gut microbiota in the diet-induced cognitive impairment. Furthermore, Dr. Leigh will present data outlining a role for minocycline, the potent anti-inflammatory and broad-spectrum antibiotic, in diet-induced inflammation and cognitive deficits.

Finally, **Dr Christopher Choy** (MIPS) will discuss behavioural makers of neurodevelopmental trajectories during adolescence into adulthood in mice, providing new opportunities to use preclinical models to map how early genetic and/or environmental insults that disrupt inflammatory pathways can change the normal trajectories in cognitive development, leading to cognitive dysfunction in neurodevelopmental disorders.

Cross talk between the brain and body - preclinical insights into the role of inflammation

Understanding how gut inflammation affects the brain in neurodevelopmental disorders

Dr Suzanne Hosie, School of Health and Biomedical Sciences, RMIT, Bundoora, Melbourne, Vic

Abstract: Interactions between the gut and the brain via the gut-brain-microbiota axis affect mood and behaviour in health and disease, however the underlying biological mechanisms are unclear. Using preclinical models of neurodevelopmental disorders, recent discoveries begin to explain how bacteria may stimulate inflammation in the gut to affect behaviour. Gastrointestinal dysfunction is commonly reported by people with autism and their caregivers and contributes to significant reductions in quality of life. Families living with autism also report higher prevalence of inflammatory disorders. An autism-associated gene mutation in the Neuroligin-3 (Nlgn3) gene affects synapse function in the CNS and the inflammatory response in mice. Nlgn3R451C mice also show a behavioural phenotype mimicking complex behavioural traits in people on the autism spectrum. In addition, Nlgn3R451C mice have an altered enteric nervous system resulting in abnormal gastrointestinal motility, permeability and altered proportions of major gut neuron populations. Strikingly, we show that this mutation additionally affects the gut microbiome in mice and immune cells in the gut-associated lymphoid tissue. This presentation will describe interactions between bacteria and the nervous system including enteric and central changes in inflammation in the context of neurodevelopmental disorders. Insights into the role of the gut-brain axis in behaviour are provided in addition to histopathological assessments of CNS microglial responses to inflammation and structural and functional analyses of gut function and microbial communities in transgenic mice.

Biography: Dr Suzie Hosie's interest in neurophysiology began at the pharmaceutical company Pfizer within the Ion Channel Pharmacology group under the supervision of Dr Derek Leishman where she studied the effects of novel compounds on long QT syndrome. Dr Hosie was subsequently sponsored by Pfizer to complete a doctorate studying tonotopic gradients of ion channel expression in the cochlear at Sussex University, UK. Dr Hosie then moved to Australia to join the Ion channels and Disease laboratory at the Florey Institute of Neuroscience and Mental Health in Melbourne under the supervision of Prof Steven Petrou and A/Prof Elisa Hill-Yardin. Here she investigated neuronal activity in genetic mouse models of epilepsy using electrophysiological and whole animal behavioural techniques. In 2012, Dr Hosie was recruited to the University of Melbourne where she contributed to research showing reduced seizure susceptibility, elevated aggressive behaviour and altered neuronal activity in the amygdala region of a mouse model of autism. This work also showed that targeting endocannabinoid pathways improved behaviour in these mice. Since moving to RMIT, Bundoora in 2017, Dr Hosie has applied her neurophysiological expertise to understanding the role of neuroinflammation in neurodevelopmental disorders including characterising interactions between the microbiome, enteric nervous system and the brain. Current work includes understanding how modulating microbes might reduce inflammation and benefit both brain function and behaviour in neurodevelopmental disorders.

Cross talk between the brain and body - preclinical insights into the role of inflammation

Contributions of inflammatory and gut microbiota changes to the cognitive deficits induced by cafeteria diet

Dr Sarah-Jane Leigh, Environmental Determinants of Obesity Group, Department of Pharmacology, School of Medical Sciences, UNSW Sydney, Australia

Abstract: Diets rich in fat and sugar impair hippocampal-dependent cognition in both humans and rodents. We examined two potential underlying mechanisms, inflammation and gut microbiome composition, using male Sprague-Dawley rats fed a high-fat, high-sugar western-style Cafeteria diet. Cafeteria-fed rats exhibit impaired spatial recognition memory, metabolic disturbances and faecal microbiome alterations, including reductions in relative Lactobacillus abundance. Moreover, Cafeteria diet consistently increases dorsal hippocampus Aif1 expression, with less consistent upregulation of Il6 and Gfap gene expression. Here, we first examined whether co-administration of the antibiotic and anti-inflammatory drug minocycline prevented diet-induced cognitive impairment across six weeks, and secondly effects of minocycline on established diet-induced cognitive impairment. Minocycline both prevented and reversed cognitive impairment and hippocampal pro-inflammatory gene upregulation in Cafeteria-fed rats, while impairing cognition in chow-fed controls. Minocycline treatment and Cafeteria diet independently altered faecal microbiome composition, and Desulfovibrio piger abundance was significantly associated with cognition in both protocols. To investigate causality we treated Cafeteria-fed rats with a targeted Lactobacillus probiotic based on the species depleted by the diet, demonstrating transient improvement in Cafeteria diet-induced cognitive impairment and altered white adipose gene expression. In summary, microbiome-modifying interventions restored cognition in cafeteria-fed rats. However, probiotic benefits were transient, and minocycline caused adverse outcomes in healthy controls. These results highlight the fundamental role of inflammation and gut microbiome composition in Cafeteria diet-induced cognitive impairment and provide new insight into the interconnectedness of inflammatory processes and microbiota responses to dietary interventions.

Biography: Dr Sarah-Jane Leigh (BSc (Hons I) PhD 2020) is an early-career behavioural neuroscientist with an interest in the effects of diet and systemic disease on brain health and function. Her doctoral research at UNSW Sydney examined the relationship between diet-induced obesity and cognitive health in rats. Specifically, she examined the role of peripheral and central inflammation, and the gut microbiota in cafeteria-diet induced deficits in spatial recognition memory using multiple interventions targeting these underlying mechanisms. This work has led to 6 publications (6 first-author; 2 empirical papers). Two of her recent publications of particular relevance to this symposium are:

-Leigh SJ, Kaakoush NO, Westbrook RF & Morris MJ (2020) Minocycline-induced microbiome alterations predict cafeteria diet-induced spatial recognition memory impairments in rats, Translational Psychiatry, 10:92, doi: 10.1038/s41398-020-0774-1.
-Leigh SJ, Morris MJ (2018) The role of reward circuitry and food addiction in the obesity epidemic: An update, Biological Psychology, 131:31-42, doi: 10.1016/j.biopsycho.2016.12.013.

Cross talk between the brain and body - preclinical insights into the role of inflammation

Cognitive behavioral markers of neurodevelopmental trajectory in rodents

Dr Christopher Choy, Monash Institute of Pharmaceutical Sciences, Melbourne Victoria, Australia

Abstract: From birth to adulthood, the brain undergoes enormous growth and maturation, supporting the adaptation of cognitive development. Particularly, between adolescence and adulthood, maturation and refinement of synaptic and neural circuits shape the more specialized aspects of cognitive processing. Adolescence also represents a vulnerable developmental stage for the onset of symptoms in neurodevelopmental psychiatric disorders. Approaching the understanding of psychiatric disorders from a brain maturation or neurodevelopmental perspective allows us to disentangle the neurobiological basis of these disorders at multiple levels of analyses from the involvement of genes and environment, on the development and refinement of brain circuits that underlie cognitive processing. Furthermore, understanding how developmental insults including early inflammatory challenges, may alter brain connectivity and thus behavior relies on having a foundational understanding of normal cognitive development. Towards addressing these perspectives, we have begun to capture changes in behavioral trajectories during adolescence into adulthood in male and female mice on distinct cognitive tasks that include an adapted visuospatial paired associate learning touchscreen task. We see that the developmental trajectory of performance on these tests are dissociable, and that measures of motivation and learning are lower during adolescence compared to adulthood. These findings highlight we can measure behavioral makers of neurodevelopmental trajectories during adolescence into adulthood in mice, providing new opportunities to use preclinical models to map how early genetic and/or environmental insults that disrupt inflammatory pathways can change the normal trajectories in cognitive development, leading to cognitive dysfunction in neurodevelopmental disorders.

Biography: Dr Christopher Choy trained as a neuroscientist using animal behavioural models to understand the risk factors contributing to the mental illness such as schizophrenia. Christopher completed his PhD in 2008 under the supervision of Prof. Maarten van den Buuse supported by an Ian Scott Scholarship awarded by the Australian Rotary Health Research Fund. His work focused on a two-hit model of schizophrenia and its effects on molecular changes and memory performance. Following his PhD, Christopher worked with Prof. Ashley Bush and Dr. Dmitry Mayorov assessing memory in rodent models. In 2011, Christopher joined the Monash Institute of Pharmaceutical Sciences (MIPS) in Melbourne as a post-doctoral researcher with Prof. Arthur Christopoulos studying the psychopharmacology of novel muscarinic receptor compounds as potential therapeutic targets for schizophrenia. Christopher is currently leading the behavioural analysis on a collaborative project between A/Prof. Jess Nithianantharajah, Prof. Chris Pantelis and Prof. Arthur Christopoulos mapping the developmental trajectory of cognitive function and dysfunction in neurodevelopmental disorders.

Treating Schizophrenia: clinical challenges and preclinical hope

Chair
Dr Tertia Purves-Tyson

Discussant
Professor Xu-Feng Huang

Overall Abstract

Biological psychiatry is positioned at the intersection of the clinic and the laboratory, with the ultimate goal of providing better outcomes for those suffering from mental illness. This symposium brings together two psychiatrists and two preclinical researchers that share the common aim of improving treatments for schizophrenia and other neuropsychiatric disorders. **Prof Sundram** will provide an overview of the limitations of current treatment for schizophrenia and outline how precision psychiatry can overcome these limitations. In order to enact precision psychiatry to help those with schizophrenia, it is essential to identify and understand dysregulation of the multiple neurobiological pathways that lead to the diverse set of symptoms that characterise the disorder. Preclinical research is instrumental in this understanding. **A/Prof Newell** will discuss preclinical and clinical studies of novel compounds that target the glutamatergic system, highlighting considerations for future research. **Dr Vernon** will discuss the effects of chronic antipsychotic treatment on cortical thinning in a preclinical model with relevance for schizophrenia, to demonstrate the avenues that preclinical research provides to both support and challenge clinical understandings of neuropsychiatric disorders and treatments. Despite these advances, it often seems that preclinical research is divorced from the daily struggles faced by people with schizophrenia and other neuropsychiatric disorders, and the clinicians grappling with suboptimal treatments. **Dr Mohan**, a consultant neuropsychiatrist, will provide a perspective on the daily challenges facing clinicians in their quest for for real-world, clinically meaningful outcomes for their patients.

Treating Schizophrenia: clinical challenges and preclinical hope

Schizophrenia as a template disorder for precision psychiatry

Professor Suresh Sundram, Head, Department of Psychiatry, School of Clinical Sciences, Monash University and Director of Research, Mental Health Program, Monash Health

Abstract: Schizophrenia and its brethren disorders constitute a leading cause of global disability burden due to the early age of onset, chronic course and diversity of symptom domains. Current treatments are only symptomatic and only effective for psychotic symptoms. There are no course modifying interventions and no capacity to target treatments. This is because the extant treatments for schizophrenia were discovered serendipitously 70 years ago, and although have had some minor improvements in the decades hence, there have been no significant advances. There is a desperate need for treatments that have better efficacy; improved tolerability; treat additional symptom domains; alter disease course; and can be targeted to clinical profile. In short, there is a desperate need for a precision psychiatry.

Creating a translational pipeline using a recursive bedside to bench approach in conjunction with leveraging large “omics” datasets provides a path to precision medicines for schizophrenia. Components of this approach have generated candidates at various points of preclinical and clinical development. These have included agents targeting clinically the glutamate system, the muscarinic M1 receptor, the endocannabinoid system, trace amine associated receptor 1 as well as promising preclinical targets from ours and other laboratories. Recognising the challenges imposed by pleiotropy and polygenic complexity requires rigorous validation of targets and betacellulin and Arx serve as exemplars of recursive validation. This will allow focussing upon specific target treatments for specific sub-types and symptom clusters within this disorder spectrum and bring closer the promise of precision medicine for schizophrenia.

Biography: Professor Sundram is the Head, Department of Psychiatry, School of Clinical Sciences, Monash University and Director of Research, Mental Health Program, Monash Health. He is a research psychiatrist and neuroscientist. He has been investigating the molecular pathology of schizophrenia and related psychotic disorders using pharmacological, neurochemical and neuropathological approaches. These inter-related methods have been applied to parse components of the disorder such as treatment resistance and suicide to better understand their neurobiological substrates. He undertook his doctoral and post-doctoral studies at the Mental Health Research Institute in Melbourne before establishing his laboratory there and subsequently at the Florey Institute, and concurrently establishing a clinical research laboratory undertaking clinical trial and biomarker research in psychotic disorders. He then transferred and integrated his research program to Monash University and Monash Medical Centre. Here, he has been able to establish a Translational Molecular Psychiatry program that has permitted rapid and seamless translational research between molecular and clinical approaches. The work has resulted in more than 150 published scientific articles, books, book chapters and conference abstracts. He has presented as plenary and invited speaker at international and national conferences, served on a number of editorial boards and as deputy editor for the Asian Journal of Psychiatry and is an advisor to the UN, national and state governments.

Treating Schizophrenia: clinical challenges and preclinical hope

The promise of glutamatergic agents for the treatment of schizophrenia: what have we learned and where to now?

A/Prof Kelly Newell, Molecular Horizons and School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong; Illawarra Health and Medical Research Institute Wollongong NSW

Abstract: Although the dopamine system contributes to the symptoms of schizophrenia, the lack of effectiveness of dopaminergic antipsychotics in many people with this illness implicates the involvement of other systems. The glutamatergic system has long been implicated in the pathophysiology of schizophrenia, leading to substantial investment in the identification and development of glutamatergic drug targets. To date, much of this has focused on drugs that directly or indirectly target the glutamatergic NMDA receptor (e.g. glycine site agonists; metabotropic glutamate receptor 5 agonists) or regulate glutamate release/levels (e.g. metabotropic glutamate receptor 2/3 agonists; kynurenine amino acid transferase inhibitors). However, studies of glutamatergic-targeted drugs have not successfully led to new approved treatments. Does this suggest that the identified glutamatergic targets are not appropriate, or could study design considerations have led to an inability to realise the true potential of these drug targets? This presentation will discuss the findings of preclinical and clinical research that have investigated the therapeutic potential of glutamatergic targets, highlighting considerations for future research.

Biography: Dr Kelly Newell is an Associate Professor in the School of Medicine at the University of Wollongong. She completed her PhD in Neuroscience in 2007 and has been in academic roles at the University of Wollongong since 2008. She has recently established a new laboratory in the University's state of the art research institute, Molecular Horizons. Her research involves examination of neurochemical aberrations in human brain tissue to understand the molecular mechanisms underlying psychiatric disorders including schizophrenia and depression. She has a particular interest in the role of the glutamatergic system in these disorders. Through the use of preclinical rodent models she investigate the potential of novel therapeutic targets as well as the impacts of these disorders and their treatment on neurodevelopment. Her research has led to over 50 publications which have been cited >1800 times.

Treating Schizophrenia: clinical challenges and preclinical hope

Effects of chronic antipsychotic treatment in adulthood on cortical thickness in rats exposed to maternal immune activation in utero

Dr Anthony Vernon, King's College London

Abstract: Clinical and pre-clinical evidence suggest that chronic antipsychotic exposure may lead to cortical thinning. We investigated cortical thinning in a rat maternal infection model, with relevance for schizophrenia following chronic antipsychotic treatment in adulthood. Adult male offspring from control (CON; saline; GD15; n=5 dams) and maternal immune activation (MIA) exposed dams (poly (I:C); 4mg/kg i.v. GD15; n=5 dams) were allocated to one of four groups: CON/vehicle; CON/haloperidol; MIA/vehicle and MIA/haloperidol (n=10/group). Vehicle or haloperidol (0.5mg/kg/d) was administered subcutaneously using osmotic mini-pumps for 28 days, starting on post-natal day 90. T2-weighted ex vivo MR images were acquired and analysed using an automated rat cortical thickness pipeline. Differences between groups in cortical thickness were assessed using linear models in R and corrected for multiple comparisons using the False Discovery Rate (5%). Significant MIA*treatment interactions were found for parieto-temporal lobe thickness. Specifically, parieto-temporal cortical thickness significantly increased in the MIA/vehicle group ($p<0.05$; $q<0.05$), whilst MIA/haloperidol offspring showed decreased cortical thickness that did not differ from CON/vehicle or CON/haloperidol treated offspring ($p<0.05$; $q<0.05$). Frontal and parietal cortical thickness is increased in adulthood in rats exposed to MIA. In the parietal cortex, chronic exposure to haloperidol induces cortical thinning, such that MIA offspring no longer differed from controls. These data suggest haloperidol may "normalize" abnormal cortical thickness in MIA-exposed rats. This provides a framework to investigate the functional relevance of these changes and their underlying mechanisms.

Biography: Anthony Vernon trained in Biochemistry (BSc) and Neuropharmacology (PhD) at Imperial College London. After post-doctoral training in the Modo and Kapur labs at the Institute of Psychiatry, Anthony started his own lab as a Lecturer in 2013 and is currently a Senior lecturer in the Department of Neuroscience, Institute of Psychiatry and a Group leader at the MRC Centre for Neurodevelopmental Disorders, both at King's College London. Research in the Vernon laboratory is focussed on two main themes:
(1) Translational Neuropsychopharmacology - drugs used to treat serious mental illness (including antipsychotics, lithium, and antidepressants) have broad effects on the nervous, immune and endocrine systems. We aim to map how these effects relate to the beneficial and adverse effects of these drugs with the goal of informing their clinical use through improved understanding of drug risk: benefit ratios.
(2) Prenatal Programming of Brain Disorders - Physiological disturbances compromising the quality of fetal development and growth, such as maternal infection, affect developmental trajectories in a manner that predisposes the offspring to chronic psychiatric or neurological diseases. We aim to determine the causative biological pathways involved and elucidate factors that promote susceptibility and resilience to perinatal insults.
In both themes we utilise rodent models, but also human induced pluripotent stem cells (hiPSC) differentiated towards neural and glial cell fates. We employ a broad range of methods including: small animal magnetic resonance imaging (MRI; clinically comparable technology), quantitative autoradiography, 3D (CLARITY) and 2D histopathology, biochemistry and transcriptomics. We are however interested to exploit any new advances in technology to address our research questions.

Treating Schizophrenia: clinical challenges and preclinical hope

Dr Adith Mohan, Neuropsychiatric Institute, Prince of Wales Hospital

Abstract: The 2010 National Psychosis Survey estimated that 64,000 people in Australia aged 18–64 experienced a psychotic illness and were in contact with public specialised mental health services each year. The most commonly recorded diagnosis in nearly half of these individuals was that of Schizophrenia. Two thirds (64.8%) experienced their first episode before the age of 25 years. Despite breakthroughs in polygenic complexity, functional genomics, neuropathology, psychoneuroimmunology and clinical and preclinical candidate discovery, the treatment of psychosis in the clinic remains stagnant and disease modifying therapies, frustratingly out of reach.

A non-clinical observer peering into the psychiatric clinic from the vantage point of psychosis could be forgiven for seeing only gloom and pessimism for both patients and their care providers, both seemingly left waiting for the translational breakthroughs promised by the 'decade of the brain'. The daily reality of the psychiatric clinic is however frequently different. More often than not, patients, their families and clinicians find themselves partnered in a mission to achieve the best outcomes possible, therapeutic limitations notwithstanding. The day-to-day business of clinical psychiatry recognises the validity of a multitude of treatment targets. The clinic is where attenuation of positive symptoms stands shoulder to shoulder with the restoration of social agency and the attenuation of self-stigma in the quest for real-world, clinically meaningful outcomes for the many with psychosis who present themselves in our waiting rooms and inpatient wards. Here, there is no place for therapeutic nihilism and the credo of "the perfect cannot be allowed to be the enemy of the good" rings truer than ever.

Biography: Dr Mohan is a consultant neuropsychiatrist at the Neuropsychiatric Institute (NPI), Prince of Wales Hospital, Sydney, Australia. The NPI is a leading neuropsychiatric facility in Australia with an excellent reputation for tertiary specialised services. Here, he is involved in the care of patients with a range of neuropsychiatric and neurocognitive disorders, including functional neurological disorders, neurodevelopmental disorders, the neuropsychiatry of epilepsy, immune mediated and degenerative neuropsychiatric disease, and drug-induced movement disorders. He is also a Research Fellow with the Centre for Healthy Brain Ageing (CHeBA), and a Senior Lecturer with the School of Psychiatry, UNSW. His research interests include novel pharmacological interventions in neuropsychiatry, genomics of human brain ageing, as well as therapeutic neuromodulation in neuropsychiatric disorders. He is involved in studies of deep brain stimulation (DBS) in Tourette syndrome and obsessive-compulsive disorder and the use of transcranial direct current stimulation (tDCS) in mild cognitive impairment. He is enrolled in a higher degree research program investigating changes in the human brain transcriptome during ageing using post-mortem brain tissue and RNA sequencing. He is actively involved in the Section of Neuropsychiatry (SoN) of the Royal Australian and New Zealand College of Psychiatrists, is the jurisdictional representative for the state of New South Wales on the SoN, and is currently involved in the development of a competency-based training curriculum for Neuropsychiatry.

Computational psychiatry

Chair
A/Prof Marta Garrido

Discussant
Dr Ilvana Dzafic

Overall Abstract

The emergent field of Computational Psychiatry employs mathematical approaches in order to translate advances in neuroscience into clinical applications for psychiatric populations. It allows the aberrations in the brain\'s neurobiology to be explored in a mechanistic manner, for the purpose of unveiling the process components of psychiatric illness, and to drive precision diagnosis and treatment. It comprises two distinct approaches, a theoretically motivated approach and a data-driven approach based on machine learning methods. Here we will focus on theoretically motivated approaches that strive to uncover the underlying altered mechanisms that lead to psychopathology. Examples of these include using algorithmic models drawn from reinforcement learning (Bennet) and Bayesian approaches to modelling behaviour (Dzafic and Powers) and brain (Weber). In this symposium, we will present computational modelling work applied to a range of psychiatric symptoms, such as hallucinations (**Powers**), depression and mania (**Bennet**), as well as psychiatric conditions, such as schizophrenia (**Weber and Dzafic**), major depression and bipolar disorder (**Bennet**). This proposal showcases the work done by researchers at different career stages (two early, a mid and a senior), including three international speakers (USA and UK), while simultaneously having gender balance (two male and two female).

Computational psychiatry

Albert Powers, Yale University Department of Psychiatry

Abstract: Psychiatry, unlike most medical specialties, lacks a well-formed, biologically-based nosology. Computational neuroscience, by describing brain function in terms of quantitative models of information processing, offers a particularly promising way to make the needed link between physiology and psychopathology. Perception is an active process in which we infer the causes of our sensations, testing our current internal model of the world against incoming sensory input. In this setting, hallucinations may be viewed as arising because of an increased influence of that existing model (priors, in Bayesian terms) over incoming sensory evidence. Using a sensory conditioning paradigm that induces hallucinations via classical conditioning, we have demonstrated that individuals who hear voices (both with and without psychosis) are particularly susceptible to these conditioned hallucinations. Using a generative model for perception, we demonstrate that this increased rate of conditioned hallucinations is due to an over-weighting of priors relative to incoming sensory evidence. We then apply these principles to several follow-up studies, demonstrating sensitivity of these measures to the clinical high risk for psychosis (CHR-P) state and speaking to relationships between phenomenology and the role of priors in hallucinations. Lastly, we discuss direct clinical applications to this knowledge. Thus, using hallucinations as an illustrative example, we make the case that the use of formal computational models may aid in the formation of a psychiatric nosology rooted in distal causes rather than symptomatology.

Biography: Dr. Powers is an Assistant Professor in the Yale University Department of Psychiatry and Medical Director of the Yale PRIME Psychosis Research Clinic. He studied Cognitive Science at Yale before moving to Nashville for Vanderbilt's M.D.-Ph.D. program. There he studied sensory neuroscience under the mentorship of Dr. Mark Wallace. His graduate work focused on the process by which the brain combines information from the different senses and how that process changes with perceptual learning. He returned to Yale for psychiatry residency as part of the Neuroscience Research Training Program. Working with Drs. Philip Corlett and Christoph Mathys, Al devised a study to test a predictive-coding model of hallucinations. The work that resulted, published in Schizophrenia Bulletin and Science in 2017, is the first evidence for a computational model that views hallucinations as an overweighting of Bayesian priors during perception. Dr. Powers joined the faculty at the Yale Department of Psychiatry on July 1, 2018 as an Assistant Professor. His work, funded by a K23 Career Development Award and an R21 from the NIMH as well as a Career Award for Medical Scientists from the Burroughs-Wellcome Fund, focuses on applying the computational tools he has developed toward early detection and novel treatment development in psychosis. His clinical work is focused upon treatment of patients experiencing attenuated psychotic symptoms, as Medical Director of the Yale PRIME Psychosis Prodrome Research Clinic.

Computational psychiatry

Dr. Ilvana Dzafic, The University of Melbourne

Abstract: There exists conflicting evidence within the predictive coding framework about psychosis. One line of evidence finds decreased precision in prior beliefs, leading to delusional mood and misattribution of inner speech to external voices. In contrast, a different line of evidence finds increased precision in prior beliefs, leading to rigid delusions and greater susceptibility to conditioned hallucinations. It is argued that these inconsistent findings can be reconciled, such that impaired learning of prior beliefs (low precision) is compensated by a stronger reliance on already attained beliefs. This study aims to empirically test this theory. 21 outpatients with schizophrenia spectrum disorders (SZS) and 30 non-clinical controls (NC) completed a 'birds signing' version of an auditory oddball task. We used neuroimaging while behaviorally measuring statistical learning of beliefs. We also examined the rigidity of beliefs by cueing participants and then measuring reversal learning during volatile conditions. Finally, we conducted computational modeling to gauge precision in prior beliefs. We found that SZS have impaired statistical learning and that errors increase with severity of delusions in volatile conditions after being cued. In addition, cued beliefs impaired reversal learning in participants that reported more psychotic-like experiences. At the brain level, we found altered anterior cingulate activity in SZS during volatile conditions after being cued. Finally, we found increased belief stability and precision in SZS compared to NC. Our findings reconcile previous contradictory evidence by showing that in psychosis there is impaired statistical learning and at the same time stronger reliance on already attained beliefs.

Biography: Dr. Dzafic is a postdoctoral research fellow in the Cognitive Neuroscience and Computational Psychiatry Lab headed by A/Prof Marta Garrido. She investigates social cognition and learning in individuals suffering from different mental health conditions, particularly, psychotic disorders. She uses neuroimaging techniques: Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG), as well as computational modeling of brain and behaviour, to explore the emergence of psychotic experiences. She is also exploring whether psychosis is on a continuum, which extends into the non-clinical "healthy" population. Dr. Dzafic completed her Ph.D. in 2017 at the Queensland Brain Institute, the University of Queensland. She has delivered oral presentations at numerous international conferences, including the Schizophrenia International Research Society and the European Conference on Schizophrenia Research, and has delivered invited talks at internationally renowned institutions such as the Institute of Psychiatry at King's College and at the Wellcome Trust Centre for Neuroimaging at UCL. Her research has been published in prominent journals such as the Journal of Neuroscience and Human Brain Mapping. She has received an MRI Research Funding award, as well as an Australian Research Council travel award.

Computational psychiatry

Dr. Lilian A. Weber, University of Oxford

Abstract: The auditory mismatch negativity (MMN) has been suggested as a translational biomarker for NMDA receptor (NMDAR) dysfunction in schizophrenia. Pathophysiological theories suggest that such dysfunction might be caused by aberrant interactions of different neurotransmitter systems with the NMDAR, which could explain heterogeneity among schizophrenic patients and their treatment response. To translate the clinical potential of signals like the MMN, we need to be able to relate them to specific pathophysiological mechanisms that allow for differential diagnosis and targeted treatment. In this talk, I will present results from a series of studies where we have used a combination of EEG, pharmacology, and computational modeling to understand the NMDAR dependence of the MMN in terms of hierarchical belief updates during auditory perceptual inference. Our results suggest that blocking NMDARs with ketamine specifically interferes with hierarchical precision estimation during auditory processing in volatile task environments. Moreover, we find that the MMN is differentially sensitive to muscarinergic (cholinergic) versus dopaminergic modulations of synaptic plasticity at NMDARs, rendering it useful for predicting differential treatment responses in schizophrenia. In an ongoing observational patient study, we therefore test its ability to identify subgroups of patients with schizophrenia who will profit from a change in medication towards antipsychotics with a prominent muscarinergic profile like olanzapine or clozapine. If successful, this would be a first step to reduce the amount of trial-and-error that doctors and patients have to go through during the treatment of schizophrenia.

Biography: Dr. Weber has a background in Psychology and Physics and did her Ph.D. at ETH Zurich under the supervision of Prof. Klaas Enno Stephan and Dr. Frederike Petzschner in Zurich. There she used hierarchical Bayesian models, pharmacology, and EEG to understand how we process sensory signals in the auditory domain (using mismatch negativity paradigms) and in the interoceptive domain (using heartbeat evoked potential paradigms). She is currently a postdoc in the Cognitive Computational Neuroscience Lab led by Dr. Laurence Hunt at the Department of Psychiatry at University of Oxford. She is interested in how humans adapt their temporal windows of integration when making decisions in dynamic environments, and how failures to do so might underlie psychiatric symptoms.

Computational psychiatry

Dr. Daniel Bennett, Princeton University

Abstract: Extreme mood states are a cardinal symptom of both bipolar disorder (manic and/or depressive episodes) and major depression (depressive episodes only). A recent neurocomputational model proposes that these extreme mood states may result from dysfunctional interactions between mood and reinforcement learning. Specifically, mood-congruent changes in perceived pleasantness of stimuli may set up a positive feedback loop between mood and learning that can produce either mania or depression. To date, the predictions of this model have not been tested in individuals with diagnosed mood disorders. 59 adult participants (37 with depression or bipolar disorder, 22 matched controls) completed a reinforcement-learning task designed to measure the strength of the positive feedback loop between mood and reinforcement learning. During the task, participants were exposed to both positive and negative mood inductions (in separate blocks). We used a computational model to quantify the interaction between mood and reinforcement learning. The model predicts an association between mood instability and a bias for (or against) stimuli encountered in a positive (or negative) mood. Consistent with this prediction, across all participants there was a positive association ($r = 0.35$, $p = .01$) between self-reported hypomanic traits and mood-congruent changes in valuation after a positive mood induction, and no significant differences between diagnostic groups. Results are consistent with a dimensional association between hypomania and mood/learning interaction. This suggests that interactions between mood and reinforcement learning may be related to the occurrence of extreme mood states across disorders.

Biography: Dr. Bennett is a postdoctoral research fellow in the Princeton Neuroscience Institute at Princeton University, advised by Professor Yael Niv. In his work, he brings together computational modeling of human behaviour with neuroimaging to understand human decision making, both in healthy individuals and in those with a psychiatric disorder. His postdoctoral research involves applying the techniques and perspectives of computational psychiatry to the study of mood disorders. Specifically, he uses reinforcement learning models to investigate how interactions between mood and learning might underlie mood disorders such as major depression and bipolar disorder. Dr. Bennett has presented this work at fora including the Institute for Pure and Applied Mathematics at UCLA and the Kavli Summer Institute in Cognitive Neuroscience at Lake Tahoe. He received his Ph.D. in 2017 from the School of Psychological Sciences at the University of Melbourne. Dr. Bennett is supported by a CJ Martin Early Career Fellowship from the NHMRC and a Sir Keith Murdoch scholarship from the American Australian Association, and is the recipient of a 2020 Travel Fellowship Award from the Society of Biological Psychiatry (USA).

Inaugural Ambassador Programme Symposium: Breaking Down Professional Silos and Investigating Youth Mental Health

Louise Birrell[1,a], **Katie Douglas**[2,b], **Yara Toenders**[3,4,c], Jennifer Nicholas[3,b], Yann Quidé[5,6,a,c], Hannah Savage[7,c], Louise Thornton[1,a], Tamsyn van Rheenen[7,b], Thomas Burne[8,9,c], Olivia Dean[10,b], Darryl Eyles[8,9,c], Frances Kay-Lambkin[11,a]

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2. *Department of Psychological Medicine, University of Otago, Christchurch, New Zealand*
3. *Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, VIC, Australia*
4. *Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia*
5. *School of Psychiatry, University of new South Wales (UNSW), Sydney, NSW, Australia*
6. *Neuroscience Research Australia, Randwick, NSW, Australia*
7. *Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, Victoria, Australia*
8. *Queensland Brain Institute, University of Queensland, Brisbane Australia*
9. *Queensland Centre for Mental Health Research, Wacol, Australia School of Medicine and Public Health, The University of Newcastle, Callaghan, Australia*
10. *IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia*
11. *School of Medicine and Public Health, The University of Newcastle, Callaghan, Australia*

[a] *On behalf of the Society for Mental Health Research (SMHR)*
[b] *On behalf of the Australasian Society for Bipolar and Depressive Disorders (ASBDD)*
[c] *On behalf of Biological Psychiatry Australia (BPA)*

SYMPOSIUM ABSTRACT

Biological Psychiatry Australia (BPA), the Australasian Society for Bipolar and Depressive Disorders (ASBDD) and the Society for Mental Health Research (SMHR) represent key areas of strength and growth in mental health research in Australia and New Zealand. This symposium represents the first step in working across our societies in support of mental wellness. In order for Australian medical research, and ultimately the lives of people with mental illness, to move forward it is critical that we all work together towards common goals, and we hope other Societies will join us in the future so that we can work together to support mental health research in all its forms.

This inaugural “Ambassador Programme” symposium brings together researchers and executive members of BPA, ASBDD and SMHR and will showcase the work of early- and mid- career researchers (EMCRs) from each of these societies. The symposium will open with a brief introduction to the three societies, followed by EMCR presentations that will highlight diverse and exciting approaches to better understand, prevent and treat mental health and substance use disorders among young people. A facilitated panel discussion will then take place featuring the presenters, EMCR committee representatives and the Presidents of each of the societies. This discussion will explore how to facilitate potential collaborations across societies, potential opportunities for networking, how to create and promote inter-society groups and translational work around specific themes and how these societies, particularly their support of EMCR members, might be improved.

Inaugural Ambassador Programme Symposium: Breaking Down Professional Silos and Investigating Youth Mental Health

PRESENTER 1: Biological Psychiatry Australia

Predicting depression onset in young people based on clinical, cognitive, environmental and neurobiological data.

Yara J. Toenders[1,2], Akhil Kottaram[1,2], Richard Dinga[3], Christopher G. Davey[4], Lianne Schmaal[1,2], IMAGEN Consortium

[1] *Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, VIC, Australia*
[2] *Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia*
[3] *Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands*
[4] *Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia*

Early onset of depression is associated with long-lasting negative consequences. Identifying adolescents at risk for developing depression would enable the monitoring of risk-factors and the development of early intervention strategies. Using machine learning to combine several risk factors from multiple modalities allows prediction of depression onset at the individual level. This presentation will focus on findings from a subsample of a multi-site longitudinal study in adolescents, the IMAGEN study, in which future (subthreshold) depression onset in healthy adolescents was predicted. Based on 2-year and 5-year follow-up data, participants were grouped into: 1) developing an MDD diagnosis or subthreshold MDD and 2) healthy controls. Baseline predictors of 145 variables from different modalities (clinical, cognitive, environmental and neurobiological) at age 14 were used as input to penalized logistic regression to predict depression onset in a training dataset (N=407). The features contributing highest to the prediction were validated in an independent hold-out sample from the IMAGEN study (3 independent sites; N=137). Baseline severity of depressive symptoms, female sex, neuroticism, stressful life events and surface area of the supramarginal gyrus contributed most to the predictive model and predicted onset of depression in the independent validation sample. This study showed that depression onset in adolescents can be predicted based on a combination of clinical, demographic, life events, personality traits and neurobiological variables.

Bio: Yara is a PhD candidate at the University of Melbourne and the Centre for Youth Mental Health (Orygen), supervised by A/Prof Lianne Schmaal and Prof Chris Davey. Her PhD research focuses on predicting onset of depression based on clinical and neuroimaging data. She also examined data-driven symptom subtypes of depression and examined their neurobiological correlates. Yara is the Orygen host representative in the BPA ECRN committee this year.

Inaugural Ambassador Programme Symposium: Breaking Down Professional Silos and Investigating Youth Mental Health

PRESENTER 2: Australasian Society for Bipolar and Depressive Disorders
Enhancing Cognitive and Functional Recovery in Mood Disorders

K. M. Douglas[1]

[1] *Department of Psychological Medicine, University of Otago, Christchurch, New Zealand*

In alignment with the ASBDD, this presentation focuses on enhancing long-term recovery in recurrent mood disorders (bipolar disorder and major depressive disorder).

Current first-line treatments for mood disorders have limited beneficial impact on cognitive functioning, and cognitive impairment often persists into recovery. Cognitive impairment is associated with difficulties in occupational and interpersonal functioning, and thus, has a major impact on patients' quality of life. It is therefore crucial to focus not only on clinical outcomes in mood disorder intervention studies, but also cognitive and functional outcomes.

This presentation will provide an overview of several innovative clinical trials conducted at the Department of Psychological Medicine that have aimed to enhance longer-term recovery in mood disorders. Presented studies include (i) an open-label pilot study of a short-term, intensive 'Activation Therapy' (cognitive activation combined with behavioural activation) for severely depressed inpatients, (ii) an RCT of metacognitive therapy versus cognitive behavioural therapy for depression, and (iii) an RCT of cognitively-enhanced IPSRT versus IPSRT alone for recurrent mood disorders. Methodological considerations in planning clinical trials targeting cognitive impairment will be discussed.

Bio: Katie is a Senior Research Fellow (Sir Charles Hercus Fellow) and Clinical Psychologist. Her research interests include biological and cognitive aspects of mood and anxiety disorders (including earthquake-related trauma), and interventions aimed at improving cognitive and functional recovery in mood disorders. Katie has been awarded 13 research grants; six grants as Principal Investigator. This includes the prestigious Sir Charles Hercus Fellowship from the Health Research Council of New Zealand. Katie has extensive experience in clinical trial methodology and is named investigator on several clinical trials of non-pharmacological treatments for mood disorders. She is currently leading two innovative clinical trials; 1) a randomised controlled trial of group-based Cognitive Remediation in mood disorders, and 2) an open label study of Social Rhythm Therapy and Bright Light for treatment-resistant bipolar disorder. She is the Deputy Chair of the Australasian Society of Bipolar and Depressive Disorders.

Inaugural Ambassador Programme Symposium: Breaking Down Professional Silos and Investigating Youth Mental Health

PRESENTER 3: Society for Mental Health Research

A smartphone peer support app to increase help seeking, prevent mental health and substance use problems in adolescence

Louise Birrell[1], Ainsley Furneaux-Bate[1], Cath Chapman[1], Nicola Newton[1]

[1] *The Matilda Centre for Research in Mental Health and Substance Use, The University of Sydney, Sydney, Australia*

Social network theory has demonstrated peers play a powerful role in relation to one's health behaviours, including mental health and substance use. However, many adolescents are not equipped with the knowledge, skills, or are aware of appropriate referral services to provide adequate support to their peers. Despite recognition of the key role peers play in health behaviour, adolescent peer training and interventions are lacking, and online programs non-existent.

This presentation will outline the co-design process and planned effectiveness trial of an online peer intervention (*Mind your Mate*) in the form of a smartphone app to prevent problematic mental health and substance use in adolescents. A CONSORT compliant RCT will be run with approximately 1,400 Year 9 students in 14 high-schools. Schools will be randomly allocated to receive; 1) the online peer intervention, or 2) waitlist control. Participating students will complete self-report assessments at baseline, 6- and 12-month follow-up.

The effectiveness of the intervention will be assessed in relation to the following primary outcomes: a) mental health symptoms, b) substance use, c) help-seeking behaviour. Secondary outcomes include: stigma and knowledge about mental health and substance use.

The development of a novel online tool for young people to support their peers and improve their own mental health represents an innovative applied approach to the prevention of mental disorders in a real-world setting. If effective, the intervention is easily scalable, low cost and will link to the existing high-school syllabus, making it easy to implement and roll out.

Bio: Dr Louise Birrell is an Australian Rotary Health Bruce Edwards Post-doctoral Research Fellow at the Matilda Centre for Research in Mental Health and Substance Use. Her research examines the link between substance use and mental health to inform effective and innovative prevention strategies. In 2019 she was awarded a competitive fellowship to develop and trial an online intervention, in the form of a smartphone app (Mind your Mate), to upskill adolescents to better support their friends around with mental health and/or substance use and encourage early help-seeking.

Louise has extensive experience trialling substance use and mental health prevention programs, particularly developing and evaluating online programs including mobile apps. Louise coordinated the first online preventative trial to combine substance use education with depression and anxiety education for high-school students and is currently a Chief Investigator of a 7-year longitudinal follow-up of this study. She is also part of the leadership team for the Cracks in the Ice portal, funded by the Australian Government Department of Health, and Chief Investigator on a trial of the Preventure program delivered by school staff.

Prior to joining the University of Sydney, Louise worked at the National Drug and Alcohol Research Centre. Louise has completed a Bachelor of Psychology (First Class Honours) and Bachelor of Social Science. Her work has been recognised through numerous awards including the Society for Mental Health Research Early Career Researcher Award (2019) and the Jennifer McLaren Award for Outstanding Research Achievement while at the National Drug and Alcohol Research Centre.

2. Poster Abstracts

2.1 Psychoses

2.1.1 Schizophrenia: Behavioural Phenotype

GPR52 agonism reverses schizophrenia-relevant spatial working memory deficits in mice

Cassandra J Hatzipantelis - Monash University
Monica Langiu - Monash University
Gregory D Stewart - Monash University
Jess Nithianantharajah - The Florey Institute / University of Melbourne
Christopher J Langmead - Monash University

Background
Deficits in working memory constitute one of the most common and severe of cognitive impairments associated with schizophrenia (CIAS). While the severity of CIAS is the most accurate predictor of patient outcomes, there remains no antipsychotic meaningfully able to improve cognition in patients. The orphan GPCR, GPR52 has been highlighted as a prospective therapeutic target for the treatment of working memory deficits in CIAS due to its enrichment in key brain regions implicated in working memory processes. The pro-cognitive capacity of GPR52 ligands, however, is yet to be assessed using state of the art, translationally-relevant behavioural tests of working memory.
Methods
Working memory performance was assessed using the translationally-relevant mouse touchscreen-based spatial working memory task, TUNL (trial-unique, delayed nonmatching-to-location). To determine if the acute MK-801 NMDA receptor hypofunction model of CIAS would produce deficits in TUNL, a dose-response relationship was established for task performance. We then used this MK-801 model of working memory impairment to assess the pro-cognitive capacity of the GPR52 agonist, 3-BTBZ. Neuronal activation in brain regions implicated in CIAS following treatment with MK-801 and 3-BTBZ was measured by c-fos induction in perfusion-fixed mouse brain slices, visualised by confocal microscopy.
Results
0.15mg/kg MK-801 impaired performance accuracy in TUNL compared to saline as working memory load increased. 10mg/kg 3-BTBZ reversed MK-801-induced working memory deficits in TUNL and, in the absence of MK-801, improved performance over vehicle at high working memory loads. 3-BTBZ reversed MK-801-induced c-fos expression in the infralimbic and prelimbic areas of the prefrontal cortex and the nucleus reuniens, although not in other brain regions implicated in CIAS such as the basolateral amygdala and entorhinal cortex. In the absence of MK-801, 3-BTBZ increased c-fos induction in the nucleus reuniens over vehicle.
Conclusions
Herein we demonstrate the pro-cognitive efficacy of the GPR52 agonist, 3-BTBZ using preclinical, translationally-relevant measures. We showed that 3-BTBZ improves poor working memory performance induced by MK-801, and above baseline levels at high working memory loads, in the mouse touchscreen-based task, TUNL. This study further implicates activity in key nodes specifically involved in working memory function and known to be dysfunctional in schizophrenia patients; the medial prefrontal cortex and nucleus reuniens, as a mechanism for GPR52-mediated pro-cognitive effects. Ultimately this study provides preclinical validation for GPR52 agonists in the treatment of working memory deficits in schizophrenia.

No Effect of Schizotypy on Visual Surround Suppression for Luminance, Contrast or Size

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Background
Perception is influenced by context. For example, a high-contrast surround typically decreases the perceived contrast of a central region. This visual surround suppression effect is reduced in people with schizophrenia, a finding commonly attributed to an imbalance between neural excitation and inhibition. However, studies in patients can be confounded by the effects of medication, illness duration, and interference from other deficits such as reduced attention. Accordingly, we investigated the relationship between surround suppression and psychometrically defined schizotypy, a range of normal personality traits that resemble symptoms of schizophrenia at a sub-clinical level.
Methods
In a sample of psychologically healthy individuals (N = 120), we measured the point at which a surrounded reference stimulus and a test with no surround were perceptually matched for each of three properties: luminance, contrast, and size. Scores on the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) were used as a dimensional measure of schizotypy.
Results
Bayesian correlation analyses suggest no relationship between the magnitude of surround suppression effects and O-LIFE subscale scores.
Conclusions
Such absence of a relationship suggests that surround suppression for luminance, contrast and size may represent informative conditions in which schizophrenia and schizotypy are disassociated, with implications for our understanding of the similarities and differences in their underlying neurobiology. Alternatively, previous reports of reduced surround suppression in schizophrenia may have been influenced by medication or other extraneous factors.

The impact of smoking status on cognition and brain morphology in schizophrenia spectrum disorders

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Background
Cigarette smoking is commonly associated with worse cognition and decreased cortical volume and thickness in healthy cohorts. Chronic cigarette smoking is highly prevalent in schizophrenia spectrum disorders (SSD), but the effects of smoking status on the brain and cognition in SSD is not clear. This study aimed to better understand whether cognitive performance and brain morphology differed between smoking and non-smoking individuals with SSD compared to healthy controls.

Methods
Cognitive, clinical, and cigarette smoking data were obtained from the Australian Schizophrenia Research Bank (ASRB). Cognitive functioning was measured in 299 healthy controls and 455 SSD patients with the Repeatable Battery for Assessment of Neuropsychological Status. Cortical volume, thickness, and surface area data were analysed from T1-weighted structural scans obtained in a subset of the sample (n = 82 controls, n=201 SSD). Associations between smoking status (smoker/non-smoker) and cognition, brain volume, thickness, and surface area were tested using multivariate analyses of covariance, including diagnosis as a moderator.

Results
No smoking by diagnosis interactions were evident, and no significant differences were revealed between smokers and non-smokers across any of the variables measured, with the exception of a significantly thinner left posterior cingulate in smokers compared to non-smokers.

Conclusions
In this sample, cognitive and brain morphological abnormalities in SSD do not appear to be associated with smoking status. Future investigation of this topic is encouraged to confirm and expand on our findings.

Interneuron-specific deletion of 14-3-3ζ leads to male-specific dopaminergic behavioural sensitisation

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Background
14-3-3ζ is involved in neurodevelopment, neurogenesis and cell death in the brain. Mutations in the 14-3-3ζ gene have been found in schizophrenia and autism, and levels of the protein have been shown to be reduced in these conditions, however how these abnormalities play a role in pathophysiology is unknown. Previous studies have shown that mice lacking 14-3-3ζ displayed hyperactivity in an open field and disrupted sensorimotor gating. These behavioural deficits were accompanied by neurodevelopmental abnormalities in the brain, including specific reduction of cortical parvalbumin interneurons, modelling a predominant defect seen in schizophrenia patients.

Methods
To further study the role of 14-3-3ζ in interneuron development, an Olig2Cre;14-3-3ζfl/fl mouse model was generated to remove 14-3-3ζ prior to neurogenesis. These mice have interneuron-specific deletion of 14-3-3ζ which replicates the PV interneuron deficiency of 14-3-3ζ-/- mice without gene deletion in other cell types. Male and female Olig2Cre;14-3-3ζfl/fl (KO) and 14-3-3ζfl/fl (WT) mice were aged to adulthood then underwent tests of psychosis-like behaviour. First, prepulse inhibition (PPI) was tested following the administration of 1, 3 or 5 mg/kg apomorphine (Apo). Following this, locomotor hyperactivity was measure following the administration of 3 or 5 mg/kg methamphetamine (Meth).

Results
KO mice showed no differences in baseline PPI or locomotor activity compared to WT mice. In male, but not female, KO mice there was a significantly greater effect of Apo to reduce PPI compared to WT mice at the highest dose of 5 mg/kg ($P = 0.008$) while there was no differential effect at 1 mg/kg. Male KO mice also showed significantly greater Meth-induced locomotor hyperactivity compared to females ($P = 0.029$) at the 5 mg/kg dose, with no sex difference in WT mice. There was no genotype effect following 3 mg/kg Meth.

Conclusions
Interneuron-specific deletion of 14-3-3ζ leads to male-specific dopaminergic sensitisation in two different models of psychosis-like behaviour.

Does adolescent stress lead to dopaminergic behavioural sensitisation in adulthood?

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Background
Sensitisation of dopaminergic activity has been suggested as an underlying mechanism in the psychotic symptoms of schizophrenia. Adolescent stress and chronic abuse of methamphetamine (Meth) are well-known risk factors for psychosis and schizophrenia; however it remains unknown how these risk factors compare in terms of dopaminergic behavioural sensitisation in adulthood. In addition, while brain-derived neurotrophic factor (BDNF) has been implicated in dopaminergic activity and schizophrenia, its role in behavioural sensitisation remains unclear.

Methods
In this study we compared the effect of chronic adolescent treatment with the stress hormone, corticosterone (Cort), or with Meth on two dopaminergic endophenotypes of psychosis in BDNF heterozygous mice and their wild-type controls in adulthood. Between 6 and 9 weeks of age, the animals either received Cort in the drinking water or were treated with an escalating Meth dose protocol. Mice then underwent behavioural testing from 11 weeks of age, using prepulse inhibition (PPI) with apomorphine administration or a locomotor hyperactivity test with acute Meth administration.

Results
In adulthood, Cort-pretreated mice showed significantly reduced Meth-induced locomotor hyperactivity compared to vehicle-pretreated mice ($p<0.05$). In contrast, Meth-hyperlocomotion was significantly enhanced in animals pretreated with an escalating dose of Meth in adolescence ($p < 0.001$). There were no effects of either pretreatment on prepulse inhibition or the response to apomorphine. BDNF Het mice showed greater Meth-induced hyperlocomotion ($p <0.05$) and lower prepulse inhibition than WT mice ($p<0.05$), however this was independent of pretreatment.

Conclusions
These results suggest that chronic adolescent stress, here modelled by glucocorticoid administration, does not cause dopaminergic sensitization, in contrast to the effect of chronic Meth treatment in the same age period. BDNF is involved in the acute behavioural response to Meth treatment as well as prepulse inhibition, but not the effects of chronic Cort or chronic Meth.

Can speech analysis be an objective diagnostic tool for schizophrenia spectrum disorders?

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Background
Speech deficits are an established aspect of schizophrenia spectrum disorders (SSD), and speech analysis is a growing focus in the development of objective clinical tests in psychiatry. This study used two machine learning techniques to explore and identify the speech variables that best differentiated SSD patients and healthy controls (HC).
Methods
43 schizophrenia/schizoaffective disorder patients (M=41.67, SD=9.89) and 46 HCs (M=38.89, SD=14.30) were recorded in general conversation with the interviewer. Recordings were blindly transcribed and language analysis software was used to generate over 100 speech variables of interest (e.g. type-token ratio, number of omitted words, etc). Two machine learning techniques were used for classification: binary logistic regression and a random forest (RF) algorithm, with a 0.8/0.2 training and validation split for both.
Results
The results for logistic regression analysis achieved 72.73% (training) and 90% (validation) sensitivity and 86.11% (training) and 100% (validation) specificity respectively, with only number of utterances with omissions and part-word revisions significantly differentiating the groups. RF analysis confirmed the discriminating utility of these two speech variables and a number of other utterance variables (e.g. omitted words, word repetition), achieving 78.79% (training) and 80% (validation) sensitivity and 94.44% (training) and 90% (validation) specificity respectively.
Conclusions
The findings successfully identified speech variables that best differentiated SSD patients and HCs. The relatively small sample size is augmented by the congruence between two separate analyses and support the utility of speech assessment for classification. Potential future uses include objective and rapid SSD speech screening tools, with promising implications for diagnosis and illness management.

Effect of Maternal Immune Activation and Adolescent Cannabinoid Exposure on Mismatch Negativity in rats

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Background
Mismatch negativity (MMN), an auditory prediction error signal, is reduced in schizophrenia and is linked with cognitive impairments and poor functional outcomes in the disorder. This has led to a strong interest in MMN as a potential clinical and preclinical biomarker of cognitive deficits. Previous studies have shown that rat brain is capable of generating human-like mismatch responses (MMRs). We aimed to determine a) whether manipulations of stimulus condition changes rat MMR as they do for human MMN and b) the effect of risk factors for schizophrenia (maternal immune activation (MIA) and adolescent cannabis exposure (ACE)) on these measures.

Methods
Pregnant dams were exposed to MIA (5 mg/kg Poly I:C at gestational day 19) and the offspring received ACE from postnatal day 35-48 (0.075 - 0.1 mg/kg/day HU-210). MMRs were studied in awake, freely moving male and female Wistar rats using wireless telemetry. Epidural electroencephalographic electrodes were surgically implanted within the skull of adult rats. The effects of three manipulations were examined: the physical difference between the frequency of expected and unexpected stimuli, the probability of the unexpected stimulus, and variability or 'jitter' in the timing of the stimuli.

Results
We found that MMR amplitude was largest in the high deviance difference, low probability and no jitter stimulus conditions and the schizophrenia-like MMR reductions were observed in the low probability condition in Two hit (MIA followed by ACE) male rats.

Conclusions
Interestingly, by employing these new manipulations, we have been able to hone in on the most MMN-like component of the rodent ERP, the N54 component. This is in agreement with the previous research in the lab and it meets other criteria of human MMN, suggesting that this will be a promising avenue for further research. Overall, our findings will improve the reliability of schizophrenia rodent model validation, as we will be able to directly measure the same neurophysiological processes that are altered in schizophrenia patients.

Better than chance: establishing a probabilistic reversal learning task in mice

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Background
Probabilistic reversal learning (PRL) is frequently used to assess abnormalities in reward learning and decision-making. The PRL paradigm examines flexible decision-making following the presentation of two stimuli, where one stimulus is rewarded more frequently than the other. People with schizophrenia often have difficulty navigating these probabilistic contingencies. To investigate the mechanisms underlying these impairments, PRL tasks have been adapted for use in animal models. However, mice often perform at levels only modestly above chance. The aim of this study was to develop an operant protocol for PRL in mice that demonstrated clear above chance performance and high levels of reversals/session.

Methods
32 male C57BL/6JArc mice completed training (3 sub-stages), deterministic reversal learning (DRL) and PRL stages. In the DRL stage, only the correct hole was rewarded (i.e. target rewarded 100% of responses and the non-target 0%). After 6 consecutive correct responses, reward contingencies were reversed (i.e. the target hole became the non-target hole). To progress from the DRL to the PRL stage, mice were required to achieve ≥70% win-stay use over 5 days or ≥80% win-stay use over 3 days. For PRL testing the reward contingencies were altered to 80%:20% (i.e. target rewarded 80% of responses and the non-target 20%).

Results
A primary strategy used to navigate both the DRL and PRL stages, win-stay, occurs when the same hole is selected after a being rewarded on the previous trial. On average, mice progressed to the DRL stage by day 15 (ranging between 9-23 days) and had completed the DRL stage after 23 days (ranging between 14-37 days). In the DRL stage, mice averaged 392 trials and 22 reversals, with 77% win-stay and 57% lose-shift use. In the PRL stage, mice are currently averaging 435 trials and 19 reversals, with 77% win-stay and 51% lose-shift use.

Conclusions
Prior work has suggested that when navigating PRL contingencies, mice tend to perform slightly above chance level for reversal learning (up to 5 reversals over 400 trials). As a consequence, PRL protocols are often simplified to increase reversals and performance. However, our protocol has identified that mice are able to complete reversals well above chance. Moreover, they maintain high win-stay strategy use and adapt lose-shift behaviour as expected when moving from DRL to PRL. The success of this paradigm in mice is an exciting development and has the potential to aid in further understanding cognitive and behavioural deficits in schizophrenia.

Sex-specific schizophrenia-relevant behaviour and contextual fear conditioning generalization in mGluR5 knockout mice

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Background
The glutamatergic system has been widely implicated in the development of psychiatric illnesses, including schizophrenia. Accumulating evidence in humans and animal studies points to N-methyl-D-aspartate receptor (NMDAR) hypofunction as a convergence point for various symptoms, where metabotropic glutamate receptor 5 (mGluR5) plays a crucial role, by being physically linked to NMDAR at the postsynaptic membrane and enhancing NMDAR function. Mice lacking mGluR5 display schizophrenia-like behaviours and have been studied as a model of the disease. However, no one has yet assessed the behavioural differences between males and females thereby considering both heterozygous (HET) and homozygous (HOMO) mGlu5R knockout mice.

Methods
We examined schizophrenia-relevant behaviours in adult (3-4 months of age) wild type-like (WT), heterozygous (HET) and homozygous (HOMO) mGluR5 knockout mice of both sexes. We assessed locomotion, sensorimotor gating, learning and memory (novel object recognition and fear conditioning), and social interaction. We also examined context fear conditioning to assess memory generalization.

Results
HOMO mice of both sexes showed higher locomotion and anxiolytic-like behaviour in the open field. HOMO females exhibited reduced sensorimotor gating compared to WT females. In the fear conditioning cue test, HOMO males showed greater freezing prior to presentation of the fear-associated cue, compared to WT males. When tested for memory generalization, only HOMO mice of both sexes exhibited elevated freezing in a new context, suggesting mGluR5 HOMO mice generalized the fear response. There were no effects of genotype or sex on novel object recognition or social interaction. HET mice of both sexes showed a similar behavioural profile to WTs.

Conclusions
Germline homozygous deletion of mGluR5 modulates schizophrenia-relevant behaviours in a sex-dependent manner, including locomotion and sensorimotor gating. We also established for the first time that mGluR5 HOMO mice of both sexes generalize contextual fear conditioning memory, and this may be related to memory impairment found in humans with schizophrenia. Our results show the importance of analyzing a variety of behavioural domains including cognition in great detail, and also considering sex-specific effects.

Effects of handling on the behavioural phenotype of the neuregulin 1 type III transgenic mouse model for schizophrenia

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Background
Handling of laboratory mice affects animal wellbeing and behavioural test outcomes. However, present research has focused on handling effects in common strains of laboratory mice despite the knowledge that environmental factors can modify established phenotypes of genetic mouse models as well. Thus, we examined the impact of handling on the face validity of a transgenic mouse model for the schizophrenia risk gene neuregulin 1 (i.e. Nrg1 type III overexpression model, i.e. Nrg1 III tg).

Methods
3 month old Nrg1 III tg and wild type-like (WT) control mice of both sexes underwent tail or tunnel handling before being assessed in the open field (OF), elevated plus maze (EPM), social preference/novelty, prepulse inhibition, and fear conditioning tests.

Results
Tunnel-handling reduced the startle response in all mice, increased OF locomotion and exploration in males and reduced anxiety in males (OF) and females (EPM) compared to tail-handling. Importantly, tunnel handled Nrg1 III tg females exhibited a more pronounced startle response to increasing startle stimuli compared to respective control females, a phenomenon absent in tail-handled females. Furthermore, Nrg1 III tg males displayed reduced OF exploration and centre locomotion and Nrg1 III tg females displayed increased cue freezing over time compared to WT mice of the same sex.

Conclusions
Handling methods have a significant impact on a variety of behavioural domains thus the impact of routine handling procedures need be considered when testing behavioural phenotypes. Handling did not modify the main schizophrenia-relevant characteristics of Nrg1 III tg mice but affected the acoustic startle-response in a genotype- and sex-specific manner. Future research should evaluate the effect of handling on other genetic models.

Childhood trauma, schizotypy and subcortical grey matter volume: An ENIGMA mega-analysis

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Background
Childhood trauma is a risk factor for psychotic disorders and is associated with increased schizotypal traits in the general population as well as morphological brain aberrations. Childhood trauma exposure may also interact with dimensions of schizotypy to impact brain morphology. However, methodological differences among previous studies have precluded understanding of these relationships. This mega-analysis from the ENIGMA Schizotypy Working Group aimed to determine if the severity of childhood trauma exposure moderates relationships between schizotypal personality dimensions and regional brain morphology.

Methods
A total of 1,081 healthy participants from seven sites worldwide were included. Schizotypal personality dimensions (total score, and Cognitive-Perceptual, Interpersonal, Disorganised dimensions) were measured using the Schizotypal Personality Questionnaire Brief version (SPQ-B), and severity of trauma exposure using the Childhood Trauma Questionnaire (CTQ). Indices of subcortical grey matter volume (n=16 regions for interest, ROI) were extracted from T1-weighted brain MRI scans processed using FreeSurfer at each site. A series of multiple linear regressions examined the main and interactive effects of schizotypy and trauma on volumes of each ROI (age, sex, site, and total intracranial volume entered as covariates).

Results
The interaction between both SPQ total score (p=0.010) and Cognitive-Perceptual dimension (p=0.002), and CTQ total score were significantly associated with right putamen volume. Moderation analysis indicated that larger putamen volume was associated with increased SPQ Cognitive-Perceptual scores (but not SPQ total scores) only in individuals exposed to low levels of trauma (p=0.012). The interaction between SPQ Disorganised dimension and CTQ total score was significantly associated with left caudate volume (p=0.006); higher SPQ Disorganised scores were associated with larger left caudate volume among those exposed to low levels of trauma only (p=0.033).

Conclusions
Using a large cohort of healthy individuals for whom childhood trauma and schizotypy were assessed with identical measures, these results indicate that higher schizotypal Cognitive-Perceptual traits are associated with larger putamen volume, and that higher Disorganised traits are associated with larger left caudate volume. Importantly, these findings were evident only in individuals exposed to low levels of childhood trauma, and may thus represent brain abnormalities associated with these dimensions of schizotypy unconfounded by childhood trauma.

2.1 Psychoses

2.1.2 Schizophrenia: Physiological Phenotype

Comprehensive integrative analyses identify causal variants and genes associated with schizophrenia using RNA guided genome editing

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Background
Schizophrenia and related psychotic disorders are among the world's most debilitating brain diseases. Despite having a significant heritability, the syndrome's complexity and polygenic architecture has made genetic association challenging. While the Psychiatric Genomics Consortium (PGC) now provides very strong clues to the location of genetically significant variation affecting the regulation and composition of cellular componentry, we now need to uncover variants which modulate processes including gene expression. This study aims to identify the altered gene, their causal mutations and characterize their biological influence in schizophrenia using genome editing approaches (CRISPR).

Methods
To specifically identify the causal mutations and to characterize their biological influence on schizophrenia, this project combined bioinformatics and functional genomics with innovations in cell biology and genome editing. The summary statistics from the large schizophrenia GWAS (PGC) and brain eQTLs data from GTEx were integrated using a range of approaches. These candidates then were ranked before being specifically modified within human cell models (such as SH-SY5Y cell line) using the RNA-guided genome editing technique known as CRISPR.

Results
My bioinformatic analyses combined several approaches to prioritise candidate genes and their putative causal variants. This including the top 16 prioritized genes among undifferentiated loci with high likelihood of functional variants contributing risk for schizophrenia. I prioritised candidate SNPs which are most likely to modulate eQTLs after in vitro analysis through CRISPR/Cas9 gene editing. In this stage, I targeted the most significant genes including PCCB, SF3B1, SNX19, PITPNM2 and ITHI4 as they showed the most significant association with schizophrenia compared to other than genes located in the same locus.

Conclusions
This analysis suggests there are several gene candidates among undifferentiated loci with high likelihood of functional variants contributing risk for schizophrenia. To further validate these candidates, we are now using RNA-guided genome editing (CRISPR) to generate isogenic cell lines for and allelic expression analysis in vitro.

Adult EDiPS animals show subtle abnormalities in baseline dopamine levels, and in amphetamine-induced behaviours

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Background
The EDiPS (Enhanced Dopamine in Prodromal Schizophrenia) model is designed to recapitulate a key finding in patients with schizophrenia; increased synthesis and release of dopamine in the dorsal striatum. We have already shown that EDiPS animals release more dopamine in the dorsal striatum following amphetamine administration. Since patients also show an increase in baseline synaptic dopamine levels, we wanted to assess whether, as predicted, baseline extracellular dopamine levels are increased in EDiPS animals. We further probed pre-synaptic striatal dopamine in EDiPS animals using a stereotypy-inducing dose of amphetamine. Stereotyped behaviours are associated with dopamine release in the dorsal striatum.

Methods
EDiPS animals were generated by injecting a construct coding for tyrosine hydroxylase and GTP cyclohydrolase 1 into the pars compacta of juvenile (P35) rats. These enzymes are transported to the dorsal striatum, where they increase dopamine synthesis capacity. We measured baseline extracellular dopamine in adult EDiPS animals using no-net flux microdialysis. We assessed potassium-induced dopamine release during the same microdialysis procedure. In a separate cohort of animals, we examined the behavioural response to 5mg/kg amphetamine. Locomotion was quantified automatically using Ethovision software, however stereotyped behaviours were scored manually throughout two 10-minute bins at 30-40- and 60-70-minutes following amphetamine administration.

Results
Unexpectedly, we found that mean levels of baseline extracellular dopamine were unaltered in EDiPS animals compared to control animals ($p=0.66$). However, we did find that EDiPS animals have increased variability in baseline dopamine levels compared to controls ($p=0.013$). We confirmed that potassium-induced dopamine release is normal in EDiPS animals ($p=0.52$), with no difference in variability between groups for this measure ($p=0.63$). Although we found no significant difference in overall stereotyped behaviours following 5mg/kg amphetamine, EDiPS animals did show significantly decreased locomotion compared to controls ($p=0.0061$). We may have been underpowered to a difference in stereotyped behaviours in EDiPS animals.

Conclusions
Although no overall differences in stereotypies was evident, there are indications that the response of EDiPS animals to 5mg/kg amphetamine is abnormal. Baseline dopamine levels are normal in EDiPS animals, which may suggest that the molecular mechanisms which normally regulate dopamine synthesis have been recruited. However, the increased variability for baseline dopamine in EDiPS animals may reflect considerable inter-animal differences in how well these mechanisms are recruited. Interestingly, an increase in variability for synaptic dopamine has also been seen in patients with schizophrenia. Therefore, the EDiPS model may be crucial to understanding this aspect of the dopaminergic dysfunction in patients.

Differential expression of estrogen receptor, dopamine-related and pro-inflammatory cytokine transcripts in the male rat brain

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Background
Dopamine dysregulation is involved in cognitive deficits and psychosis in schizophrenia. Estrogen receptor modulation can attenuate psychosis and improve cognition. Neuroinflammation is identified in many brain regions in schizophrenia, including the midbrain and cortex. To understand the propensity for different brain regions of the mesocortical, mesolimbic and nigrostriatal dopaminergic pathways to respond to estrogens and alter pro-inflammatory signals, we examined dopamine-, estrogen-, and inflammatory-related gene expression in five brain regions in normal male rats. We hypothesised that gene expression of these molecules would be differentially expressed across the dopamine cell bodies and dopamine terminal regions investigated.

Methods
Tissue was collected from adult male Sprague-Dawley rats (n=11-14/group) at postnatal day 88 from prefrontal cortex (PFC), dorsal striatum (DS), ventral striatum (VS), substantia nigra (SN), and ventral tegmental area (VTA). Dopamine receptor (Drd2s, Drd2l, Drd1, and Drd3), estrogen receptor alpha (ERa) and beta (ERB) and IL-6, TNF, and IL-1beta transcripts were measured using quantitative PCR. mRNA levels were normalised to an internal control and the geomean of four housekeepers using the delta-delta Ct method. Data was analysed using one-way ANOVA and Bonferroni post-hoc tests.

Results
All transcripts were differentially expressed across the five brain regions. As expected, Drd1, Drd2s and Drd2l mRNAs were most highly expressed in DS, followed by VS, relative to PFC, SN, and VTA [$F(4,61\text{-}62)=131.6\text{-}360.7$, $p<0.0001$]. Drd3 was most highly expressed in the VS [$F(4,61)=207.6$, $p<0.0001$]. ERa mRNA levels were highest in the VTA compared to all other brain regions [$F(4,62)=32.9$, $p<0.0001$], whereas ERB mRNA levels were highest in SN and VTA compared to PFC, VS and DS [$F(4,61)=50.0$, $p<0.0001$]. Pro-inflammatory cytokine transcript levels were highest in midbrain regions (either the SN or VTA), compared to VS, DS and PFC [$F(4,61\text{-}63)=6.8\text{-}22.8$, $p<0.0001$].

Conclusions
For the first time, we show differential gene expression of multiple transcripts across key dopaminergic regions of male rat brain. ER mRNAs were most highly expressed in the midbrain and dopamine receptor mRNAs in the striatum. Of the regions examined, pro-inflammatory transcripts were most highly expressed in the midbrain, and thus the midbrain may be particularly sensitive to inflammatory stimuli and neuroinflammation-induced damage under pathological conditions. These data suggest the midbrain, the main locus of dopamine cell bodies, is poised to respond robustly to estrogen-based therapies including raloxifene, and thus be a locus for modulation of dopamine-related behaviour and cognition.

The betacellulin knock-out mouse: Behavioural characterisation of a novel model with relevance to schizophrenia

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Background
Clozapine uniquely relieves psychotic symptoms in 30-50% of treatment resistant (TR) schizophrenia patients, however, the underlying mechanism remains unclear and given its severe side effects, alternative treatment options are needed. Our body of work indicates that clozapine may augment signalling through the epidermal growth factor (EGF) system. Betacellulin (BTC) is a protein of this system and is markedly decreased in SZ patients, particularly in the TR subpopulation; and in SZ patients with severe cognitive impairment, suggesting its important role in these aspects of schizophrenia.

Methods
Here, we characterized adult BTC KO mice using a behavioural battery of tests to measure short-term memory, social recognition, anxiety, and locomotor activity. To investigate whether BTC interferes with the dopaminergic or the glutamatergic system, mice were challenged with a single i.p. injection of either the dopamine releaser, amphetamine (5mg/kg), or the glutamatergic antagonist, MK-801 (0.25mg/kg) during the locomotor test.

Results
Both male and female BTC KO mice showed an increased startle response to an auditory stimulus and an anxiety-like phenotype as compared to controls. While MK-801 induced hyper-locomotion in all female mice, male BTC KO did not respond to MK-801 as opposed to their WT littermates. Conversely, female BTC KO mice showed a diminished response to amphetamine on locomotion as compared to controls, while no difference was seen in male mice. This suggests that BTC may play a significant role in the glutamatergic signalling in males, while it appears to be crucial for the dopaminergic signalling in females.

Conclusions
Our results show for the first time that BTC regulates specific behavioural domains with relevance to SZ in a sex specific manner and BTC KO mouse may represent a new model relevant to treatment resistant SZ, enabling the investigation of more targeted treatment options for this debilitating mental illness.

A 1H MRS study investigating the relationships between cortical GSH and Cognition and Negative Symptoms in Chronic Schizophrenia

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Background
Evidence suggests that the major intracellular antioxidant glutathione (GSH) may be reduced in schizophrenia, potentially contributing to the pathophysiology of the disorder. The present study aimed to investigate whether cortical GSH concentrations derived from proton magnetic resonance spectroscopy (1H MRS) were altered in a homogenous group of chronic, treatment-resistant schizophrenia participants. In addition, we explored correlations between cortical GSH concentrations, and both cognition and negative symptoms.

Methods
15 chronic schizophrenia participants and 12 age- and gender-matched healthy controls took part in the study. Levels of GSH were obtained through a 30x30x30mm voxel placed in the occipital lobe, positioned using an axial T1-weighted gradient-echo image. A long echo (TE=131) acquisition MEGA-PRESS pulse sequence was performed using a Siemens scanner at 3T (TR=2000ms). Spectral processing was performed using jMRUI. Clinical variables were assessed through the positive and negative syndrome scale (PANSS) and the scale for the assessment of negative symptoms (SANS). Cognitive performance was measured using the MATRICS consensus cognitive battery (MCCB).

Results
Cortical GSH concentration was not different between individuals with schizophrenia and HCs $F(1,25)=0.00$, $p=0.997$. Additionally, there were no significant associations between negative symptoms or cognition and cortical GSH concentrations.

Conclusions
Given all schizophrenia participants had chronic and treatment-resistant residual symptoms, the findings of no difference in GSH concentrations from the present study are particularly pertinent. A number of possible reasons for this finding are discussed, including the suggestion that oxidative stress in schizophrenia may arise from peripheral GSH abnormalities.

Microbiome profiling reveals gut dysbiosis in the metabotropic glutamate receptor 5 knockout mouse model of schizophrenia

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Background
Schizophrenia (SZ) is a psychiatric disorder that constitutes one of the top 10 global causes of disability. More recently a potential pathogenic role for the gut microbial community (microbiota) has been highlighted, with numerous studies describing dysregulated microbial profiles in SZ patients when compared to healthy controls. However, no animal model of SZ has previously recapitulated the gut dysbiosis observed clinically.
Methods
Since the metabotropic glutamate receptor 5 (mGlu5) knockout mouse is a preclinical model of SZ with strong face and predictive validity, in the present study we performed gut microbiome profiling of mGlu5 knockout (KO) and wild-type (WT) mice by 16S rRNA sequencing of bacterial genomic DNA from fecal samples.
Results
We found a significant genotype difference in microbial beta diversity and in the relative abundance of Verrucomicrobiaceae, Bacteroidaceae and Erysipelotrichaceae families in this mouse model of SZ. We also identified a signature of bacteria discriminating both genotypes (KO and WT), consisting of the Erysipelotrichales, Bacteroidales and Clostridiales orders. We thus uncovered an imbalance in the gut microbiota profile between mGlu5 KO and WT mice, outlining the first evidence for gut dysbiosis in a genetic animal model of SZ.
Conclusions
Our findings suggest that this widely used preclinical model of SZ also has substantial utility for investigations of gut dysbiosis, and associated signalling via the microbiota-gut-brain axis, as potential modulators of SZ pathogenesis. Our discovery opens up new avenues to explore gut dysbiosis and its proposed links to brain dysfunction in SZ, as well as novel therapeutic approaches to this devastating disorder.

Kynurenine pathway enzymes and increased astrocyte presence in midbrain of people with schizophrenia

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Background
The kynurenine pathway (KP), important in immune system regulation, produces neuroactive metabolites implicated in schizophrenia pathophysiology. The KP metabolite kynurenic acid and mRNAs encoding KP enzymes, tryptophan 2,3-diooxygenase (TDO2), kynurenine aminotransferases II (KAT II) are elevated and kynurenine 3-monooxygenase (KMO) decreased in schizophrenia cortex. We previously identified inflammation in the midbrain of people with schizophrenia that may contribute to dopamine dysregulation. The extent to which gene expression of KP enzymes in the midbrain in schizophrenia may be altered is unknown. We aimed to determine KP transcript levels and their relationship with cytokine and glial cell transcripts in the schizophrenia midbrain.

Methods
A matched cohort of 29 healthy control and 28 schizophrenia midbrain samples was used for these studies. The cohort was previously clustered by immune biotype producing low inflammation/control (n=29), low inflammation/schizophrenia (n=15), and high inflammation/schizophrenia (n=13) subgroups. We performed qRT-PCR to assess KP enzyme mRNAs (TDO, KATI, KATII, KMO) and in situ hybridisation of the astrocyte marker GFAP mRNA to determine astrocyte expression. Western blot was performed to measure GFAP protein (4 bands detected). Group differences were assessed by ANOVA or ANCOVA. Relationships between cytokine, glial and KP enzyme gene expression was explored with multiple regression analyses.

Results
Only TDO2 mRNA significantly differed between inflammatory groups, with the greatest difference exhibited between high and low inflammation schizophrenia subgroups ($p=0.043$). GFAP mRNA was elevated in high inflammatory schizophrenia substantia nigra ($p=0.002$). Total GFAP protein was increased by 37% in schizophrenia compared to control cases ($p=0.05$). Increased IL-1B and IL-6 mRNA levels predicted higher TDO2 mRNA in high inflammation/schizophrenia subgroup ($p<0.01$). Higher KMO and TDO2 mRNAs predicted greater GFAP mRNA levels ($p<0.001$) in schizophrenia. In the high inflammation/schizophrenia subgroup, KMO mRNA positively and KAT I mRNA negatively related to GFAP mRNA ($p<0.001$).

Conclusions
Our finding of increased GFAP mRNA and protein points to astrogliosis, a sign of neuronal damage, suggesting a higher state of astrocytic reactivity, particularly in the substantia nigra where the majority of dopamine neurons are located. Our results suggest that in the midbrain, the normal functions of TDO, KAT 1 and KAT II enzymes necessary for kynurenine and kynurenic acid syntheses, may be altered by reactive astrocytes and pro-inflammatory cytokines, further exacerbating dopamine dysregulation.

Differential Expression and Editing of Small Non-Coding RNAs in Lymphocytes of Individuals with Schizophrenia

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Background
Schizophrenia (SZ) is a debilitating, complex and heterogeneous neuropsychiatric disorder associated with a combination of genetic and environmental factors. Dysregulation of short non-coding microRNA (miRNA) and associated miRNA-mRNA interactions has recently been identified in individuals with the disorder, however other classes of short non-coding RNAs (sncRNAs) remain poorly characterised. Alteration of RNA editing has additionally emerged as a potential causal factor in SZ neuropathology, however it is unclear whether this affects sncRNAs. In the current study, we aimed to characterise patterns of sncRNA differential expression associated with SZ and examine whether these RNAs are subjected to differential RNA editing.

Methods
We collected peripheral blood mononuclear cell (PBMS) tissue from a cohort of 15 healthy controls (7 males, 8 females) and 36 age-matched SZ-affected individuals (18 males, 18 females) obtained from the Australian Schizophrenia Research Bank. Total RNA was extracted and subjected to small RNA sequencing (BGI). Expression of sncRNAs and sequence mismatches were analysed via the small non-coding RNA annotation pipeline optimized for rRNA and tRNA-derived small RNA tool, which was utilized for sequential alignment of sncRNA fragments to rRNA, tRNA, miRNA, snoRNA, snRNA and piRNA. Differential expression of sncRNAs was determined using EdgeR.

Results
Comparison of control and SZ samples revealed significant differential expression of sncRNA fragments derived from 15 tRNAs, 3 mitochondrial tRNAs, 7 snoRNAs, 1 piRNA, 1 YRNA and 19 miRNAs (FDR < 0.1). When stratified for sex, a further 47 tRNAs, 6 snoRNAs, 1 YRNA and 10 miRNAs were differentially expressed amongst males, whereas females showed no significant changes. Analysis of sncRNA sequence mismatches revealed that males with SZ exhibited significantly lower mismatch rates for tRNA-derived small RNA fragments compared to controls (FDR1 mismatch = 0.0002, FDR ≤ 2 mismatches = 0.0883), which affected fragments derived from the 5´ and 3´ ends equally.

Conclusions
These results indicate that in addition to miRNAs, sncRNA fragments derived from tRNAs, snoRNAs, piRNAs and YRNAs are subjected to differential expression in the periphery of individuals with SZ, while editing of tRNAs also appears to be decreased. Furthermore, our findings suggest SZ-associated sncRNA expression and editing is subjected to considerable sexual dimorphism, with males predominantly affected. We consequently suspect alteration of sncRNA expression and editing could substantially disrupt temporospatial gene regulation in SZ, and may subsequently contribute to pathophysiology of the disorder.

Polygenic risk score for schizophrenia moderates the effects of childhood trauma on schizotypy across the health-psychosis spectrum

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Background
Cognitive and behavioural expressions of psychosis risk in the general population, referred to as schizotypy, may be relevant to the development of a range of clinical disorders with psychotic features. Recent evidence shows that both genetic and environmental risk factors for psychotic disorders are associated with increased schizotypy in the general population. However, little is known about the interactive effect of genetic and environmental risk factors on schizotypal expression across the psychosis spectrum.

Methods
Participants were 56 individuals with schizophrenia, 61 individuals with bipolar disorder, and 51 healthy individuals. Schizotypy was measured using the Schizotypal Personality Questionnaire (SPQ) with analyses conducted separately for the total SPQ score, and each of the SPQ Cognitive-Perceptual, SPQ Interpersonal, and SPQ Disorganised dimensions. Childhood trauma exposure was measured with the Childhood Trauma Questionnaire (CTQ total score), summed to index trauma severity. Polygenic risk scores (PRS) for schizophrenia were calculated for all participants using effect sizes from genome-wide association studies (GWAS) of schizophrenia reported by the Psychiatric Genomics Consortium.

Results
A series of multiple linear regression models, with age, sex and population stratification included as covariates showed that childhood trauma was associated with greater expression of all dimensions of schizotypy. Moderation analyses showed that the PRS was a significant moderator of the association between childhood trauma and interpersonal and disorganised schizotypy. In particular, increased severity of childhood trauma exposure was associated with increased scores on these two dimensions of schizotypy in individuals with low or average PRS for schizophrenia, but not in individuals with high PRS for schizophrenia.

Conclusions
Increasing severity of childhood trauma exposure was associated with higher schizotypy scores among all individuals across the health and psychosis spectrum. However, the strength of this relationship was dependent on an individual's genetic risk for schizophrenia: stronger associations between trauma and the interpersonal and disorganised dimensions of schizotypy in individuals with low to average genetic loadings for schizophrenia suggests that these features of schizotypy may be less genetically influenced among those with a history of trauma.

BDNF and TrkB splice variants are altered in post-mortem midbrain in schizophrenia and exacerbated by inflammation

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Background
Subcortical hyperdopaminergia likely underlies psychosis in schizophrenia. Elevated pro-inflammatory markers (SERPINA3, IL6, IL1, TNF) found in the midbrain of ~50% of schizophrenia cases may damage dopamine neurons. Dopamine neurons are not considered to be lost in schizophrenia, suggesting trophic factors such as Brain-Derived Neurotrophic Factor (BDNF), signaling via the full-length Tropomyosin kinase B receptor (TrkBTK+), may promote dopamine neuron survival. However, BDNF binding to the truncated receptor (TrkBTK-) on glial cells diverts trophic support away from neurons. We hypothesised that BDNF and TrkB gene expression would be altered in the schizophrenia midbrain and be exacerbated in inflammatory states.

Methods
BDNF (exon IV), TrkBTK+ and TrkBTK- mRNA levels were quantified by qPCR in post-mortem midbrain tissue (28 control/28 schizophrenia) from the NSW Brain Tissue Resource Centre. TrkBTK+ localization was visualized using in situ hybridization (20 control/10 schizophrenia from the Clinical Brain Disorders Branch). Gene expression was analysed by diagnosis and by previously assigned high/low inflammation biotypes. Relationships between BDNF, TrkBTK+ and TrkBTK- mRNA levels with a previously published marker for dopamine synthesis (TH mRNA) and an indicator of neuropathology pertaining to astrocytosis (GFAP mRNA) were assessed using correlation analyses in the entire cohort and separately in each diagnostic group.

Results
Gene expression of BDNF IV (31%) and TrkBTK+ (19%) was significantly reduced, while TrkBTK- (29%) mRNA levels were increased in the midbrain of schizophrenia cases compared to controls ($p<0.05$). Schizophrenia cases with a high inflammation biotype displayed the greatest magnitude of alterations in BDNF IV, TrkBTK+ and TrkBTK- mRNA levels compared to low inflammatory controls ($p<0.05$). TH mRNA was significantly positively correlated with both BDNF ($r=0.535$) and TrkBTK+ ($r=0.393$) gene expression (both $p<0.05$); while, TrkBTK- was positively correlated with GFAP mRNA expression ($r=0.523$, $p<0.01$) in the entire cohort.

Conclusions
Our study provides the first evidence for altered BDNF and TrkB gene expression in the schizophrenia midbrain, which are augmented by elevated inflammatory markers. These alterations do not reflect the hypothesized elevated trophic support to overcome damage by neuroinflammation; instead, the lack of trophic support may further diminish the health of dopamine neurons, known to be dysregulated in schizophrenia. Future work will quantify midbrain dopamine neurons in schizophrenia as a measure of the consequence of downregulated trophic and upregulated inflammatory pathways. Overall, heightened overlapping neuropathologies of inflammation and reduced trophic support imply unhealthy midbrain dopamine neuron status in schizophrenia.

Chemogenetic activation of dorsal and ventral striatal pathways differentially impairs goal-directed action in mice

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Background
Symptoms of schizophrenia include impaired motivation and cognitive deficits, and one of the most robust pathophysiological findings is increased dorsomedial striatal dopamine (DA) neurotransmission. The dorsomedial striatum is involved with the coordination of motor and action-planning, decision-making and reward learning, and dopamine is known to modulate a number of cognitive processes. This study aimed to examine the effects of chemogenetic activation of the dorsal and ventral dopaminergic striatal pathways, to unpick their differing roles on reward learning and goal-directed action in mice using the Outcome-specific Devaluation Task (ODT).
Methods
Excitatory DREADDs were expressed in two different striatal pathways in adult C57BL/6J mice, one projecting from the substantia nigra to the dorsomedial striatum (SN-DMS) and the other from the ventral tegmental area to the nucleus accumbens (VTA-ACB). Surgery was completed prior to training on the ODT, where mice learned two sets of action-outcome associations via instrumental training. Post-training, one of the outcomes was devalued and mice then had to make a choice between two competing actions, allowing for the exploration of goal-directed behaviour. DREADDS were activated with CNO at different timepoints during testing to differentiate learning from decision-making processes.
Results
Initially, DREADDs were activated during instrumental training but not during the choice and value tests. Activation of both the SN-DMS and VTA-ACB pathways impaired goal-directed action (preference bias during the choice test). This suggests that elevated striatal DA impairs the ability to form appropriate action-outcome associations to guide choice. Animals were then retrained on the instrumental contingencies (i.e. action-outcome associations) without activation, followed by the choice and value tests with DREADDs activation. VTA-ACB activation, during choice testing, impaired goal-directed action while SN-DMS activation did not. Reward valuation processing was not affected under any condition.
Conclusions
We suggest that in line with the pathophysiological findings in schizophrenia, elevated DA in the DMS disrupts associative learning resulting in action selection impairments. While elevated DA in the ACB may disrupt the encoding of the motivational values of a reward to guide choice, whether it be during learning or during action selection itself. Identifying the underlying neurobiology that contributes to these functional impairments will help to identify approaches to improve the quality of life of those living with schizophrenia.

miRNA binding site variation is associated with psychiatric disorders

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Background
Small, non-coding RNAs known as microRNA (miRNA) are thought to contribute to the pathophysiology of psychiatric disorders such as schizophrenia. Evidence for their involvement comes from both gene expression studies and genome-wide association studies: several miRNAs have been observed to be consistently differentially expressed in the brain and periphery between healthy and affected individuals; and one of the most significant genetic associations with schizophrenia is located within the MIR137 locus. However, not much is known about the impact common variation within miRNA binding sites has on disease.

Methods
We utilised the miRNA target site database (dbMTS) for variant annotation and obtained publicly available GWAS summary statistics to identify potential miRNA binding site variants (MBSVs) associated with nine psychiatric disorders: schizophrenia, bipolar disorder, depression, autism, PTSD, ADHD, anorexia, OCD and Tourette's syndrome. We compared the distribution of p-values for MBSVs to that of all variants using the Kolmogorov-Smirnov test. We also assessed enrichment of genome-wide associated MBSVs using Fisher's exact test. MAGMA was used to investigate association of MBSV-affected gene sets with each disorder, and meta-analysis was performed to assess joint gene set association across all nine psychiatric disorders.

Results
We observed a significant five- and six-fold enrichment of genome-wide associated MBSVs in SCZ and MDD, and a genome-wide significant association of MBSVs following p-value aggregation. Analysis of specific miRNA families revealed genome-wide significant associations of miR-335-5p, miR-21-5p, miR-361-5p and miR-577 in both SCZ and MDD, and a suggestive association ($p = 7.3x10-8$) for the miR-132-3p/212-3p family with SCZ. We also identified a significant relationship between reduced miR-132-3p/212-3p binding affinity and SCZ risk. Gene-set association of MBSV affected genes using MAGMA revealed a significant association of genes involved in synaptic protein localisation in a meta-analysis of all psychiatric disorders.

Conclusions
These results suggest that MBSVs are functionally significant variants that may contribute to psychiatric disorders, particularly SCZ and MDD. We also found supporting evidence for a relationship between reduced miR-132-3p/212-3p function and SCZ risk. The gene set association results further suggest that MBSVs may affect protein localisation to the synapse in psychiatric disorders. Thus, the results of this study warrant further investigation into the neurobiological impact of MBSVs on gene networks and disease pathophysiology.

mRNA Destruction in Dendrites Regulates Synaptic Plasticity and Schizophrenia-Related Behavior

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Background
Synaptic plasticity requires a tight control of mRNA levels in dendrites. Specifically, mRNAs are actively translated and degraded to modulate the local synthesis of proteins which enable adaptive plasticity. The Nonsense-Mediated mRNA Decay pathway (NMD) regulates mRNA degradation, and has been recently associated with neuropsychiatric diseases (e.g. schizophrenia) in GWAS studies. In particular, this comprises association with Up-Frameshift factors such as UPF2, however the functionality of these factors in neurons remains unknown. Therefore, the role of NMD in neuronal physiology has remained an almost completely unexplored regulatory mechanism for synaptic deficits related to brain disorders such as schizophrenia.

Methods
To access neuronal compartments of pre- and post-synaptic neurons (e.g. dendrites vs axons and cell-bodies), we custom fabricated microfluidic devices in a nano-biomaterials lab. To induce disruption of the NMD pathway and monitor outcomes, we utilized various methods including conditional genetics (UPF2fl/fl; αCaMKII:CreERT2) for mouse and behavioral experiments, viral manipulations for in vitro manipulation of NMD (UPF2:GFP-shRNA lentivirus), electrophysiology (patch clamping for E-LTP, L-LTP, LTD), FISH for mRNA localization in dendrites, CLICK-Chemistry to monitor dendritic protein synthesis, receptor internalization assays, as well as spine assays to examine the effects of chemical manipulations on structural plasticity.

Results
We discovered that neuron- specific disruption of UPF2, an NMD component, in adulthood attenuates learning, memory, hippocampal spine density, and hippocampal synaptic plasticity (L-LTP via patch clamping) in mice. Utilizing microfluidic devices, we identified that the NMD pathway operates within dendrites to specifically regulate GLUR1 surface levels via increased internalization and altered dendritic protein synthesis of GLUR1. Utilizing viruses, siRNAs and microfluidics to achieve post-synaptic knockdown of NMD targets, we mechanistically determined that co-regulation of endogenous NMD mRNA targets (Arc and Prkag3 mRNAs) in dendrites rescued surface GLUR1 expression and rescued the spine density of NMD-deficient hippocampal neurons in vivo.

Conclusions
We describe the first mechanisms for how NMD factors identified in GWAS likely contribute to schizophrenia risk at the synaptic level. In controlled experiments within microfluidic devices, we could isolate individual neuronal compartments (e.g. dendrites) to identify and biochemically manipulate physiological mRNAs undergoing degradation. This allowed us to determine how the NMD pathway regulates neuronal GLUR1 signaling and spine density. Specifically, we found that the NMD pathway operates in dendrites to specifically regulate synaptic plasticity and cognition by modulating local GLUR1 internalization and synthesis. Our work therefore explains the physiological role of mRNA destruction and its potential role in schizophrenia.

Dysregulation of glucocorticoid stress signalling transcripts in the midbrain in schizophrenia

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Background
Stress and inflammation are known risk factors for schizophrenia. Psychosocial stress can increase striatal dopamine release, consistent with a role for subcortical hyperdopaminergia in schizophrenia pathophysiology. Increased dopamine neurotransmission is also associated with greater levels of oxidative stress and neuroinflammation, which may exacerbate dopamine dysregulation in the midbrain in schizophrenia. However, it is not known whether molecular abnormalities in glucocorticoid receptor (GR)-mediated stress signalling occur in the midbrain in people with schizophrenia. We therefore investigated whether alterations in stress-responsive genes in the midbrain would correspond with a state of chronic stress, indicated by impaired stress responsivity, in people with schizophrenia.
Methods
To identify whether a molecular signature consistent with a state of chronic stress exists within the midbrain in schizophrenia, we compared the mRNA expression of the key stress signalling molecules GR, mineralocorticoid receptor (MR/NR3C2), and GR co-factors FK506-binding protein 51 (FKBP51/FKBP5) and 52 (FKBP52/FKBP4) in the post-mortem midbrain between 28 people with schizophrenia and 28 controls using qRT-PCR. We then assessed the extent to which alterations in these mRNA transcripts were related to, or distinct from, increased neuroinflammation previously identified in the midbrain in ~46% of people with schizophrenia.
Results
We found a robust increase in FKBP5 and a modest decrease in FKBP4 mRNA expression in the midbrain in schizophrenia relative to controls (154.77% [$p<0.0001$ and 11.43% [$p<0.05$]). FKBP5 mRNA expression was increased in high inflammation schizophrenia relative to controls (310.37%, $p<0.0001$) and low inflammation schizophrenia (151.37%, $p<0.0001$). There was a trend overall effect for GR mRNA expression and planned post-hoc comparisons revealed a decrease in GR mRNA expression in high compared to low inflammation schizophrenia (20.39%, $p<0.05$). We found no effect of diagnosis or inflammation on MR mRNA expression.
Conclusions
We show, for the first time, alterations in glucocorticoid-mediated stress signalling in the midbrain in schizophrenia consistent with a state of chronic stress. Our findings suggest overexpression of FKBP5 mRNA may be associated with impaired negative feedback of the stress hormone response in people with schizophrenia, particularly in those who also exhibit high levels of neuroinflammation. Decreased FKBP4 mRNA expression may also contribute to impaired stress-responsivity in schizophrenia, though this appears to occur in the absence of neuroinflammation. Future work will determine whether stress-induced changes in dopamine neurotransmission are concomitant with alterations in stress-responsive genes in the midbrain in schizophrenia.

Alterations in synaptic architecture in an animal model of relevance to schizophrenia; EDiPS (Enhanced Dopamine in Prodromal Schizophrenia) prevents dysregulation of markers of cognitive function during antipsychotic drug treatment in rats

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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 been successful in developing a novel animal model of relevance to schizophrenia termed as EDiPS (Enhanced Dopamine in Prodromal Schizophrenia). Using this model, the major aim of this study is to explore if, increased DA synthesis capacity in EDiPS has altered architecture of high probability dopamine release sites in the striatum.

Methods
EDiPS rats were produced using an AAV vector containing human-tyrosine hydroxylase (Hu-TH) and human-GTP-Cyclo-Hydrolase-1 (HuGCH-1) in rat substantia-nigra, whereas controls received only HuGCH-1. Six-week post-viral delivery, brains were harvested and fixed. Paraffin processed striatal-tissues were sectioned at 10µm using a microtome. Immunostaining for TH, a presynaptic marker Bassoon, and a postsynaptic marker PSD95 was done. Bassoon within TH axons are defined as sites of high probability dopamine release, and PSD95 located within 600nm from Bassoon (within TH) is defined as an activated DA synapse. Images were captured using confocal microscope, deconvolved using Huygens-Professional, and synaptic components were analysed using Imaris.

Results
We selected four regions to compare synaptic elements between control and EDiPS. Two regions in dorsal striatum (medial and lateral) and two regions in nucleus accumbens (shell and core). MANOVA analysis showed no interactions between striatal sub-regions and groups. However, the analysis also indicated an overall effect of EDiPS, increasing the number of TH surfaces ($F=4.396$, $p=0.041$, $n=7$), number of high probability DA release sites ($F=7.552$, $p=0.008$, $n=7$) and activated dopamine synapses ($F=4.927$, $p=0.031$, $n=7$).

Conclusions
EDiPS is a robust model recapitulating the clinical finding of increased DA synthesis and release in schizophrenia. As expected TH surfaces were elevated. Perhaps more importantly there was also an increase in DA release sites and DA-related synapses across the striatum however there was no regional selectivity. This indicates that whilst the current EDiPs construct alters striatal synaptic architecture this was not selective for the dorsal striatum as expected. Future studies using a more nigral specific EDiPS construct are now warranted.

Schizophrenia gene and gene-set associations shared with other psychiatric disorders and their implications for precision drug repurposing

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Background
Schizophrenia displays significant genetic correlation with several other psychiatric disorders, which supports the observed overlaps in clinical presentation. However, the biological underpinnings of this shared genetic architecture require further exploration. We believe that genes and pathways which display pleiotropy amongst psychiatric phenotypes may be particularly biologically salient, and this could have implications for the future treatment of schizophrenia.

Methods
We utilised a multimarker approach to identify overlapping gene-based associations between schizophrenia and seven additional psychiatric disorders. A transcriptome-wide association study (TWAS) using SNP weights from brain and blood was then leveraged to refine the biological mechanisms of shared schizophrenia genes. Furthermore, a pairwise meta-analysis of schizophrenia with each disorder individually was performed via Stouffer's method. We then implemented the previously developed pharmagenic enrichment score (PES) method to identify candidate trans-diagnostic drug repurposing candidates. Briefly, the PES framework seeks to identify druggable gene-sets enriched with common variant associations which can then be utilised to construct pathway specific polygenic scores.

Results
Gene-based analysis of common variation revealed 67 schizophrenia-associated genes shared with other psychiatric phenotypes. TWAS provided some mechanistic insights into the direction of effect for these pleiotropic genes – for instance, overexpression of the serine/threonine-protein kinase NEK4 was associated with both schizophrenia and bipolar. Pairwise meta-analysis of schizophrenia and each psychiatric phenotype identified 330 novel associated genes that were only nominally associated with each disorder individually. The pharmagenic enrichment score methodology revealed several interesting trans-diagnostic drug repurposing candidates for schizophrenia and at least one other disorder, including the antioxidant N-acetylcysteine and the anticonvulsant Lamotrigine.

Conclusions
We uncovered widespread sharing of genic associations between schizophrenia and a variety of psychiatric disorders, with TWAS revealing that predicted expression of a subset of these pleiotropic genes was correlated with multiple phenotypes. Several novel associations were detected by meta-analysis of schizophrenia with each disorder individually, consolidating their genetic overlap and further supporting the gain in power afforded by cross-disorder analysis. We further demonstrated that druggable schizophrenia associated pathways shared with other psychiatric disorders may provide biologically salient trans-diagnostic drug repurposing opportunities.

Prenatal Poly I:C challenge affects adolescent behaviours and neurotransmission in female juvenile rats

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Background
Exposure of polyriboinosinic-polyribocytidylic acid (Poly I:C) in pregnant rats has been reported to cause schizophrenia-like behaviours and abnormal neurotransmissions in adult, particularly male, offspring. This study aims to investigate the effects of maternal Poly I:C exposure on adolescent behaviours and neurotransmission in female juvenile rats.

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 conducted for behavioural tests during postnatal days (PD) 35-60. Rats were sacrificed on PD60 for measuring inflammation and neurotransmission markers by RT-qPCR.

Results
Prenatal Poly I:C exposure increased Il-1a in the prefrontal cortex (PFC), hippocampus (Hip) and nucleus accumbens (NAc) of female adolescent offspring. Poly I:C exposure decreased GABAA subunit Gabrb1 in the Hip and Gabrb3 in PFC. NMDA receptor subunit Grin1 was decreased in the Hip, while Grin2a was increased in the PFC. D2R was decreased in the Hip, but increased in NAc. 5-HT2AR was also decreased in the PFC. Female adolescent Poly I:C offspring showed anxiety-like and depressive-like behaviour, and deficits in pre-pulse inhibition and social interaction. Unexpectedly, these animals showed a better performance in a novel object recognition test.

Conclusions
These results suggested that prenatal Poly I:C exposure had long-lasting effects on inflammation marker and neurotransmissions in the brain, as well as behaviour and cognitive function in female adolescent offspring rats.

Acute effect of corticosterone and RU486 on dorsal striatal dopamine release

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Background
Stress is regarded as one of the major risk exposures for the development of schizophrenia. Since the major dopaminergic abnormality in schizophrenia is an increase in presynaptic dopamine synthesis and release within the dorsal striatum, we would like to examine the effect of acute stress on dopamine release in this brain region. To achieve this, we used corticosterone injections to mimic the physiological effect of acute stress, as activation of the hypothalamic-pituitary-adrenal (HPA) axis is the most robust neurochemical representation of stress. We measured dopaminergic changes in the dorsal striatum in response to corticosterone and blockade of the corticosterone receptor.

Methods
Adult male Sprague Dawley rats underwent anaesthetized microdialysis to assess dopamine release after systemic drug administration. Four groups were included (n = 6-7 for each group). Briefly, once surgery was complete, baseline samples were collected for 80 minutes. Animals then received a subcutaneous injection (T80 min) of either 100% dimethyl sulphoxide (DMSO) or 20 mg/kg RU486 (glucocorticoid receptor antagonist), followed by an intraperitoneal injection (T100 min) of either 100% DMSO or 2.0 mg/kg corticosterone. Then all animals received an intraperitoneal injection (T140 min) of 0.6 mg/kg amphetamine. Sampling continued for a further 2 hours.

Results
Neither corticosterone nor RU486 alone significantly changed baseline extracellular dopamine levels in the dorsal striatum ($p > 0.05$). However, cumulative post-amphetamine extracellular dopamine levels (expressed as area under the curve using all post-amphetamine samples) were significantly higher in corticosterone pre-treated rats than in vehicle (DMSO pre-treated) controls ($p = 0.0061$) and RU486 pre-treated rats ($p = 0.0004$). There were no differences in cumulative post-amphetamine extracellular dopamine levels between RU486 pre-treated rats and vehicle controls ($p > 0.05$). Experiments investigating the combinatory effects of RU486 and corticosterone on baseline and amphetamine-induced dopamine release are still ongoing.

Conclusions
Although the dorsal striatum has been repeatedly implicated in schizophrenia, the impact of stress on the dopamine system in this region has been less studied. To address this, we pharmacologically manipulated the HPA axis and examined changes in extracellular dopamine levels in the striatum using in vivo microdialysis. We found a combinatory effect of corticosterone and amphetamine, but no effect of corticosterone or RU486 alone, or any combinatory effects of RU486 and amphetamine. This study will help us to better understand the interaction between the HPA axis and the striatal dopamine system, and their association in schizophrenia.

2.1 Psychoses

2.1.3 Schizophrenia: Pharmacology

Cannabidiol as a potential preventative treatment in a neuregulin 1 mouse model of schizophrenia

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Background
Schizophrenia is a neurological disorder that develops in late adolescence/early adulthood due to interaction of genetic and environmental risk factors. Established antipsychotic medication shows limited efficacy for negative and cognitive symptoms, is ineffective for approximately 30% of patients, and has side effects impacting treatment compliance. Recently, the role of neuroinflammation in the development of disorder has received increasing attention. Cannabidiol (CBD) is a non-toxic phytocannabinoid that has anti-inflammatory and potentially antipsychotic-like properties. We hypothesise that adolescent CBD treatment could potentially limit neuroinflammatory events and prevent development of a schizophrenia-relevant phenotype in a mouse model for risk gene neuregulin 1 (NRG1).

Methods
Heterozygous Nrg1 transmembrane domain (Nrg1 TM HET) males and wild type-like (WT) littermates were treated with 30 mg/kg of CBD or vehicle intraperitoneally during adolescence (PND 35-60). Mice were tested in adulthood (5-6 months) in tasks relevant to schizophrenia including open field, social interaction and prepulse inhibition (PPI). One week later, the behavioural response of the same mice to acute treatment with 3 mg/kg of Δ^9-tetrahydrocannabinol (THC) was also evaluated to determine if adolescent CBD treatment modulates the sensitivity to a cannabis challenge.

Results
Adolescent CBD treatment reduced social interaction in all mice, reduced open field locomotion in WT mice, and tended to reduce PPI in Nrg1 TM HET mice, suggesting that Nrg1 may modulate some effects of CBD. THC-treated Nrg1 TM HET mice showed a reduction in distance travelled in the open field when they had received CBD during adolescence. THC also tended to further reduce the CBD-induced decrease in social interaction and the reduction in startle caused by THC was potentiated in CBD-treated Nrg1 mice. Importantly, THC-CBD interactions were only evident in Nrg1 but not WT mice.

Conclusions
These results suggest that CBD does not function as a neuroprotective drug during adolescence in the Nrg1 mutant mouse model. Interestingly, Nrg1 mice appeared to be more susceptible to the potentiating effects of adolescent CBD treatment on later THC-induced behaviours. These findings suggest persistent brain changes following adolescent exposure to CBD. Further investigations following up on these findings is utilising proteomics analysis to determine the neuroinflammatory and endocannabinoid profile of Nrg1 TM HET mice.

Liraglutide prevents dysregulation of markers of cognitive function during antipsychotic drug treatment in rats

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Background
Antipsychotic drugs (APDs) olanzapine and clozapine are used to treat schizophrenia; however, they do not effectively treat the cognitive symptoms of the disorder and can cause serious metabolic side effects, leading to medication non-compliance. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that has the potential to address both of these problems, and we have previously shown it can improve aspects of cognition and prevent the metabolic side effects of APDs in a rodent model. The effect of liraglutide on central markers of cognitive function during APD treatment has yet to be elucidated.

Methods
Female Sprague-Dawley rats were administered olanzapine (2 mg/kg), clozapine (12 mg/kg), liraglutide (0.2 mg/kg), olanzapine + liraglutide co-treatment, clozapine + liraglutide co-treatment or vehicle for six weeks. Markers of cholinergic, GABAergic and endocannabinoid function were examined in the hippocampus (HPC) and prefrontal cortex (PFC) using western blot and receptor autoradiography techniques. Specifically, choline acetyltransferase (ChAT; acetylcholine synthesis), acetylcholinesterase (AChE; acetylcholine degradation), glutamate decarboxylase (GAD67; GABA synthesis) and fatty acid amide hydrolase (FAAH; endocannabinoid degradation) protein expression, as well as muscarinic acetylcholine receptor M1/M4 (M1/M4R) and endocannabinoid CB1 receptor (CB1R) binding density were examined.

Results
Olanzapine increased ChAT ($p<0.05$), AChE ($p<0.01$) and GAD67 ($p<0.001$) protein expression as well as M1/M4R binding density ($p<0.05$) in the HPC vs. controls, whilst olanzapine + liraglutide co-treatment reduced AChE ($p<0.05$) and GAD67 ($p<0.01$) expression compared to olanzapine treatment alone. In the PFC, olanzapine reduced ChAT ($p<0.05$), increased FAAH ($p<0.01$) and increased GAD67 ($p<0.01$) protein expression vs. controls, while olanzapine + liraglutide co-treatment reduced GAD67 protein expression ($p<0.05$) vs. olanzapine. Additionally, clozapine reduced M1/M4R density in the HPC vs. control ($p<0.01$) and clozapine + liraglutide co-treatment increased M1/M4R density vs. clozapine alone ($p<0.05$).

Conclusions
These findings suggest that liraglutide co-administration can prevent the antipsychotic drug-induced dysregulation of key central markers of cognitive function. This research offers an insight into the potential mechanisms underlying the therapeutic efficacy of liraglutide co-administration during APD treatment and provides justification for further investigation.

Serum estradiol as a blood-based biomarker predicting hormonal treatment outcomes in women with schizophrenia

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Background
Patients diagnosed with schizophrenia display substantial heterogeneity in terms of their clinical presentations, and treatment response. Accumulating research suggests that such high diversity may reflect distinct biological subtypes with differentially affected underlying neurobiology. Novel treatments, including sex hormone estradiol treatments, provide alternative efficacious treatment avenues. Associated treatment-response biomarkers that can stratify patients according to biological subgroup may further assist clinical practice through personalised medicine approaches.

Methods
This repeated-measures study characterised the association between hormone levels (estrogen, progesterone, testosterone, prolactin, FSH, LH, DHEA) and symptom treatment outcomes (defined by The Positive and Negative Syndrome Scale (PANSS)) across a 56-day study of 200ug adjunctive estradiol treatment in women with schizophrenia. Group-based trajectory models was used to account for potential heterogeneity (subgroups). Receiver operating characteristic (ROC) curves were evaluated to define the predictive value of endogenous estradiol levels as a treatment-response biomarker of estradiol treatment.

Results
The results generated two subgroups; a treatment-responder group who demonstrated decreasing PANSS scores across time, and a treatment non-responder group, demonstrating stable PANSS scores across time. The treatment-responder subgroup was significantly negatively predicted by estradiol blood level (b= - 2.34, SE=1.17, p=0.047), while FSH blood level was positively associated with the treatment non-responders (b= 7.14, SE=2.54, p=0.008). ROC for day 28, 56 time points yielded area under the curve of 0.52 and 0.55, respectively. Harrell's C-statistic = 0.59.

Conclusions
This is the first study to identify endocrine markers in blood serum predicting response estradiol treatment in female schizophrenia patients, highlighting heterogeneity in response. It provides promising data suggesting that multiple sampling of estradiol levels may lead to the development of a molecular blood test that could be used to help psychiatrists determine if endocrine modulation if a viable treatment option for each patient. The continued identification of new biomarkers specific to disease subtypes and individual patients is essential for translation into the personalised medicine era in psychiatry.

The Gut Microbiome and Treatment Response in Schizophrenia

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Background
Patients with schizophrenia who do not respond to first-line treatment with atypical antipsychotics, termed treatment resistant schizophrenia (TRS), are often prescribed clozapine. Clozapine is the only drug recommended for TRS, but it frequently induces significant side effects including blood dyscrasias, metabolic syndrome and severe constipation. In the past ten years, researchers have identified significant differences in the microbiome composition of individuals with schizophrenia. However, no one has explored the differences of gut microbiome composition amongst people with varying degrees of treatment response. The aim of this research is to understand if gut microbiome may mediate some of these side-effects.

Methods
In our planned study I will obtain faecal matter from 100 participants (25 healthy controls, 25 patients with schizophrenia taking atypical antipsychotics different from clozapine, 25 patients with treatment resistant schizophrenia who respond to clozapine and 25 patients with treatment resistant schizophrenia who do not respond to clozapine). After sequencing the samples through an Illumina pair-end shotgun platform (Novoseq), relative microbial abundances and microbial diversity will be recorded. In addition, GC-MS and LC-MS analysis will be performed to record any metabolomic differences associated with microbiome changes. I will control for BMI, sex, age, physical exercise, and diet.

Results
We predict there will be significant microbiotic and metabolomic differences between healthy controls and people with schizophrenia. In particular, I expect to find decreased microbial diversity in patients with schizophrenia and decreased levels of short-chain fatty acids. In addition, we predict there will be specific microbiome and metabolomic profiles amongst people within the different treatment response groups to clozapine.

Conclusions
This research will help to understand whether gut microbiome mediates treatment response/side-effect profiles in patients. In the future an understanding of patient microbiome may aid clinicians in tailoring treatments specifically for each patient in order to avoid inducing these debilitating side-effects. Results from this study will help in the selection of specific biome taxa in future experiments employing gnotobiotic animals to better understand the contribution of gut/brain mechanisms to disease.

2.1 Psychoses

2.1.4 Bipolar disorder, Psychosis

Medical morbidity and mortality in Australians with Bipolar Disorder from linked administrative data

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Background
Bipolar disorder (BD) is associated with a wide range of medical comorbidities, contributing to a reduced life expectancy of 8 to 12 years compared to the general population. Increased rates of suicidal ideation and suicide attempts are associated with BD and contribute to this mortality gap, and suicide attempts have been associated with increased rates of physical morbidity. Linked administrative health data provides the opportunity to examine rates of comorbid illness and associated causes of mortality within a large sample of Australians with BD.

Methods
The Sax Institute's "45 and Up Study" comprises 267,153 residents of New South Wales, aged 45 years and over at baseline (2006-2009). Questionnaire data were linked by CHeReL to ~157 million records sourced from NSW Government data collections including Mental Health Ambulatory, Emergency Department, Admitted Patient, death registrations and cause of death (COD) data. Pharmaceutical Benefits Scheme and Medicare Benefits Schedule data were supplied by Services Australia (formerly the Australian Government Department of Human Services). Identification of BD-cases employed cumulative evidence across multiple data sources. Medical morbidities and mortality were identified from linked administrative data which spanned the period 2001-2017.

Results
BD-cases (n=4789) were identified from ICD-10-AM codes and records of BD medication supply. After controlling for relevant demographic variables (age, gender, socioeconomic-disadvantage, smoking, alcohol consumption, physical activity and body-mass-index), BD-cases had significantly increased prevalence of numerous medical comorbidities compared to non-BD cases (n=248,945) including cardiovascular (OR~1.2-2.0), metabolic (OR~1.6-1.9), gastrointestinal (OR~1.5-2.3) and respiratory (OR~2.1-2.3) illness. Admitted-patient records revealed a higher prevalence of suicidal ideation (OR=35.3; frequency=8.72%) and attempt (OR=45.5; 13.99%) among BD-cases compared to non-BD-cases (~0.20-0.26%). Preliminary analysis demonstrated increased mortality in BD after ~115-months follow-up (22% vs 12.8%), with deaths most commonly attributed to cardio-/cerebro-vascular diseases.

Conclusions
Administrative health data has the potential to advance our understanding of long-term health outcomes and effective treatment strategies for BD. Specifically, establishing the prevalence of medical morbidity and mortality in Australians with BD may provide key health targets for clinical intervention, improved service provision, and enable relationships between pharmaceutical treatment regimens and health outcomes to be modelled. However, caution should be taken in generalising from this older adult sample with average age ~62 years, which may not be representative of wider populations. Future work will quantify and examine cumulative comorbidity burden, comorbidity treatment rates, and relationships to pharmaceutical treatments.

Shorter telomere length associated with cognitively impaired subgroup in psychosis

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Background
Schizophrenia (SZ) and bipolar disorder (BD) are complex mental illnesses that are associated with cognitive deficits. There is considerable cognitive heterogeneity that exists within both disorders. Studies that cluster schizophrenia and bipolar patients into subgroups based on their cognitive profile increasingly demonstrate that, relative to healthy controls, there is a severely compromised subgroup and a relatively intact subgroup. There is emerging evidence that telomere shortening, a marker of cellular senescence, may be associated with cognitive impairments. The aim of the current study was to explore the relationship between cognitive subgroups in psychosis and telomere shortening.

Methods
Participants included 73 clinical cases (26 SZ/47 BD) and 113 healthy controls (HC). A transdiagnostic framework was used to first determine cognitive clusters within the patient group, based on current cognitive functioning (MATRICS Consensus Cognitive Battery T scores) . Emergent clusters were then compared to each other and the HC group on telomere length and clinical variables (cognitive scores / diagnostic groupings / premorbid IQ).

Results
Two clusters emerged within the patient group which were deemed to reflect a relatively intact cognitive group and a cognitively impaired subgroup. Telomere length was significantly shorter for the severely impaired cognitive subgroup, as compared to the HC group.

Conclusions
This study replicates previous findings of transdiagnostic cognitive subgroups and associates shorter telomere length with the severely impaired cognitive subgroup. These findings support emerging literature associating cognitive impairments in psychiatric disorders to accelerated cellular aging as indexed by telomere length

Macrophage inhibitory cytokine-1 elevation in affective psychoses in the second Australian national survey of High Impact Psychosis (SHIP) study

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Background
Peripheral blood cytokine alterations are found in people with psychotic disorders. Recently Kumar et al., 2017 determined elevated macrophage inhibitory cytokine-1 (MIC-1) levels in those with psychoses compared with healthy controls and an inverse association with severity. Dependent on the cellular microenvironment MIC-1 is known to act as an immune modulator. However dysregulated cytokine levels are not evident in all people with psychoses. We aimed to determine peripheral blood MIC-1 levels in those with affective psychoses compared with non-affective psychoses and whether course of disorder or psychosocial functioning was an independent predictor of altered MIC-1 levels.

Methods
The SHIP study involved collection of clinical data and peripheral blood samples. Diagnoses were made according to the International Statistical Classification of Diseases (ICD-10). We used a standard ELISA to measure MIC-1 in 416 plasma samples. We compared MIC-1 levels between participants with affective and non-affective psychoses, adjusting a priori for sex, age, current smoking and BMI. A multivariable log linear regression model was applied to study the association between the clinical variables course of disorder or psychosocial functioning and MIC-1 levels.

Results
We found participants diagnosed with affective psychoses were 1.28 times (p=0.014) more likely to have higher levels of peripheral MIC-1 than those diagnosed with non-affective psychoses (N=167) adjusting for age, BMI, smoking and sex. Our multivariable model found higher levels of MIC-1 in those with a continuous chronic course of disorder without deterioration (N=20), compared with participants who experienced either a single episode of psychosis (N=7) (p=0.03, OR=2.20, 95% CI 1.06, 4.56) or multiple episodes with either good recovery (N=73) (p<0.001, OR=1.68, 95% CI 1.22, 2.11) or partial recovery (N=58) (p<0.001, OR=1.74, 95% CI 1.38, 2.20).

Conclusions
Our results provide evidence that levels of peripheral MIC-1 differ between affective and non-affective psychosis. Interestingly a continuous chronic form of the disorder without deterioration is more likely to predict elevated MIC-1 levels whereas a continuous chronic form with deterioration is associated with lower MIC-1 levels in those with affective psychosis. This suggests that elevated MIC-1 levels may have an anti-inflammatory effect and contribute to protection against the deteriorating effects of a continuous chronic course of disorder.

Reduced chemokine and chemokine receptor expression are associated with deficits in neurogenesis and inhibitory interneurons in psychiatric disorders

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Background
Neural stem cells in the subependymal zone (SEZ) continue to generate cortical inhibitory interneurons in the postnatal human brain. Schizophrenia and bipolar disorder are characterised by both reduced neurogenesis in the SEZ and decreased inhibitory interneuron function in the dorsolateral prefrontal cortex (DLPFC). Signalling of the CXC motif chemokine 12 (CXCL12) through CXC motif chemokine receptors 4 (CXCR4) and 7 (CXCR7) regulates the generation, migration and survival of inhibitory interneurons. We hypothesised that reduced expression of CXC chemokine family members is associated with deficits in both neurogenesis and inhibitory interneuron function in schizophrenia and bipolar disorder.

Methods
Post-mortem tissue was obtained from 35 schizophrenia, 35 bipolar disorder and 35 control cases from the Stanley Medical Research Institute. CXCL12, CXCR4 and CXCR7 expression were determined in the SEZ and DLPFC by quantitative polymerase chain reactions. Analyses of covariance were used to assess diagnostic differences followed by Fisher's least significant difference tests. Semi-partial correlations were performed to assess the relationships between CXC chemokine family members and markers of neural stem cells (PROM1, GFAPD) and neuronal progenitors (SOX2, ASCL1), and inhibitory interneurons (SST, PVALB, VIP, NPY, CR, CCK, CALB) that were previously measured in the SEZ and DLPFC, respectively.

Results
In the SEZ, CXCL12 mRNA was decreased in schizophrenia compared to controls (24%, $p=0.001$). CXCR4 and CXCR7 mRNAs were reduced in schizophrenia and bipolar disorder compared to controls (9-33%, $p\leq0.05$). CXCL12, CXCR4 and CXCR7 expression positively correlated with PROM1, GFAPD, SOX2 and ASCL1 mRNAs ($sr\geq0.28$). In the DLPFC, CXCL12 mRNA was decreased in schizophrenia compared to controls (25%, $p=0.004$). CXCR4 and CXCR7 expression did not significantly differ across diagnostic groups. CXCL12 expression positively correlated with VIP mRNA ($sr=0.37$). CXCR4 expression negatively correlated with VIP, CR and CCK mRNAs ($sr\leq-0.22$). CXCR7 expression negatively correlated with SST and NPY mRNAs ($sr\leq-0.29$).

Conclusions
These findings provide the first molecular evidence of decreased CXC chemokine family member expression in the SEZ and DLPFC in psychiatric disorders, with exacerbated deficits in schizophrenia compared to bipolar disorder. Dysregulated CXC signaling capacity may hamper the generation of neuronal progenitor cells, which may contribute to cortical inhibitory interneuron deficits in psychiatric disorders. Triple-labelling immunohistochemistry will be used to identify the cellular localisation of CXCR4 and CXCR7 in the SEZ and DLPFC to further disentangle the regulatory role of CXCL12 signaling in the generation and maintenance of inhibitory interneurons in the human brain.

Interactive effects of polygenic risk and trauma exposure on systemic inflammation in schizophrenia and bipolar disorder.

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Background
Schizophrenia (SZ) and bipolar-I disorder (BD) are characterised by increased peripheral inflammation. Childhood trauma exposure is a critical risk factor for these disorders, also associated with elevated inflammation. Recent genome wide association studies (GWAS) have identified shared genetic risk for SZ and BD in loci involved in inflammatory responses. How environmental and genetic risks interact to impact inflammatory responses in these disorders remains unclear. This study aimed to determine whether childhood trauma differentially moderates the effects of genetic risk for SZ/BD (limited to genes involved in inflammatory responses) on systemic inflammation, among cases with SZ/BD, and healthy individuals.

Methods
Participants were 46 cases diagnosed with SZ, 49 diagnosed with BD and 43 healthy controls (HC). A polygenic risk score (PRS) limited to the 767 genes involved in inflammatory response from the most recent GWAS (for SZ and BD phenotypes combined) was calculated using published effect sizes. Systemic inflammation was measured using a composite z-score derived from serum concentrations of interleukin 6, tumour necrosis factor alpha and C-reactive protein. An index of childhood trauma exposure (exposed vs. non-exposed) was derived from the Childhood Trauma Questionnaire (CTQ).

Results
A series of multiple linear regressions (age, sex and population stratification as covariates), showed a marginally significant three-way interaction (PRS-by-trauma-by-group; p=0.052). An exploratory post-hoc moderated moderation analysis further indicated that as PRS increased, systemic inflammation increased in HC exposed to trauma (p=0.047). However, this association was not evident among HC who were not exposed to trauma (p=0.133), nor among any clinical cases (non-exposed: p=0.909; exposed: p=0.410). The effect of the PRS-by-trauma interaction on systemic inflammation (p=0.016) was significant, but there were no significant independent effects of PRS, trauma or group, nor PRS-by-group or trauma-by-group interactions.

Conclusions
Contrary to our primary hypothesis, trauma exposure did not moderate the relationship between genetic risk loci involved in inflammatory responses, and systemic inflammation in SZ and BD cases. Other mechanisms (e.g., stress, medication, physical health, other environmental/sociodemographic factors) may have a stronger influence on systemic inflammation in SZ and BD. Nevertheless, increased genetic risk for SZ/BD was associated with increased systemic inflammation in trauma-exposed healthy individuals only. This may reflect potential mechanisms by which trauma-related inflammation leads to immune-related pathology in trauma-exposed ostensibly healthy populations. Future studies are needed to replicate these findings.

The activity and connectivity of the facial emotion processing neural circuitry in bipolar disorder: a systematic review

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Background
Facial emotion processing abnormalities may be a trait feature of bipolar disorder (BD). These social cognitive impairments may be due to abnormalities in the neural processing of facial affective information in visual ("core"), and limbic and prefrontal ("extended") networks, however, the precise underlying neurobiological mechanism(s) underlying this symptom are unclear.

Methods
We conducted a systematic review to appraise the literature on the activity and connectivity of the facial emotion processing neural circuitry in BD. Two reviewers undertook a search of the electronic databases PubMed, Scopus and PsycINFO. Study eligibility criteria included; BD participants, neuroimaging, and facial emotion processing tasks.

Results
Out of an initial yield of 6121 articles, 66 were eligible for inclusion in this review. We identified differences in neural activity and connectivity within and between occipitotemporal, limbic, and prefrontal regions, in response to facial affective stimuli, in BD compared to healthy controls.

Conclusions
The findings from this review suggest abnormalities in both the activity and connectivity of facial emotion processing neural circuitry in BD. It is recommended that future research aims to further define the connectivity and spatiotemporal course of neural events within and between occipitotemporal, limbic, and prefrontal regions.

Resting-State Functional Connectivity Changes in Medicated and Unmedicated Psychosis: A longitudinal, triple blind, placebo-control MRI study

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Background
Psychotic symptoms are widely thought to arise from disturbed communication between brain regions and resting-state functional connectivity (rs-fMRI) has been used extensively to map patterns of disturbed functional connectivity (FC) in patients with psychotic disorders. One limitation affecting all existing longitudinal studies conducted thus far is that they have only examined previously medicated patients. This is problematic because previous exposure to medication may result in brain changes that could mask or be mistaken for illness-related processes. Thus, no prospective study to date has been able to distinguish the natural effects of psychotic illness from antipsychotic medication in driving these changes.
Methods
We conducted a clinical trial where 62 antipsychotic-naive people with First Episode Psychosis received either an atypical-antipsychotic or placebo over 6 months. A healthy-control group (n=27) was also recruited. rs-fMRI scans were acquired at baseline, 3-months and 12-months. We mapped FC between each pair of 316 regions and distinguished illness and medication-related effects using mixed-effects models combined with bootstrapping and the Network-Based Statistic. Canonical correlational analysis (CCA) was used to examine associations between changes in illness-related connectivity and trial outcome measures (SOFAS,BPRS), as well as associations between connectivity changes and gene expression, as quantified in the Allen Human Brain Atlas.
Results
Group-by-time interactions ($p<0.05$,FWE-corrected) were detected within illness-related (placebo vs control) and medication-related (antipsychotic vs placebo & control) contrasts. Illness-related connectivity decreases were predominantly located in thalamus, striatal, default and somatomotor networks, whereas increases were present within the limbic and default networks. Medication-related decreases were present between hippocampal, ventral attention, and frontoparietal networks, whereas increases were detected between the thalamus and all other networks. Illness-related connectivity changes were associated with pre-registered clinical outcome measures over 3 months ($R=0.901$, $p=.005$). Additionally, spatial topography of regional illness-related changes correlated with gene expression related to synaptic function, glutamate transmission, and immune processes ($R=0.419$,$p=.009$).
Conclusions
Psychotic illness and antipsychotic medication exert differential effects on longitudinal changes in resting-state functional connectivity. Illness-related changes are associated with changes in functional outcome. Spatial correlations between illness-related changes and gene expression implicate interactions between immunological and synaptic function. Additionally, our design establishes the feasibility of conducting placebo-controlled MRI research in early psychosis.

DNA methylation differences between high and low polygenic risk burden in youth at familial risk of bipolar disorder

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Background
Environmental factors along with genetic predisposition may impact the development of Bipolar Disorder (BD). Epigenetic modulations (chemical modifications of the DNA sequence) are a possible mechanism through which environmental factors can affect gene expression and development of psychiatric symptomatology in people at high familial risk (high-risk; HR). We sought to examine the burden of genetic variants associated with relevant psychiatric disorders in young HR and healthy controls (CON) using polygenic risk scores (PRS), and investigate DNA methylation differences in HR subjects with high- versus low-PRS to identify epigenetic processes relating to environmental factors operating beyond genotypic risk burden.

Methods
PRS were calculated for 2806 research participants using summary statistics from genome-wide association studies of the Psychiatric Genomics Consortium for three psychiatric phenotypes: Bipolar Disorder, Major Depressive Disorder (MDD) and cross-disorder. DNA derived from peripheral blood in a subset of an Australian HR cohort (175 HR; 129 CON subjects) were assayed using Illumina Methylation 450K and EPIC BeadChips. PRS were compared between HR and CON groups using Generalised Estimating Equations (GEE) to account for family relationships. An epigenome-wide association study was performed on HR subjects with high and low genetic burden for BD using linear models.

Results
The BD-PRS significantly distinguished Caucasians with established BD (n=264) from controls (n=1115) at pT=0.105, R2= 0.057, p=5.36e-12. After selecting 128 HR participants in the top/bottom 40% of the population distribution for BD-PRS, those in the high BD-PRS group also had significantly higher cross-disorder PRS (GEE Wald-χ2=5.478, p=0.02) and significantly higher MDD-PRS (GEE Wald-χ2=3.668, p=0.05). Data analysis for PRS-stratified EWAS is underway and results on differentially methylated CpG sites will be reported.

Conclusions
A higher burden of genetic variants associated with a variety of different mental illnesses in first-degree relatives of BD cases supports the non-specificity of psychopathology in those at familial risk of BD. While analysis of differential methylation is currently underway, the integration of approaches considering both the genetic and epigenetic components of risk is promising for improving our understanding of the complex interplay between genetic and environmental factors in mental illness. Alongside environmental stimuli, DNA methylation might be influenced by genetic modifications, providing insight on the molecular mechanisms through which genomic variants contribute to complex psychiatric disorders.

2.2 Affect

2.2.1 Depression

Abnormal default mode network effective connectivity in young people with depression

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Background
Depression has been consistently linked to dysfunction in the brain's default mode network (DMN). This network is important for self-referential processing, including negative repetitive thoughts. However, few studies have examined how the directional interactions within this network are altered by depression.
Methods
We compared the fMRI resting-state effective connectivity of 110 unmedicated young people with moderate to severe depression with 101 healthy controls. Using spectral dynamic causal modelling, we examined seven brain regions implicated in the extended DMN: the bilateral inferior parietal lobules (IPL), bilateral hippocampi, posterior cingulate cortex (PCC), and the ventral and dorsal medial prefrontal cortices (dmPFC and vmPFC).
Results
Group differences were compared using Parametric Empirical Bayes. Those with depression demonstrated greater negative connectivity from the dmPFC to vmPFC, PCC, and right IPL, and from the PCC to right hippocampus. They also demonstrated greater positive connectivity from the right IPL to PCC and vmPFC, and from the left hippocampus to PCC. Using leave-one-out cross-validation we observed a correlation between the predicted and observed scores of $r = .28$ ($p > .001$), illustrating that this effect was sufficiently large to predict group allocation.
Conclusions
These findings illustrate that at rest, those with depression demonstrate diffuse changes between regions of the DMN. Moreover, while these alterations may aid in distinguishing those with and without depression, they alone are not sufficiently large to provide clinical utility. Further work will examine whether these alterations are also predictive of treatment response in this patient population.

Electroconvulsive Therapy (ECT) Modulates Network-Based Connectivity and Spectral Power in Patients with Major Depressive Disorder: A Resting-State EEG Analysis

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Background
Major depressive disorder (MDD) is a common and often debilitating illness with a complex and incompletely understood pathophysiology. Electroconvulsive therapy (ECT) has proven to be an effective intervention for severe treatment-resistant MDD. The core therapeutic effects of ECT stem from the elicitation of a generalised seizure. However, despite decades of use, the precise neurobiological mechanisms which drive clinical response to ECT remain poorly understood. Electroencephalography (EEG) provides a cost-effective method for studying neural activity, making it practicable for implementation in clinical settings. Here, we used resting-state EEG (RS-EEG) recordings to examine the physiological effects of an acute course of ECT.

Methods
Data from 23 patients (14 female, mean age 47.29±16.75 years) carrying a DSM-IV diagnosis of MDD were analysed. All patients were classified as having treatment resistant depression, defined as no meaningful clinical response to at least two separate antidepressant trials. 10-minutes of RS-EEG (64-channel cap) was recorded both prior to initiation of the ECT course, and again within 48-hours following the final treatment session. ECT was administered 2-3 times per week according to an open-label protocol (average 13.87±5.32 treatments). Functional connectivity was analysed using the Network-Based Statistic. Changes in oscillatory power and network topology were also explored.

Results
Our results demonstrate that ECT was able to enhance connectivity within lower (delta and theta) frequency bands across subnetworks largely confined to fronto-central channels, while, conversely, more widespread subnetworks of reduced connectivity emerged within faster (alpha and beta) bands following treatment. Graph-based topological analyses revealed changes in measures of functional segregation (clustering coefficient), integration (characteristic path length), and small-world architecture following ECT. Finally, robust post-treatment enhancement of delta and theta spectral power was observed, which showed a positive association with the number of ECT sessions received.

Conclusions
Overall, our findings indicate that RS-EEG can provide a sensitive measure of dynamic neural activity following ECT and highlight network-based analyses as a promising avenue for furthering mechanistic understanding of the effects of convulsive therapies. Future prospective studies could extend these analyses to examine a broader range of brain-behaviour relationships, including specific cognitive and clinical outcome measures.

Pro-inflammatory cytokines: interleukin 6 and interleukin 1 alpha, are dysregulated in depression and correlated with the measures of the psychopathology

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Background
Major depressive disorder (MDD) is associated with increased risk of cardiometabolic disease (CMD); however, the pathophysiology underlying the relationship between MDD and CMD is unclear. One proposed mechanism for this association, which is under-researched, is the inflammatory response produced by the cytokines interleukin 6 (IL6) and interleukin-1 alpha (IL1-α). Inflammation is hypothesised as a leading cause of depression, linked to different psychopathologies and stress, and associated with CMD risk indices including blood pressure and obesity. This positions IL6 and IL1-α as important markers to be analysed in the context of MDD to understand the relationship of MDD with CMD risk.

Methods
Plasma of 120 participants (n=60 meeting DSM 5 criteria for MDD and n=60 control; age and sex matched) were analysed to assess the levels of IL1-α and IL6. Biometric data (BMI, waist circumference, blood pressure and heart rate) were collected, and participants completed the Brief Symptom Inventory (BSI) and Depression Anxiety Stress Scale (DASS). Two-way ANOVA was used to compare IL6 and IL1-α between depressed and control groups, and by sex. Correlations were conducted to determine associations between IL6 and IL1-α and biometric and psychometric data.

Results
Participants' age range was 18 to 54 years (mean=25.05, SD=6.61, 68 females). Plasma IL6 and IL1-α levels were higher in the MDD group than healthy controls, but not different between males and females. However, for IL6, there was significant group by sex interaction, whereby, females in the MDD group had higher IL6 level, but in the control group had lower IL6 level, than males. Neither IL6 nor IL1-α correlated with the biometric data but both correlated with several psychopathology measures and distress (Somatization, Obsessive Compulsive, Interpersonal Sensitivity, Depressive symptoms, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism, Global Severity and Stress).

Conclusions
Both IL6 and IL1-α were higher in MDD than controls supporting an inflammation theory of MDD and a potential role as biomarkers in MDD. Correlations between IL6 and IL1-α and broad measures of psychopathology and distress highlight their potential role in general mental health. Neither IL6 nor IL1-α correlated with CMD risk indices of BMI or blood pressure. However, inclusion of additional CMD risk indices such as plasma lipids, visceral fat, fasting blood glucose and insulin resistance in future studies, would facilitate more comprehensive examination of any associations between IL6 and IL1-α and CMD risk among individuals with MDD.

The clinical effectiveness of vortioxetine augmented with celecoxib or placebo in the treatment of depression: a randomised controlled trial

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Background
Several studies show a role of inflammation in the pathophysiology of major depressive disorder (MDD) and suggest that anti-inflammatory strategies may improve treatment outcomes. This 6-week, randomised, controlled trial aimed to measure the efficacy of anti-inflammatory augmentation of antidepressant treatment in the treatment of MDD, and investigated whether the effect was dependent on baseline inflammation levels.

Methods
Study participants (N=119) were divided according to blood high sensitivity C-reactive protein (hsCRP) concentration, then randomised to receive either vortioxetine and celecoxib or vortioxetine and placebo for six weeks. Vortioxetine was offered optionally for a further 29 weeks. The primary outcome was change in Montgomery–Åsberg Depression Rating Scale (MADRS) score, with a primary endpoint of a score reduction by 50% from baseline to six weeks. Secondary outcomes included the Functioning Assessment Short Test (FAST), Clinical Global Impression-Severity (CGI-S), and THINC-integrated tool (THINC-it) Codebreaker task (i.e. digit symbol substitution test).

Results
There was a significant improvement of depressive symptoms (MADRS total score) in the entire cohort; however, stratified analyses showed that only the celecoxib-augmented group showed significant improvement over 8 weeks. Cognitive function (number of correct answers on the Codebreaker) improved significantly over time in the entire cohort, and also in both treatment groups in stratified analyses. Changes over time in the FAST and CGI scores did not reach significance in the entire cohort. However, only celecoxib augmentation reduced symptom severity (CGI-S), while the placebo group performed better in psychosocial functioning (FAST) than the celecoxib-augmented group.

Conclusions
While mood, cognitive function and disease severity were improved by antidepressant augmentation with celecoxib, such an effect was not found for psychosocial functioning. As the celecoxib-augmented group showed greater improvement in cognitive functioning than placebo in particular, further investigation of the treatment in the subset of patients with MDD and cognitive impairment is warranted. Interestingly, hsCRP levels at baseline were neither predictive of treatment outcome nor did they interact with the treatment group. Despite evidence of advantages in clinical outcomes with adjunctive anti-inflammatory treatment of MDD, the study suggests that hsCRP is not an appropriate predictive biomarker of the treatment.

Saliva Lithium Monitoring as an Alternative to Blood Sampling in Patients Taking Lithium Medications

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Background
Lithium was first used as clinical treatment for manic depressive illness in 1949, and remains the predominant first line of treatment for bipolar disorder. However, lithium therapy has a narrow therapeutic window (0.5 – 1.2 mM), and frequent blood tests are required to regulate the dose. The use of saliva as a biofluid has many advantages over blood, as it is non-invasive, easier and safer to collect, requires less processing, and can be collected at home without the need for trained personnel. This study investigated the potential utility of saliva over blood as a longitudinal means of monitoring lithium levels.

Methods
Individuals 65 years and under on lithium medication were recruited from the University of California Irvine Medical Center (UCIMC) and Veterans Affairs San Diego Mood Disorders Clinic, University of California San Diego (UCSD). Saliva samples were collected via the passive drool method and lithium levels analysed using Inductively coupled plasma atomic emission spectroscopy. Time-matched blood was collected and serum lithium levels were analysed by the pathology laboratory at each site. A short health and lifestyle questionnaire was completed at the time of sample collection, and relevant clinical history and blood chemistry data was collected from the patient's electronic medical file.

Results
Recruitment site cohorts differed significantly in gender ratios, age, blood serum lithium (bLi) and saliva lithium (sLi) levels (all $p \leq 0.002$). Outcome was therefore analysed by site. BLi and sLi were correlated at both UCIMC ($r^2=0.67$, $p<0.0001$; $n=26$) and UCSD ($r^2=0.46$, $p<0.0001$; $n=34$). These levels, and the saliva/serum lithium ratio (s/bLi), was not affected by time from saliva to blood collection, or daily lithium dose. S/bLi correlated with time from last dose to collection ($r^2=0.42$, $p=0.01$). The average intrasubject s/bLi from 3 appointments was used to estimate bLi at the 4th appointment; this estimation correlated with the observed bLi ($r^2=0.87$, $p=0.0007$).

Conclusions
These data show that saliva lithium levels may be used an alternative to blood measurements in patients who present with a stable saliva/serum lithium ratio. Further investigation into the impact of health and lifestyle factors, and clinical history, on saliva and serum lithium levels will help determine the limitations and eligibility criteria for this measure within a clinical setting. Refinement and application of this measure may significantly improve quality of life and clinical outcome for patients prescribed lithium prophylaxis, with an emphasis on those who are unable to provide routine blood samples.

Relationships between cortisol, problematic eating behaviours and weight symptom profiles in Major Depressive Disorder

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Background
Major Depressive Disorder (MDD) is associated with an increased risk of chronic diseases. A proposed pathway between MDD and chronic diseases is weight gain linked to an increased prevalence of problematic eating behaviours and changes in neuroendocrine pathways. The most prominent neuroendocrine change observed in MDD is cortisol dysregulation linked to altered hypothalamic-pituitary-adrenal (HPA) axis activity. Cortisol is the main hormone of the stress response and is involved in regulating energy balance and food intake. While cortisol has been linked to both weight gain and weight loss, little research has examined the relationships between cortisol and overeating behaviours in MDD.

Methods
Plasma cortisol concentrations, anthropometric and health measures, and psychopathology were compared between 80 participants with MDD and 60 healthy controls. Participants with MDD were sub-categorised into those reporting increased or decreased appetite and/or weight. Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II) and the Depression, Anxiety and Stress Scale (DASS-21). Problematic eating behaviours were quantified with the Dutch Eating Behaviours Questionnaire (DEBQ) and the Yale Food Addiction Scale (YFAS).

Results
Plasma cortisol was higher in participants with MDD than controls and in males than females, and was negatively associated with waist circumference and body mass index (BMI). Depressed participants reporting appetite and weight loss had higher cortisol levels than those reporting appetite and weight gain. Problematic eating behaviours were higher in depressed participants with weight gain compared to weight loss, and in females than males. When stratified by sex, cortisol was positively associated with depression, anxiety and stress-related psychopathology in females, and negatively associated with problematic eating behaviours, waist circumference and BMI in males.

Conclusions
The results indicate that cortisol is linked to appetite and weight loss in MDD, with different effects across sexes. Higher cortisol may contribute towards the tendency for appetite and weight loss in males with MDD, whereas lower cortisol may contribute to a greater propensity towards weight gain in females with MDD. These findings support that differences in cortisol production may contribute to observed sex differences in symptom presentation, as well as weight gain and associated chronic health risks, in MDD.

Exercise during pregnancy and its impact on depression and anxiety: A systematic literature review

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Background
Antenatal depression has a worldwide prevalence of 10-13% of the pregnant population. Treatment of depression in this population is challenging due to the potential or perceived risks of prescribed drugs for both the mother and developing infant. Growing evidence has shown that exercise can prevent and alleviate symptoms of clinical depression, including anxiety, in the general population, however it is not clear if this therapeutic effect extends to the pregnant population. The aim of this systemic literature review was therefore to synthesize the evidence that examines whether exercise/physical activity during pregnancy impacts depressive and/or anxiety symptoms during and/or after pregnancy.

Methods
We conducted a systematic review of the literature in accordance with the PRISMA guidelines. PubMed, Scopus and Web of Science electronic databases were searched for clinical studies using the keywords: depression OR anxiety, AND, pregnancy, AND, exercise or variations on these keywords. Articles were included if they were 1) peer reviewed and written in English, 2) conducted a defined exercise protocol during pregnancy in a human population, 3) included a control group that was not exposed to the exercise protocol, 4) measured depressive and/or anxiety symptoms during and/ or after pregnancy.

Results
Thirty-one articles were selected for the final qualitative synthesis. The included studies recruited women from 14 to 50 years old at 9-32 weeks gestation. Exercise interventions lasted 6 to 20 weeks. Twenty-six of the 31 articles showed that the exercise intervention during pregnancy significantly improved depressive and/or anxiety symptoms during and/or after pregnancy compared to the control group. Five of the studies showed no improvement in symptoms and one study showed a worsening of depressive symptoms. Only six of the 31 studies recruited women with a clinical diagnosis of depression, five of which showed significant improvements in depressive symptoms.

Conclusions
There is limited evidence of the therapeutic effects of exercise in pregnancy on antenatal depression. Nevertheless, the evidence to date suggests antenatal exercise can improve depressive and anxiety symptoms during and post-pregnancy. It is not known how the potential therapeutic effect of antenatal exercise compares to that of antidepressant drug treatment in this population or whether exercise can enhance the therapeutic effect of antidepressant drugs. Further investigations are needed to determine the extent and nature of this potential therapeutic effect.

Omega-3 polyunsaturated fatty acid levels in individuals with Major Depressive Disorder compared to healthy controls

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Background
Omega-3 polyunsaturated fatty acids (ω-3PUFA) are essential to neuronal and heart health and must be obtained through dietary sources. Low consumption of ω-3PUFA has been linked to depressive symptoms in epidemiological studies, however there is little research comparing ω-3PUFA levels in people with and without MDD (Major Depressive Disorder). The omega-3 index, the percentage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in erythrocytes, is associated with cardiovascular disease risk, having cut-points of 8% for high risk and low risk respectively. The omega-3 index is also considered an important emerging biomarker of neuropsychiatric risk.

Methods
Sixty individuals meeting DSM 5 criteria for MDD and 60 matched controls (18-54 years) participated. MDD diagnoses were confirmed through semi-structured interviews. Participants gave a blood sample and completed the Brief Symptom Inventory and the Depression, Anxiety and Stress Scales. Plasma levels of individual fatty acids were quantified and fatty acid peaks were identified by comparison with known fatty acid standards. Additionally, established methods were used to compare plasma EPA+DHA levels to corresponding to Omega-3 Index equivalents, with 2.9%, 4.0%, 5.2%, 6.4% of total plasma lipids corresponding to 4%, 6%, 8%, 10%, respectively. Two-way ANOVAs and correlational analyses were performed.

Results
Levels of ω-3PUFA were well below the recognised high-risk ω-3 index cut-off of <4%, which converts to 2.9% in plasma levels of EPA+DHA. The mean plasma EPA+DHA across participants was only 2.2%. There were no significant differences in the plasma EPA+DHA levels between the MDD (2.16%) and control (2.18%) groups. Females had higher EPA+DHA levels (2.3%) than males (2.0%) across groups. There were few significant correlations between fatty acid levels and mental health symptoms. As expected, severity of psychopathology was higher in the MDD than control groups. Additionally, anxiety was higher in females than males overall.

Conclusions
Our results indicate that participants generally, regardless of MDD status, were deficient in plasma ω-3PUFA. Our results are consistent with previous dietary research findings of deficiencies in ω-3PUFA intake in Australia and other countries. MDD participants had higher mental health symptoms than controls, as expected, however these symptoms were not directly correlated with ω-3PUFA. Our results suggest that the local population sampled here may be at heightened risk of both mood disorders and cardiovascular health problems due to low ω-3PUFA levels. Further dietary studies and public education regarding recommended levels of consumption of ω-3PUFA may be warranted.

Evidence of kynurenine pathway dysfunction and glutamate pathology in depression

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Background
Emerging evidence suggests alterations in the kynurenine pathway (KP) is a novel contributor to the aetiology of depression and disorders involving psychosis. Stimulation of the kynurenine pathway leads to the formation of neuroactive metabolites, including kynurenic acid and quinolinic acid, which are antagonists and agonists of the glutamate N-methyl-D-aspartate (NMDA) receptor, respectively. Kynurenic acid is predominantly produced within astrocytes and quinolinic acid is produced in microglia. It was hypothesised that increases in the microglial quinolinic acid arm of the KP would be evident in depression, potentially resulting in increased glutamatergic neurotransmission.

Methods
The Stanley Medical Research Institute provided RNA from the anterior cingulate cortex (ACC) from depression subjects with psychosis (n=12) and without psychosis (n=12) and non-psychiatric controls (n=12). qRT-PCR was used to measure gene expression of KP enzymes, including tryptophan 2,3-dioxygenase (TDO2), kynurenine aminotransferase I and II (KAT I/II) which produce kynurenic acid and kynurenine 3-monooxygenase (KMO) which ultimately produces quinolinic acid. We also measured gene expression of the NMDA receptor subunits; GRIN1, GRIN2A, GRIN2B, and glial markers; IBA1, GFAP and the excitatory amino acid transporter-2 (EAAT2).

Results
mRNA expression of KAT I, KAT II, and the astrocyte marker, EAAT2 was significantly increased (+15% [p=0.010], +26% [p=0.002], +46% [p=0.017], respectively) in depression, when including those with and without psychosis. There was a significant increase in GRIN2B (+36% [p=0.009]) in depression overall and a borderline increase in GRIN1 (+24% [p=0.056]). We report no change in mRNA expression of TDO2, KMO, GFAP, IBA1 or GRIN2A (all p>0.050).

Conclusions
The increased KATI/II indicates that depression is associated with increased activation of the kynurenic acid arm of the KP in the ACC, which may suggest an overt astrocyte response in depression, alongside increased production of the NMDA receptor antagonist. Taken together with the finding of increased EAAT2 and evidence of increased GluN2B containing NMDA receptor expression in the ACC in depression, these KP changes may be associated with glutamatergic pathology in depression. Future studies should explore if enzymatic mRNA changes lead to altered metabolite levels of the KP in the brain and how they interact with glutamatergic signalling in depression.

Neurobiological Alterations in the CB2 Receptor Relevant to Depression: A Systematic Review

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Background
The mechanisms underlying the aetiology of depression remain unclear. Current antidepressant drugs (ADDs) are challenged by a high incidence of treatment resistance and delayed onset of therapeutic action, highlighting a need for novel treatment targets. Studies have suggested the involvement of the Endocannabinoid System (ECS), particularly the cannabinoid CB1 receptor (CB1R) in the pathology of depression; however, it is unclear whether the lesser-known cannabinoid CB2 receptor (CB2R) also plays a role. The aim of this review was to evaluate existing preclinical and clinical literature investigating alterations in the CB2R relevant to depression.

Methods
A systematic literature search was conducted across the following electronic databases; PubMed, Scopus, and Web of Science following PRISMA guidelines, using search terms “depression” and “CB2”. Publication dates up until March 2020 were included. Studies that manipulated the ECS through receptor modulation via the use of an external agonist and/or antagonist were excluded. A total of 14 studies (9 preclinical and 5 clinical) were included in the present review. These studies examined changes in the CB2R in altered neurological states relevant to depression.

Results
CB2R expression was upregulated in the dorsolateral prefrontal cortex (PFC) in ADD-naïve suicide victims (without depression diagnosis), not in clinically depressed cohorts administered chronic ADDs (including suicide victims). CB2R Q63R polymorphism could predispose clinical depression. Preclinical studies employed several depression models (male dominated). CB2R expression was differentially upregulated in early life and chronic unpredictable stress paradigms, and Wistar Kyoto rats (PFC, hippocampus, striatum, cerebellum). Conversely, CB2R expression decreased in olfactory bulbectomized rats (PFC, hippocampus), with no changes in C57BL/6J anxiety, inflammatory (interferon α-induced) or post-stroke models. CB2R gene overexpression induces resistance, while deletion increases vulnerability to depressive-like stimuli.

Conclusions
The limited evidence suggests a role for the CB2R in the neurobiology of depression; however, there appear to be conflicting findings that could be a result of the diversity within the limited clinical population samples and the heterogeneity of the rodent models of depression. Further studies are needed to examine CB2R alterations in clinical and pre-clinical models of depression that include consideration of sex differences and effects of ADDs, among other factors, in order to elucidate the role of the CB2R in depression and its potential as a novel therapeutic target.

Effect of deferiprone on the serotonin transporter knock-out mouse model of depression

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Background
Current therapeutics for major depressive disorder (MDD) which modulate monoamine neurotransmitter levels either lack efficacy for the broader population or cause deleterious side effects. MDD is most distinctively identified by a prolonged period of depressed mood and aberrant stress-coping mechanisms. Individuals with a genetic predisposition involving the serotonin transporter have an increased propensity for developing MDD and are also more resistant to the therapeutic effects of currently available treatments for MDD. To tackle this issue, non-monoaminergic therapeutics must be explored. Deferiprone is primarily an iron chelator which has also been shown to reduce serotonin neurotransmitter synthesis.

Methods
The present study aims to characterise the effects of deferiprone in the serotonin transporter knock-out (5-HTT KO) mouse model of MDD. To assess the therapeutic viability of deferiprone on depression associated behaviours, acutely following deferiprone treatment, the forced-swim test (FST) was conducted. To determine the relevant brain regions activated by deferiprone, immunohistochemical staining of c-fos was conducted following acute deferiprone intraperitoneal administration, with or without forced-swim exposure.

Results
Acute delivery of deferiprone reduced immobility time in the 5-HTT KO group in the forced-swim test. In addition, deferiprone administration without forced-swim exposure resulted in increased c-fos expression in the hypothalamus (paraventricular nucleus), nucleus accumbens shell, amygdala (medial, lateral, central and basolateral) and bed nucleus of the stria terminalis regardless of genotype. Furthermore, there was a reduction in c-fos expression following acute deferiprone and forced-swim exposure in the paraventricular nucleus of the hypothalamus in both genotypes.

Conclusions
Based on these results, acute deferiprone is effective in ameliorating the depression associated behaviour displayed by 5-HTT KO model in the FST, and seems to activate brain regions associated with the actions of clinically available antidepressants. These findings provide compelling evidence for the potential use of deferiprone in alleviating symptoms associated with MDD. Further investigation must now be carried out to replicate these therapeutic effects using different behavioural paradigms relevant to depression.

2.2 Affect

2.2.2 Anxiety

From Bowels to Behaviour: Neonatal Immune Challenge Impact on Adult Anxiety Behaviour and Gastrointestinal Changes

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Background

There is a distinct relationship between anxiety disorders and the gastrointestinal (GI) tract, with GI abnormalities considered a significant comorbidity of anxiety disorders and vice versa. While, the aetiology of some anxiety disorders remains unknown, the gut-brain-axis (GBA), a bidirectional communication system between the GI tract and the brain, is a possible mechanism for this relationship. The GBA is crucial throughout neurodevelopment, with early life stress (ELS) believed to influence GI and mental health in later life. This project uses our neonatal immune challenge model to investigate the effect of ELS on GI inflammation and anxiety-like behaviour in adulthood.

Methods

Wistar rats were injected with lipopolysaccharide (LPS; 0.05 mg/kg), an endotoxin, in the treatment group to induce early life stress or equivolume saline in the control group, on postnatal days (PNDs) 3 and 5. Behaviour tests were conducted at PND 90 to assess anxiety-like behaviours. Evidence of GI inflammation and barrier integrity were assessed in the colon at PND 90 using qPCR and histological methods. Both males and females were assessed.

Results

Behaviour results showed that early life stress induces behavioural changes, however these results are sex dependent. Exposed males displayed increased anxiety, evidenced by decreased exploration and social interaction and increased rearing. Whereas exposed females displayed more complex behaviour with increased locomotion and social interaction.

In the gut we found early life stress leads to gut changes, again this was sex dependent. Exposed males displayed increased inflammation with significant alterations of cytokines such as IL1B and TNF, and increased lymphocytes. Exposed females found increased stress hormones (CRH) in the gut. Early life stress disrupted the intestinal barrier independent of sex.

Conclusions

We have found that early life stress alters the gut brain axis with lasting effects. Animals who received LPS as neonates displayed altered anxiety behaviours and gastrointestinal changes in adulthood. Importantly, these results were sex dependent highlighting the need for more sex specific research into both mechanisms and symptoms of psychological and gastrointestinal disorders. Combined, these findings illustrate the profound impact of early life stress and the entwined network of our bowels and brains and the impact on behaviour.

Restraint stress enhances cancer progression and alters anxiety-like behaviour in a mouse model of breast cancer

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Background
Anxiety in cancer patients is approximately 3-times more prevalent compared to the general population and 22% of cancer survivors suffer from a long-term PTSD like syndrome. It is possible that these symptoms are caused by the anxiety/stress of a cancer diagnosis or by the cancer. Given the neuroimmune and neuroendocrine systems interact, it is plausible that both cancer and stress synergistically enhance anxiety in cancer patients. To disambiguate the role of cancer versus stress, we examined anxiety-like behaviour in tumour and non-tumour bearing mice exposed to restraint stress (vs no stress) using a mouse model of metastatic breast cancer.

Methods
Female BALB/c mice were injected with 4T1.2 mammary adenocarcinoma cells into the 4th left mammary fat pad or a sham injection of sterile PBS. To model the physiological impact of stress caused by a cancer diagnosis, mice underwent 2 h of restraint stress (vs handling) from days 3-9 after tumour cell injection, and then were assessed on a battery of anxiety-related behavioural tests. At study completion, mice were euthanized with CO2 and blood and spleens were collected. Brains and lungs were collected after cardiac perfusion with PBS and paraformaldehyde.

Results
Restraint stress significantly enhanced tumour growth, and cancer caused splenomegaly, indicating cancer-induced inflammation. Restraint stress and cancer each induced anxiety-like behaviour on the elevated plus maze. Cancer increased anxiety-like behaviour in the light/dark box. Surprisingly restraint stress caused tumour-bearing mice to spend more time in the light section of the light/dark box. This is possibly due to the anti-inflammatory actions of glucocorticoids induced by stress, which will be determined by assessment of plasma corticosterone. Neither cancer nor stress affected behaviour in the open field test.

Conclusions
The findings provide evidence confirming brain-to-tumour communication as stress enhanced cancer progression. However, the behavioural findings indicate that the interaction between cancer and stress is more complex than originally anticipated, and the insensitivity of the behavioural assays could be impeding the identification of nuanced biology. Therefore, we are examining the brains for microglial activation to determine how stress and cancer impact glial cell activation. This study aims to close the gap in our understanding of the physiological impact of stress and neuroinflammation in cancer-associated anxiety, and identify novel targets for interventions for those that suffer from cancer-related mood disorders.

Threat and safety reversal learning in social anxiety disorder - an fMRI study.

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Background
Social anxiety disorder (SAD) has been linked to maladaptive forms of fear regulation, including the capacity to distinguish between learned threat and safety signals in a flexible manner. However, few studies have directly examined such flexible fear-related processing in young, unmedicated SAD patients, including its neural basis. Our study aimed to address this issue by characterizing the neural, subjective and autonomic correlates of threat and safety reversal learning in patients with SAD and comparing them to demographically matched patients with major depressive disorder and to healthy control participants.

Methods
All participants completed a threat-safety reversal learning task during functional magnetic resonance imaging. Our primary group analyses were focused on the three key regions of the 'extended fear network', the dorsal anterior cingulate cortex, anterior insula cortex and the ventromedial prefrontal cortex. We supplemented these analyses by investigating associations between participants' task evoked subjective and neural responses, and their scores on the Liebowitz Social Anxiety Scale (LSAS).

Results
While successful threat-safety updating was associated with significant activation of the regions of interest across the groups, there were no significant differences observed between them, which was consistent with subjective reports of anxiety and affect. For subjective reports, however, higher scores on the LSAS were found to predict greater safety reversal learning.

Conclusions
We did not observe threat and safety reversal learning to be significantly impaired in young people with SAD. Our study raises interesting questions about the nature of maladaptive threat and safety learning in the disorder and the direction of future studies.

EEG Correlates of Attentional Control in Anxiety Disorders: Error-Related Negativity and Correct-Response Negativity findings.

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Background

Anxiety disorders are highly prevalent and cause substantial personal, social and economic burden. Current treatment approaches are largely ineffective, with both psychological, and pharmacological, interventions having moderate effects at best. As over 33% of individuals have more than one anxiety disorder simultaneously this suggests that there may be some underlying similarities that are found across anxiety disorders i.e. transdiagnostically. Altered attentional control is one such similarity found across anxiety disorders and is associated with specific changes in brain activity which can be recorded by electroencephalogram (EEG). These include Error-Related Negativity (ERN) and Correct-Response Negativity (CRN).

Methods

A systematic review was undertaken to assess the research on EEG correlates of attentional control (ERN and CRN) in individuals with clinical anxiety and healthy controls.

Results

A consistent increase in ERN amplitude was found in individuals with clinical anxiety compared to healthy controls, for both non-emotional and emotional attentional control across ~87% of studies extracted. Of the studies that measured CRN, only ~20% found significant differences between individuals with clinical anxiety compared to healthy controls, however of these studies, all showed the consistent pattern of an increase in CRN amplitude in individuals with clinical anxiety compared to those without.

Conclusions

Findings indicate the promising utility of ERN in attentional control as a robust, transdiagnostic trait marker of clinical anxiety.

Reproductive experience alters the influence of estrous cycle on the sensitivity to diazepam

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Background
Research indicates that fluctuating sex hormones across the estrous cycle in female rats modulate their sensitivity to benzodiazepines, which are commonly prescribed for anxiety disorders. However, these studies were conducted in females without prior reproductive experience. In female rats and women, reproductive experience alters the nature of sex hormonal fluctuations, and the impact of these fluctuations on the regulation of anxiety. Therefore, this study aimed to compare the dose response function of the benzodiazepine diazepam across the estrous cycle in female rats with and without reproductive experience.
Methods
Naturally cycling virgin female rats (n=47) and reproductively experienced rats (n=50) were injected with a low or high dose of diazepam (1.3mg/kg or 1.7mg/kg, i.p.) or vehicle, in the proestrus (high sex hormones) or metestrus (low sex hormones) phase of the estrous cycle. Thirty minutes post-injection rats were tested on the elevated plus maze.
Results
Replicating past research, in virgin female rats, the low dose of diazepam reduced anxiety-like behaviour in proestrus ($p=.022$), but only the high dose of diazepam reduced anxiety-like behaviour in metestrus ($p=.002$), relative to vehicle-treated rats. In contrast, in reproductively experienced rats, relative to vehicle-treated rats, both the low and high dose of diazepam reduced anxiety-like behaviour in proestrus ($ps<.009$) and metestrus ($ps<.003$).
Conclusions
Reproductive experience may mitigate the influence of estrous cycle on the sensitivity to diazepam. These findings extend previous research by demonstrating that not only menstrual cycle, but also reproductive history, are potentially important factors to consider when prescribing doses of benzodiazepines in females.

Characterizing human safety learning via Pavlovian conditioned inhibition

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Background
Deficient safety learning has been proposed as a consequential phenotype in the pathogenesis of anxiety disorders. Despite increased translational interest in this phenomenon, there has been only limited research on the fundamental basis of safety learning in humans.
Methods
We examined safety learning in 73 healthy participants using a modified Pavlovian conditioned inhibition paradigm. The paradigm featured a threat stimulus that was reinforced alone (A+), but not reinforced when combined with a second stimulus (the conditioned inhibitor, AX-). During a subsequent test phase, X and a control safety cue (C) were each combined with a second threat stimulus (CS+) to assess their suppression of threat responses. Learning was assessed via skin conductance responses (SCRs) and US-expectancy ratings.
Results
Both stimuli successfully suppressed SCRs and ratings at test, but the conditioned inhibitor (X) suppressed ratings by a greater magnitude than the control safety cue (C). Increased expectancy ratings for X were also associated with higher trait anxiety and younger age. These findings suggest that an additive level of conditioned safety accrues to a Pavlovian conditioned inhibitor (exposed to A+/AX- conditioning) compared to a merely unreinforced safety signal (or CS-), and that responses to the conditioned inhibitor are more sensitive to individual differences in trait anxiety.
Conclusions
Learning from expectancy violation (or prediction error, where the omission of threat is surprising) may confer a more robust form of safety learning than learning from stimuli that are merely non-reinforced. We conclude that the Pavlovian conditioned inhibition procedure, so far under-examined human fear conditioning, could provide a valid experimental model of human safety learning, with particular utility for investigating the role of safety learning in anxiety-related pathology.

A state of glucose depletion promotes anxiety-like behaviour in C57BL/6 mice

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Background
The ventromedial hypothalamus (VMH) is largely known for its importance in regulating energy homeostasis. Many studies have shown it is necessary for the counter-regulatory response to hypoglycaemia. The VMH has also been shown to regulate behaviour, including anxiety-like behaviour. This study aimed to investigate the impact of glucose depletion on mood and behaviour, and how the VMH may be involved in driving anxiety-like behaviour.

Methods
55 male C57BL/6 mice underwent behavioural testing in a light dark box and open field 25 min following an intraperitoneal injection of insulin (0.75 U/kg, 1 U/kg or 1.1 U/kg). 24 male C57BL/6 mice were implanted with an intra-cerebroventricular (ICV) cannula in the lateral ventricle, and tested in a light dark box and open field 25 min following an ICV injection of 2-deoxy-glucose (2DG; 0.5mg). Brains were perfused in 4% PFA, cryo-sectioned and stained for c-fos expression after an acute ICV treatment with 2DG.

Results
Insulin-induced low blood glucose is correlated with lower locomotion and time spent in the light zone of the light-dark box, as well as reduced exploratory behaviour in an open field. Similarly, 2DG-treated mice showed significantly reduced locomotor activity, exploratory behaviour and increased anxiety-like behaviour compared to controls. An acute ICV injection of 2DG significantly increases c-fos positive cells in the VMH, but not in the arcuate nucleus, paraventricular nucleus, lateral hypothalamus or medial amygdala.

Conclusions
An acute state of energy deficit caused by insulin or 2DG promotes anxiety-like behaviour and reduces exploratory behaviour in C57BL/6 mice, and the VMH is sensitive to a 2DG-induced glucose deficit. Future experiments should explore the role of the VMH in driving hypoglycaemia associated behaviours.

2.2 Affect

2.2.3 Stress

Evidence that severe stress rewires the brain: association of severe stress exposure with orbitofrontal cortex dendritic spine loss in psychiatric disorders

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Background
Severe stress is one of the strongest risk factors contributing to psychopathology risk, yet the mechanisms underpinning this process are poorly understood. Animal studies indicate that cortical dendritic spines are persistently modified by stress, with similar effects identified in models of psychiatric disorders. However, confirmation in the human brain in the context of stress or psychopathology is lacking. This study aimed to determine the impact of childhood vs adulthood stress on dendritic spines in the human orbitofrontal cortex (OFC) (Brodmann Area 11), a region highly involved in the stress response and implicated in the pathology of psychiatric disorders.

Methods
Postmortem OFC tissue derived from individuals with (1) psychopathology and childhood stress exposure, (2) psychopathology and adulthood stress exposure, (3) psychopathology and no severe stress exposure, and matched controls (n=32) was acquired from the NSW Brain Bank, Sydney (HE2018/351). Apical dendritic spines on pyramidal neurons in cortical layers II/III and V were quantified and morphologically categorised using Golgi-Cox staining (FD Rapid GolgiStain); >20,000 spines were manually categorised and analysed in R. Individual average spine density was compared between groups using analyses of covariance. Linear regression modelling was used to compare segment distance from soma with spine density between groups.

Results
Total spine density was reduced in the superficial layers of the OFC ($F(3,28)=3.059, P=0.0445$) in psychiatric cases with childhood stress compared to cases with no severe stress ($P=0.0280$). This difference was specific to mushroom spines ($F(3,27)=6.710, P=0.0016$), with both cases exposed to childhood and adulthood stress having significantly less mushroom spines compared to controls ($P=0.0060$, $P=0.0488$, respectively) or cases with no stress history ($P=0.0008$, $P=0.0440$, respectively). No significant variance in mushroom spines was detected in the deeper cortical layers ($F(3,27)=2.776, P=0.0605$). No interactive effect of segment distance from soma and total/mushroom spine density in both superficial and deeper layers were identifiable between groups.

Conclusions
We identified persistent reductions in mature dendritic spines in psychiatric cases exposed to severe stress compared to psychiatric cases with no severe stress exposure and controls. These changes were most pronounced in cases with childhood stress exposure, and most notably in the superficial layers (II/III). The findings indicate that there are likely long-term impacts of severe stress exposure on dendritic spines at any age, but that stress during childhood has an exaggerated effect. We hypothesise stress during early life may cause changes in brain connections, setting individuals on a trajectory to develop psychopathology later in life.

Prenatal stress outcomes on the GABA/glutamatergic balance is altered by maternal separation in the neonatal period

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Background
Prenatal stress is associated with the development of neurobehavioral disorders such as Attention Deficit Hyperactivity Disorder (ADHD) in childhood, with susceptibility greater in males. Optimal neurodevelopment relies on the complex interplay between the inhibitory GABAergic and excitatory glutamatergic pathways in the brain. We propose that excessive cortisol exposure in neurodevelopmental periods (prenatal psychosocial stress) will disrupt the balance between these inhibitory/excitatory pathways, and that these imbalances may explain adverse behavioural outcomes. Further, we aimed to examine the role of stress in the neonatal period following prenatal stress exposure in utero, on offspring behaviour and GABAergic/glutamatergic pathways.

Methods
Pregnant guinea pigs were exposed to control-handling or psychosocial stress (2hrs/day strobe light) on gestational age (GA) 50, 55, 60 and 65 (term ~GA71). Following delivery, a cohort of prenatally-stressed pups were subjected to a second stress event (2hrs/day maternal separation) on postnatal day (PND) 1-7, while another group received no postnatal stress. Control, prenatal stress and pre+postnatal stress groups underwent behavioural testing on PND28 (childhood equivalence), and following euthanasia on PND30, hippocampal tissue was collected for real-time PCR analysis of GABA/Glutamatergic pathways. A linear mixed model was used to compare between stress and control groups.

Results
Male guinea pig pups exposed to prenatal stress alone displayed significant increases in locomotor behaviour, compared to controls, indicating a hyperactive phenotype. The hippocampus of these males showed an imbalance in GABAergic/glutamatergic gene expression; the GABAA receptor α1 and α2 subunit ratio (GABRA1/GABRA2) was significantly upregulated ($p=0.006$), as was the ratio of GABA production enzymes GAD1(25)/GAD1(67) ($p=0.002$) and chloride co-transporters NKCC1/KCC2 ($p=0.014$). The ratio of ionotropic glutamate receptors GRIN2A/GRIN2B was also upregulated ($p=0.014$), compared to control. Pre+postnatal stress restored both the adverse behavioural phenotypes and GABAergic/glutamatergic changes to control levels.

Conclusions
The stress-induced changes in GABAergic and glutamatergic components involved in the control of inhibition/excitation balance in this study suggests increased cortisol from prenatal stress mediates behavioural abnormalities in childhood. The complete restoration of these disruptions to control levels following a 'double-hit' of stress (prenatal stress followed by stressful stimuli in the early neonatal period) suggests this time in development is susceptible to further developmental programming. These observations further suggest this period may be a window in which behavioural or therapeutic treatment be used to improve long-term outcomes.

The α9-nACh receptor regulates coping to experimental and environmental stress in mice

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Background
Stress can trigger or exacerbate depression and anxiety disorders, which have less than a 50% success rate of treatments. alpha9-nicotinic acetylcholine receptors (nAChR) are expressed in the adrenal and pituitary glands and may be a promising novel target for treating or preventing stress-related mental health disorders. We aimed to better characterise the functional role of alpha9-nAChRs in regulating stress responses in mice.

Methods
Congenital alpha9-nACh knockout (KO) mice were compared to wildtype (WT) to characterize the stress phenotype that arises in the absence of alpha9-nAChRs. The effect of experimental restraint stress was previously tested on the elevated plus maze, forced swim test, and in corticosterone levels. Environmental stress subsequently arose via ground-borne vibrations from an adjacent construction site. Mice housed during the environmental stress, and those born 1 to 2 generations after the cessation of the stressor, were tested for anxiety on the elevated plus maze.

Results
Naïve alpha9-nACh KO mice showed normal behaviour and physiology on all measures. After experimental stress, alpha9-nACh KO mice exhibit marked anxiety-like behaviour and stress-induced arousal and dysregulated corticosterone levels compared to WT mice. During environmental stress, KO mice fertility decreased while WT was stable. After environmental stress, behavioural tests showed high levels of anxiety in naïve animals. This anxiety phenotype persisted for at least 6 months after the cessation of stress.

Conclusions
alpha9-nAChRs regulate responses to stress and KO mice show a marked inability to cope with moderate experimental or environmental stress. alpha9-nAChRs are important in feedback mechanisms that are activated by stress, and a potential target for treatments of stress-related disorders such as anxiety.

2.2 Affect

2.2.4 Mood disorders

Oral microbiome composition, but not diversity, is associated with adolescent anxiety and depression symptoms

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Background
Depression and anxiety are highly prevalent disorders, whose significant burden is compounded in the presence of oral disease. Mental health disorders and oral health may be associated via changes to the oral microbiome, involving increased pro-inflammatory communication and cortisol in saliva. The present study provides the first culture-independent investigation of the oral microbiome considering depression and anxiety symptoms in adolescence, a critical age where these conditions begin to emerge and co-occur. It also investigates whether inflammation and cortisol moderate these relationships.

Methods
Participants (N = 66) aged 14–18 years (69.70% female) self-reported oral health, depression and anxiety symptoms, and collected saliva samples across two days. Saliva was assayed for cortisol and C-reactive protein (CRP), and used for 16S rRNA gene sequencing to estimate the oral microbiome. Multivariate statistical analyses examined associations.

Results
Overall diversity of the oral microbiome did not differ between adolescents by anxiety or depression grouping (low versus high symptoms), and was not associated with symptom measures. Depression and anxiety symptoms were instead associated with differential abundance of specific bacterial taxa, including Spirochaetaceae, Actinomyces, Treponema, Fusobacterium and Leptotrichia spp. Several host mood-microbial relationships were moderated by proposed mechanisms, including salivary cortisol and CRP.

Conclusions
Oral microbiome composition, but not diversity, was associated with adolescent anxiety and depression symptoms. Longitudinal studies considering these associations would improve mechanistic understanding and adolescence remains an essential developmental period to identify early targets for intervention.

The gut microbiota in anxiety and depression– a systematic review

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Background
Growing evidence indicates the community of microorganisms throughout the gastrointestinal tract, (i.e., gut microbiota), is associated with anxiety and depressive disorders. We present the first systematic review of the gut microbiota in anxiety disorders, along with an update in depression. Consideration of shared underlying features is essential due to the high rates of comorbidity.
Methods
Systematic searches, following PRISMA guidelines, identified 26 studies (two case-control comparisons of the gut microbiota in generalized anxiety disorder, 17 in depression, one incorporating both anxiety/depression, and six including symptom-only measures).
Results
Alpha and beta diversity findings were inconsistent; however, differences in bacterial taxa indicated disorders may be characterized by higher abundance of pro-inflammatory species (e.g., Enterobacteriaceae and Escherichia/Shigella), and lower short-chain fatty acid producing-bacteria (e.g., Prevotellaceae and Faecalibacterium).
Conclusions
Several taxa, and their mechanisms of action, may relate to anxiety and depression pathophysiology via communication of peripheral inflammation to the brain. Although the gut microbiota remains a promising target for prevention and therapy, future research should assess confounds, particularly diet and psychotropics, and examine microorganism function.

Dimensions of interoception and daily emotion during coronavirus lockdown

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Background
The coronavirus pandemic presents multiple psychological stressors. Emotions are influenced by an individual's interoceptive sense. Psychological data on interoception may help develop evidence-driven strategies to reduce negative psychological effects. The aim of the present study was to investigate the relationship between dimensions of interoception and daily emotion in medical students during the coronavirus pandemic. We tested the hypothesis that interoceptive trait predictive error (ITPE) would be positively associated with daily negative affect.

Methods
Nineteen participants (mean age 22.5, 53% male) completed heartbeat detection tasks prior to the coronavirus lockdown. Interoceptive accuracy was examined by a heartbeat counting task and a six-interval heartbeat discrimination task to calibrate an appropriate synchronous interval for the subsequent two-interval task heartbeat discrimination task. Interoceptive awareness was gauged by a confidence-accuracy correspondence and receiver-operator correspondence. Interoceptive sensibility was gauged by the Body Perception Questionnaire. ITPE was calculated as the discrepancy between interoceptive sensibility and interoceptive accuracy. During coronavirus lockdown, participants completed the Positive and Negative Affect Schedule for 14 days.

Results
A Spearman's analysis revealed that ITPE was significantly positively associated with mean daily negative affect over 2 weeks ($r_s = 0.456$, $p = 0.025$, 1-tailed). Interoceptive awareness was negatively associated with negative affect ($r_s = -0.437$, $p = 0.032$, 1-tailed). Interoceptive sensibility was positively associated with negative affect ($r_s = 0.463$, $p = 0.023$, 1-tailed).

Conclusions
These preliminary findings suggest that the degree of interoceptive error may be a predictive factor when determining individuals at greater risk of negative effects on psychological well-being in isolation. Equally, results may indicate a role for interoception related interventions to be implemented in tools developed to mitigate negative responses to heightened isolation.

Associations between mental wellbeing and neural bases of positive emotion recognition in a twin sample using fMRI

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Background
Deficits in basic emotion recognition have been well-documented in clinical disorders including depression and schizophrenia. This highlights the importance of intact emotion processing in mental health and wellbeing. However, it is not yet clear what the underlying neurobiological bases of such an emotion-wellbeing link may be, and whether this association is driven by genetic or environmental factors. Therefore, our aim here was to use fMRI in order to investigate the relationship between wellbeing and neural correlates of emotion, and the extent to which such associations may be heritable.

Methods
230 healthy monozygotic and dizygotic twins from the TWIN-E cohort were included in the current study. A simple emotion recognition task consisting of 240 standardised faces depicting happiness, anger, fear, disgust, sadness, or a neutral expression was used to probe neural activity associated with these basic emotion types. Wellbeing, as well as negative mood symptoms (consisting of depression, anxiety, and stress symptoms), were measured using the COMPAS-W and DASS-42 scales, respectively. Twin modelling was used to determine the heritability of emotion-related neural activity, as well as the genetic and environment covariance between wellbeing, negative mood symptoms, and brain activity.

Results
We found that individuals with high levels of wellbeing (while controlling for negative mood symptoms) displayed greater neural activity in the right inferior frontal gyrus (IFG) in response to happy faces (positive emotion). This region also showed 20% heritability when comparing twin pairs. Using multivariate twin modelling, we identified a significant unique environmental correlation between IFG activity and wellbeing (r = .208), suggesting that unique life events (i.e., life experiences not shared between twins) contribute in common to both constructs, more so than common genetics or shared family environment.

Conclusions
Previous mental health research into emotion processing has mostly focused on the presence of emotion-related deficits in clinical populations. Our observation of a link between neural correlates of positive emotion and wellbeing is in line with the notion of a mutual relationship between these two constructs, and indicate that positive emotion processing (which may be heritable) plays an important role in optimal psychological functioning. This is compatible with the idea that happiness is an important factor in people's lives, and that one's wellbeing state can be impacted by how emotional information is processed.

Predictors of change in wellbeing over a 12-month period in 1399 twins

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Background
The neuroscience of both subjective (hedonic) and psychological (eudaimonic) wellbeing is a highly active area of research in science and medicine given its sparser focus and understanding relative to other mental health conditions. The aim of this study was to identify the psychological, cognitive and physical health predictors of wellbeing change over a 12-month period.
Methods
This talk will report on the significant predictors of wellbeing change over a 12-month period in a sample of 1,399 healthy adult twins (18-60 years) tested across Australia from the TWIN-E study. Wellbeing was measured using the COMPAS-W Wellbeing Scale which provides a composite index of both subjective and psychological wellbeing.
Results
Multiple linear regression modelling was used to evaluate the comparative predictive value of various markers in predicting change in wellbeing over time. We will report on the key significant predictors selected from a range of diverse measures which includes basic demographic information (age, sex, education, and marital status), life events (childhood trauma and recent positive/negative life events), health/lifestyle variables (BMI, sleep, diet, exercise, and socialisation activities), personality, work engagement, and neurocognitive performance.
Conclusions
Mental wellbeing is an independent construct from mental illness symptoms and so it is important to measure predictors of wellbeing change in order to capture a comprehensive understanding of mental health predictors.

Using EEG & ERPs to understand wellbeing

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Background
Despite a recent surge in mental wellbeing research, its underlying neural mechanisms remain largely unknown. This presentation focuses on findings from the TWIN-E study of wellbeing testing associations between EEG measures and mental wellbeing.
Methods
The sample included 422 monozygotic and dizygotic twins aged 18-63. Resting EEG and event-related potentials were measured from 26 electrode sites. EEG bands alpha, beta, delta, and theta were calculated from resting state data, while emotion-related ERPs were measured during an emotional face paradigm. Linear mixed models were used to test for associations between these measures and mental wellbeing. A heritability analysis and correlated factors model were also conducted using the classical twin design.
Results
A significant association was found between mental wellbeing and resting EEG, specifically a profile of high alpha, high delta, and low beta power indicating high wellbeing. The heritability of this EEG profile was driven primarily by common genetic factors (r = -.19). The patterns of association between wellbeing and ERPs to emotional faces will also be discussed.
Conclusions
The findings indicate that different measures of EEG are associated with wellbeing independently from anxiety or depression symptoms. This indicates that individuals with higher wellbeing show altered neuronal firing both at rest and while completing emotional processing tasks.

Dynamic neural interactions supporting the cognitive reappraisal of emotion

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Background
The cognitive reappraisal of emotion is hypothesized to involve frontal regions modulating the activity of subcortical regions such as the amygdala. However, the pathways by which structurally disparate frontal regions interact with the amygdala remains unclear.
Methods
In this study one hundred and four healthy young people completed a cognitive reappraisal task and dynamic causal modeling (DCM) was used to map functional interactions within a frontoamygdalar network engaged during emotion regulation.
Results
Five regions were identified to form the network: the amygdala, the pre-supplementary motor area (preSMA), and the ventrolateral (vlPFC), dorsolateral (dlPFC) and ventromedial prefrontal cortices (vmPFC). Bayesian Model Selection was used to compare 256 candidate models, with our winning model featuring modulations of vmPFC-to-amygdala and amygdala-to-preSMA pathways during reappraisal. Moreover, the strength of amygdala-to-preSMA modulation was associated with the habitual use of cognitive reappraisal.
Conclusions
Our findings support the vmPFC serving as the primary conduit through which prefrontal regions directly modulate amygdala activity, with amygdala-to-preSMA connectivity acting to shape ongoing affective motor responses. We propose that these two frontoamygdalar pathways constitute a recursive feedback loop which computes the effectiveness of emotion-regulatory actions and drives model-based behavior.

2.3 Neurodegeneration, Dementias

Cellular changes in the substantia nigra and subthalamic nucleus in Parkinson's disease following deep brain stimulation

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Background
Parkinson's disease (PD) is a progressive neurodegenerative disorder pathologically hallmarked by the loss of dopamine neurons in the substantia nigra (SN) and alpha synuclein aggregation. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a common target to treat the motor symptoms in PD. However, we have limited understanding of the cellular changes in the STN during PD and our knowledge concerning the impact of DBS on the STN and SN is limited.

Methods
Post-mortem tissue from 6 PD non STN-DBS patients, 5 PD STN-DBS and 7 age-matched controls were stained with markers for neuroinflammation (glial fibrillary acidic protein (GFAP) and Iba1) and neurodegeneration (tyrosine hydroxylase (TH), alpha-synuclein and NeuN). Changes were assessed using quantitative and semi-quantitative microscopy techniques.

Results
This study confirms previous findings of significant neuronal loss ($p<0.001$), increased neuroinflammation ($p<0.018$) and increased alpha synuclein (p0.639 for all variables). However, increased alpha-synuclein deposition was observed in the STN following STN-DBS ($p=0.030$).

Conclusions
This study does not identify any change in inflammation or neuronal loss in the STN or SN following STN-DBS. However, significant alpha-synuclein pathology was present in the STN in all PD cases and was significantly increased in cases with STN-DBS.

Effects of gene-environment interactions on gut dysbiosis and function in the R6/1 mouse model of Huntington's disease

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Background
Huntington's Disease (HD) is a devastating autosomal dominant neurodegenerative disorder, with no current cure or treatment. HD is characterised by impaired motor, cognitive and psychiatric symptoms and is caused by a tandem repeat mutation in the huntingtin gene. Trinucleotide (CAG) repeat length affects the onset, however, is not the sole predictor, and there is evidence for gene-environment interactions. Studies exploring gene-environment interactions in HD mice have found that exercise and environmental enrichment can both delay the onset of symptoms. Exercise and environmental enrichment can also positively modulate the gut and its microbiota, however, this interaction is unexplored in HD.

Methods
We aimed to understand how environmental enrichment (addition of novel objects into the home cage) and exercise (addition of running wheels into the home cage) influence gut physiology and microbiota composition in HD mice, following our recent discovery of altered gut microbiota as a potential therapeutic target for HD. We used the R6/1 transgenic HD mouse model, assessing motor parameters, food and water intake as well as body weight changes. We also assessed faecal output and water content, gut morphology and gut physiology parameters.

Results
We observed expected decreases in motor parameters in HD mice, which was rescued by enrichment and exercise. No differences in gut transit time, faecal output, faecal water content or markers for mucous damage were observed at 12 weeks of age. However, increased gut permeability was observed in HD mice at 12 weeks. We also observed main housing effects on gut morphology, influencing caecum weight:length ratio and colon length.

Conclusions
No differences in gut transit time and faecal output suggest that the gastrointestinal motility of HD mice is intact in the early stages of the disease. Furthermore, no differences in faecal water content or mucosal damage markers suggest that water absorption of the small intestine and mucosal layers are relatively intact in HD mice at 12 weeks of age. However, we did observe an increase in gut permeability at the same age that dysbiosis was previously reported, indicating an imbalance in gastrointestinal function. Further investigation is required to assess the effects of the microbiota and their by-products on these parameters.

Underlying biopsychosocial mechanisms of disinhibited behaviours in dementia and a systematic review of management approaches

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Background
Despite being associated with multiple negative outcomes, disinhibited behaviours in dementia including sexual disinhibition, are reported and researched less often than other behaviours and psychological symptoms associated with dementia. They can cause significant distress for families, carers, other residents, as well as individuals who experience them. Our aims were to: 1) review the literature of underlying biopsychosocial factors (including neurochemical mechanisms) involved in disinhibited behaviours and develop a conceptual model to aid understanding, and 2) systematically review pharmacological and nonpharmacological approaches that included outcome measures of disinhibited behaviours in dementia. We also discuss issues around measuring disinhibited behaviours.

Methods
Aim 1: A scoping review identified papers investigating biopsychosocial mechanisms underpinning disinhibited behaviours and impulsivity. A conceptual model of associated factors was developed and case vignettes were described. Aim 2: Systematic searches of the databases MEDLINE, EMBASE and PsychINFO were conducted for publications that included measures of disinhibited behaviours in dementia published between 2002 and March 2020. We included reviews, original articles, case reports, cohort studies and randomised controlled trials. All studies were rated for research quality. Statistical and clinical significance were considered. Effect sizes were included where provided or calculated where possible.

Results
Aim 1: As with other behaviours and psychological symptoms, biological factors alone do not explain disinhibited behaviours but are integrated with psychological, social and environmental factors. Our conceptual model incorporates associated factors and we provide case vignettes to build on understanding of underlying causes of behaviours. Aim 2: Nine pharmacological (including pain management and antidepressants) and seven nonpharmacological studies (models of care, education/ training, physical activity, and music) showed significant effects for reducing disinhibited behaviours in dementia ($p < 0.05$; mean Cohen's $d = 0.53$ and 1.13 respectively). The measure used most often was the Neuropsychiatric Inventory disinhibition subscale.

Conclusions
We demonstrated clinical effectiveness for several pharmacological and nonpharmacological approaches. Clinical effectiveness was higher for nonpharmacological approaches. Disinhibited behaviours exhibit considerable heterogeneity in their presentation, underlying mechanisms and effective management approaches; likely driven by several associated factors including individual differences. Our conceptual model aims to address these and to provide future directions for research and clinical guidance.

Cannabidiol (CBD) treatment improves spatial memory in 14-month-old female TAU58/2 transgenic mice

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Background
Frontotemporal dementia (FTD) and Alzheimer's disease (AD) share the pathological hallmark of intracellular neurofibrillary tangles (NFT), which result from the hyperphosphorylation of microtubule associated protein tau (i.e. caused by mutations in the MAPT gene). The P301S mutation in human tau carried by TAU58/2 transgenic mice results in brain pathology and behavioural deficits relevant to FTD and AD. The phytocannabinoid cannabidiol (CBD) exhibits properties potentially beneficial for multiple pathological processes in FTD and AD.

Methods
We treated 14-month-old female TAU58/2 transgenic and wild type-like (WT) littermates with 100 mg/kg CBD for three weeks via intraperitoneal injection prior to conducting a battery of behavioural tests relevant to FTD and AD. These included the elevated plus maze, motor function tests, the social preference test, the cheeseboard task and fear conditioning.

Results
TAU58/2 females had reduced motor function, bodyweight and anxiety compared to WT. The moderate reduction in sociability, and defective spatial recognition memory of vehicle-treated transgenic mice was restored by CBD treatment. Average speed on the cheeseboard was increased in CBD-treated mice although this effect was strongest in TAU58/2 mice. CBD treatment also reduced anxiety-like behaviour and reduce contextual fear-associated freezing in both TAU58/2 and WT mice.

Conclusions
Chronic administration of 100 mg/kg CBD ameliorated several dementia-relevant phenotypes in TAU58/2 mice, suggesting this phytocannabinoid may be useful for treating aspects of tauopathy-related neurodegenerative diseases.

Chain Length Alterations to Sphingolipids in the Caudate of advanced Huntington's Disease Patients

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Background
Huntington's Disease (HD) is an autosomal, dominant, neurodegenerative disorder characterised by progressive and terminal psychiatric, cognitive, and motor disturbances. HD is caused by a polyglutamine mutation in the huntingtin gene (HTT) and subsequent protein (mhtt). Brain-region specific disturbances are a feature of HD, despite ubiquitous expression of mhtt. The unique lipid profiles of these regions may contribute to their vulnerability. Sphingolipids act as second messengers and membrane components. Alterations to the concentrations of these molecules, and their enzymes occur in multiple neurodegenerative diseases and HD mouse models. There is limited research on sphingolipid pathways in HD human tissue.

Methods
Post-mortem human caudate from 13 advanced HD subjects and 13 age and sex-matched controls was supplied by the Victorian Brain Bank. All HD subjects had a Vonsattel pathological grading of IV, the most severe. Sphingolipids were extracted and measured using targeted mass spectrometry techniques. Proteins were extracted and analysed via western blot.

Results
We identified alterations to sphingolipid species governed by the length of their fatty acyl chain. Long chain (C16-C21) species were increased in HD caudate, with a simultaneous decrease in very long chain (C22-C26) species. This specific pattern was observed in several subclasses of lipids: ceramides, sphingomyelins and lactosylceramides, and did not occur in sulfatides. Expression of ceramide synthases 1 and 2, which produce long and very long chain ceramides respectively, was not different in HD caudate. Western blots of ceramide synthase 2 identified additional banding above the molecular weight of the protein, in HD subjects only.

Conclusions
The increased concentration of long chain species and decreased concentration of very long chain sphingolipid species may reflect changes to the lipid profile of neurons in HD caudate. The western blots of ceramide synthase 2 indicate that this enzyme may be modified in HD, affecting the availability of very long chain species. Increased long chain and decreased very long chain sphingolipid species has been identified in other neurological illnesses.

Effects of dance on cognitive skills in people with Parkinson's disease

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Background
Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system which manifests as a broad spectrum of motor and non-motor symptoms. While there is accumulating evidence supporting dance for improving motor features in PD, it is not yet clear if the benefits extend to non-motor features. This study aimed to determine the impact of dance classes based on the Dance for Parkinson's Disease (DfPD®) model, on objectively assessed cognitive skills in people with PD.

Methods
A quasi-experimental parallel group, pre- and post-test design was used. The participants were allocated to a Dance Group (DG; n= 17) or Control Group (CG: n=16). Participants had early-stage PD (Hoehn & Yahr: DG=1.6 ± 0.7, CG =1.5 ± 0.8) with no cognitive impairment (Addenbrooke's score: DG= 93.2 ± 3.6, CG = 92.6 ± 4.3). The DG undertook a one-hour class, twice weekly-12 weeks, while the CG had treatment as usual. The NIH Toolbox® cognition battery and the Trail Making Test (TMT) A and B were used to assess the cognitive skills.

Results
There were no differences between groups at baseline on any measure. Compared to the CG, the DG had significant pre-post improvement on the episodic memory measured through auditory verbal learning test of the NIH-TB, $F(1,31)=4.25$, $p=0.048$ and the executive function measured using the TMT (TMT-B, $F(1,31)=5.73$, $p=0.023$; TMT B-A, $F(1,31)=5.55$, $p=0.025$). Remaining cognitive skills assessed through NIH-TB (processing speed, attention, inhibitory control, cognitive flexibility, and language) did not improve significantly.

Conclusions
Dance classes based on the DfPD® model had mix results on cognitive skills. A larger RCT with periodic follow-up assessment is required to confirm these effects.

Anhedonia as a primary feature in frontotemporal dementia

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Background
Much of human behaviour is motivated by the drive to experience pleasure. This capacity to experience pleasure depends upon the integrity of frontostriatal circuits in the brain. A breakdown in these circuits leads to the inability to experience pleasure, otherwise known as anhedonia. Despite increasing attention in the neuropsychiatric literature, the nature and severity of anhedonia in dementia remains unclear. This is the first study to explore the prevalence and neural correlates of anhedonia in frontotemporal lobar degeneration (FTLD), and its potential overlap with apathy and depression.

Methods
A total of 172 participants took part in this study including 87 FTLD patients, 34 Alzheimer's disease, and 51 healthy older Control participants. Within the FTLD group, 55 cases were diagnosed with clinically probable behavioural-variant FTD, 24 presented with semantic dementia, and 8 cases had received a diagnosis of progressive non-fluent aphasia. Premorbid and current anhedonia was measured using the Snaith-Hamilton Pleasure Scale (SHAPS), while apathy was assessed using the Dimensional Apathy Rating Scale (DApS). Voxel-based morphometry analysis was used to examine associations between anhedonia and patterns of grey matter atrophy in the brain.

Results
Relative to Controls, behavioural-variant FTD and semantic dementia patients showed a significant increase in anhedonia, representing a departure from their pre-morbid levels. Voxel-based morphometry analyses revealed that anhedonia was associated with atrophy in an extended fronto-striatal network including orbitofrontal, medial prefrontal and insular cortices, paracingulate gyrus and the putamen. The neural correlates of anhedonia were largely dissociable from that of apathy, with only a small region of overlap in the right orbitofrontal cortices.

Conclusions
This is the first study, to our knowledge, to demonstrate striking levels of anhedonia in FTLD syndromes, reflecting atrophy of predominantly right-sided fronto-striatal brain regions specialised for hedonic tone. The presence of anhedonia cannot be entirely explained in terms of apathy, depression, or disease staging, and points to the importance of expanding current diagnostic criteria for FTLD to consider anhedonia as a primary feature. Future studies addressing the impact of anhedonia on everyday activities are critical for developing targeted interventions to improve the quality of life of FTLD patients and their carers.

Cannabidiol prolongs lifespan and prevents neurite degeneration in a Caenorhabditis elegans model of Alzheimer's disease

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Background
Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. It is characterised by the accumulation of amyloid-β (Aβ) protein, which is involved in neurite degeneration. Cannabidiol (CBD), a phytocannabinoid from the Cannabis sativa plant, has a broad spectrum of potential therapeutic properties in preventing neurodegenerative pathology. The mechanisms responsible for these effects, however, are still poorly understood.

Methods
In this study, we used the transgenic CL2355 strain of Caenorhabditis elegans (C. elegans), which expresses the human Aβ peptide throughout the nervous system to investigate the effects of CBD in lifespan and health span. The neuroprotective effect of CBD was further explored by observing the dopaminergic neurons using transgenic dat-1 :: GFP strains using the confocal microscope.

Results
CBD treatment extended the lifespan of the transgenic Aβ nematodes. In addition, CBD significantly improved age-dependent changes in reproductive behaviour (egg-laying) compared with the control strain. Moreover, we found that the Aβ-expressing model showed substantial degeneration of dopaminergic neurons after 3 days, which was rescued by CBD treatment. Lastly, we evaluated the effect of CBD on the various behavioural responses in the Aβ model. The results showed that CBD treatment led to increased exploratory behaviour, increased pharyngeal pumping in the aged animals, and an improved chemotaxis response in the Aβ-expressing animals.

Conclusions
In summary, our study shows that CBD treatment extended lifespan and improved health span in transgenic Aβ-expressing worms. We further demonstrate that CBD prevented dopaminergic neuron degeneration induced by Aβ. Our findings highlight the neuroprotective benefits of CBD and its potential therapeutic approach for the treatment of AD patients.

2.4 Substance use and associated disorders

Maternal Exposure to Methadone or Buprenorphine in the Prenatal Period and During Lactation Induces Sex-Specific Developmental and Cognitive Deficits in Rat Pups

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Background
Opioid use and abuse in women of reproductive age has escalated in the last decade, increasing the number of infants with Neonatal Abstinence Syndrome (NAS) by 300% in some countries. Methadone (MET) is the gold standard therapy for pregnant women; however, buprenorphine (BUPE) is increasingly prescribed due to improved compliance. The long-term developmental trajectories for offspring exposed to BUPE versus MET is not clear. Here we use an animal model to compare the impact of pre-natal MET or BUPE on early development and cognition in male and female rat offspring.

Methods
From gestational day 11 pregnant female Sprague-Dawley rats received no treatment, slow-release MET (9 mg/kg/day) or BUPE (1 mg/kg/day) across gestation and until weaning (post-natal day 21). Physical and behavioural milestones of pups were recorded, and cognitive capacity assessed using the novel object recognition (NOR) and novel place recognition (NPR) tasks.

Results
Pups born to MET- or BUPE-treated dams showed a reduced growth trajectory, delayed eye opening and delayed motoric development, as well as impaired performance on the NOR and NPR tasks. The extent of these deficits was less severe with the use of BUPE over MET, although across pups from BUPE treated dams, female pups had worse outcomes than males.

Conclusions
Pre- and post-natal MET and BUPE exposure had a marked physical and cognitive impact on rat offspring, although exposure to BUPE may have less pronounced negative consequences compared to MET. These findings highlight the ongoing and pressing need for new approaches in treating opioid dependent pregnant women.

A systematic review investigating the effect of opioid misuse on the gut microbiome

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Background
Cognitive impairment is a core component of opioid use disorders, and can inform disease severity and recovery. The pathogenesis underlying cognitive impairments resulting from opioid use disorder is poorly understood and treatment options are lacking. The commensal gut microbiota may influence brain function, including cognition and addiction, and could serve as a key candidate for future targeted treatments. Gut microbiota imbalances have been identified in alcohol addiction; however, whether dysbiosis is evident during the misuse of other substances is unclear. Therefore, the aim of this review was to outline patterns of dysbiosis in studies investigating clinical and preclinical opioid misuse.

Methods
A systematic literature review was conducted using PRISMA guidelines. Major databases (SCOPUS, PubMed, and Web of Science) were examined using the terms (“opiate” OR “opioid”) AND (gut microbiota OR microbiome OR microbiota) up to April, 2020. Articles were included if they investigated a cohort misusing opioids, or a pre-clinical model of opioid misuse, and provided data on the microbiota profiles of the subjects. 14 articles investigating the effects of various opioids on the microbiota were included. Of these, two were clinical studies and 12 were preclinical studies (one primate and 11 rodent models).

Results
Five microbiota families (Bacteroidaceae, Clostridiales XIV, Lachnospiraceae, Peptostreptococcaceae, Ruminococcaceae) and 2 genera (Bifidobacterium, Parasutterella) were altered in opioid users with comorbid cirrhosis, and two genera (Bifidobacterium, Prevotella) in subjects with comorbid type 2 diabetes. In primates, morphine misuse with comorbid simian immunodeficiency virus altered 3 families (Leuconostocaceae, Methanobacteriaceae, Streptococcaceae) and 4 genera (Actinobacillus, Dialister, Haemophilus, Methanosphaera). In rodents, 6 bacterial phyla, 20 families, 25 genera and 20 species imbalances were identified, with consistent Enterococcus faecalis upregulation and differential changes in Akkermansia, Allobaculum, Bifidobacterium, Clostridium, Enterococcus, Lactobacillus, Parabacteroides, Prevotella, Ruminococcus, Streptococcus, Sutterella across studies.

Conclusions
Research examining the effect of opioids on microbiota is limited, particularly in human subjects. Existing research suggests a dysbiotic effect of opioid misuse on microbiota. We identified several strains commonly disrupted at the genus level. Phyla and species-level alterations have not been reported in humans and primates. Given the emerging evidence showing that certain bacteria are implicated in key signalling pathways (eg dopaminergic, endocannabinoid, neurotrophic factors) and metabolite production (short chain fatty acids), further research is needed to understand the pathophysiological consequence of microbiota dysbiosis on brain function (including cognition and reward pathways underpinning addiction) in people undertaking opioid misuse.

Acute and sub-chronic cannabidiol have effects on different symptoms of opioid withdrawal in mice

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Background
The opioid epidemic is the deadliest drug crisis in American history, taking 130 lives each day, more than guns or car accidents. The current situation can be directly linked to the over-prescription of opioids, which usurp the brain's reward system while creating tolerance and withdrawal, gating the transition to using more dangerous opioids. Emerging epidemiological evidence suggests a potential role for medicinal cannabis in treating opioid use disorder (OUD); for example, opioid use decreased by 40-60% in chronic pain populations using medicinal cannabis and opioid mortality rates are lower in US states that have legalised medicinal cannabis.

Methods
We explored the efficacy of CBD, a non-psychoactive component of medicinal cannabis for oxycodone withdrawal using murine models of spontaneous and naloxone-precipitated oxycodone withdrawal. We administered escalating doses of oxycodone, twice daily over a 9 days. In the acute dosing studies, we administered a single dose of CBD prior to precipitation of opioid withdrawal with naloxone or testing for spontaneous withdrawal 24 h after the final oxycodone injection. In the co-dosing studies, CBD was administered prior to each oxycodone administration. Our key measures of interest covered the gastrointestinal, somatic and negative affective symptoms of opioid withdrawal.

Results
We have shown that acute CBD dose dependently inhibits some somatic symptoms of opioid withdrawal in mice, and causes pronounced inhibition of gastrointestinal symptoms. Further, we discovered that chronic co-administration of CBD alongside oxycodone dose dependently inhibits opioid withdrawal-induced jumps, an escape behaviour thought to be caused by withdrawal-induced dysphoria. We have repeated the acute CBD experiments in female mice showing a consistent therapeutic effect of CBD for naloxone-precipitated withdrawal, however, female mice did not show a robust spontaneous withdrawal syndrome.

Conclusions
To compliment these behavioural findings, pharmacological studies are underway to explore one potential mechanism of action, CB1 negative allosteric modulation. Further, we are currently conducting immunohistochemistry studies to reveal brain regions involved in CBD interference with opioid withdrawal, which will subsequently be assessed in greater detail using fibre photometry.

Risk factors for adolescent-onset methamphetamine use disorder: a role for poor inhibitory control and gene polymorphisms

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Background
Methamphetamine is the second most widely abused illicit drug worldwide and represents one of the greatest health threats. More alarming, over 4% of Australians aged 14-19 have reported using methamphetamine in a given year. This is a major concern, as adolescence is a period of heightened vulnerability to substance use disorders, and young people are more prone to relapse. Evidence suggests that early life adversity, cognitive deficits, and gene polymorphisms in addiction-related genes may be contributing factors. We therefore investigated the relationship between the age of onset of methamphetamine use and potential risk factors in people with methamphetamine use disorder.

Methods
We recruited thirty-five current methamphetamine users (last use within 7 days) with a DSM-5 diagnosis of methamphetamine use disorder, and matched-controls. Participants were administered the Childhood Trauma Questionnaire, the Barratt Impulsiveness Scale, and a cognitive task battery assessing speed of processing, cognitive flexibility, working memory, and inhibitory control. Inhibitory control was also assessed using a novel cue reactivity task that we developed, consisting of the pseudo-randomised presentation of methamphetamine-related cues counterbalanced with food-related cues. Skin conductance response and self-reported cravings were recorded throughout the task. Whole blood was collected for genotyping and assessment of polymorphisms in key addiction-related genes.

Results
Correlation analyses revealed that inhibitory control was positively associated with age of onset of methamphetamine use ($n=35$; $p<0.01$), but not length or severity of use. Inhibitory deficits were not mediated by early life adversity or poor impulse control. There was also a strong association between poor inhibition and cue-induced cravings on the cue reactivity task ($n=35$; $p<0.01$). Preliminary chi-square analyses of addiction-related polymorphisms revealed that the Pro4Thr variant of the vesicular monoamine transporter 1 gene conferred a risk for methamphetamine use disorder ($n=58$; OR=2.82), with minor allele carriers more likely to have started using methamphetamine earlier in life ($n=28$; $p=0.041$).

Conclusions
Our results suggest that impaired inhibition during adolescence may be a risk factor perpetuating methamphetamine use after experimentation, contributing to the development of methamphetamine use disorder. In addition, poor inhibition may lead to heightened cue-induced cravings and may be a risk factor for cue-induced relapse in young people. The Pro4Thr polymorphism in the vesicular monoamine transporter 1 gene may also play a role in adolescent vulnerability to methamphetamine use disorder, although its exact role is still unclear. Future directions include creating a model to understand predictors and/or consequences of early onset methamphetamine use and identify new therapeutic targets.

Repeated methamphetamine exposure and subsequent withdrawal alters parvalbumin interneuron excitability in the prefrontal cortex

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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 (*$p < 0.05$). Action potential firing frequency of PV interneurons in response to depolarising current injections was significantly increased in male and female mice after METH administration compared to saline controls (*$p < 0.05$). Resting membrane potential was significantly lower in the female group following METH exposure compared to saline controls (*$p < 0.05$), with no other alterations in intrinsic properties observed.

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 results in an increase in PV excitability, as seen as an increase in action potential firing frequency. This is consistent with increase in GABA and GABAergic neurotransmission in PFC during psychostimulant withdrawal, and functional hypoactivity in the PFC during withdrawal. It appears that PV output and excitability may vary across intoxication/withdrawal states, thus future studies aim to elucidate the activity of PV interneurons in vivo across different addiction states.

The effect of cannabigerol on methamphetamine addiction and psychosis

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Background
The psychostimulant methamphetamine (METH) is a highly addictive illicit drug associated with physical and mental health problems, especially psychosis. Pharmacological approaches for METH dependence suffer limitations due to poor efficacy. Cannabis constituents demonstrate therapeutic potential because of their anxiolytic and neuroprotective properties. We have previously shown that cannabidiol (CBD) reduces the motivation to self-administer METH and decreases the sensitised hyperactive response to METH in rats. Cannabigerol (CBG) displays emerging therapeutic properties. As such, we aimed to test the ability of CBG to reduce METH psychosis and motivation for METH reward in rat models of chronic drug use.

Methods
12 rats underwent a sensitization protocol where they received daily METH injections for 7 days. After withdrawal phase, CBG (20, 40, 80 mg/kg) was administered 30 minutes prior to METH (1mg/kg), and locomotor activity was measured. 16 rats were trained to intravenously self-administer METH via lever press (fixed ratio 1 schedule of reinforcement) then advanced to a progressive ratio schedule to examine the effects of CBG (same previous doses) on reward motivation. We tested a combination of CBG and CBD (20+80mg/kg), to see if it would inhibit reward motivation, using a known effective dose of CBD (80 mg/kg) as control.

Results
None of the doses of CBG tested were able to reduce locomotor activity in METH sensitised rats and the motivation to self-administer METH. As expected, CBD administration reduced the motivation to self-administer METH, and the co-administration of CBG reversed this effect.

Conclusions
This is the first study analysing the effects of CBG on psychosis and METH seeking behaviour and suggests that, at least at the doses tested, CBG might not have the same pharmacological mechanisms and neurochemical interactions as CBD, and potentially could be antagonizing CBD effects.

Effects of Ibogaine on cocaine-conditioned place preference on male and female rats

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Background

Psychostimulants, such as cocaine, have significant abuse potential and studies shows that women are more vulnerable to addiction development, probably due to the influence of sex hormones. Cocaine addiction has no specific pharmacological treatments, despite its burden on public health. Ibogaine has shown interesting results for different drugs of abuse. However, ibogaine has shown to change locomotion with acute and sub-cronic administration. We aimed to verify whether the treatment with ibogaine affects preference for cocaine in male and female rats in the conditioned preference place protocol (CPP) and if ibogaine influences open field (OF) measures with a sub-acute dose.

Methods

Wistar albino male (n=40) and female (n=34) rats on postnatal day (PND) 21 were allocated in standard housing. At PND 50, a classical CPP was initiated. Pretesting and testing lasted 15 min, while conditioning sessions lasted 30 min. Treatment was administered on day PND 61 (Testing) and 62 (OF) around 5 hours before procedures: vehicle (VEH: DMSO 80% + saline 20%); ibogaine (IBO): 40 mg/kg. Vaginal smear cytology was done daily to verify the female estrus cycle. Experiments followed the guidelines of the International Laboratory Animal Science Council and were approved by UFCSPA's Ethics Committee for Research (#233/18).

Results

In IBO male rats, the time spent in the cocaine chamber at testing was reduced compared to pretesting ($P = 0,026$) and compared to VEH ($P = 0,049$). In females, no statistical significant differences were found for any group in CPP. No interaction with estrous cycle or treatment was found either. OF measures: IBO males and females demonstrated decreased total locomotion (sum of total quadrants crossings) ($P< 0,001$) and rearing ($P < 0,001$) compared to VEH groups. Time in center showed no statistical differences. These results show promising findings for treatment with ibogaine in males.

Conclusions

Here, we have seen a different response between sexes in CPP procedure. Actually, in females, both VEH and IBO showed propensity to increase time spent in the cocaine chamber at testing, although no statistical significance was found, suggesting females vulnerability to cocaine's properties. However, no influence of the estrus cycle was found. Data on females are scarce for ibogaine treatment and should be more thoroughly investigated. IBO seemed to influence locomotion in OF test even after 5h, increasing anxiety, as it can be seen by decreased rearings and this corroborates other studies with ibogaine which show reduction in locomotion.

Cocaine and amphetamine regulated transcript (CART) signalling in the central nucleus of the amygdala modulates stress-induced alcohol seeking

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Background
The central nucleus of the amygdala (CeA) is a key hub regulating alcohol and stress interactions, however the exact neuronal populations that govern this interaction are not well defined. Here we examine the neuropeptide cocaine and amphetamine regulated transcript (CART) within the CeA in stress-induced alcohol seeking.
Methods
We used dual immunohistochemistry and RNA scope to investigate the neuronal populations in the CeA and activation of CART cells following stress-induced alcohol seeking. We used yohimbine (1 mg/kg, i.p.) as a pharmacological stressor and examined the effects of CART neutralisation in the CeA on stress-induced reinstatement of reward seeking, motivation to consume alcohol and anxiety-like behaviour in alcohol-experienced and alcohol-naïve rats.
Results
We found that CART cells are predominantly expressed in the capsular/lateral division of the CeA and are a subpopulation of protein kinase Cδ (PKCδ) cells, distinct from corticotrophin releasing factor (CRF)-expressing cells. Both stress (yohimbine) and stress-induced alcohol seeking activated CART cells in the CeA, while neutralisation of endogenous CeA CART signalling attenuated stress-induced alcohol, but not sucrose seeking. Consistent with this, blocking CART signalling within the CeA did not alter the motivation to obtain and consume alcohol, but did attenuate stressor-induced anxiety-like behaviour during abstinence from alcohol.
Conclusions
Together, these data identify CeA CART cells as a subpopulation of PKCδ cells that influence stress x alcohol interactions and mediate stress-induced alcohol seeking behaviours.

The role of ventral subiculum M4 muscarinic receptors in alcohol seeking

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Background
Alcohol Use Disorder (AUD) is a chronic relapsing disease, with limited therapeutic treatment options despite its large socioeconomic burden. Relapse propensity is a significant hurdle in AUD treatment. One trigger for relapse is returning to a context previously associated with alcohol. The ventral subiculum (vSub) has been implicated in the processing of contextual cues, with a projection from the vSub to nucleus accumbens shell (ACbSh) thought to mediate this role. M4 muscarinic acetylcholine receptors (mAChRs) are expressed within the vSub, however, the distribution and role of vSub M4 mAChRs in relapse to alcohol seeking are unknown.
Methods
We first examined the regulation of M4 mRNA within the vSub, using both our translationally relevant rodent model of long-term alcohol consumption/withdrawal and qPCR. Next, to examine the expression of M4 receptors on vSub to AcbSh projection neurons, we combined retrograde tracing with RNAscope. Finally, we examined the functional role of M4 mAChRs in context-induced relapse to alcohol seeking. To do this, we used an ABA renewal paradigm, and tested both systemic and intra-vSub administration of the selective M4 mAChR positive allosteric modulator (PAM), VU0467154. VU0467154's impact on rotarod performance, locomotor activity, and food/water consumption were also assessed.
Results
Long-term alcohol consumption/withdrawal led to a significant downregulation of Chrm4 expression (M4 mRNA) within the vSub. Further, RNAscope analysis revealed dense vSub M4 mAChR expression, including specifically on neurons projecting to the AcbSh. Systemic administration of the selective M4 PAM VU0467154 (30mg/kg, p.o) significantly reduced ABA renewal of alcohol seeking in rats but did not affect rotarod performance. Moreover, this effect is likely mediated in the vSub as intra-vSub administration of VU0467154 (3 µmol/ hemisphere) also significantly reduced ABA renewal of alcohol seeking. Intra-vSub VU0467154 administration had no impact on locomotor activity, food or water consumption.
Conclusions
Together our data suggest that long term alcohol consumption downregulates M4 mAChRs in the vSub, where they likely play a role in linking contextual cues with reward, and that administration of a selective M4 PAM can counteract this and prevent context-induced relapse to alcohol. Thus, M4 mAChR allosteric modulation is a potential candidate for the treatment of AUD, and aspects of this are mediated in the vSub.

Sex differences in binge drinking: The role of cocaine and amphetamine regulated transcript

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Background
More than 25% of Australians binge drink alcohol to harmful levels at least once a month. This is alarming given binge drinkers are almost 20 times more likely to develop alcohol dependence compared to non-binge drinkers. Further, rates of risky binge drinking are rising, especially in women, with an 80% increase observed over the last 15 years. Nevertheless, the neural mechanisms that underpin binge drinking are not well understood.
Methods
We explored the role of the neuropeptide, cocaine and amphetamine regulated transcript (CART) in binge drinking. Using a novel CART KO mouse line, we examined binge drinking of (10% alcohol, 5% sucrose or sucrose + alcohol combination) compared to wildtype (WT) littermates. As both emotional state and taste preferences are thought to contribute to sex differences in alcohol consumption, we examined the role of CART in anxiety-like behaviour and taste hedonics.
Results
Females lacking CART had lower binge alcohol consumption, while male CART KO mice had higher binge alcohol consumption compared to WT littermates. No differences in binge sucrose consumption were observed in female mice; however, supplementing alcohol with increasing concentrations of sucrose increased their alcohol consumption in a dose-related manner relative to WT levels. Female CART KO mice showed no difference in saccharin (sweet), salty (NaCl) or sour (citric acid) preference, but a decrease in quinine (bitter) solution preference. Additionally, we found no difference in anxiety-like behaviour in female CART KO vs WT mice.
Conclusions
Our results identify a novel, sexually dimorphic role for the neuropeptide CART in binge drinking. Further, in female mice, this appears to be driven through differences in taste hedonics rather than anxiety-based responses. Together our data suggest CART as a potential target for the treatment of binge drinking and prevention of alcohol dependence.

Sex-dependent behavioural effects of adolescent alcohol binge drinking and adult methamphetamine self-administration in rats

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Background
Alcopop beverages are well known for their high levels of both sugar and alcohol and they are generally the first alcoholic beverage that young people start drinking. The over-consumption of alcohol by adolescents may encourage co-administration with other drugs, and the prevalence of alcohol and methamphetamine (METH) co-abuse is high. The main aim of this study was to evaluate the consequences of prior alcohol binge drinking history in adolescents on METH self-administration in adult rats.
Methods
Adolescent male (*n*=60) and female (*n*=54) Sprague Dawley rats were trained to lever press for alcohol (5-15% Alcopop or Ethanol; v/v) or control solutions (Water or 10% Sucrose) in 1-hour oral self-administration sessions for 28 days. After jugular catheter implantation while adults, they were then trained to nose-poke for intravenous METH in 2-hour sessions (IVSA; 0.03-0.1 mg/kg) for 17 days. Rats then underwent 3 days of sequential alcohol and METH access, where alcohol or control solutions were available for the first hour, followed by 1-hour of intravenous METH access. Relapse to oral- and METH-cues were performed after 1-month withdrawal.
Results
Male and female Alcopop rats had greater ethanol intake compared to Ethanol rats in general with both alcohol concentrations. Alcopop rats had more infusions compared to Ethanol rats at 5% alcohol concentration, but no difference at 15%. At the low METH dose, female rats had more infusions compared to males, but no difference across conditions at the high METH dose. During sequential access, METH intake was not affected by alcohol intake. On oral-cue relapse testing, Sucrose rats relapsed more than Alcopop and Ethanol rats. On METH-cue relapse testing, except for the Ethanol group, female rats relapsed more than male rats.
Conclusions
Sweetened alcoholic beverages can stimulate higher ethanol intake in both male and female rats. However, our findings show that adolescence alcohol exposure partially affects only female rats as they took more METH at low dose. During sequential sessions, Alcopop females had greater ethanol intake than males but had a similar pattern of METH intake. However, Alcopop females exhibited greater METH-seeking behaviour than males on relapse. Overall, this could suggest a possible sex-dependent difference in sensitivity to METH, particularly at the lower dose. Also, it seems that sugar may be affecting the drinking behaviour and METH relapse only in female rats.

Topographic cholinergic projections from pontine nuclei to dorsal striatum: A retro-grade tracing study in Indiana alcohol-preferring (iP) rats

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Background
Acetylcholine plays a vital role in reward-related learning and decision-making. The striatum is involved in the transition from goal-directed to habitual behavior and our lab has implicated striatal muscarinic receptors in alcohol consumption and relapse. Historically it was believed that cholinergic activity in the striatum was mediated by cholinergic interneurons; however, direct cholinergic innervations from the pedunculopontine tegmentum and laterodorsal tegmentum to the striatum also exist.

Methods
To map out these brainstem cholinergic projections to the dorsal striatum, retrograde tracer (cholera toxin ß) was injected into dorsolateral striatum (DLS) or dorsomedial striatum (DMS) in iP rats. After transcardial perfusion, immunohistochemistry was performed to double-label for choline acetyltransferase (ChAT+) and retrograde tracer Cholera toxin subunit ß.

Results
Findings from iP rats suggested that more than 70% of PPTg and LDTg innervations to dorsal striatum are cholinergic. For the DLS, these cholinergic projections are distributed equally across the PPTg. In contrast, projections to the DMS were largely confined to LDTg with limited expression in the caudal PPTg. The remaining non-cholinergic population may be glutamatergic or GABAergic.

Conclusions
Here I confirmed that the pontine PPTg and LDTg provide an external source of acetylcholine to the striatum in the alcohol-preferring iP rat. Comprehensive mapping of these projection neurons showed that more than 70% of brainstem projections to the dorsal striatum are cholinergic. Furthermore, cholinergic neurons within the PPTg and LDTg send both ipsilateral and contralateral projections to the dorsal striatum. Characterizing these cholinergic projections could potentially uncover a novel mechanism for alcohol use disorder.

Investigating the propensity to relapse following punishment-imposed abstinence from alcohol seeking in female iP-rats

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Background
Sex is a well-known factor that can influence drug-associated craving and relapse-like behaviour. However, there are few preclinical studies investigating alcohol consumption and relapse-like behaviour in female rodents. Our lab has recently shown an increased propensity to relapse to alcohol seeking following long-term abstinence in male iP-rats. This study investigated relapse to alcohol seeking following long-term abstinence in female iP-rats.

Methods
Female iP-rats were given intermittent voluntary access to 20% v/v alcohol for 12 home-cage sessions. Rats then completed operant self-administration training in Context A, where alcohol was available following active lever pressing. Subsequently, rats were introduced to a different context (B), where active lever pressing resulted in the same delivery of alcohol but also paired with footshock delivered randomly on 50% of lever presses. Footshock intensity was increased until alcohol seeking ceased. Rats were tested in either Context A or Context B on Day 1 abstinence for alcohol seeking, then again on Day 30 abstinence in the same context.

Results
There was a significant interaction between Test Context x Abstinence Day [$F(1,15) = 8.285$, $p = 0.011$]. There was a significant main effect of Abstinence Day on alcohol seeking behaviour in Context B [$F(1,11) = 26.230$, $p=0.000$], with active lever presses being significantly higher on Day 30 testing compared to Day 1 testing. There was no significant main effect of Abstinence Day on alcohol seeking behaviour in Context A [$F(1,6) = 0.335$, $p=0.584$]. Furthermore, there was no significant main effect of Context on alcohol seeking behaviour for Day 30 abstinence testing [$F(1, 18) = 1.183$, $p=0.291$].

Conclusions
The current study demonstrates an increased propensity to relapse in Context B following long-term abstinence in female iP-rats. Importantly, relapse-like behaviour was not influenced by estrous cycle. These results are comparable to our previous data in male iP-rats (Campbell et al., 2019), suggesting a lack of sex differences in this form of relapse to alcohol seeking, thereby excluding sex as a biological variable. Ongoing studies will investigate factors that may influence the propensity to relapse in both male and female iP-rats to predict relapse-prone rats for intervention studies.

Dependent smokers exhibit greater prefrontal cortex activity during preparatory control but blunted anterior cingulate cortex activity during reactive control when inhibiting over rewards

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Background
Reduced inhibitory control and a hypersensitivity to rewards are amongst the key deficits in addiction. These deficits may contribute to the high persistence in drug-seeking behaviors and impulsive decision-making found in people with a drug-dependence. Moreover, a reduced inhibitory control may significantly contribute to a higher chance of relapse. A better understanding of these processes may offer insight into ways of decreasing drug-seeking behaviors and avoiding relapse by exercising control over immediate rewards. These differential processes of inhibiting a response and the hypersensitivity to rewards have been relatively well studied; but is typically studied independently.

Methods
We sought to better understand how the brain exerts inhibitory control over rewards in dependent smokers and healthy controls. We used a novel variant of the monetary incentive delay task, where we added a stop signal component such that participants had to inhibit responses to earn a larger monetary reward. Brain activity was recorded using functional magnetic resonance imaging (fMRI) while participants performed this task. Using the horse-race model we were able to estimate the stop signal reaction times (SSRT), an indicator of difficulty in inhibiting a response, as well as a measure of impulsivity.

Results
Inhibitory accuracy scores did not differ between control and dependant groups. However, the dependant group had slower SSRTs, suggesting that responses may be harder to inhibit for the dependent group. Brain data showed that the dependent group had greater preparatory control activity in the middle frontal gyrus and inferior frontal gyrus prior to successful inhibitions over reward. However, the control group had greater reactive control with more activity in the anterior cingulate cortex during successful inhibitions. Our model-based approach to relating SSRT with brain activity revealed that the dependant group with slower SSRTs engaged more control related prefrontal brain regions.

Conclusions
Overall, we show that whilst the inhibition accuracy scores are similar between groups, differential neural and computational processes are used to achieve this. The dependent group has a greater difficulty in exerting control over rewards, and as a result engages more prefrontal control regions prior to successful inhibitions.

A Systematic Literature Review of Cannabinoid-Related Changes in fMRI-Based Brain Resting State Functional Connectivity

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Background
Cannabis is a complex substance, containing over 144 different cannabinoids with distinct effects on behaviour. The two most commonly studied cannabinoids are delta-9-tetrahydrocannabinol (THC), which drives cannabis' psychoactive effects and has been associated with higher anxiety and psychotic symptoms, and cannabidiol (CBD), which has been shown to mitigate THC-related effects. Broad systematic reviews show that cannabinoids' distinct effects on behaviour might be ascribed to distinct changes in brain structure and function. However, there lacks a focused and comprehensive review of the differential effects of cannabinoids on brain function, particularly in the absence of task demands, and associated changes in behaviour.

Methods
A systematic literature search was run in APA PsycInfo, PubMed, and Scopus, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Inclusion criteria were: (i) Human sample, (ii) acute exposure to cannabinoids, and (iii) brain function measured using functional magnetic resonance imaging resting state functional connectivity (rsFC). Key exclusion criteria were: (i) Animal sample, (ii) participants had a lifetime history of Axis I psychological disorders or neurological disorders, (iii) non-experimental, (iv) non-peer reviewed. This process led to the selection of ten studies.

Results
The reviewed studies comprised 217 predominantly male participants (mean age= 24 years) and exposed participants to THC (n=7), CBD (n=2), and cannabis plant matter (n=2). THC and cannabis plant matter exposure, versus placebo, was consistently associated with lower rsFC, most commonly between the striatum and prefrontal, parietal and occipital cortices. One study reported higher striatal-prefrontal rsFC after CBD versus placebo exposure. Four studies additionally ran brain-behaviour correlations, finding that lower THC- and cannabis plant matter-related rsFC associated with THC and cannabis plant matter exposure, and poorer sustained attention (n=2), higher impulsivity (n=1) and higher self-reported symptoms of cannabinoid exposure (n=3).

Conclusions
Based on these preliminary findings, a consistent trend emerged for lower rsFC between striatal and prefrontal, parietal and occipital regions associated with exposure to THC and cannabis plant matter. There is also early evidence of THC and CBD's opposing effects on brain function, particularly in the striatal-prefrontal pathway. Finally, evidence emerged for behavioural outcomes associated with THC and cannabis plant matter, indicating an underlying neurobiological basis for behaviours associated with cannabinoid exposure. However, more research is needed to strengthen understanding of the effects of different cannabinoids and strains of cannabis on brain function, and associated changes in behaviour.

Resting-state functional connectivity differences predating cannabis use onset; findings from the IMAGEN consortium study into adolescents

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Background
Adolescence is often when cannabis use first starts and is a period of rapid brain maturation. By age 17, 31% of Australians have used cannabis. Adolescent cannabis use is linked to lower school attainment, early school dropout, depression, anxiety, psychosis, suicidal ideation and addiction. Such outcomes have been ascribed to the impact of cannabis use on the developing brain. Indeed, adolescent cannabis use has been associated with aberrant function of brain prefrontal-striatal pathways that support emotional and cognitive functioning. Critically, no fMRI study has examined if altered brain function predate youth cannabis use onset.

Methods
We extracted resting state functional connectivity (rsFC) fMRI, substance use and clinical data from a large longitudinal consortium (IMAGEN) from 68 youth. At age 19 we examined 27 cannabis users and 41 controls. We examined the sample groups at age 14 before cannabis use onset. Groups were matched at age 14 and age 16 by age, sex, risk for mental health disorders, AUDIT score, monthly standard drinks, and general ability index. Whole brain resting-state functional connectivity analysis was compared between 14 year old who did and did not commence using cannabis at age 19.

Results
At age 14, there were differences in resting-state connectivity in youth who did vs did not use cannabis by age 19, specifically, greater connectivity between the lateral orbitofrontal cortex (OFC) and calcarine sulcus and lower between the medial OFC and the inferior temporal gyrus. Resting-state connectivity in youth aged 14 and impulsive personality scores, significantly predicted cannabis use by age 19.

Conclusions
To our knowledge, this is the first study to investigate and demonstrate rsFC alterations predate and predict youth cannabis use. Future research are warranted to explore if such group differences persist with regular cannabis use at age 19, and if these alterations change as users increase/decrease their use, and dissipate with use cessation.

Hippocampal, Nucleus Accumbens, and Orbitofrontal Cortex Volume in Cannabis Use Disorder

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Background
Regular cannabis use is associated with smaller volumes in brain regions implicated in Cannabis Use Disorder (CUD), these include: the hippocampus, which is involved in memory and learning processes; nucleus accumbens (NAc), which plays a key role in reward processing; and the orbitofrontal cortex (OFC) which is ascribed to motivation. It is unclear whether volumetric alterations in these regions represent a distinct neural signature associated with CUD severity. The objective of this ongoing study was to investigate whether hippocampal, NAc, and OFC volumes are smaller in regular cannabis users with severe CUD, compared to mild-to-moderate CUD and non-using controls.

Methods
Thus far, we have examined a sample of 47 participants. Of these, 39 were regular cannabis users stratified into mild-to-moderate CUD (n=21) and severe CUD (n=18) groups using the Structured Clinical Interview for DSM-V, and 8 were non-using controls. All groups were matched for age, sex and IQ. Participants underwent structural MRI brain scans to quantify hippocampal, NAc and OFC volumes using Freesurfer v.6. Participants also completed a series of structured interviews and questionnaires to assess demographic, substance use and psychiatric history.

Results
Our preliminary results showed significant volumetric differences between the control group, mild-to-moderate CUD group and severe CUD group ($p < .001$) whereby smaller hippocampal volumes were observed in the severe CUD group. There were no significant differences in OFC or NAc volumes between either CUD groups or CUD groups and controls.

Conclusions
Our preliminary findings suggest that smaller hippocampal volumes in regular cannabis users may be associated with CUD severity, supporting neurobiological models of addiction implicating the hippocampus in the chronic stages of addiction. This study suggests no association between OFC and NAc volumes and CUD severity, however these findings are limited by our small sample size, particularly that of the control group, and the cross-sectional design. Recruitment for this study is continuing toward a larger sample, with all current participants undertaking longitudinal follow-ups to inform whether volumetric alterations persist or dissipate over time.

Patterns of brain function associated with cue-reactivity in regular cannabis users: A systematic review of fMRI studies

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Background
Cannabis is used globally by ~200 million people, of which ~10-30% meet criteria for a cannabis use disorder. Cue-reactivity (including behavioural, physiological, psychological, and neural responses to substance-related stimuli) may reflect motivational processes underlying continued cannabis use. To date, the fMRI studies examining whether regular cannabis use is associated with alterations in brain function implicated in cue-reactivity to cannabis-related stimuli has not been reviewed. This systematic review aims to summarise the findings from fMRI studies using a cue reactivity task (viewing cannabis versus neutral stimuli), in (i) cannabis users and (ii) versus non-using controls.

Methods
A systematic search of PsychInfo, PubMed, and Scopus databases was conducted. Studies were included if they were written in English, peer reviewed, had a sample of regular cannabis users aged between 14-65 years, and employed a fMRI cue-reactivity task (cannabis versus neutral stimuli). Studies were excluded if they included samples with comorbid substance use disorders (except alcohol, nicotine), psychopathology, or employed imaging techniques other than fMRI. A total of eighteen studies met inclusion/exclusion criteria (six studies included a non-using control group), comprising a total of 829 participants (209 female) of which 619 were regular cannabis users and 210 non-using controls

Results
There was consistent higher activity in striatal, prefrontal, and parietal regions in cannabis users versus controls while viewing cannabis compared neutral stimuli. In the striatum, there was higher activity in the dorsal striatum in dependent, high problem, and early-onset samples, and higher activity in the ventral striatum in non-dependent, low problem, and late-onset samples. A positive association between increased function in the striatum, OFC, ACC, amygdala, insula, and PCC with higher levels of craving, and cannabis dependence/problem severity, however associations were inconsistent across studies. Further, there was no evidence for an association with cannabis use levels (i.e., frequency, quantity).

Conclusions
Overall, the reviewed literature is characterised by methodological limitations that prevent a direct comparison of findings across studies. These include heterogenous measurements of patterns of cannabis use, the nature of problematic use, craving, dependence severity, and limited reporting of comorbid mental health and substance use. This is furthered by variability of fMRI cue-reactivity tasks (e.g., type of stimuli, presentation). Despite these limitations, studies consistently reported increased brain function in reward pathways and associations with craving and dependence severity. This review supports the notion that cannabis-related neuroadaptations associated with craving are involved in sensitisation of reward pathways to cannabis cues.

Resting State Functional Connectivity in Cannabis Users versus Non-Using Controls: A Systematic Review of the Literature

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Background
Cannabis is a commonly used illicit drug worldwide. Regular cannabis use is associated with adverse psychosocial and health outcomes, which may have neurobiological underpinnings. Task-based fMRI studies have predominantly revealed differences in frontostriatal regions during executive function and reward processing in regular cannabis users (vs. controls). However, our understanding of alterations in brain function during rest (without the constraints of cognitive tasks) remains to be elucidated in regular cannabis users. This review aims to systematically summarise the resting-state functional connectivity (rsFC) evidence in cannabis users compared to controls that will include brain-behaviour associations (cannabis use levels, cognitive performance, and psychopathology).

Methods
This review followed the PRISMA guidelines and was pre-registered with Prospero (ID:180355). Searches were conducted across 8 databases, uncovering 416 studies. Key inclusion criteria required: human participants, comparison between regular cannabis users and controls, measurement of functional connectivity using resting-state fMRI, English language, and publication in peer-reviewed journals. Studies were excluded that: were non-empirical, were reviews or meta-analyses, or examined a drug other than cannabis. Twenty-one studies were selected, which included 1,222 participants (404 females), aged 23 years (range 16-42). Of these, 630 were regular cannabis users and 592 controls.

Results
Eighteen (of 21) studies showed significant differences in rsFC between regular cannabis users and controls, typically between striatal and frontotemporal regions. Twelve studies examined rsFC and cannabis use levels associations, 7 of which found both positive and negative associations in frontal, parietal, and cerebellar regions. Four studies examined rsFC and psychopathology associations with both positive and negative associations reported in frontal, temporal, parietal, occipital, and subcortical regions. Two studies examined rsFC and cognitive associations with both positive and negative associations reported in frontal, parietal, and temporal regions.

Conclusions
Emerging evidence of rsFC alterations in regular cannabis users suggests alterations in frontotemporal and striatal pathways that are implicated in executive function and reward processing and susceptible to endocannabinoid down-regulation. Findings must be interpreted with caution, in light of key methodological issues including but not limited to the cross-sectional nature of the designs. Future work is warranted to examine causal relationships between cannabis use and brain integrity, to ascertain if alterations predate use, vary with use fluctuations, and dissipate with abstinence.

Gamma oscillations in a pragmatic open-label trial of prolonged cannabidiol administration in cannabis users

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Background
Altered gamma oscillations are observed in clinical and cognitive disorders including major depressive disorder, with restorative changes indexing therapeutic recovery. Increased gamma power has been reported in regular cannabis users compared to controls and modulation of hippocampal cannabinoid receptors has been shown to alter gamma oscillations important for cognition. We recently reported restorative effects of prolonged cannabidiol (CBD) administration in regular cannabis users on total and subfield hippocampal volumes, and depressive and psychotic-like symptoms. Here, we investigate the effects of prolonged cannabidiol administration on spontaneous gamma oscillations in regular cannabis users and associations with improved neural and clinical outcomes.

Methods
Eighteen regular cannabis users (mean 25.37 years; 15 males) completed a ~12-week open-label trial of daily CBD administration (200mg; 99.5% pure crystalline CBD). Electroencephalograph (EEG) was recorded during 5-minutes of rest with eyes open at baseline and post-treatment. EEG data recorded from 32 scalp electrodes were subjected to a Fast Fourier Transform (Hanning window, 10%) and mean amplitude spectra were quantified for gamma frequency (35Hz-45Hz). Electrodes were collapsed into three sagittal (frontal, central, parietal) and two lateral (left, right) planes to assess changes in gamma EEG power. Correlations were performed between gamma EEG and neural, clinical, and cannabis use measures.

Results
A repeated measures ANOVA found no interaction between treatment time-point (baseline versus post-treatment) and lateral or sagittal planes for gamma EEG power. Gamma power was collapsed across hemisphere to reduce the number of correlations. Higher baseline gamma power was associated with reduced (from pre- to post) depression scores following CBD treatment (central, rho=-.56; parietal, rho=-.61). Higher baseline gamma power was also associated with smaller volume increases in CA1 in the hippocampus (central, rho=-.55) and left entorhinal cortex in the medial temporal lobe (frontal, rho=-.53; parietal, rho=-.54). No associations were observed for psychotic-like symptoms or cannabis related measures.

Conclusions
Our preliminary data did not support overall changes in gamma EEG power following ~12-weeks of CBD administration. However, associations between higher baseline gamma and improved depression scores suggest that gamma oscillations may mediate CBD's effects on these symptoms in regular cannabis users. Higher gamma power at baseline was associated with smaller volume increases in brain regions implicated in depression, which may index reduced capacity for neuroplasticity changes over the duration of the treatment period. These interpretations are preliminary and warrant further investigation, including the effects of CBD administration on gamma oscillations in treatment-seeking and abstinent cannabis users.

2.5 Learning and Decision Making

Role of zona incerta RXFP3+ neurons in context-dependent Pavlovian conditioning and extinction

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Background
RXFP3, the cognate receptor for relaxin-3, is implicated in stress and arousal. We recently identified a dense population of RXFP3+ cells in the zona incerta (ZI). The functional role of this region is poorly understood, however anterograde tracing showed that this population of cells projects to the periaqueductal gray, lateral habenula, and lateral septum, which are implicated in associative memory and control of defensive behaviours. Therefore, it seems likely that these neurons may mediate Pavlovian fear conditioning and extinction.

Methods
Transgenic RXFP3-Cre mice received a bilateral dorsal ZI injection of a Cre-dependent adeno-associated virus containing either the hM3Dq DREADD tethered to mCherry, or mCherry alone. After 6 weeks, mice received 9 pairings of a tone conditioned stimulus (CS) with a 1mA footshock in context A. The next day (extinction), mice were injected with clozapine-N-oxide (CNO - 3mg/kg i.p) to activate targeted cells, placed in context A or a distinguishable context (B), and exposed to 30 CS presentations without shock. On the third day (test), mice were placed into either context and exposed to a further 30 CS presentations without shock.

Results
Following an injection of CNO, hM3Dq transfected mice displayed decreased freezing to CS presentations during extinction compared to mCherry controls. However, during test (conducted drug-free), mice expressing the hM3Dq DREADD displayed less freezing only when extinguished and tested in a context different from the conditioning context (i.e. group ABB). No differences were found in freezing levels of mice extinguished in context A (i.e. groups AAA, AAB). In other words, extinction retrieval was greatest in mice that were extinguished and tested in a different context from conditioning, but only where RXFP3+ cells were activated during extinction.

Conclusions
We showed that activation of ZI RXFP3+ inhibited expression of conditioned fear, and promoted the encoding of extinction learning in a context-dependent manner. Future studies will confirm these results by examining the effect of an inhibitory DREADD expressed in the same population. We will also examine the effect of exciting and/or inhibiting specific projections from ZI RXFP3+ cells. These results clarify the ZI's role in associative memory and control of defensive behaviours, and highlight the therapeutic potential of targeting RXFP3 in treating fear related disorders, such as PTSD.

Automated and experimenter-free assessment of cognition and behaviour in rats: Introducing the PhenoSys

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Background
Animal models of psychiatric disease are essential for revealing causal relationships between specific biological mechanisms and human pathologies, and are necessary for predicting drug effects and developing novel therapeutics. It is now well-appreciated that repeated intervention and idiosyncratic handling techniques can affect stress reactivity and have a dramatic influence on experimental outcomes in animal models. Therefore, the impact of the experimenters themselves can hamper reproducibility within and between laboratories. In order to effectively utilise animal models to uncover the biological underpinnings of human disease, it is important to reduce experimenter influence on behavioural outcomes.

Methods
We utilised the “PhenoSys” - a fully-automated modular behavioural testing system that includes home-cages and touchscreen operant testing chambers - to assess visual discrimination and reversal learning in female Sprague-Dawley rats (n=8). Group-housed rats were implanted with subcutaneous RFID transponders, enabling an automated “ID Sorter” to allow rats to move between a living and testing chamber using a short tunnel positioned above a weight scale. The approach removes all experimenter influence besides olfactory cues. Rats were not only subject to performance-based testing, but were also continuously monitored in their home cages to examine aspects of social, locomotor and exploratory behaviour.

Results
We found that compared to traditional touchscreen testing, the rate at which rats learned visual discrimination and reversal tasks in the PhenoSys increased approximately 3-fold. Because animals can enter the touchscreen chamber at any time of the day or night when they are curious and motivated to perform, automation also unmasked the broad spectrum of learning abilities among animals. We saw a proportional increase in the rate of learning, with “fast learners” acquiring tasks ~4 times as fast as their counterparts in traditional touchscreens and “slow learners” (that may be less motivated to work for sucrose) only twice as fast.

Conclusions
This pilot study confirmed that the PhenoSys accelerates learning rates in female rats. The continuous monitoring of animals using RFID technology also allows deeper consideration of inter-animal variability and behavioural complexity and to match these with specific aspects of performance. The broader adoption of automated behavioural testing systems that eliminate the need for experimenter intervention will likely improve both the reliability of behavioural assessment in rats and mice and reproducibility within and between laboratories. We believe this represents a new “gold-standard” in behavioural neuroscience and anticipate a shift in the way the way these experiments are conducted and interpreted.

The Biophysics of Cognition – Effects of Potassium Channel (Kv) Modulators on Cognition-related Brain Oscillations in Mice

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Background
Voltage gated ion channels modulators are known to affect the excitability of single neurons, and would be expected to modulate network excitability. Here, we measured the effects of Kv modulators 4-aminopyridine (4AP), tetraethylammonium (TEA), retigabine (RET) and E4031 on power spectral density, coherence and cross-frequency coupling from depth electrode recordings in prefrontal cortex (PFC) and dorsal hippocampus (dHIP) of awake mice.
Methods
56 adult male C57BL/6 mice (aged 6-10 weeks) were implanted with 50um insulated tungsten electrodes in PFC and dHIP. Local field potential (LFP) signals were recorded continuously at 20kHz and power spectra were divided into theta (4-12Hz), beta (12-32Hz), low gamma (32-60) and high gamma (60-100Hz) bands. Coherence and cross-frequency-coupling (CFC) measures were derived from these spectra. Chronux and Fieldtrip software packages from Matlab and custom scripts were used for analysis. Drugs were administered via intraperitoneal injection. One-way-ANOVA with repeated measures were used for all outcome measures, with Bonferroni correction. Statistical significance was set at $p<0.05$.
Results
In hippocampus TEA (0. 5 mg/kg) reduced theta power by 36%, beta (38%), slow-gamma (23%) and fast-gamma power (46%). The hERG channel blocker E4031(30 mg/kg) suppressed slow-gamma (24%) and fast gamma (39%). Retigabine (20 mg/kg, 12.5 mg/kg) showed the strongest inhibition of both slow-gamma and fast-gamma power, with a maximal reduction of 42% and 63% respectively. 4AP had quite different effects, enhancing slow gamma power (2 mg/kg,56%; 1 mg/kg, 15%). Retigabine reduced coherence between PFC and dHIP in the theta and fast gamma bands ($p<0.05$), and also reduced the modulation index measure of CFC by 10% ($p<0.01$).
Conclusions
The current observations appear to be the first to directly test the effects of voltage gated ion channels modulators on network activity in vivo. The effects of Kv modulators apart from 4AP are reminiscent of antipsychotic drug effects and should be tested for therapeutic relevance. We speculate that the enhancement of theta and gamma power by 4AP may have a cognition-enhancing effect that will be interesting to test in freely behaving animals.

Probing individual differences to dissect lateral orbitofrontal cortex contributions to distinct perseverative behaviors

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Background
Neuroimaging studies implicate orbitofrontal cortex (OFC) dysfunction in obsessive compulsive disorder (OCD), with OFC hyperactivity observed during symptom provocation, and impaired OFC recruitment observed during tasks probing perseverative decision-making including reversal learning. In vivo imaging in the Sapap3 knockout mouse (KO), which displays OCD-relevant perseverative grooming and perseverative incorrect responding on a reversal learning task, can be used to determine whether overlapping or distinct activity patterns in OFC contribute to these behaviours.

Methods
Male and female mice were injected with virus encoding fluorescent calcium indicator (AAV5-hysn-GCaMP6f) and implanted with gradient-index (GRIN) lenses in lateral OFC (lOFC) to visualize neural activity using Inscopix miniature microscopes (n=12KO/8 wildtype (WT) littermate controls, ~5 months of age). Calcium imaging was performed during grooming assessment and reversal learning, and aligned to behaviours of interest (correct/ incorrect responses during reversal learning, initiation of grooming).

Results
Significantly more lOFC neurons were suppressed at the start of grooming in Sapap3-KOs relative to WT ($p<0.05$). Severity of compulsive grooming varied across KO mice (7-70% of time spent grooming), and increased severity was associated with more lOFC neurons showing inhibition at the onset of grooming ($p=0.01$). During reversal learning a subset of KOs (n=6) show elevated perseverative incorrect responding; no correlation was seen between this behaviour and levels of perseverative grooming. In KOs, elevated incorrect responding was correlated with a larger proportion of neurons being activated during these perseverative lever presses ($p=0.008$).

Conclusions
These data suggest that Sapap3-KOs show distinct patterns of lOFC activity change associated with severity distinct perseverative behaviours. Ongoing experiments are determining whether distinct striatal output populations contribute to these different OCD-relevant behaviours.

Mouse hippocampus neural ensembles are tuned near criticality during a cognition task

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Background
Dynamical systems exhibit transitions between ordered and disordered states and "criticality" occurs when the system lies at the borderline and achieves higher dynamical range where the input is neither strongly damped nor excessively amplified. Long-range temporal correlations in brain activity such as memory may be manifestations of criticality. Thus, impairments in brain function such as dementia or epilepsy could arise from failure of adaptive criticality, and deviation from criticality may be a potential biomarker for cognition-related neurological and psychiatric impairments. For the first time, we report strong evidence of criticality properties in freely behaving animals using widefield neural calcium imaging.
Methods
We utilized 15-minute episodes of widefield calcium imaging from several hundred hippocampal CA1 neurons using "Miniscopes" in freely behaving mice to study criticality measures during cognitive tasks such as novel object recognition (NOR). On an 8-core, 1.5TB-RAM supercomputing system, a Constrained Non-negative Matrix Factorization algorithm was performed to extract neuronal spatial footprints and temporal traces. Temporal vectors were weighed with the estimated firing rates and after thresholding, spikewords were derived. We identified neural avalanches using another thresholding step on the ensemble activity and derived 4 independent criticality measures: power-law distribution, deviation from criticality (DCC), shape collapse, and branching ratio (BR).
Results
The 4 criticality parameters were measured in 7 recording sessions from 6 freely behaving mice consisting of 3 inactive sessions and 4 sessions during NOR. We find that while the hippocampus neural network exhibits characteristics of a near-critical system at rest (power law expands less than 2 orders of magnitude, DCC = 0.77±0.72, shape collapse error = 0.260±0.032, BR = 0.9583±0.0069 in mean±SD), the system shifts even closer to the critical state when engaged in cognitive tasks (power law expands at least 2 orders of magnitude, DCC = 0.29±0.19, shape collapse error = 0.090±0.066, BR = 0.9787±0.0354 in mean±SD).
Conclusions
Our results utilizing a novel calcium imaging technique and analyzing 4 independent measures of criticality for the first time in the hippocampus neural network suggest that switching from inactivity to a cognitively active state modulates the system's distance from criticality; meaning it decreases DCC and shape collapse error while increasing BR. At criticality, the dynamical range and the information content and transmission are maximized. It will be of great interest to extend these observations to brain areas such as frontal cortex, and to examine whether there are derangements of these parameters with naturally or artificially induced states of cognitive impairment.

Temporal control of AgRP neurons is required for a context-induced overeating response in mice

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Background

Context is integral to the learned over-eating response. When sated rats and mice are re-exposed to contexts in which they were previously hungry, they exhibit avid over-eating compared to mice that were never hungry. This suggests a key role of hunger circuits in regulating context-conditioned feeding behaviour. The perception of hunger is centrally mediated via increased signalling of Agouti related peptide (AgRP) neurons, an effect that relies on increased levels of the “hunger hormone” ghrelin. Therefore, the aim of this study was to investigate role of ghrelin-responsive AgRP neurons in the acquisition of a conditioned overeating response to context.

Methods

We used a context-induced feeding (CIF) paradigm whereby fasting produces a conditioned response (CR). We first confirmed that ghrelin was sufficient to precipitate both an unconditioned response (UR) and CR. Because ghrelin engages arcuate AgRP neurons to precipitate feeding, we next sought to investigate the specific contribution of AgRP neurons with chemogenetics and optogenetics. We utilised adult male AgRP-IRES-cre mice (AgRP), or wild-type (WT) littermates, that were administered either a Cre-dependent excitatory DREADD (AAV-HM4Dq; AgRP-Gq) or excitatory opsin (AAV-socoChR2; AgRP-ChR2) into the Arc. With these, we sought to evaluate temporal dynamics of AgRP neurons required for a CIF response

Results

Activation of AgRP-Gq with CNO resulted in a robust feeding response within the conditioning context, consistent with a robust unconditioned response (UR) (p0.05). Because these artificial signals are sustained for hours following CNO administration, we considered the possibility that we were masking a “true response”, and so repeated the experiments with AgRP-ChR2 mice that received stimulation (20Hz; 3s ON, 1s OFF) specifically within the training context.

Conclusions

This study shows that both ghrelin and AgRP signalling are sufficient for context-conditioned feeding behaviour, and highlights the important role of temporal specificity for AgRP activation in forming context-conditioned associations. Future studies aim to investigate the role of "downstream" orexin neurons, and the involvement of striatal dopamine.

Are impulsive actions habitual?

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Background
Impulsive actions occur without forethought of the consequences and are often triggered by internal or external stimuli. These features suggest a link between impulsivity and habits. This study aimed to determine if impulsive actions are associated with habit formation.
Methods
Individual differences in efficiency on the DRL task provided a baseline measure of impulsivity. Rats with lower impulsivity reduced premature responses under devalued compared to valued and baseline conditions with no change in correct presses. However, rats with high impulsivity reduced premature presses and increased correct presses on both tests compared to baseline, but did not show sensitivity to devaluation.
Results
Individual differences in efficiency on the DRL task provided a baseline measure of impulsivity. Rats with lower impulsivity reduced premature responses under devalued compared to valued and baseline conditions with no change in correct presses. However, rats with high impulsivity reduced premature presses and increased correct presses on both tests compared to baseline, but did not show sensitivity to devaluation.
Conclusions
These results suggest that low impulsive rats were able to think through their actions to consider the outcome and respond appropriately, however high impulsive rats did not. High impulsive rats did reduce their impulsive responses when motivation was reduced but failed to show outcome-specific updating. If we can understand the associative learning mechanisms that underlie impulse control disorders, then novel therapeutic strategies can be developed.

Connections between the valuation and executive control systems encode value-setting and delay discounting in the brain.

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Background
The process of valuation assists in determining if an object or course of action is rewarding and worthy of effort. Delay discounting is the observed decay of a rewards' subjective value over time, a decision-making process modulated by the valuation and executive control systems. The valuation system (VS) encodes reward value across different delays, while the executive control system (ECS) integrates contextual and mnemonic information with salience signals. We investigated the resting-state functional connectivity relationship between the VS and ECS with delay discounting in a large (n=992) cohort of healthy young adults from the Human Connectome Project (HCP).

Methods
A single brain mask comprising regions recruited by the VS and ECS (referred to as the Valuation-Control Complex, VCC), based on the Desikan-Killiany atlas. Resting-state functional MRI signal was extracted from HCP participants, and the Pearson correlation coefficient was then computed between all pairs of VCC regions, yielding a single connectivity matrix per subject. The network-based statistic (NBS) was used to identify functional circuits and subnetworks of the VCC associated with delay discounting and subjective value setting trials. Each pairwise connection in the VCC was then regressed for the demographic variables of age, gender, cognition, education, employment and income.

Results
VCC connections were negatively correlated with delay discounting and value-setting behaviour. Of note was the correlation between the ventrolateral prefrontal cortex and amygdala correlated with delay discounting behaviour of small ($200, $p<0.05$, $\beta=-0.18$) and large ($40,000, $p<0.01$, $\beta=-0.43$) rewards and between the ventromedial prefrontal cortex and posterior parietal cortex in value setting of small ($200, $p<0.01$, $-20<\beta<-200$) and large rewards ($40,000, $p<0.01$, $\beta<-20,000$). While some connections were influenced by demographic variables, many remained independent of external influence, suggesting that connections between the VS and ECS play a role in value-setting and delay discounting.

Conclusions
These findings suggest a basic neuroscientific framework for understanding brain connections involved in subjectively valuing small and large rewards over different delays, and how these valuations go on to influence delay discounting behaviour. Connections between the VS and ECS could play a major role in encoding delay-centric, value-based decision-making, with the prefrontal cortex emerging as a key hub, owing to its numerous significant associations with other VS and ECS regions.

Unlocking animal feelings for better welfare and drug discoveries

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Background
Just as humans, individual animals differ in their propensity to see if glass is “half-full”, or “half-empty”. Animals cannot talk, but they can react to ambiguous situations and cues in a way that suggests expectations of a positive outcome (optimism) or expectations of a negative outcome (pessimism). For example, when black bowl is associated with sweet food, and white bowl with bitter food, how would animals react to grey bowl? A “judgement bias test” based on this phenomenon, is not only a window into animals’ inner lives, but also a potential tool for improving animal welfare and developing new psychopharmaceuticals.
Methods
To validate judgement bias test’s potential promises in non-human animal research, we conducted two meta-analyses, collecting data from empirical studies using this assay on species ranging from insects to primates. Our first meta-analysis summarises studies using judgement bias assays as a measure of animal welfare, whereas the second meta-analysis synthesises studies measuring effects of psychoactive drugs.
Results
Our meta-analytic works revealed that “judgement bias test” is valid and widely applicable in both contexts. We show that both non-pharmacological and pharmacological manipulations usually alter judgement bias as predicted. However, average measured effect on animal behavioural responses to test cues is small to moderate, and highly heterogeneous among studies. We also uncovered several potential moderators of the effect size, e.g. drug type, cue ambiguity level, sex of animals, task type and reinforcement scheme used.
Conclusions
Meta-analytic syntheses show validity of judgement bias assay as a measure of a positive or negative affective state in non-human animals. Our work also reveals how to improve and customise design of this increasingly popular behavioural assay.

The role of NMDA receptors in the BLA in aversive higher-order Pavlovian conditioning

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Background
NMDAR activity is crucial for learning across a wide range of behavioural protocols in rodents. In the basolateral amygdala complex (BLA), NMDAR activity is necessary for animals to develop defensive responses (e.g., freezing) to conditioned stimuli (CSs) that predict aversive outcomes, including first-order CSs that are directly paired with an innately aversive unconditioned stimulus (US; e.g., foot shock), and second-order CSs that are directly paired with a learned source of danger, such as an already-conditioned CS. Here, we used a range of behavioural protocols to assess the conditions under which NMDAR in the BLA are required for aversive higher-order conditioning.

Methods
Long Evans rats were implanted with cannulae targeting the BLA and infused with either drug or vehicle immediately prior to the target training session. For experiment 1, rats were infused with either vehicle or the competitive, non-selective AMPAR antagonist, NBQX. For experiments 2-6, rats were infused with either vehicle or the competitive, non-selective NMDAR antagonist, D-AP5. These experiments used a serial-order conditioning protocol in which a novel CS (S1) is directly paired with a foot shock US in stage 1, followed by serial-order pairings of a second novel CS (S2) with S1 and shock (i.e., S2-S1-shock) in stage 2.

Results
Blockade of AMPAR in the BLA impaired the acquisition of serial-order conditioned freezing to S2 (Exp 1). However, acquisition of freezing to S2 was not affected by NMDAR blockade (Exp 2, 3). NMDAR activity in the BLA was necessary for animals to acquire freezing to S2 when: (1) the first stage of training was omitted (i.e., S1-shock; Exp 3); (2) the shock US was omitted from stage 2 of training (Exp 4); (3) the already-conditioned S1 was omitted from stage 2 of training (Exp 5); and (4) when both stages of training occurred in different contexts (Exp 6).

Conclusions
These experiments establish 4 necessary conditions for rats to acquire freezing to S2 independently of NMDAR activity in the BLA:
1) Rats must undergo S1-shock training in stage 1 (Exp 3).
2) The shock US must be present in stage 2 (Exp 4).
3) The already-conditioned S1 must be present in stage 2 (Exp 5).
4) Both stages of training must occur in the same context (Exp 6).
These results demonstrate that the role of NMDAR activity in aversive Pavlovian conditioning depends on the animal's training history and the nature of the protocol, and may be regulated by animal's expectations.

BDNF val66met is a strong predictor of decision making and attention performance on virtual reality cognitive battery

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Background
The val66met polymorphism of the brain-derived neurotrophic factor (BDNF) gene has been associated with changes in executive functioning. Decision making may be affected by val66met, however this relationship is understudied. Changes in attention and visual processing speed related to val66met may explain potential changes in decision making. There is increasing evidence that chronic stress disrupts executive functions, however potential relationships between val66met and cognition have not been studied in the context of chronic stress or stress-related autonomic changes. Some evidence suggests val66met alters autonomic activity as measured by heart rate variability (HRV), however these studies are few and far between.

Methods
55 healthy full-time university students (val/val = 29; val/met = 26) completed self-report measures of chronic stress and mental wellbeing (10-item Perceived Stress Scale and 12-item Short Form Health survey). Participants completed a virtual reality cognitive test battery (CONVIRT) measuring decision making, attention, and visual processing reaction times. To measure autonomic functioning, saliva alpha amylase and HRV were assessed at baseline and after CONVIRT testing. Saliva samples were sent to the Australian Genome Research Facility to identify the val66met genotype.

Results
Hierarchal regression demonstrated that the val66met genotype was the strongest predictor of decision making and attention, but not visual processing, where val/met participants had faster reaction times than val/val participants. Val/met participants demonstrated higher perceived chronic stress and heightened increases in sympathetic activity, but not parasympathetic activity. Despite this, neither stress nor autonomic activity moderated the effect of val66met on decision making or attention.

Conclusions
This study was the first to investigate the effect of val66met on decision making, attention, and visual processing while concurrently considering the roles of chronic stress and autonomic activity. Although the val66met and cognition literature has been conflicted, this multifaceted approach allowed us to demonstrate that carriers of the val/met gene variant may have better decision making and attention than val/val carriers. This study enhances our understanding of the role of BDNF in executive functioning. Further, this study demonstrates the importance of including measures of chronic stress and autonomic activity when investigating the role of val66met in cognition.

Punishment insensitivity: Roles for impaired contingency awareness and medial orbitofrontal cortex

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Background
In principle, we seek rewards and avoid harm, adapting our behaviour to our environment. However, research show individuals, either human or non-human, differ markedly in their avoidance of harm (i.e. their sensitivity to punishment). On top of non-clinical implications for this variability, insensitivity and hypersensitivity to punishment have been linked to various psychopathologies, including addiction, psychopathy, and depression. The underpinnings of this variability are poorly understood; it could be due to differences in aversion, motivation for reward, and/or instrumental control, as well as the biological substrates that support these functions.

Methods
To address this, we trained rats in a task that concurrently assessed punishment, reward-seeking and Pavlovian fear. For behaviour analysis, rats (N = 48) were trained to press two levers for food (VI30sec). They then received conditioned punishment training; pressing continued to yield food, but pressing the "punished" lever yielded a stimulus (VI60sec CS+) co-terminating with footshock, whereas the unpunished lever yielded an inconsequential stimulus (VI60sec CS-). In follow-up experiments, rats received NMDA or sham lesion of medial orbitofrontal cortex (mOFC) before (N = 32) or after (N = 40) conditioned punishment. Lever-pressing was subsequently assessed under extinction conditions.

Results
In general, rats exhibited fear (conditioned suppression) to the CS+ but not CS-, and selectively avoided the punished lever. However, avoidance was bimodally distributed and unrelated to fear and unpunished reward-seeking. Cluster analysis of all behaviour identified punishment sensitive, insensitive and hyper-sensitive phenotypes. Crucially, insensitive animals exhibited normal conditioned suppression, but failed to avoid the punished lever in a manner consistent with contingency blindness. Lesions of mOFC caused impairments in acquiring, but not retrieving, punishment avoidance without affecting reward-seeking or fear. mOFC lesioned animals also failed to maintain punishment avoidance in extinction tests, unlike sham animals.

Conclusions
Propensity to avoid harm differs vastly across individuals; this was assumed to be due to differences in aversive or appetitive motivation. Here, we show punishment insensitivity can emerge independently of these reasons and, in this case, appears primarily due to failures in detecting Action-Punisher relationships. Lesions of the mOFC cause this punishment insensitive phenotype; mOFC is likely a key structure in acquiring and maintaining punishment associations, conforming with findings that punishment-related disorders are associated with mOFC dysfunction. Follow-up experiments, including in humans, are currently underway.

Amygdala-cortical control of striatal plasticity drives the acquisition of goal-directed action

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Background
In mammalian species the capacity for goal-directed action relies on a process of cognitive-emotional integration, which melds the causal and incentive learning processes that link action-goal associations with the current value of the goal. Recent evidence suggests that such integration depends on a cortical-limbic-striatal circuit centered on the posterior dorsomedial striatum (pDMS). Learning-related plasticity has been described at both classes of principal neuron in the pDMS; the direct (dSPNs) and indirect (iSPNs) pathway spiny projection neurons and is thought to depend on inputs from prelimbic cortex (PL) and the basolateral amygdala (BLA).

Methods
The relative contribution of these structures to the cellular changes associated with goal-directed learning has not been assessed, nor is it known whether any plasticity specific to the PL and BLA inputs to the pDMS is localised to dSPNs, iSPNs or both cell types. Here, by combining instrumental conditioning with circuit-specific manipulations and ex vivo optogenetics in mice, we address these questions.

Results
We discovered that the PL and not the BLA input to pDMS is pivotal for goal-directed learning, and that plasticity in the PL-pDMS pathway was bilateral and specific to direct pathway spiny projection neurons (dSPNs) in the pDMS. Subsequent experiments revealed the BLA is critically, but indirectly, involved in striatal plasticity via its input to the PL; inactivation of the BLA projection to PL blocked goal-directed learning and prevented learning-related plasticity at dSPNs in pDMS.

Conclusions
This series of experiments demonstrates that the BLA provides information to the PL necessary for learning-related plasticity in the PL-pDMS pathway; and, therefore, for a limbic-prefronto-striatal circuit that is necessary for the acquisition of goal-directed action. This circuit is critical to normal decision-making; i.e., the capacity to decide between competing courses of action, which is crucial to maintaining good health and wellbeing. Impairments in decision making are well established in normal aging, as well as a range of neuropsychological disorders, and this circuit provides a candidate target for therapeutic interventions relating to these impairments.

2.6 Post-traumatic stress disorder

Stress Hypersensibility in Autism Spectrum Disorder is a Risk Factor for PTSD-like Memory Formation

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Background
The interaction between Autism Spectrum Disorder (ASD) and anxiety traits has been extensively documented. However, the consequences of such interplay upon cognition remains unknown. ASD does not only encompass core deficits in behavioural domains such as social behaviour and repetitive behaviours, but also hyperreactivity to sensory stimuli, making patients potentially more susceptible to developing post-traumatic stress disorder (PTSD). Despite sharing common alterations, the overlap between ASD and PTSD is poorly explored.

Methods
To assess the susceptibility of developing traumatic memory in ASD, we tested the Contactin-associated protein 2 knock out (Cntnap2 KO) mouse model of ASD in an unpaired tone-shock fear conditioning paradigm, modified from a previously used model of PTSD-like memory, combined with a 30min-restraint stress. Behavioural testing was combined with mapping of recall-induced brain activities, by quantifying c-Fos levels. To manipulate PTSD-like memory formation, we optogenetically modulated the PFC activity during conditioning. Finally, we aimed to develop a behavior-based rehabilitation strategy to rescue pathological memory, through re-exposure to the tone in the conditioning context.

Results
Unlike control mice, which displayed a strong fear of the conditioning context (i.e. normal memory), Cntnap2 KO mice showed a strong fear to the tone, and little fear to the context. Such memory profile is characteristic of a PTSD-like memory: hypermnesia for an irrelevant cue, combined with an amnesia for the context surrounding the traumatic event. We show that such pathological memory was associated with a broad dysfunction of the prefrontal-hippocampo-amygdalar network. Optogenetic manipulation of the PFC successfully prevented PTSD-like memory formation in Cntnap2 KO mice. Finally, recontextualizing the trauma restored normal memory, even after long-term retention of PTSD-like memory.

Conclusions
Here we demonstrate that ASD is a risk factor for developing PTSD-like memory, in response to acute mild stress. Our study shows that a stressful situation, that does not exceed the threshold for pathological memory in control population, gives rise to PTSD in ASD. By revealing that autistic mice display the classic qualitative alterations of PTSD-like memory, we open the path to better diagnostic of trauma in ASD. Once detected, we hope to pave the way for successful behavioural-based rehabilitations of PTSD in ASD, through reexposure to the elements of the trauma, which successfully restored normal fear memory in mice.

Traumatic brain injury and post-traumatic stress disorder are associated with persistent white matter disruption in Vietnam War veterans

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Background
To date, Diffusion Tensor Imaging (DTI) studies have revealed structural changes in major white matter (WM) tracts shortly following traumatic brain injury (TBI) and in patients with post-traumatic stress disorder (PTSD), but the long-term persistence of these changes is unknown. We utilized DTI to investigate WM alterations in TBI and/or PTSD survivors, five decades after the trauma.
Methods
Data from 160 Vietnam War veterans recruited by the US Department of Defense Alzheimer's Disease Neuroimaging Initiative, underwent a neuropsychological Assessment, structural MRI, and DTI, and were divided into TBI (n = 23), PTSD (n = 53), TBI+PTSD (n = 36), and control (n = 48). We tested for group differences in WM's fractional anisotropy (FA) and mean diffusivity (MD) (tract-based spatial statistics), and calculated correlations between WM alterations with neuropsychological scores (Voxel-wise).
Results
The PTSD and TBI+PTSD groups showed greater neuropsychological and cognitive impairments as compared to the TBI and control groups. Compared to controls, decreased FA and increased MD were observed in major WM tracts including the corpus callosum, external and internal capsule, inferior longitudinal fasciculus, cingulum, and superior longitudinal fasciculus. Furthermore, FA alterations correlated positively with the Boston Naming Test and Montreal Cognitive Assessment, while MD correlated negatively with Boston Naming Test and Mini-Mental State Exam scores, implying a relationship between disruption of WM axons and present cognitive performance.
Conclusions
DTI detected distinct patterns of WM changes in veterans with TBI and PTSD almost half a century post-trauma, and the extent of WM alterations correlated with poor clinical outcomes.

Activating Attachments Modulates Neural Responses to Threat in Refugees with PTSD Experiencing Separation Grief

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Background
Refugees exposed to forcible displacement also experience significant disruptions to their social attachment systems - including family separation and destruction of social networks. This can lead to attachment insecurity or grief relating to separation from loved ones. These experiences might impact on how the brain engages the attachment system to mitigate neural responses to threat. This study tested the functioning of the attachment system during threat coping in refugees with PTSD.

Methods
Refugees with (N = 28) and without (N = 22) PTSD participated in an fMRI study where they were presented with prime cues to engage the attachment system prior to processing threat or neutral images. We examined PTSD (vs no-PTSD) group differences in neural activation and connectivity patterns to attachment primed threat, and how these group differences were moderated by avoidant or anxious attachment style, or by grief relating to separated family.

Results
We found significant PTSD group differences in neural responses to threat but that these differences were substantially moderated in different ways by separation grief and attachment style. Increased separation grief was linked to increased amygdala but decreased ventromedial prefrontal cortex and hippocampal activity to attachment primed threat in PTSD (vs no PTSD). Avoidant attachment style was associated with increased activity in the dorsal attention network to attachment primed threat and neutral cues in the PTSD (vs no PTSD) group). Anxious attachment style was linked to reduced amygdala connectivity with medial prefrontal regions in the PTSD (vs no-PTSD group).

Conclusions
Separation grief emerged as the strongest predictor of the erosion of the buffering effect of the attachment system on threat-related neural activity in refugees in PTSD. Avoidant and anxious attachment style appeared to moderate attention and prefrontal regulation mechanisms in PTSD. The findings highlight the importance of considering disrupted social attachments in the post-trauma recovery of refugees, which may be based on significant changes in key emotional and regulatory neural systems.

The Functional Connectome in Posttraumatic Stress Disorder

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Background
Previous fMRI studies of posttraumatic stress disorder (PTSD) have investigated region-specific alterations in resting-state connectivity but global changes in connectivity are yet to be characterized. Understanding the neuropathology of this is important to develop novel treatment interventions for PTSD. This study aims to conduct the first connectome-wide investigation in PTSD to provide a more comprehensive analysis of neural networks in this disorder.
Methods
A functional MRI scan was completed by138 individuals (67 PTSD and 71 non-trauma-exposed healthy controls [HC]). 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 PTSD and HC were investigated using network-based statistics at a family-wise error rate of $p<0.05$. Significant network differences were then further investigated in 27 individuals with trauma exposure but no PTSD [TC]).
Results
Compared to HC, PTSD displayed decreased intrinsic functional connectivity in a network of 203 connections between 420 regions within and between mid-posterior default mode, central executive, limbic, visual and somatomotor regions. Additionally, PTSD displayed increased connectivity across a network of 50 connections from thalamic and limbic to sensory and default-mode regions. Connectivity in TC in both these networks was intermediate and significantly different to PTSD and HC.
Conclusions
A large-scale imbalance between hypoconnectivity of higher-order cortical networks and hyperconnectivity of emotional and arousal response systems seems to occur on a sliding scale from trauma exposure to clinical manifestation as PTSD. Novel interventions that target this systemic functional imbalance could provide potential mitigation of PTSD.

Neural Activity During Response Inhibition in Mild Traumatic Brain Injury and Posttraumatic Stress Disorder

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Background
Mild traumatic brain injury (mTBI) is often characterized by deficits in response inhibition, which can contribute to marked social and occupational dysfunction. mTBI often occurs in the context of psychologically traumatic events. This can cause posttraumatic stress disorder (PTSD), which also impedes response inhibition. The overlap or distinction in these inhibitory deficits in mTBI and PTSD is unclear. This study aimed to assess behavioral, neurophysiological, and neuroimaging indices of response inhibition in mTBI by also assessing these parameters in healthy controls (HC) and PTSD participants.

Methods
Participants with mTBI (without PTSD) (n=46), PTSD (without mTBI) (n=41), and HC (n=40) were assessed during a response inhibition task (the Go/NoGo task) during separate functional magnetic imaging (fMRI) and event-related potentials (ERP) sessions. PTSD symptom severity was assessed with the Clinician-Administered PTSD Scale.

Results
Both mTBI and PTSD participants performed more omission errors on the Go/NoGo task and were associated with greater N2 amplitude, greater left inferior parietal activation and reduced connectivity of the left inferior parietal cluster and left angular gyrus compared to HC. There were no differences between mTBI and PTSD on any of these measures.

Conclusions
These findings highlight that both mTBI and PTSD contribute to neural dysfunction in mTBI during response inhibition, and arguably these occur due to distinct mechanisms. In the context of the common comorbidity between these two conditions, strategies to address response inhibition deficits in mTBI may need to consider causative factors underpinning neurological insult of mTBI and psychological effects associated with PTSD.

Acute changes in functional connectivity within the default-mode network are associated with the development of posttraumatic stress disorder in women exposed to sexual assault

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Background
Women are more likely to be exposed to sexual violence, often leading to the development of posttraumatic stress disorder (PTSD). However, the neurobiological changes occurring early following exposure to a traumatic event and involved in the late development of PTSD are not clear. Changes in resting-state functional connectivity have been proposed as markers of chronic PTSD, but there is only little evidence for its use in predicting the development of the disorder. This study aimed to determine if acute changes in patterns of functional connectivity would be evident in women who developed PTSD six months following exposure to sexual assault.
Methods
Participants were 25 women recruited three weeks following exposure to sexual assault (T1) and 19 age-matched healthy controls (HC). Among the victims, 10 participants met (PTSD) and 15 did not meet (trauma-exposed controls, TEC) DSM-IV criteria for PTSD six months post-trauma (T2). Independent component analysis was applied to resting-state functional magnetic resonance images at T1. A series of analyses of variance compared patterns of connectivity among groups at T2 (HC, TEC, PTSD) within selected independent components that correlated ($r^2>0.25$) with templates of known connectivity networks available through the FIND Lab (Stanford University).
Results
Among the selected components, only one showed a significant main effect of group. This component spatially correlated with the default mode network (DMN; $r^2=0.31$). Main effects of group were evident in the posterior cingulate cortex (PCC; $pFWE=0.011$) and in the postcentral gyrus (PCG; $pFWE=0.038$). Post-hoc analyses indicated that the PTSD group showed significant increased PCC connectivity compared to both the TEC and HC groups (all $p<0.001$), and that both the TEC and PTSD groups showed decreased connectivity in the PCG compared to both the HC group (all $p<0.001$).
Conclusions
Changes in functional connectivity within the DMN are evident as early as three weeks following exposure to sexual assault. Notably, within this network, increased connectivity in the PCC may represent an early marker of the later development of PTSD, while increased connectivity in the PCG may represent a marker of trauma exposure. These regions are involved in processing self-related and somatosensory information, respectively. It is thus possible that delivering early interventions acting upon these brain regions (e.g., trauma-focused cognitive-behavioural therapy or eye movement desensitisation and reprocessing) may prevent the development of PTSD in women exposed to sexual assault.

2.7 Disordered Eating: Obesity, Anorexia, Body Image

Dual plasticity and protection role of hippocampal perineuronal nets revealed by improvement and impairment of memory function

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Background
Perineuronal nets (PNNs) are condensed extracellular matrix (ECM) structures that surround specific neurons. Here they regulate neuronal plasticity and also protect neurons from damage. PNNs frequently surround parvalbumin (PV+) interneurons in the cortex, a key neuronal population for cognitive functioning, dysfunction of which is linked to several neuropsychiatric conditions. Harnessing the structural integrity of PNNs represents a mechanism by which neuroplasticity can be modulated, but comes with the caveat that without PNNs, neurons are vulnerable to damage. Here we designed several experiments to assess these two functions of PNNs, in the context of dietary-obesity induced memory impairment.
Methods
Hippocampal PNNs were degraded using the enzyme chondroitinase ABC (or PNase control). The degradation of PNNs was conducted either following 4 weeks of high fat / high sugar (HFHS) diet consumption, or before the 4 weeks of HFHS diet administration. Behavioural testing was conducted using modified versions of a spontaneous location recognition (SLR) task, which have different spatial configurations reliant upon increasing levels of hippocampal plasticity. Following testing, immunofluorescent analysis was conducted to examine the numbers of parvalbumin neurons, PNNs and mirogliosis in the hippocampus.
Results
Memory performance was restored in HFHS diet mice when PNNs were ablated following 4 weeks of HFHS diet consumption and then tested one week later. Moreover, control diet mice treated with chABC showed enhanced memory performance. However, memory deficits in the SLR task were exacerbated when PNNs were removed prior to the 4-week HFHS diet consumption period, and no improvement was seen in control diet fed mice. Parvalbumin neuron immunoreactivity was reduced in the HFHS diet mice, and microgliosis was increased, indicating that chABC treatment may only transiently provide improvements in memory performance.
Conclusions
These studies provide evidence, in the same experimental setting, for the dual role of PNNs in plasticity and protection of PV neurons, and provide further evidence for PNNs as a novel therapeutic target, but with the critical caveat that both beneficial and detrimental effects of PNN manipulations can obtain depending on the timing of PNN manipulation.

Obesity in adolescence leads to dysregulated regional and distributed neural circuits

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Background
Emerging evidence suggests the adolescent brain may be particularly vulnerable to the impact of obesity and overconsumption of nutrient deprived calorie-dense foods. Excessive consumption of obesogenic “junk foods” has tangible influences on brain structure and function - altering neural dynamics, white matter, neurogenesis, and plasticity, disruption of which is associated with cognitive impairments and neuropsychiatric conditions, including ADHD, depression and anxiety. Obesity in adolescence is especially insidious as derailment of neurodevelopment can drastically alter the typical maturational arc. Here, we used non-invasive neurophysiological imaging in adolescents with obesity to study intrinsic activity in regional and distributed neural circuits and networks.

Methods
We scanned 26 adolescents using resting-state magnetoencephalography (MEG), including those with obesity (n=6, age M=14.2 years, 2 females, BMI > 30) enrolled in the SickKids Team Obesity Management Program (STOMP) and typical controls (n=20, age M=13.1 years, 10 females, normal BMI range). Regional neural dynamics and interareal synchrony (or functional connectivity) were measured across the whole brain. We examined alpha (8-14 Hz), beta (15-30 Hz) and gamma (30-80 Hz) oscillations, which are implicated in inhibition and excitation, thalamo-cortical resonance and connectivity.

Results
Regional contrasts revealed significant elevated gamma in obese individuals, particularly in bilateral prefrontal and medial parietal cortices, and posterior cingulate cortex – key regions for cognitive control. Trending alpha oscillatory decreases were also found in the medial superior frontal cortex. Network-based analysis identified significantly reduced functional network connectivity in the alpha and beta frequencies across a distributed set of regions, including fronto-parietal and temporal areas, and key nodes in the Default Mode Network (DMN). The greatest reduction in function coupling was observed in the superior parietal lobule and precuneus – two critical regions for attention and higher-order cognition.

Conclusions
Here, we report the first evidence of reduced neurophysiological functioning in adolescents with obesity. We observed significant dysregulation of neural rhythms associated with excitation and inhibition, which may underlie cognitive changes and precipitate the development of neuropsychiatric conditions. A striking feature of our results was the disruption of connectivity within the DMN in adolescents with obesity, a neural signature commonly observed in neurological and neuropsychiatric disorders. These novel findings demonstrate the neurophysiological impact of obesity during a key period of neurodevelopment, which may lead to enduring functional deficits that persist into adulthood and predispose those to mental health challenges.

N-Acetylcysteine reduces compulsive-like behavior towards high-fat high-sugar food in diet-induced obese rats

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Background
Compulsive overeating displayed by some people with obesity shares similarities with compulsive drug taking behaviour. In both cases it is a chronic, relapsing condition where individuals display compulsive substance-seeking and use despite known negative consequences. This raises the possibility that drug addiction treatments may show utility in the treatment of compulsive overeating. N-Acetylcysteine (NAC) is a cysteine pro-drug which has shown some success in clinical trials for reducing cocaine, marijuana, and cigarette use, as well as compulsive behaviours such as gambling and trichotillomania.
Methods
We assessed the impact of NAC on addiction-like behaviour towards highly palatable food in a well-established rat model of diet-induced obesity. Diet-induced obesity-prone (DIO) and resistant (DR) rats were tested for differences in their eating behaviour and for presence of compulsive overeating. We measured consumption in home cages and in the classic operant self-administration paradigm where rats could lever press for high-fat high-sugar food (HFHS) pellets. Loss of control was defined as a persistence of HFHS food-seeking in the presence of cues that signalled reward unavailability.
Results
DIO animals ate more, earned more food pellets, and responded more during signalled reward-unavailability periods. This persistent responding in the absence of reward displayed by DIO rats was ameliorated by daily injections of NAC (100 mg/kg, i.p.) and after 14 days NAC-treated DIO performance resembled that of DR rats. Moreover, Vehicle-treated DIO rats continue to increase their lever presses for food pellets over the 2-week self-administration period, but this escalation was absent in NAC-treated DIO rats.
Conclusions
These findings suggest that NAC modifies important aspects of compulsive-like food-seeking behaviour in DIO rats and supports the further investigation of this compound in compulsive overeating.

Protocol: Investigating the Cause and maintenance of Anorexia Nervosa (the I-CAN study): A comprehensive neurobiopsychosocial investigation of the underlying mechanisms involved in anorexia nervosa

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Background
The biopsychosocial model of anorexia nervosa (AN) is well accepted, yet, the different biological, psychological and sociocolutural factors involved in the development and maintenance of AN remain poorly understood. Furthermore, the majority of the literature focuses on single or specific aspects of the model without integrating environmental and biological components. The I-CAN study will involve a large-scale neurobiopsychosocial investigation of the factors and mechanisms that contribute to AN.
Methods
Over 300 participants will be recruited including people with a current or past history of AN; siblings of participants with AN; and healthy controls. A comprehensive neurobiopsychosocial battery of assessments will be administered, including an extensive range of psychological and sociocultural measures, cognitive assessments and biological data collection (i.e. magnetic resonance imaging (MRI), and blood, saliva and faecal samples).
Results
Analyses will involve a combination of analyses of variance, regressions and machine learning to identify combinations of factors that are involved in AN.
Conclusions
The findings of this research will inform the development of new treatments, targeting the underlying factors and mechanisms involved in AN. In particular, this research aims to identify relationships and interactions between different variables to enable the implementation of personalised treatment for individuals with anorexia nervosa in the future.

Evaluating the rat BDNF Val68Met polymorphism as a risk factor for activity-based anorexia

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Background
Anorexia nervosa (AN) is a debilitating metabo-psychiatric disorder, characterised by extreme body weight loss through hyperactivity and minimal food intake. The single nucleotide polymorphism of the brain derived neurotrophic factor (BDNF), Val66Met, is associated with a higher reward value of starvation in AN patients as well as more severe AN symptoms. Our study is the first to investigate the effects of the rat-specific knockin gene BDNF Val68Met on susceptibility to body weight loss in activity-based anorexia (ABA). We propose that Met allele carriers are more susceptible to body weight loss in ABA, mediated by altered feeding behaviour and/or energy expenditure.

Methods
Female BDNF Val68Met rats (n=35) on a Sprague-Dawley background were housed individually at 5 weeks of age before being exposed to the activity-based anorexia (ABA) paradigm. The paradigm consists of 6 days of running wheel access followed by a maximum of 10 days of wheel access combined with time-limited access to food (90 min/day). Feeding patterns and hedonic preferences were also assessed in a separate cohort of BDNF Val68Met rats (n=44 male; n=32 female) using automated feeding cages. Finally, expression of the thermogenic marker uncoupling protein 1 (UCP1) was examined in interscapular brown adipose tissue (BAT) with western blotting.

Results
The modified protocol of ABA including one week of adolescent social isolation increased susceptibility of female rats to pathological weight loss, with 100% of animals reaching body weight criteria for removal from the paradigm (<80% baseline) before the maximum of 10 days exposure. The effects of the BDNF Val68Met polymorphism were subtle, with female Met/Met carriers running less at baseline ($p=.0395$) than Val/Met heterozygotes or wildtypes, and an increased orexigenic response to ghrelin administration for Val/Met female rats only ($p<.0001$). Male Met/Met carriers ate more food than Val/Met and wildtypes ($p=.0003$), however, preference for sucrose or high-fat food was unaltered.

Conclusions
We show that adolescent social isolation stress increases susceptibility to ABA in female rats, although possession of the BDNF Val68Met allele did not exacerbate this. This contrasts with a mouse model in which the Met allele increased anorexia-like phenotypes only in combination with this stressor, and may relate to higher stress resilience of Sprague-Dawley rats. The findings of reduced activity in female Met/Met carriers and increased food intake in male Met/Met carriers are consistent with a shift towards energy conservation and provides a signpost for further investigation into the role of this gene variant in feeding and exercise behaviour.

Investigating the cardiometabolic profile of anorexia nervosa

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Background
The energy deprivation and malnutrition associated with anorexia nervosa (AN) places immense pressure on the cardiovascular (CV) system, with up to 80% of patients suffering from CV complications. Individuals with AN also demonstrate altered autonomic nervous system (ANS) activity, thought to be implicated in the pathogenesis of cardiometabolic illnesses. Whether this impairment is sustained after weight restoration is unknown. The aim of this study was to assess CV, ANS and metabolic function in individuals with a current and previous diagnosis of AN compared with age-matched healthy individuals.

Methods
Autonomic nervous system activity was assessed in 37 participants (10 healthy controls, 10 individuals with anorexia and 17 individuals with a previous diagnosis of AN who were weight restored) using direct muscle sympathetic nerve recording (MSNA; microneurography), heart rate variability (HRV), blood pressure (BP) and arterial stiffness [Carotid to femoral pulse wave velocity (cfPWV)].

Results
Females with a current diagnosis of AN displayed low systolic BP, decreased muscle sympathetic nervous activity and reduced HRV as assessed by standard deviation of heart rate and low frequency component of HRV compared with female controls. Individuals with AN also displayed significantly increased pulse wave velocity, which persisted after weight restoration.

Conclusions
Individuals with a current diagnosis of AN demonstrated poorer vascular health, with impaired arterial stiffness, autonomic dysregulation with low muscle sympathetic nervous system activity, impaired baroreflex function and low blood pressure as well as metabolic abnormalities. Weight-restored participants also demonstrated some sustained dysregulation of the ANS despite normal blood pressure levels. Investigating these functions in individuals with AN and whether they are sustained with weight restoration will enable us to investigate the underlying cause of cardiac complications present in AN, with the potential to identify those at risk of cardiac failure.

Altered resting-state brain connectivity in body dysmorphic disorder

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Background
Body dysmorphic disorder (BDD) is a psychiatric disorder characterised by a preoccupation with a perceived defect in appearance. Functional neuroimaging research has identified hyperactivity in visual pathways and reduced fronto-limbic connectivity in BDD relative to healthy controls. While much of this research has employed task paradigms utilising visual stimuli, preliminary data suggests that abnormalities of brain function in BDD persist while at rest. However, there has been no thorough investigation of resting-state brain function in BDD. Thus, we aimed to investigate the functional connectivity of resting-state intrinsic connectivity networks in BDD as compared to healthy controls, using fMRI.

Methods
Resting-state fMRI images were acquired from 13 BDD and 19 healthy control participants, using a T2*-weighted gradient-echo, echo planar multiband imaging sequence (TR = 870ms, TE = 30ms, flip-angle = 55°, multiband acceleration factor (MB) = 6, field of view = 192mm, 96 x 96 acquisition matrix, 66 interleaved slices, 450 volumes, voxel size = 2.0 isotropic, TA = 6:40 minutes). Group independent components analysis was conducted to estimate whole-brain voxel-wise functional connectivity among all participants. Then, voxel-wise functional connectivity of identified intrinsic connectivity networks were compared between BDD and healthy control participants using t-tests.

Results
In contrast to healthy controls, BDD participants demonstrated the following significant differences: i) increased connectivity of left superior temporal gyrus with a default mode network, ii) increased coherence within a posterior visual network localized to the right middle occipital gyrus, iii) increased connectivity of right anterior insula with a cerebellar network, iv) increased connectivity of the right superior parietal lobule, right lingual gyrus and a dorsal sensorimotor network, v) increased connectivity of left antero-lateral orbitofrontal cortex with a central executive network, and vi) increased coherence within a right fronto-parietal network, localised to the right superior intraparietal sulcus.

Conclusions
These findings indicate abnormally heightened connectivity of bodily and visual processing regions with broader intrinsic brain networks in BDD, which may relate to disturbed body image and an increased body focus in self-referential processing in the disorder. Secondly, findings of altered connectivity in two cognitive-control networks (fronto-parietal and central executive) in BDD may have explanatory relevance for previous findings of neurocognitive dysfunction in BDD, including poor executive functioning and response inhibition difficulties. Importantly, these results extend previous neurobiological models of BDD by highlighting a role of widespread connectivity alterations in BDD that persist in the absence of active task paradigms.

A hindbrain noradrenergic circuit involved in food intake control

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Background
The nucleus of the solitary tract (NTS) is implicated in food intake control. Specifically, activation of NTS noradrenergic (NA) neurons suppresses food intake and appetitive behaviours. However, the neural circuits by which these neurons control feeding behaviours remain poorly understood. The parabrachial nucleus receives dense projections from the NTS and is implicated in food intake control. However, whether NTS NA projections to the PBN contribute to the control of feeding behaviours is unclear.

Methods
To characterise NTS NA projections to PBN, rats received infusions of retrograde tracer Fluorogold to the PBN, and NTS sections were stained for TH, a marker of noradrenaline synthesis. To selectively activate the NA NTS→PBN pathway, TH-Cre rats were infused with excitatory DREADD (hM3Dq) to the NTS and clozapine-N-oxide (CNO; ligand for hM3Dq) was administered to the PBN. We then examined the effects of NA NTS→PBN activation on a variety of feeding behaviours including dark cycle chow intake, deprivation re-feed, and high-fat diet intake.

Results
Retrograde tracing results revealed that 6.5% of TH-expressing neurons in the NTS projected to the PBN, and 11.6% of PBN-projecting NTS neurons were TH positive. Preliminary results indicated that activation of NA NTS→PBN pathway reduced dark cycle chow intake and body weight. In food deprived rats, there was a trend towards suppressed chow intake, after activation of NA NTS→PBN pathway. However, when given access to high fat food, activation of the pathway was insufficient to reduce food intake.

Conclusions
These results provide evidence to show that NTS NA neurons engage neurons within the PBN to reduce dark cycle chow intake, whilst suggesting the involvement of other neural pathways in regulating food intake when the motivation to consume is heightened (e.g. hunger, food palatability).

Characterisation of hindbrain - forebrain noradrenergic circuits in the control of feeding behaviours

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Background
Overeating is a major factor in obesity development. The lack of effective treatments calls for the need to better understand the neural mechanisms of food intake control. Studies from our laboratory showed that activation of noradrenergic (NA) neurons in the nucleus of the solitary tract (NTS) reduces food intake, regardless of energy state or food palatability. This suggests that these neurons control feeding behaviours, however, the neural pathways are unclear. This study explored the role of NTS NA projections to the bed nucleus of the stria terminalis (BNST; NA NTS-->BNST) and paraventricular hypothalamus (PVH; NA NTS-->PVH), in food intake control.
Methods
We characterised these projections via injection of retrograde tracer, Fluorogold, to the BNST and PVH. Immunohistochemistry was performed on NTS sections to assess colocalization of Fluorogold with NA. We then determined whether activation of NA NTS-->BNST and NA NTS-->PVH pathways reduces dark cycle chow intake, deprivation re-feed and high-fat diet intake. To selectively activate NA NTS-->BNST and NA NTS-->PVH pathways, tyrosine hydroxylase (TH) cre rats were injected with a cre-dependent AAV encoding the excitatory receptor (hM3Dq) or reporter control (eYFP) to the NTS. Cannulae were implanted into the BNST or PVH, permitting infusions of clozapine-N-oxide (ligand for hM3Dq) or vehicle.
Results
Retrograde tracing results confirmed NTS NA projections to both BNST and PVH, with approximately 50% of BNST- and PVH- projecting NTS neurons colocalising with NA. Results from behavioural studies showed that activation of the NA NTS-->PVH pathway, but not NA NTS-->BNST pathway, reduced dark cycle chow intake. Activation of NA NTS-->PVH or NA NTS-->BNST pathway, however, had no effect on chow intake after overnight deprivation or high-fat diet intake.
Conclusions
Together, these findings showed that activation of NA NTS-->PVH neurons reduced chow intake and that different NTS NA pathways are likely involved in reducing deprivation re-feed and high-fat diet intake. Future studies will characterise other hindbrain noradrenergic circuits to further elucidate the underlying mechanisms of these feeding behaviours.

Activation of the medial-prefrontal cortex to lateral hypothalamic circuit suppresses food intake and motivation to obtain sucrose reward

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Background
The medial pre-frontal cortex (mPFC) is a key brain region implicated in food reward valuation. Human imaging studies demonstrate that both obese and anorexic patients have stronger mPFC activation in response to food cues, suggesting a role for the mPFC in disordered feeding. Specific mPFC circuits may regulate different aspects of feeding behaviour, with many mPFC circuits not yet thoroughly investigated. The mPFC directly projects to the lateral hypothalamus (LH) – a brain region that coordinates both feeding and reward seeking. Here, we aim to manipulate mPFC-LH circuit in mice to determine a potential role in control of feeding behaviour.

Methods
Initially, we ablated the mPFC-LH circuit in C57BL/6 mice using a dual viral approach to target a genetically engineered caspase to the mPFC-LH projection neurons. These mice were assessed for changes in bodyweight and feeding behaviour on both standard chow and palatable diets. Next, we targeted hM3Dq designer receptors exclusively activated by designer drugs (DREADDs) to the mPFC-LH projection neurons of C57BL/6 mice and acutely activated this circuit using clozapine-N-oxide (CNO) to assess the effect of circuit activation on feeding and operant responding. Finally, we used wireless optogenetics to activate excitatory mPFC-LH projection neurons during a real-time place preference task.

Results
Caspase mediated ablation of the mPFC-LH circuit significantly increased body weight on a chow diet and increased food intake on an acute palatable diet, suggesting that this circuit exerts inhibitory control over feeding behaviour. Supporting this, both optogenetic and chemogenetic activation of the mPFC-LH circuit suppressed fasting induced re-feeding, and motivation to obtain sucrose reward in an operant conditioning task. Neither ablation nor activation of the mPFC-LH circuit influenced anxiety-like behaviour as assessed using standard behavioural tests. However, in the real-time place-preference task, mice spent less time in the stimulation zone, suggesting acute activation of the mPFC-LH circuit is aversive.

Conclusions
Our results suggest the mPFC-LH circuit is an inhibitory controller of feeding and motivated reward-seeking behaviour. Ablation of the mPFC-LH circuit suggested that this circuit is anorexigenic, as deletion resulted in increased bodyweight and food intake. Our DREADDs and optogentic studies support this idea in that stimulation of the mPFC-LH projection neurons was sufficient to override homeostatic and hedonic drives, to suppress fasting induced re-feeding and motivated sucrose-seeking. These results support a role for hyper-activation of the mPFC to LH circuit in anorexic behaviours and are consistent with human imaging data that demonstrate increased mPFC activity in patients with anorexia.

Hunger signalling via the ghrelin receptor in the olfactory bulb influences mood and metabolism

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Background
Olfactory dysfunction contributes to many metabolic and mental illnesses in humans and many animals rely on olfaction for normal exploratory behaviour and food acquisition. Interestingly, changes in metabolic state, such as reduced caloric intake during fasting, enhances olfactory processing in both humans and animals. The mechanism linking metabolic state and olfaction remains unknown. Ghrelin is a hormone that regulates metabolism, mood, and memory at various central nervous system (CNS) locations via its receptor under a state of energy deficit. Although the ghrelin receptors are highly expressed in the olfactory bulb (OB), its function remains unknown.
Methods
We investigated whether ghrelin receptors in the OB increases olfaction performance in fed and fasted conditions and whether or not this influences mood and metabolic parameters using a number of behavioural and metabolic challenges. We employed a viral genetic knockdown approach to chronically delete ghrelin receptors specifically in the OB in ghrelin receptor floxed mice crossed with cre-depednent tdTomato reporter mice to aid viral spread and knockdown validation. 10 week old adult mice were injected with AAV-cre (AAV5 pmSyn1-EBFP-Cre) in to the OB.
Results
Deletion of ghrelin receptors in the OB significantly affected olfactory performance in olfactory discrimination and habituation tasks in both fed and fasted mice, as well as increased the latency to find food under both fasted and ghrelin-induced conditions. A two-bottle choice assay for saccharin vs water indicated that mice lacking ghrelin receptors in the OB were completely anhedonic and did not show a preference for saccharin. In support of this, we observed significantly highly anxiety and reduced exploratory locomotor activity in 3 independent anxiety behavioural tasks. Intriguingly, mice increased body weight, fat mass and high blood glucose, indicating metabolic dysfunction.
Conclusions
Our results indicate a novel role for ghrelin receptors in the OB and suggest they play an important role to regulate mood in both fed and fasted conditions. These results also suggest that the ghrelin receptor is a novel molecular mechanism in the OB linking mood and metabolism, since mice gain significant fat mass and develop glucose intolerance on a chow diet relative to WT mice. These findings can potentially inform future therapies aimed at treating both olfactory and metabolic dysfunction, both of which are affected in obesity and diabetes.

2.8 Neurodevelopment: Autism, Early-Life Stress, Social Dysfunctions

Observations of the Effect of Scopolamine on Hippocampal CA1 Place Cells in Freely Moving Mice Using Widefield Calcium (“Miniscope”) Imaging

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Background
Rodent spatial navigation depends on place cells, which are a type of hippocampal pyramidal cell that fire at specific places in a familiar environment. Muscarinic blockade with scopolamine results in cognition deficits usually attributed to impaired memory encoding, but effects on memory retrieval are controversial. Here, we recorded the calcium signals of hundreds of hippocampal neurons with a miniature fluorescent microscope to study the properties of place cells in a linear track before and after the administration of scopolamine.

Methods
Normal black six mice implanted with 2mm diameter lenses in hippocampal CA1 region after AAV GCaMP6 inection 2 weeks beforehand. The mice were trained to run back and forth in a linear track and the neural activities were recorded during this time. We studied the neural firing rate, spatial information content, ensemble stability and decoding accuracy before and after the administration of scopolamine or saline separately. Drugs were administered via intraperitoneal injection.

Results
Five animals were recorded during the experiment. Scopolamine increased the neural firing threshold with fewer neurons (84.7%) appearing on the field. Besides, the neural firing rate was reduced to 83.39% ($p<0.01$). The spatial information content, which is a measure of neural information entropy, decreased to 75% ($p<0.05$) in both running directions. The ensemble stability was greatly impaired by scopolamine with more out-of-field neural firing and the decoding accuracy was reduced by a factor of 3.

Conclusions
Our results suggest that the scopolamine has a clear disruptive effect on the decoding of neural correlates of spatial memory most likely related to the blockade of mAChr. We hypothesize that these effects are related to Im, a potassium conductance modulated by muscarinic receptors, with strong effects on neuronal excitability.

Reframing social cognition: Relational mentalising, and consequences for autism

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Background
The idea that Theory of Mind or 'mindreading' is human's most high-level social ability is barely disputed. Most of this is based on an experiment where one needs to infer what another person thinks on the basis of what they have seen: The so-called false belief task. People on the autism spectrum performing atypically on such tasks has lead to a notion of them lacking mental representations, or being 'mind blind'.

Methods
We present an alternative for Theory of Mind; 'relational mentalising' (Deschrijver & Palmer, in press), where detecting the extent to which another's thinking aligns with our own, after taking note of it, is key. We reframed the philosophical assumptions and interpretation of 40 years of false belief data. We then performed a systematic review of neuroimaging studies using the false belief design, which are typically used to make claims about the temporoparietal junction (TPJ) brain area being tied to mental representations processes.

Results
On the basis of a critical analysis of the control conditions used in the 51 identified false belief neuroimaging studies, we argue that none of them can guarantee the involvement of the TPJ in mental representation processes. A minority of studies however (27%), uses a design that may tie activity in the TPJ to mental conflict monitoring processes only. Reviewing the literature on autism with this in mind, we propose that individuals on the spectrum most likely do not lack mental representations, but rather experience issues on the level of mental conflict monitoring, after having grasped what another is thinking.

Conclusions
The framework has farreaching consequences for psychological science, its neuroscientific bases, and beyond: Throughout life, the ability to detect when people are thinking differently (relational mentalising), may be more important than inferring the content of their minds per se (representational mentalising).

Exploring social avoidance in the Fragile X Mouse model of ASD using a social fear conditioning paradigm

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Background

Fragile X Syndrome (FXS), a form of intellectual disability in humans, is the most prevalent monogenetic cause of Autism Spectrum Disorder (ASD). FXS is caused by a single gene mutation in the FMR1 gene that causes loss of function to the fragile X mental retardation protein (FMRP), which plays a key role in regulating the expression of a wide range of proteins important in healthy cognitive development. Like humans with the fmr1 loss of function mutation, Fmr1(-/-) mice have deficits in social interaction and motivation, abnormal locomotion, repetitive grooming and anxiety-like behaviours.

Methods

Social anxiety and avoidance is the most prevalent social deficit in patients with Fragile X Syndrome, present in as many as 75% of males. Until recently, however, behavioural phenotyping of sociability has been limited in its ability to isolate aspects of social interaction from social fear. Using a murine social fear conditioning (SFC) task, we pair a mild foot shock with conspecific social interaction and examine fear extinction in a novel context in response to novel conspecifics.

Results

We will present data exploring how age (juvenile vs adult), sex (male vs female) and genotype (wild type vs FMR1(-/-)) impact conditioned social avoidance behaviour. This is thus the first ever work to properly model the core social anxiety deficit in Fragile X Syndrome in the FMR1(-/-) mice.

Conclusions

Having established our model, we plan to investigate potential pharmacological therapeutics and the neural correlates of the social fear response behaviour using fibre photometry to tie social avoidance behaviour to brain activity in real-time.

Neonatal LPS-induced immediate and sustained effects on cytokines and growth factors in the brain during early life.

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Background
Inflammation during critical periods of neurodevelopment profoundly shapes how the brain develops. This is of great interest given that epidemiological studies have linked early life infection with increased incidence of mental illness. In previous studies, we have used a bacterial mimetic lipopolysaccharide (LPS) to induce perinatal systemic inflammation in neonatal rats and have found subtle associations between inflammation and altered immune function, pro-inflammatory cytokines and microglial activation, with anxiety-like behavior in adulthood. Given neural circuits are organized and differentiated perinatally, neonatal period is highly important for postnatal brain maturation. Therefore, we aimed to investigate LPS-induced central effects.

Methods
Male and female pups (n=4) were administered LPS (0.05 mg/kg, i.p.) on postnatal day (PND) 3 and 5 and brains were collected on PND5 and PND13. High throughput Luminex Multiplex ELISA was performed on Magpix using 23-plex rat cytokine panel as per the manufacturer's instructions. The data was analyzed using 3-way ANOVA followed by post-hoc Bonferroni multiple comparison tests to investigate the role of three independent variables (age: PND5, PND13; sex: male, female; treatment: Saline, LPS) on the expression levels of cytokines, chemokines and growth factors in the brain.

Results
We found an increased expression of central cytokines [IL5 ($p < 0.001$), IL6 ($p < 0.01$), IFNγ] and growth factor GCSF ($p < 0.05$) in LPS-treated males but a decrease ($p < 0.001$) was observed in LPS-treated females when compared with respective saline-treated group, 6hrs post LPS injection on PND5. At PND13, the levels of these molecules normalized in males, but a significant decrease ($p < 0.05$) was observed in females compared to saline-treated group. Interestingly, the basal expression was elevated ($p < 0.05$) in saline-treated females compared to males. There were no effects on IL-1β and TNF-α levels.

Conclusions
Using a model of early life infection, we demonstrate profound sex differences in the immediate and sustained inflammatory response of the neonatal brain. These findings offer insights into the role of neuroimmune signaling in brain development and may implicate a role for neuroimunne signaling in the long-term behavioural outcomes observed in rats exposed to LPS as neonates.

Nutrition and micronutrient intake in children with a diagnosis of autism

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Background
Research suggests that children with a diagnosis of autism spectrum disorder have high rates of abnormal feeding behaviours including food selectivity and restricted diet with some research suggesting greater levels of obesity among children on the spectrum than their neurotypical peers. It is unclear however whether these differences persist in the Australian context and little is known about the influence of sensory sensitivities on the eating patterns of children on the spectrum.

Methods
This is a cross-sectional comparison of children with a diagnosis of autism spectrum disorder aged 2–18 years, their undiagnosed siblings and controls with no history of autism. Dietary intake was assessed using the Australian Child and Adolescent Eating Survey (ACAES) a validated food frequency questionnaire filled out by the parents or children. Sensory processing impairments where measured in children with autism using the second edition of Short Sensory Profile (SSP-2), autistic phenotypic traits were measured using the subscales of the 2nd edition of the Autism Diagnosis Observational Schedule (ADOS-2) and details of other child characteristics were reported by parents.

Results
Children with autism, their siblings and controls had comparable BMIs and comparable energy intakes. Children with autism consumed a greater significantly more energy-dense, nutrient-poor foods than the neurotypical controls and siblings both as a proportion of their total energy intake and more than their siblings as a proportion of their total energy intake. Among children with autism, the presence of sensory seeking behaviours was associated with a greater intake of calories overall, with a greater proportion of their total energy intake coming from the consumption of core foods. The presence of restricted and repetitive interests were associated with a more restricted diet.

Conclusions
Children with autism in the Australian context have a dietary intake consisting of a higher proportion of energy-dense, nutrient-poor foods than their neurotypical peers and siblings. Consistent with previous findings, children who seek sensory input are more likely to have a varied diet and meet their daily nutrient needs. Sensory profile stratification and autistic trait stratification could be used to identify children whose nutrition should be regularly surveyed.

A novel Posner-style cueing task to assess attention orienting in mouse models of autism

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Background
Attention orienting determines where we focus our concentration and is an essential contributor to all cognitive processes. Several studies have associated atypical attention orienting with Autism Spectrum Disorder (ASD). As yet, no effective pharmacological or behavioural treatments exist to address atypical attention orienting in ASD. Attention orienting involves endogenous (goal-directed) and exogenous (stimulus-driven) systems, both of which can be investigated using the Posner task. We have recently reverse-translated this task for use in mice using touchscreen technology. This major advancement now makes it possible to investigate attention orienting deficits in mice that will yield results translatable to human clinical studies.
Methods
The current study investigated attention orienting in mice with and without the autism-associated R451C mutation in neuroligin-3 (NL3) using our newly adapted Posner task for mice. Twenty NL3 mice and twenty wild-type (WT) mice were trained to sustain their nose-poke to a central square until a validly or invalidly cued target was displayed. The cue was a peripheral non-predictive flash in the exogenous task and a central spatially-predictive image in the endogenous task. The effects of two attention-modulating drugs, methylphenidate (MPH) and atomoxetine (ATX), on task performance were also assessed.
Results
On both tasks, mice were quicker and more accurate in the validly versus invalidly cued trials, consistent with results in the human Posner task. NL3 and WT mice were not significantly different in response times, accuracy or attention orienting. Neither MPH nor ATX altered attention orienting, but they exerted differential effects between the genotypes. MPH increased response times only in NL3 mice in the exogenous task. ATX decreased accuracy only in WT mice in the endogenous task.
Conclusions
Our study showed intact attention orienting in NL3 mice during the Posner-style cueing task. Differences in responses to MPH and ATX in NL3 mice indicate that the mutation alters key neurotransmitter systems involved in attention. This study is the first investigation of attention orienting in a mouse model of autism using our adapted human task, producing fundamental new knowledge that may facilitate behavioural and pharmaceutical treatments to improve atypical attention orienting in people with ASD.

Does Prenatal Hypoxia Alter the Early Ontogeny of Dopamine Neurons?

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Background
Dopaminergic dysfunction is a significant feature in the pathophysiology of schizophrenia. Developmental risk factors for schizophrenia as diverse as maternal immune activation or developmental vitamin D deficiency, when modelled in animals, produce abnormalities in early dopaminergic function. Disruptions to dopamine systems during early development may therefore be a convergent early aetiological pathway to psychosis in adulthood. Prenatal hypoxia is another well-known developmental risk factor for schizophrenia. It is typically induced by obstructed labour, smoking during pregnancy and preeclampsia. This project investigates whether prenatal hypoxia also adversely affects developing dopamine systems in embryonic mesencephalic dopamine neurons and in their postnatal connections.

Methods
Pregnant mice at gestational day 10 were exposed to 10% oxygen for 48 hours. Embryo brains were harvested at gestational day 12 and in a separate cohort at postnatal day 10. Prenatal samples were examined for dopamine progenitor number, postmitotic dopamine neuron positioning and gene expression by immunohistochemistry using antibodies against Lmx1a-Sox2 and Nurr1-TH. Postnatal striatum was examined for synaptic density using PSD-95, Bassoon as a presynaptic marker and PSD-95 as a postsynaptic marker. A proximity of 600nM between Bassoon within TH and PSD95 was used as criteria for a dopamine synapse. Cellprofiler and Imaris pipelines were developed for quantification.

Results
Prenatal hypoxia resulted in a significant decrease in dopaminergic progenitor cell number, where protein expression was unchanged. There was also a reduction of mediolateral migration and an increase in dorsoventral migration of progenitors in hypoxic brains. There was no effect observed of hypoxia on postmitotic dopaminergic neurons. There was no effect of hypoxia on mature cell number or protein expression, there was however, a significant decrease in mediolateral position. Striatal synaptic studies are ongoing.

Conclusions
This project aims to identify whether prenatal hypoxia gives rise to abnormal dopaminergic function in the mesencephalon. The prenatal findings to date suggest that like maternal immune activation and developmental vitamin D deficiency, early abnormalities in dopamine ontogeny may represent a convergent developmental mechanism for abnormal dopaminergic function in psychosis.

Developmental Vitamin D (DVD) deficiency increases foetal exposure to testosterone in an animal model of autism spectrum disorder (ASD)

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Background
ASD is a group of neurodevelopmental disorders which are more common in males. The 'prenatal sex-steroid' hypothesis links excessive steroid exposure during foetal life with ASD. However, the reasons why sex-steroid exposure may be excessive, remains unclear. Epidemiological studies identified several environmental risk factors associated with ASD, including DVD-deficiency. We have demonstrated in an animal model that DVD-deficiency is associated with hyper-inflammatory response in placentas from male but not female foetuses. Vitamin D also regulates expression of several steroidogenic enzymes. Therefore using this model we examined whether DVD-deficiency leads to increased sex-steroid levels in both the maternal and foetal compartments.

Methods
Female rats are fed a vitamin D deficient diet from 6 weeks before mating until tissue collection at embryonic day 18. We examined the levels of testosterone, androstenedione and corticosterone in maternal plasma, foetal brains and amniotic fluid by liquid chromatography–mass spectrometry. We further examined gene expressions of steroidogenic enzymes and DNA methylation of aromatase promotors in foetal brains as a potential molecular mechanism regulating testosterone expression. Steroid data from foetal brains and amniotic fluid were analysed by multivariate analysis of variance to determine the main effect of foetal sex, maternal diet, and foetal sex × maternal diet interactions.

Results
We show that DVD-deficiency increases testosterone levels in maternal blood. Importantly testosterone levels were also elevated in DVD-deficient foetal male brains. We also show increased levels of testosterone and androstenedione in the amniotic fluid of female but not male DVD-deficient foetuses. Vitamin D, like other steroid-related hormones, regulates gene expression via methylation. Therefore we examined whether the significant elevation in testosterone in male brains was due to such a potential gene-silencing mechanism. We show that the promoter of aromatase PII was hyper-methylated in DVD-deficient male brains compared to male controls.

Conclusions
Increased exposure to testosterone leading to increased androgenisation of the foetal brain is frequently cited as a possible causative process for the pronounced sex-bias in ASD. However this remains a difficult hypothesis to test directly in human. Here we have examined this hypothesis in a preclinical model based on epidemiologically validated risk factor for ASD. We have shown that DVD-deficiency may selectively elevate testosterone in male embryonic brains. We also uncovered a selective gene-silencing mechanism of aromatase in male brains that may in part explain this finding. These findings provide further mechanistic support for the prenatal sex-steroid theory of ASD.

Altered maternal-pup behaviours in developmental vitamin D-deficient rats

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Background
Developmental vitamin D (DVD)-deficiency is an epidemiologically recognized risk factor for autism (Lee et al. 2019). Our lab has established a rat model of DVD-deficiency to investigate the neurobiological mechanisms implicated in DVD-deficiency (Eyles et al. 2003). Previous findings in DVD-deficient animals have pointed out alterations in maternal stress response as a potential mechanism for altered behaviours in adult offspring. Indeed, studies show that postpartum maternal care, primarily the frequency of licking/ grooming and arched-back nursing, influence offspring neural development (Meaney 2001). This study aims to examine maternal care behaviours and its effect on maternal-pup interactions in DVD-deficient animals.
Methods
DVD-deficient rats were produced by methods already established in our lab (Ali et al. 2019). Postpartum maternal behaviours were video-recorded daily from postnatal day 2 (P2) to P6 in the home cages. Ultrasonic vocalizations (USVs) were recorded from each pup at P7 and P9 in a sound-attenuated chamber. Pup retrieval task was conducted in the home cage for each litter immediately after measuring their USVs at P7 and P9. Statistical significance was measured by multivariate analysis of variance (maternal behaviour and USVs) and student's t-test (pup retrieval).
Results
A total of 21 dams (DVD n=12, Control n=9) were used for the maternal behavioural analysis. We found significantly increased licking and grooming ($F_{1, 105}=9.918$, $p<0.05$) and blanket nursing ($F_{1, 105}=4.716$, $p<0.05$) in DVD-deficient dams compared to controls. Similarly, USVs measurement showed that DVD-deficient pups emitted significantly increased number of calls ($F_{1,305}=6.194$, $p<0.05$) and longer duration of calls ($F_{1, 305}=5.692$, $p<0.05$) compared to controls at P9 but not at P7. Call frequency and call amplitude were not different between control and DVD-deficient pups. The latencies to retrieve the pups were also not different between the control and DVD-deficient dams.
Conclusions
Our current results show that maternal-pup interactions are altered in DVD-deficient animals. Studies have highlighted the implication of maternal care on several mechanisms affecting brain development, including altered hypothalamus-pituitary-adrenal function, oxytocin receptor expression, and synaptic plasticity in the offspring that might lead to long term effect on offspring brain development and behaviour. However, there is also a possibility that altered maternal behaviour observed in our DVD-deficient dams might have been driven by the pup's behaviour, such as increased USVs. This latter possibility remains to be explored.

Vitamin D and SV2C effects on dopaminergic neurons development

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Background
Emerging evidence has identified Vitamin D (VitD) as an essential factor in the development of the dopamine (DA) system. Consequently, developmental VitD deficiency has been implicated in the aetiology of disorders resulting from abnormalities in this system, such as schizophrenia. Synaptic dysfunction has been hypothesised as central to the pathophysiology of schizophrenia with several studies highlighting the role of alterations in synaptic vesicle glycoproteins 2 (SV2) like SV2C, specifically in DA system function. Therefore, the aim of this study was to identify VitD's effect on DA neuronal development and SV2C-synapse formation, as well as SV2C's role in DA neuronal function.

Methods
To investigate VitD and SV2C's effects on the development of DA neurons we used 3 models: 1) our human dopaminergic cell model overexpressing the vitamin D receptor (SH-SY5Y/VDR+), 2) rat primary neuron cultures from DA-rich midbrain tissue at embryonic day (E)14, and 3) rat striatal-mesencephalon explants at (E)16. We performed immunocytochemistry to analyse DA neurons neurite outgrowth and SV2C-synapse formation. We also assessed the effects of SV2C silencing on the expression of the rate-limiting enzyme on DA synthesis tyrosine hydroxylase (TH), DA production and storage using quantitative PCR and high-performance liquid chromatography (HPLC).

Results
Our results provide further evidence of VitD's role as a mediator of dopaminergic development by showing that it increases neurite outgrowth of TH+ neurons in our cell line, primary cultures and explants. We also show the first evidence to suggest that VitD may alter the distribution of DA-associated synaptic protein SV2C specifically. Furthermore, we present SV2C as an important mediator of dopaminergic development and function demonstrating that the silencing of SV2C in SH-SY5Y/VDR+ cells increases DA production and storage.

Conclusions
This study serves to further establish VitD as an essential factor for proper dopaminergic development and maturation. Our results also suggest possible new avenues for research aimed at investigating the connection between VitD and SV2C and whether this may be harnessed to provide further insight into the molecular mechanisms underlying the disrupted DA signalling characteristic of schizophrenia.

Injury during adolescence leads to sex-specific executive function deficits in adulthood in a pre-clinical model of mild traumatic brain injury

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Background
Adolescents are more likely than adults to develop chronic symptoms, such as impulsivity and difficulty concentrating, following a mild traumatic brain injury (mTBI) which may relate to disruption of pre-frontal cortex (PFC) development. During adolescence the PFC is undergoing extensive remodelling, driving maturation of executive functions incorporating attention, motivation and impulse control. In part maturation of the PFC is driven by outgrowth of dopaminergic neurons to the PFC under the guidance of specific axonal targeting cues, including netrin-1. How a mTBI in adolescence may alter expression of axonal targeting cues, and the influence on PFC development is not yet known.
Methods
As such the effects of mTBI in mid-adolescence on executive functioning in adulthood (12 weeks) were examined via the 5-choice serial reaction task (5CSRTT) in both male and female Sprague Dawley rats. Animals at p35 (n=12-16 per group) were injured via weight drop (100g from 0.75m) and injury confirmed by a significant increase in righting reflex. At two weeks post-injury animals were trained on the 5CSRTT, once animals were performing consistently two probes were conducted- one where stimulus duration was decreased to increase attentional demand and one where the intertrial interval was randomly varied to increase inhibitory demand.
Results
Interestingly, while a mid-adolescence mTBI in females led to significantly higher omissions and decreased accuracy when task difficulty was high (stimulus duration 1s), males had significantly increased premature response rate when the intertrial interval was varied. Examination of levels of TH, as a reflection of dopaminergic innervation, found no difference in either gender post-TBI in the PFC, but a significant increase in the limbic system (nucleus accumbens) in males, but not females, chronically post-TBI, suggesting an imbalance between the regions. The increase in TH was accompanied by a chronic reduction in netrin-1 within the nucleus accumbens in males only
Conclusions
Our findings provide increased support for the heightened vulnerability of females to chronic cognitive dysfunction following TBI, and that males are at risk of alterations in impulse control. There is a pressing need to further dissect the post-injury cascades in males versus females and how sex interacts with age at time of injury to identify novel treatment targets for each population, and to determine biomarkers to predict those most likely to develop chronic symptoms post-TBI.

Developmental inhibition of long intergenic non-coding RNA, HOTAIRM1, impairs dopamine neuron differentiation and maturation

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Background
The dopaminergic (DA) system is important for a range of brain functions and subcortical DA development precedes cortical maturational processes. DA neuron fate is controlled by a complex web of transcriptional factors that dictate DA neuron specification, differentiation and maturation. A growing body of evidence suggests that these transcriptional factors are under the regulation of newly discovered non-coding RNAs. The long non-coding RNA (lncRNA) HOX-antisense intergenic RNA myeloid 1 (HOTAIRM1) is present in adult DA neurons and it is involved in the neuronal differentiation in human stem cells suggesting it may also play a role in early DA neuron development.
Methods
To determine its role in early DA neuron development, we knocked down HOTAIRM1 using RNAi in vitro in a human neuroblastoma cell line, and in vivo in mouse DA progenitors using a novel in utero electroporation technique. The expression of DA neuron specification and maturation factors in the developing mesencephalon and neuroblastoma cell lines were assessed using real-time PCR.
Results
HOTAIRM1 inhibition decreased the expression of a range of key DA neuron specification factors and impaired DA neuron differentiation and maturation. These results provide evidence of a functional role for HOTAIRM1 in DA neuron development and differentiation.
Conclusions
In conclusion, our in vitro and in vivo data have consistently shown that knockdown of HOTAIRM1 attenuated retinoic acid-mediated DA neuron differentiation, suggesting a role of this lncRNA in DA neuron development. These novel data highlights that HOTAIRM1, even when expressed at low abundance in DA neurons, plays an important regulatory role in neuronal specification and maturation. Understanding of the role of lncRNAs in the development of DA systems may have broader implications for brain development and neurodevelopmental disorders such as schizophrenia.

Negative association between the insula and resilience during a continuous performance task: an fMRI twin study

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Background
Inability to sustain attention is often a symptom of poor mental health. However, it is unknown how wellbeing and resilience to adversities influence the underlying neural mechanisms of sustained attention and whether genetic versus environmental factors contribute to these relationships. The aim of this study was to examine the associations between wellbeing and resilience to childhood trauma with the sustained attention neural circuitry during functional magnetic resonance imaging (fMRI), as well as the genetic and environmental contributions to these relationships in a sample of twins.

Methods
A sample of 253 adult twins, including 187 trauma exposed twins with fMRI data from the TWIN-E study of Wellbeing were included in this study. Wellbeing was measured using the COMPAS-W Wellbeing Scale and resilience was defined as a higher level of wellbeing despite trauma exposure. fMRI activity was measured during a Continuous Performance Test task. The regions of interest defining the attention neural circuit included the medial superior prefrontal cortex, lateral prefrontal cortex, insula, inferior parietal lobules, and precuneus. Association analyses were conducted, in addition to heritability analysis and correlated factor models to assess common genetic and environmental variance.

Results
While no effects were found for wellbeing, significant negative associations were found between resilience and activation in the insula. The heritability in this region was estimated at 31%, and the association between the insula activation and resilience was mostly driven by common genetic factors (r = -0.70).

Conclusions
The findings suggest that higher resilience to trauma is associated with a neural profile of reduced activation in the insula region. This possibly indicates a pattern of 'neural efficiency' (i.e., more efficient and/or attenuated activity) in people who may be more resilient to trauma, which requires confirmation in future studies.

Unraveling the consequences of childhood maltreatment: deviations from typical functional neurodevelopment mediate the relationship between maltreatment history and depressive symptoms

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Background
Childhood maltreatment is associated with lifelong psychiatric sequalae. However, our understanding of neurobiological mechanisms responsible for this association is limited. One way childhood maltreatment may confer risk for psychopathology is by altering neurodevelopmental trajectories during childhood and adolescence. However, longitudinal research, which is essential for examining this question, on the development of neural circuitry, has been limited.
Methods
In the current study, associations between childhood maltreatment and the longitudinal development of resting state functional connectivity (rsFC) were examined in 130 community residing adolescents. fMRI data was acquired at age 16 (T1; M age = 16.46 years, SD = 0.52, 66F) and age 19 (T2; mean follow up period: 2.35 years). Childhood maltreatment history was assessed prior to T1. We used whole-brain functional connectivity analysis to examine maltreatment-associated alterations in the development of neural circuitry.
Results
We found maltreatment to be associated with widespread longitudinal increases in rsFC, primarily between default mode, dorsal attention, and frontoparietal systems. We also found sex-dependent increased maltreatment-associated rsFC in males in salience and cortical limbic circuits. Cross-sectional analyses revealed a shift in maltreatment-related rsFC alterations, which were localized to subcortical and sensory circuits at T1 to frontal circuits at T2. Finally, longitudinal increases in rsFC connectivity mediated the relationship between childhood maltreatment and increased depressive symptoms.
Conclusions
To our knowledge, this is the first study to longitudinally examine maltreatment-related alterations in rsFC in adolescents. Our findings extend the current literature by demonstrating links between childhood maltreatment, widespread rsFC across adolescent development, and depressive symptoms. zThe present study sheds light on the long-term adverse effects of childhood maltreatment on neurodevelopment, and highlights the importance of identifying early markers of risk in order to guide intervention and prevention efforts to ameliorate the long-term consequences of childhood maltreatment.

Exercise reverses the effects of early-life social isolation on adolescent extinction learning in male but not female rats

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Background
The impaired extinction of acquired fear is a symptom of anxiety- and fear-related disorders. Early-life environmental factors, like social isolation and exercise, can alter the ability to extinguish fear. The effect of and interplay between these factors in adolescence and underlying neurophysiological mechanisms underpinning these changes is unknown. The present experiments examine whether early-life social isolation and exercise affect cued fear extinction in adolescent rats. Hippocampal neurogenesis is also examined as a potential mediator of these effects.
Methods
In Experiment 1, male and female Sprague-Dawley rats were isolated or group-housed between post-natal days (P)21-49 in home-cages with a locked or unlocked running-wheel (n=7-10/group). All groups then underwent fear conditioning (P43), extinction (P43-5) and test (P48). In Experiment 2, we additionally injected a neurogenesis-inhibiting agent TMZ (25 mg/kg, i.p) or vehicle from P21-37 (n=7-9/group). We further examined differences in Ki-67 (a proliferating cell marker) and doublecortin (DCX; marker of immature neurons) immunolabelling in the dentate gyrus of the hippocampus to quantify changes in neurogenesis in both experiments.
Results
Social isolation significantly impaired extinction recall (ps<0.05) in adolescent males and exercise rescued this effect (ps<0.05). In contrast, exercise disrupted extinction recall in isolated adolescent females (ps<0.05). Exercise increased the number of cells expressing Ki-67 and DCX in the dentate gyrus in all groups except isolated adolescent males (ps<0.05). In Experiment 2, suppression of neurogenesis was sufficient to mitigate the effects of exercise on fear extinction recall in both sexes (ps<0.05). However, extinction recall ability correlated with the number of immature neurons (DCX+) in the ventral hippocampus of female adolescents only (ps<0.05).
Conclusions
Our results highlight that early-life social isolation and exercise have sex-specific effects on the extinction of conditioned fear in adolescent rats. Neurogenesis prior to adolescence may be an underlying neurobiological mechanism by which stress and exercise alter adolescent fear inhibition in a sex-specific manner. As impaired extinction is a model used to understand anxiety- and fear- disorders, our findings emphasise the need for sex-specific and personalised approaches to understand emotional regulation in adolescence.

Adolescent oxytocin treatment prevents early life stress induced depression-like outcomes in male and female rats

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Background
Early life stress (ELS) is associated with increased vulnerability for mental illness later in life, including depression. Despite this known link, there are no available pharmacotherapies. Recently, administration of the neuropeptide oxytocin in adulthood was shown to reduce depression-like behaviours in male rats with a history of ELS. However, it is unknown whether oxytocin treatment during adolescence, a crucial developmental window for the oxytocin system, can prevent depression-like behaviours after ELS in both males and females. Thus, this study aimed to determine whether oxytocin administration during adolescence can ameliorate the enduring effects of ELS on depression-like behaviours in both sexes.

Methods
Long Evans rat pups underwent maternal separation (MS) for either 15 or 360 minutes on postnatal days (PND) 1 to 21. During adolescence (PND 28-42), rats received a daily intraperitoneal injection of either oxytocin (1mg/kg) or saline. In adulthood (PND 57 onwards), anhedonia was measured using an effortful choice paradigm and learned helplessness was measured using the forced swim test. Body weight was measured across the lifespan and lastly the spleen, thymus, and adrenal glands were weighed due to their involvement in immune and endocrine system functions that can be impacted by ELS.

Results
We found that in both sexes, MS increased learned helplessness, but had no impact on anhedonia. Importantly, both males and females exposed to MS who received adolescent oxytocin injections displayed a reduction in learned helplessness to a level consistent with non-separated controls. Additionally, post weaning, MS resulted in persistent reductions in body weight in both sexes and increased spleen weight in males and adrenal weight in females. Additionally, oxytocin treatment had no impact on body weight in either sex, increased thymus weight in control males, and reduced ELS-induced adrenal hypertrophy in MS exposed females.

Conclusions
Altogether, this suggests that an adolescent oxytocin treatment schedule is capable of preventing the emergence of depression-like symptoms in both sexes, and adrenal hypertrophy in females, who have experienced ELS.

Timing of maltreatment in childhood and the effect on brain structure and function in adulthood: a systematic review

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Background
The effects of childhood maltreatment on the structure and function of the brain have been widely researched. However, there is less data assessing specific impact of timing at which the abuse or neglect occurs. The timing of maltreatment may have a profound impact on brain development, and identifying sensitive periods may enable us to develop crucial protective and therapeutic interventions for those affected by abuse and neglect. The aim of this systematic review was to identify and evaluate studies that assess the role of timing of maltreatment on the structure and function of the adult brain.

Methods
A systematic review of the literature was conducted in PubMed, Web of Science, and Scopus. The PRISMA guidelines for systematic literature reviews were followed. The inclusion criteria were articles published: (1) in English; (2) in human populations; (3) in a peer-reviewed journal; (4) studying populations where maltreatment was experienced between 0-18 years of age; (5) that included data on the timing at which maltreatment was experienced; and (6) that included data on any structural or functional brain outcome in adulthood. Exclusion criteria included letters, conference presentations, book chapters, meta-analyses, and reviews.

Results
In total 6033 unique articles were identified and screened. From these, a total of just 8 articles studied imaging phenotypes in the context of childhood maltreatment with information on specific timing of that exposure. Some preliminary evidence was identified for two sensitive periods to maltreatment for the hippocampus; one early in childhood, and one in pre-puberty. There was also some evidence for a pre-pubertal sensitive period to maltreatment affecting the visual cortices. However, the scarcity of studies in this area that collect timing of maltreatment exposure presents a lack of sufficient evidence to draw firm conclusions.

Conclusions
There were several significant methodological issues identified within the studies, as well as large heterogeneity between the studies' methods. A need for improvement and consistency in methodology, as well as a strong need for continued research on the timing of childhood maltreatment was identified. The strengths of the studies and directions for future research will be discussed.

Detrimental Impacts of Oxidative Stress on the Transcriptome of Differentiating Neuroblastoma Cells: Implication for Psychiatric Disorders

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Background
Perinatal environmental exposures, such as smoking and drinking alcohol during pregnancy, which are known risk factors for schizophrenia and other psychiatric and neurodevelopmental disorders, have been shown to induce oxidative stress in cells. Although the role of oxidative stress in the etiology of neurodegenerative diseases is well studied, it remains unknown if and how it contributes to the genomic dysregulation associated with psychiatric disorders. In this study we used the SH-SY5Y neuroblastoma cell line model to explore changes in the transcriptome in response to oxidative stress before or during neural differentiation, a process found to be defective in these diseases.

Methods
Oxidative stress was chemically induced in cultured neuroblasts by the addition of 10M H2O2 either during 7 days of differentiation with ATRA, or 72 hours before inducing differentiation. Having extracted RNA and checked its integrity, total RNA-Sequencing was performed by Novaseq 6000. FASTQ, Cutadapt, HISAT2, and HTSEQ bioinformatic tools were used for quality control, trimming, alignment to the reference genome, and quantifying of sequencing reads, respectively. Differential expression analysis of genes was done by the R package edgeR, and the online tool ToppFun was applied to determine the biological processes and signalling pathways that were enriched for differentially expressed genes.

Results
We observed differential expression of many genes, most of which are functionally localised in synapses, and involved in neurogenesis and neuronal differentiation. These also featured in three schizophrenia-associated signalling pathways, including axon guidance, PI3K-Act, and signalling by retinoic acid. Interestingly, circulatory system development was also affected by both treatment timings, which might contribute some of the risk for the higher incidence of cardiovascular diseases observed in patients with neurodevelopmental disorders. There was also a very large (up to 400-fold) increase in the expression of immunity-related genes, which is interesting given the well-established link between immune system activation and psychiatric disorders.

Conclusions
In conclusion, we predict that early life exposure to oxidative stress has a disturbing effect on neuronal differentiation even before its initiation, suggesting that it is a key risk factor for the onset of neurodevelopmental disorders, and the neuronal progenitor cells in fetal nervous system may be particularly vulnerable to this exposure in the very early months or even weeks of pregnancy, because of its capacity for producing significant genomic risk for psychiatric diseases later in life.

Heterogeneous neural noise induces breakdown of structure-function coupling in ADHD

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Background
Adult attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattentive and hyperactive-impulsive symptoms that begin in early childhood. Adults with ADHD show altered whole-brain functional connectivity. However, the underlying mechanisms that lead to an abnormal relationship between the structural wiring of the brain and its function remain uncharted. This gap in knowledge hinders the development of strategies to manage the development of life-long debilitating symptoms.
Methods
We recruited 80 psychotropic-naive adults with childhood-onset ADHD aged 18–39 years (mean 26.7 years), who fulfilled DSM-IV-TR criteria for the current diagnosis of ADHD. Results from the clinical sample were compared with the results of age- (mean 25.7years), sex-, and IQ-matched healthy controls. The final sample included 78 ADHD adults and 118 healthy controls. We built a computational brain model of ADHD to test possible neural mechanisms underpinning observed group differences. Using this model, we assessed which patterns of neural noise heterogeneity, introduced in distinct subgroups of brain regions, mapped onto patterns of structural-functional decoupling.
Results
Structural connectivity did not significantly differ between groups. However, relative to controls, ADHD showed a reduction in structure-function coupling in feeder connections linking brain hubs to peripheral regions. Specifically, this abnormality involved connections linking fronto-parietal control systems with sensory networks. Furthermore, lower structure-function coupling was associated with higher ADHD symptoms. Results from our computational brain model further suggest that the observed structure-function decoupling in ADHD is driven by heterogeneity in neural noise variability across brain regions.
Conclusions
Our cohort allowed for an unequivocal assessment of ADHD-specific structural and functional brain networks in the absence of common confounds. By highlighting a neural cause of a clinically meaningful breakdowns in the brain network structure-function relationship, our work provides novel information on the nature of chronic ADHD. Our results encourage future assessment of genetic and neurobiological underpinnings of neural noise in ADHD, particularly in the fronto-parietal system. We also suggest that noise-mediated mechanisms are essential for subsequent computational models of attention deficit disorders.

Dysregulation of the Y-chromosome gene Sry underlie sex differences in the spontaneous-hypertensive rat model of ADHD.

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Background
Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting over 5% of children worldwide. Whilst the aetiology of ADHD is unclear, males are three times more likely to be diagnosed with ADHD than females. However, the biological reasons underlying this male bias is unclear. We previously showed that the Y-chromosome gene, Sry, is expressed in ADHD-relevant brain regions (e.g. prefrontal cortex, hippocampus) and regulates dopamine transmission in males. We propose that Sry dysregulation contributes to male susceptibility to ADHD. To test this, we investigated the regulation and function of Sry in the spontaneously-hypertensive rat (SHR) model of ADHD.
Methods
In study 1, brain Sry mRNA expression was compared between 4 and 12-week-old male SHRs and wild-type Wistar Kyoto (WKY) rats. In study 2, the effect of reducing brain Sry expression – via by intracerebroventricular Sry antisense oligonucleotide (ASO) infusion – on behaviour and gene expression was assessed in male SHRs and WKYs. At day 7 of ASO (or vehicle) infusion, locomotor and cognitive functions were assessed in the open field, novel object recognition and spontaneous alternation tests, followed by brain isolation for post-mortem analysis.
Results
We found that Sry mRNA expression was markedly reduced in the prefrontal cortex, hippocampus, striatum, and hypothalamus of 4 and 12-week-old male SHRs when compared to the male WKYs. Moreover, developmental increase in Sry expression observed in the male WKYs was absent in the male SHRs. Repeated intracerebroventricular antisense oligonucleotide (ASO) infusions in male WKYs induced recognition and spatial memory deficits in the novel object recognition test and spontaneous alternation test, similar to those observed in the male SHRs. The ASO-induced cognitive deficits in the male WKYs were associated reduced hippocampal and striatal SRY expression.
Conclusions
In summary, our findings show that brain Sry expression is developmentally stunted in male SHRs, which contributes to the cognitive deficits observed in the male SHRs. Taken together, these findings suggest that dysregulation of the male-specific gene, Sry, could predispose males to ADHD and that normalization of brain Sry expression may be a novel sex-specific therapeutic strategy for ADHD.

Oxytocin and vasopressin inhibit hyper-aggressive behaviour in socially isolated mice

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Background
Despite the high prevalence of aggression across a wide range of disorders, there is a severe lack of pharmacological treatments. Recent rodent studies have shown both centrally and peripherally administered oxytocin is effective in reducing territorial aggression, an adaptive form of aggression not reflective of pathological hyper-aggression. The current study tested i.p. administered oxytocin and vasopressin in a model of non-territorial hyper-aggression and examined the involvement of oxytocin receptors (OXTR) and vasopressin V1a receptors (V1aR).

Methods
Male Swiss mice (N = 160) were either socially isolated or group housed for 6 weeks prior to the commencement of testing; wherein two unfamiliar weight and condition matched mice were placed into a neutral context for 10 min.

Results
Socially isolated mice exhibited heightened aggression that was powerfully and dose-dependently inhibited by oxytocin and vasopressin and that was accompanied by dose-dependent increases in close social contact (huddling) and grooming. These anti-aggressive effects of oxytocin were blocked by pre-treatment with a higher dose of selective V1aR antagonist SR49059 (20 mg/kg i.p.), but not a lower dose of SR49059 (5 mg/kg i.p.) or selective OXTR antagonist L-368,899 (10 mg/kg i.p.). Interestingly, the highest dose of the OXTR agonist TGOT (10 mg/kg) also reduced isolation-induced aggression.

Conclusions
Overall our findings are consistent with a growing number of studies linking a range of effects of exogenous oxytocin to actions at the V1a receptor.Interestingly, the highest dose of the OXTR agonist TGOT (10 mg/kg) also reduced isolation-induced aggression. These results suggest that while activation of the V1a receptor appears critical for the anti-aggressive effects of oxytocin, activation of the oxytocin receptor cannot be excluded.

2.9 Miscellaneous

Wakeful quiescence: Awakening the influence of oxytocin on sleep-wake behaviour in male rats

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Background
Oxytocin is a versatile neuropeptide implicated in diverse range of neurobehavioural processes such as stress, social behaviour, and feeding. Based on the anxiolytic, serenic effects of oxytocin, one could posit that oxytocin should prime the brain for sleep and elicit hypnogenic effects. However, as the social salience hypothesis suggests that oxytocin promotes prosocial behaviour and directs attention toward social stimuli, oxytocin may be implicated in promoting wakefulness. To-date, little research has comprehensively investigated the role of oxytocin in sleep-wake behaviour and no explanation to reconcile these two seemingly competing hypotheses has been proposed.
Methods
The current preclinical study investigated the dose-response relationship of oxytocin with sleep outcomes using radiotelemetry-based polysomnography in adult male Wistar rats. Oxytocin (0.1, 0.3 and 1 mg/kg) was administered via the intraperitoneal route, and intraperitoneal caffeine (10 mg/kg) was also administered as a wake-promoting positive control.
Results
In rats, oxytocin demonstrated dose-dependent effects on sleep-wake behaviour: oxytocin initially promoted wakeful quiescence (a restful but conscious state) at the cost of reducing both active wakefulness, NREM and REM sleep. More specifically, oxytocin reduced NREM sleep during the 1-1.5 hours post-administration, and dose-dependently delayed REMS onset and reduced the proportion of time spent in REM sleep.
Conclusions
This appears to reconcile the two competing hypotheses: in male rats, oxytocin appears to promote a state of wakeful quiescence—one of rest and relaxation, but also of responsive consciousness to environmental stimuli. Future research will elucidate the neurobiological underpinnings that mediate these oxytocin-induced effects on sleep outcomes.

Primary tumour resection improves cancer-related cognitive impairment in mouse models of breast cancer

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Background
Up to 70% of cancer patients and survivors experience cognitive impairment. Currently there is a dearth of understanding of the biological mechanisms responsible for cognitive impairment in cancer survivors, which has restricted the capacity to develop novel intervention strategies for cancer-associated cognitive impairment. Using mouse models of breast cancer, we have demonstrated that tumour-induced inflammation and chemotherapy independently cause cognitive impairment. Here, we investigate if breast cancer surgery (tumour resection) aimed at eliminating cancer-induced inflammation can reverse established cancer-induced cognitive impairment. We also demonstrate the cumulative impact of cancer, cancer surgery and chemotherapy on memory by creating “cancer survivor” mice.

Methods
67NR non-metastatic or 4T1.2 metastatic mammary carcinoma cells were implanted into the mammary fatpad of adult female mice to model breast cancer. To determine if resection of the tumour reversed tumour-induced memory impairment, we performed surgery that mimicked the impact of either minor (lumpectomy) or major (mastectomy) breast cancer surgery. To determine the cumulative impact of multiple cancer treatments on memory, the chemotherapy drug paclitaxel (10mg/Kg, i.p) was administered to mice every 2nd day for seven doses after primary tumour resection. The novel object/place recognition and Y Maze tests were used to assess memory.

Results
Both non-metastatic and metastatic tumours induced memory impairment, which was rescued by primary tumour resection (minor surgery). Primary tumour resection reduced spleen mass suggesting that removal of the tumour decreases inflammation. Major surgery increased spleen mass and induced memory impairment two weeks after surgery in tumour free and non-metastatic tumour bearing mice but not in mice with metastasis. Preliminary findings from our “survivor” mouse model indicated that the tumour plays the most dominant role in inducing memory impairment compared to surgery or chemotherapy.

Conclusions
These studies raise the possibility that cancer-induced cognitive impairment may be reversed if the source of inflammation is removed by surgery. However, this strategy will not be effective for metastatic cancer. As mice bearing metastatic tumours did not show memory improvement after primary tumour resection, it raises the possibility that disseminated cancer cells were responsible for continued impairment of memory. Ongoing studies are examining if there is a cumulative impact of cancer and cancer treatment on the brain in our survivor model.

Notch family member expression declined in the first postnatal years in post-mortem subependymal zone in a healthy human cohort

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Background
Notch signalling is essential for neural stem cell (NSC) maintenance in the adult murine subependymal zone (SEZ). We recently found an age-related decline of neurogenesis-related mRNAs, including activated NSC and proliferation markers in the human SEZ, while markers of quiescent NSCs remain stable from infancy into ageing. However, the extent to which notch signalling may change across life in the human SEZ remains unknown. To examine whether alterations in notch-related molecules are associated with neurogenesis in humans across development, we measured key notch family member transcripts and assessed the relationships between notch family members and neurogenesis markers in the SEZ.

Methods
We determined notch family gene expression levels (12 targets) throughout life in the post-mortem SEZ of healthy people (n = 70, 2 days - 103 years) using qRT-PCR. We measured expression of notch ligands (DLL1, DLL3, DLL4, JAG1, JAG2), receptors (NOTCH1, NOTCH2, NOTCH3, NOTCH4) and intracellular targets (HES1, HES4, HES5) across seven age groups (neonates, infants, children, adolescents, young adults, adults and aged adults). Age group differences were assessed using one-way analyses of covariance or analyses of variance. Semipartial and partial correlations were performed to determine the relationships between notch signalling markers and neurogenesis markers (GFAPD, NES, MKI67, and ASCL1).

Results
We found a steep, early decline in DLL1, DLL3, JAG1, NOTCH1 and NOTCH2 mRNAs (all $p<0.001$), which stabilised later in life. NOTCH3 and NOTCH4 expression also declined in early life but showed some fluctuations later in life (all $p\leq0.016$). Consistent with ligands and receptors, intracellular targets HES1 and HES5 mRNAs declined over age (all $p\leq0.007$). All notch family mRNAs showed a strong, positive correlation with NES, a marker of activated NSCs (all $p\leq0.015$), and with ASCL1, a marker of neuronal progenitors (all $p\leq0.04$). MKI67, a marker of cell proliferation, positively correlated with all targets except DLL4, HES1 and HES4 ($p\leq0.001$).

Conclusions
Our findings suggest that notch signalling is more active in early life but persists into ageing in the human SEZ. Concurrent with neurogenesis markers, notch family mRNA expression rapidly declined in early life, then remained stable into ageing. The strong positive correlations between notch family members and markers of activated NSCs and neuronal progenitors, but not quiescent NSCs, suggests a multifaceted role in activation of NSCs and neuronal cell fate decisions during neurogenesis. Further work to determine the cell type-specific roles of notch signalling in the postnatal human SEZ is required to better understand how notch regulates neurogenesis throughout life.

Bazedoxifene – a promising brain active SERM that crosses the blood brain barrier and enhances spatial memory

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Background
Over 20 years of accumulated evidence has shown that the sex hormone 17β-estradiol can enhance cognitive functioning. However, the utility of estradiol as a therapeutic cognitive enhancer is hindered by its unwanted peripheral effects (carcinogenic). Selective estrogen receptor modulators (SERMs) avoid the unwanted effects of estradiol by acting as estrogen receptor antagonists in some tissues (breast), but as agonists in others such as bone, and are currently used to treat osteoporosis. However, understanding of their actions in the brain are limited. This project aimed to determine if the third generation SERM, bazedoxifene, can enter the brain and enhance cognition.

Methods
Liquid-chromatography mass spectrometry was used to assess whether a peripheral injection of bazedoxifene enters the brain. Ovariectomized mice were treated with either saline or bazedoxifene then tested in a spatial memory paradigm to determine if bazedoxifene can improve ovariectomy induced spatial memory deficits. Ovariectomized mice carrying a luciferin tag on the estrogen response element (ERE) were treated with a peripheral injection of bazedoxifene then an intracerebroventricular injection of luciferin before bioluminescent imaging to determine if bazedoxifene activates the ERE in the brain.

Results
Using liquid chromatography-mass spectrometry, we firstly demonstrate that a peripheral injection of bazedoxifene can enter the brain. Secondly, we show that an acute intraperitoneal injection of bazedoxifene can rescue ovariectomy-induced spatial memory deficits in the Y-maze novelty preference task. And finally, using the ERE-luciferase reporter mouse, we show in vivo that bazedoxifene can activate the ERE in the brain.

Conclusions
The third generation SERM, bazedoxifene, was FDA-approved in 2013 for the treatment of menopausal symptoms and postmenopausal osteoporosis and is superior to its predecessors due to fewer cases of vasomotor side effects and fibrocystic breast disease. The evidence shown here suggest bazedoxifene could be a viable cognitive enhancer with promising clinical applicability.

Long-read sequencing of neuropsychiatric disorder risk gene isoforms in human brain

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Background
Neuropsychiatric disorders are debilitating conditions for sufferers and have a strong genetic component. Recent studies have identified hundreds of risk genes. How these contribute to disease risk through altered expression and RNA splicing is not well understood. We used long-read sequencing and long-range PCR to generate full-length sequence data for several risk genes to better understand their expression and splicing as a first step to understand their contribution to neuropsychiatric disease risk.

Methods
Risk genes from GWAS loci were selected based upon collated expression, association and pathway information. Genes with multiple lines of evidence for schizophrenia, bipolar disorder, depression and autism spectrum disorder risk were prioritised. We amplified the entire mRNA coding regions of five high-confidence risk genes from seven regions of post-mortem human brain from five control individuals. Bioinformatics packages Minimap2, Salmon, FLAIR and TAQLoRe were used to identify and quantify the different mRNA products (isoforms) present and discover novel exons and splice isoforms.

Results
The mRNA isoforms expressed by SNAP91, GRIA1, CPT1C and GRIN2A in different human brain regions were analysed in control samples (N=35). Isoform expression patterns of GRIA1 and CPT1C varied across brain regions especially between cerebellum and the cortex. A potentially novel exon in GRIA1 was also present in a highly abundant isoform for this gene. While SNAP91 expressed at least 28 high-confidence novel isoforms. Pilot sequencing using unique molecular identifiers has also improved the quantification of transcript abundance in each brain region.

Conclusions
Several potentially novel exons and isoforms were identified in control brain regions by using long-read sequencing. Novel exons and isoforms could be linked with disease and will improve our understanding of neuropsychiatric disorder causation and RNA splicing profiles in the brain. This information may also be of clinical relevance as several risk genes overlap multiple disorders and have associations with psychiatric phenotypes. The detection of altered isoform profiles combined with polygenic risk scores, for example through blood sampling, may become a useful marker of disease onset and progression in at risk individuals.

Review of analysis techniques in mental health research with consumer instruments– A guide for researchers and graduate students

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Background
To identify and synthesis literature on analysis techniques and methodological approaches used to analyse consumer measures in mental health research.
Methods
The review included papers published up to January 2020 across seven databases: CINAHL, Web of Science, Medline, PsycINFO, EMBASE, Scopus and Google Scholar. Data search and extraction was conducted according to the recommended guidelines for conducting review by Cochrane and Joanna Briggs Institute (JBI). Mixed method synthesis was used to synthesis the data.
Results
The initial search yielded 2,282 papers. A total of 32 papers were included in the synthesis. Most of the included papers (25/32;78.12%) focused on psychometric properties, whilst 14%(5/32) targeted analysis techniques, and 6.3% (2/32) addressed methodological justification. The measurement models (eg. psychometric properties) were analysed through validity and reliability testing as part of instrument development and adaptation. The structural models were analysed using techniques such as Structural Equation Modelling, Multivariable Regression Models, Intraclass correlation coefficient (ICC) and Primer on Partial Least Squares Structural Equation Modelling.
Conclusions
Although consumer instruments were analysed using techniques involving linear, hierarchical and longitudinal effects, no attempt was giving to procedures that applied complex data mining or machine learning. Consumer researchers and clinicians are encouraged to apply rigours analysis techniques.

Modelling factors associated with the quality of mental health services and consumer functionality using tertiary-based services.

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Background
This paper aims to measure the impact of consumer predisposing, enabling and need factors on the perceived quality of mental health services and consumer functionality.
Methods
This paper recruited a random sample of 510 consumers receiving out-patient and in-patient psychiatric services. Consumers were invited to complete the Verona Satisfaction Scale (54-items), together with the WHO Disability Assessment Instrument (36 items) using the Redcap application. Descriptive and inferential statistics like hierarchical multiple regression model were used.
Results
Consumers reported mixed satisfaction with the quality of mental health services (total mean =3.2; SD=56) but were largely dissatisfied with the range of interventions received (Mean=1.57; SD=0.77). Also, consumers had mild difficulties in terms of global disability (total mean = 1.79; SD=0.82). Several predisposing (age, education, and primary occupation), enabling (insurance status) and need factors (mental health status) were significantly associated with consumer perceived quality of mental health services, particularly regarding the range of interventions, efficacy and overall satisfaction. Predisposing, enabling and need factors were also significantly associated with consumers' functionality.
Conclusions
Mental health professionals and regulators are encouraged to incorporate the predisposing, enabling and need factors of consumers when planning and monitoring activities as well as developing advocacy and awareness campaign

Genetic properties of hub connectivity in the human brain

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Background
Nervous systems are intricately connected networks with complex wiring patterns. Such complexity is at least in part attributed to a heterogeneous distribution of connectivity across neural elements, such that a large fraction of network connections is concentrated on a small subset of network nodes called hubs, that play a central role in integrated brain function. The rapid evolution of network hubs in humans, coupled with evidence supporting the heritability of many different aspects of brain organization suggests an important role for genes. Here we investigate the genetic influences on brain network hubs in the human connectome.
Methods
Using the DWI data from the Human Connectome Project for 117 pairs of monozygotic and 60 pairs of dizygotic twins we performed a connectome-wide heritability analysis quantifying the genetic influences on phenotypic variance in connectivity strength. Next, we developed a pipeline for identifying genes whose expression in cortex is influenced by expression quantitative trait loci (eQTLs) preferentially related to hub connectivity. Using gene expression data from the Allen Human Brain Atlas we quantified the degree of transcriptional coupling between brain regions. Finally, we investigated whether stochastic network wiring models can reproduce the spatial distribution of hub regions.
Results
We showed that genetic influences on brain connectivity are preferentially concentrated on links between network hubs. Through analysis of genome-wide single nucleotide polymorphisms in two independent samples, we demonstrate that variants preferentially related to hub connectivity are eQTLs for genes implicated in risk for schizophrenia, intelligence, and energy metabolism. Further, connected pairs of hubs exhibit tightly coupled gene expression related to the metabolic demand and cytoarchitectonic similarity of these areas. Finally, we show that stochastic network wiring models fail to capture the spatial distribution of hub regions and therefore the precise pattern of wiring between network hubs.
Conclusions
Through a set of multi-faceted genetic analyses spanning several data modalities we demonstrate a direct link between molecular function and the large-scale network organization of the human connectome. We find that genetic influences are more strongly concentrated on costly and functionally valuable connections between network hubs. Our findings also highlight that based on the current stochastic models of network growth, generic physical and/or functional properties of the brain are not sufficient to capture the spatial distribution of hubs, hence supporting a prominent role for genes in shaping the connections between them.

Kidney plays an important role in ketogenesis induced by risperidone and exercise in juvenile female rats

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Background
The positive role of ketone body in the treatment for mental disorders has been demonstrated previously. Ketogenesis can be triggered not only by exercise and diet, but also by metabolic disorders. Our previous studies demonstrated that exercise intervention could prevent risperidone-induced dyslipidemia and gluco-metabolic disorders in female juvenile rat. In this study we will explore the role of risperidone and exercise in ketogenesis.
Methods
Thirty-two juvenile female Sprague Dawley rats were randomly assigned into 4 groups (n=8/group): Vehicle-Sedentary group, Risperidone (0.9mg/kg; b.i.d)-Sedentary group, Vehicle-Exercise (three hours daily access to running wheels) group and Risperidone-Exercise group for a period of four weeks. After completing treatment, the protein levels were detected by western blot.
Results
Exercise-intervention significantly ameliorated the risperidone-induced increase in subcutaneous (inguinal) and visceral (periovary) adipose tissue, fasting triglyceride and insulin levels. Compared to the Vehicle-Exercise group, Risperidone-Exercise group had a significant higher level of plasma β-hydroxybutyrate (β-HB), which had a positive correlation with plasma non-esterified fatty acid (NEFA) levels. Risperidone upregulated renal but not hepatic HMGCS2 (the key enzyme of ketogenesis). Exercise significantly enhanced expression of renal CPT1A, which is involved in fatty acid β-oxidation and ketogenesis. No significant difference was observed in OXCT1 (the key enzyme of ketone body utilization), in the main ketone body utilization organs, kidney and heart.
Conclusions
These results suggested that the increased plasma β-HB in Risperidone-Exercise group attributes to higher levels of plasma NEFA, renal HMGCS2 and CPT1A expression, and lower level of plasma insulin. The kidney plays an important role in ketogenesis induced by risperidone.