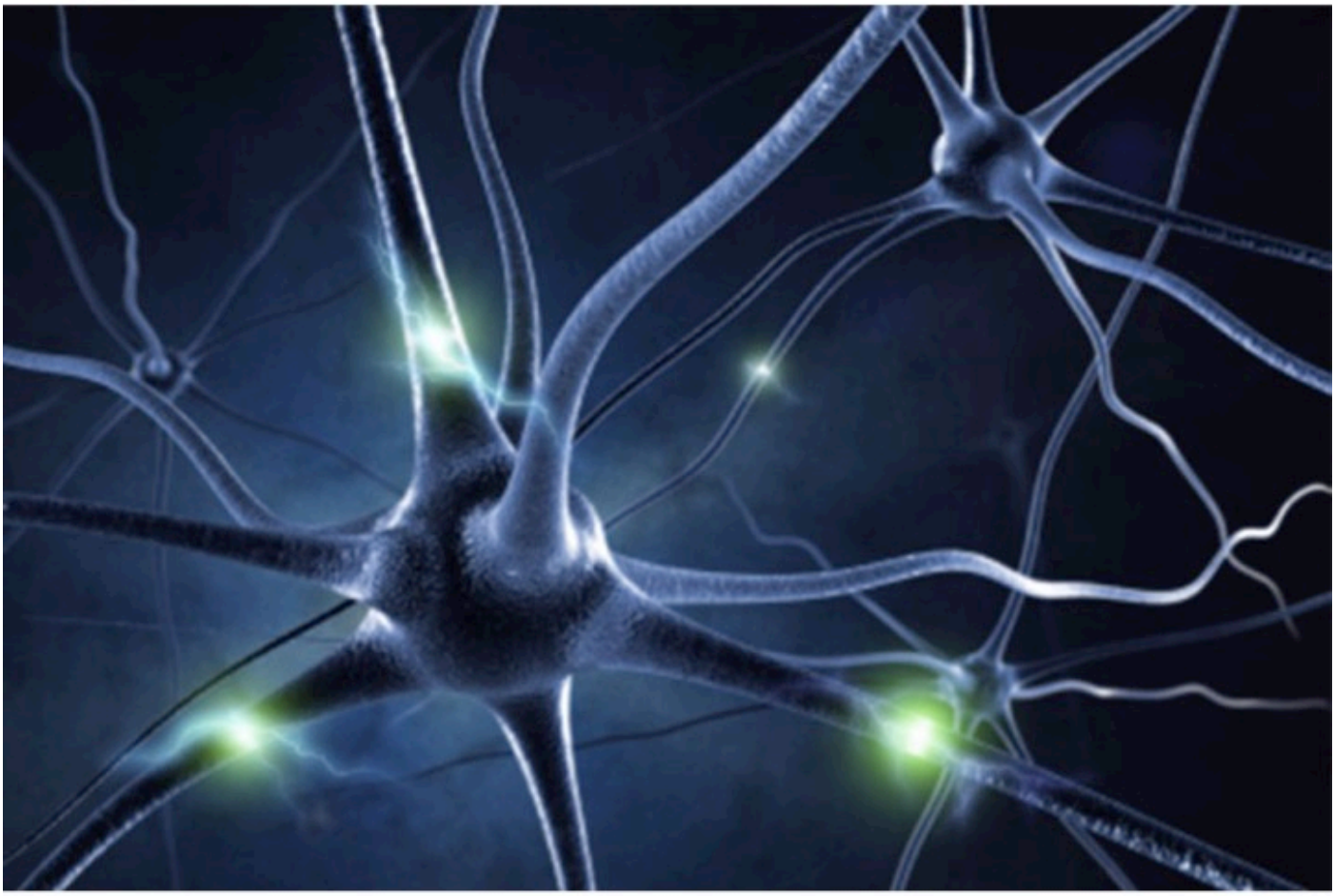
Biological Psychiatry
AUSTRALIA



Biological Psychiatry Australia

7th Annual Scientific Meeting, Wollongong

Sunday 29 – Tuesday 31 October 2017

Abstract Book

#biolpsychaus17

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PROGRAM

Sunday 29th October IC Atrium, University of Wollongong Innovation Campus			
Time	**Event**	**Speaker**	**Presentation Title**
4:00 – 5:00	Registrations open		
4:30 – 5:00	Welcome drinks		
5:00 – 5:40	Keynote presentation Chair: Prof Chao Deng	Prof Brian Dean	Translating biological psychiatry research into the clinic: A roller coaster that is worth the ride
5:40 – 7:40	Welcome Mixer/Team competition (Prize: Gourmet Gift Hamper) Hosted by Alice Petty and Jee Kim Round 1 Never Have I Ever.. Round 2 Chinese Whispers Charades Round 3 Team Name Interpretative Dance		

Monday 30 October Illawarra Room, Novotel Wollongong Northbeach			
Time	**Event**	**Speaker**	**Presentation Title**
8:00 – 9:00	Registrations open		
8:45 – 9:00	Opening Address	Dr Kelly Newell, Chair, Local Organising Committee Prof Darryl Eyles, President, Biological Psychiatry Australia	
9:00 – 10:00	8th Aubrey Lewis Lecture Chair: Prof Darryl Eyles	Dr Jee Kim	Development of memory and motivation
10:00 – 10:30	Data Blitz 1 Chair: Maximus Berger	Prof Barbara Meyer	There's something fishy about his behaviour: How does omega-3 status influence aggression and cognitive function and what can be done to ensure a better future?
		MD. Mamun Al-Amin	Vitamin D deficiency reduces hippocampal subfield volume and disrupts right-hippocampal structural connectivity: evidence from mouse and human data
		A/Prof Olivia Carter	Do sensory integration deficits represent a biomarker for schizophrenia?
		Ann-Katrin Kraeuter	Ketogenic diet normalizes behavioural abnormalities in a chronic neurodevelopmental murine model of schizophrenia
		Dr Lauren Harms	The effects of mid-late gestational maternal immune activation in rats on schizophrenia-related behaviour
10:30 – 11:00	Morning tea		
11:00 – 12:30	Symposium 1: Therapeutic potential of cannabidiol treatment for psychiatric illness. Chair: Prof Nadia Solowij Discussant: A/Prof Tim Karl	Dr Katrina Weston-Green	Cannabidiol treatment in a poly I:C model of schizophrenia: cognitive behavioural improvements and altered neurotransmission
		Prof Nadia Solowij	Prolonged administration of cannabidiol to chronic cannabis users: a pragmatic trial and its cognitive and symptomatic outcomes
		Prof Paul Amminger	The cannabidiol youth anxiety pilot study (CAPS): a 12-week open-label pilot study of cannabidiol for anxiety disorders
12:30 – 1:00	Data Blitz 2 Chair: Dr Rose Chesworth	Dr Tertia Purves-Tyson	Raloxifene modulates dopamine-related transcripts in the midbrain in male rats
		Camilla Beale	Effects of cannabidiol treatment upon hippocampal subfield volumes in current cannabis users
		Shaun Hopper	Decreased hippocampal responsiveness to muscarinic M1 receptor positive allosteric modulation in a sub-group of subjects with schizophrenia
		Samuel Millard	Maternal fluoxetine treatment alters offspring behaviour and NMDA receptor subunit profile at adolescence
		Dr Renata Pertile	Epigenetic regulation of dopaminergic neuronal differentiation by Vitamin D
1:00 – 2:30	Lunch and posters		
1:30 – 2:30	Poster presentations		
2:30 – 4:00	Symposium 2: Epigenetic mediators of brain dysfunction and psychiatric disorders. Chair/Discussant: Prof Anthony Hannan	Dr Terence Pang	Paternal lifestyle factors which alter sperm small RNAs and offspring behavioural phenotypes
		Dr Irina Voineagu	The role of non-coding RNAs in autism spectrum disorder
		Dr Xiang Li	DNA modification in fear-related learning and memory
4:00 – 4:30	Afternoon tea		
4:30 – 5:30	ECR Session Chairs: Dr Katrina Green and Jeremy Lum	Strengthening the Pillars of Biological Psychiatry: A Focus on Supporting the Early Career Researcher	
6:30	Cocktail function, Level One @ harbourfront, 2 Endeavour Drive, Wollongong		

Tuesday 31 October Illawarra Room, Novotel Wollongong Northbeach			
Time	**Event**	**Speaker**	**Presentation Title**
9:00 – 10:00	5th Isaac Schweitzer Lecture Chair: Prof Nadia Solowij	Prof Pat Michie	From clinical to pre-clinical research – using animal models to understand the neurobiology of schizophrenia
10:00 – 10:30	Data Blitz 3 Chair: Dr Lauren Harms	Dr Susan Thomas	Withdrawal from the help of friends and family in depression: Links to plasma cortisol and oxytocin levels
		Tasnim Rahman	Deficits of somatostatin and SSTR2 mRNAs in orbitofrontal cortex in schizophrenia
		Dr Wei Luan	Maternal vitamin D treatment reverses maternal immune activation induced alterations in mesencepahlic neurogenesis
		Cassandra Wannan	Network-based cortical thinning in treatment resistant schizophrenia
		Helen Cai	Changes in peripheral immune cell trafficking molecules in schizophrenia
10:30 – 11:00	Morning tea		
11:00 – 12:30	Symposium 3: Addicted to addiction – is it lack of love, too much stress, or just your personality (and genes)? Chair: Dr Jiamei Lian Discussant: Dr Jee Kim	Prof Iain McGregor	Serendipity and the Hard Slog: an insiders account of the discovery and development of a novel therapeutic for treating addiction and social deficits
		Prof Andrew Lawrence	Peptide interactions and relapse
		A/Prof Christopher Dayas	The devil is in the detail: why studying individual differences in addiction matters...
12:30 – 1:00	Annual General Meeting		
1:00 – 2:30	Lunch and Posters		
1:30 – 2:30	Poster presentations		
2:30 – 3:10	Special Symposium: Highest ranked student abstracts Chair: Dr Kelly Newell	Georgia Watt	The therapeutic potential of cannabidiol (CBD) in a transgenic mouse model of Alzheimer's disease
		Sally Grace	Intranasal oxytocin increases amygdala responses to emotional faces in body dysmorphic disorder
		Asad Ali	Altered fetal steroidogenesis and dysregulated placental immune response in a developmental vitamin D deficient rat model of autism
3:10 – 4:10	Q & A Moderator: Nick Rheinberger (ABC Illawarra) Chair: A/Prof Jeremy Crook	Prof Paul Amminger Prof Pat Michie Prof Stephen Wood Prof Iain McGregor Prof Suresh Sundram	Is Biological Psychiatry The Graveyard of Psychiatry?
4:10 – 4:30	Afternoon Tea		
4:30 – 4:45	Prizes and Awards		
4:45 – 5:00	Conference Discussant	Dr Vibeke Catts	
5:00	Conference Close		

Welcome

Dear Colleagues,

On behalf of the Local Organising Committee (LOC), I warmly welcome you to the Biological Psychiatry Australia (BPA) Conference in Wollongong!

I would like to thank our sponsors for their invaluable support. Thank you to our Major Sponsor, the Illawarra Health and Medical Research Institute and to the Faculty of Science, Medicine and Health at the University of Wollongong. I would also like to thank and acknowledge the financial support of our Gold Sponsors, Neuroscience Research Australia (NeuRA), Otsuka/Lundbeck and Creso Pharma and our Silver Sponsor, Janssen. Your generosity ensures that these meetings are possible and provides support for our many Early Career Researchers.

I would like to thank the BPA2017 LOC and the BPA Executive Committee as well as our graduate students, who have greatly assisted in organising our annual meeting in Wollongong. This year's program highlights the exciting and diverse range of biological psychiatry research that is being conducted in Australia. We are pleased to have the inaugural BPA President, Prof Brian Dean, opening our conference on Sunday evening. We are equally delighted to have Emeritus Professor Pat Michie and Dr Jee Kim presenting the Isaac Schweitzer Lecture and Aubrey Lewis Award Lecture and congratulate these outstanding Australian biological psychiatry scientists for these awards. We have three outstanding symposia in this years program, together with a student symposia, 3 data blitz sessions and two-days of poster presentations. We are excited to include a new addition to the program this year, an interactive Q & A panel moderated by Nick Rheinberger from ABC Illawarra, and would like to thank the esteemed scientists on this panel.

The BPA2017 LOC would like to offer a warm welcome to the new members of our society, and to our current members we would like to thank you for your continued support. We believe our program will provide opportunities to hear of the latest developments in biological psychiatry research from leading and emerging Australian researchers, engage in intellectual discussion and initiate new collaborations in biological-based research into mental illness. BPA2017 also provides an excellent platform for our Early Career Researchers to present their research and interact with the leaders in the field.

We thank you for coming to our beautiful city nestled between the mountains and the sea and hope that you enjoy the meeting.

Kind Regards,

Kelly Newell
Chair, Local Organising Committee
BPA 2017 Conference

Local Organising Committee

Chair: Dr Kelly Newell

Mr Jeremy Lum
Dr Katrina Green
A/Prof Jeremy Crook
Prof Nadia Solowij
Dr Yinghua Yu
Prof Darryl Eyles
Dr Jee Kim
Prof Chao Deng
Dr Jiamei Lian
Prof Xu-Feng Huang

Keynote presentation: Translating Biological Psychiatry Research into the Clinic: A Roller Coaster that is Worth the Ride.

Prof Brian Dean, The Florey Institute of Neuroscience and Mental Health and Swinburne University; Inaugural President of Biological Psychiatry Australia

Sunday, 29th Oct, 5:00 – 5:40 pm

Brian Dean currently holds the positions of Head, The Division of Biological Psychiatry and Mental Health and Head, The Molecular Psychiatry Laboratory at The Florey Institute of Neuroscience and Mental Health, Parkville and Professorial Research Fellow at the Centre for Mental Health, Swinburne University, Hawthorn, Victoria, Australia. He is also a Professor in the Department of Florey Neuroscience and Mental Health, University of Melbourne, Australia and Deputy Director of the Victorian Brian Bank Network (Psychiatry).

Brian Dean initially trained in the fields of pharmacology and parasitology whilst studying for a Higher National Diploma in Applied Biology at Sunderland University, UK. After obtaining a degree specialising in biochemistry from the University of the Southbank, London he was accepted as a Licentiate of the Institute of Biology. On moving to Australia, he was awarded Master of Science and then a Doctoral Degree from the University of Melbourne. Subsequently, he has sort to understand the changes in molecular architecture of the human brain that cause schizophrenia, bipolar disorder and major depressive disorders as well as identifying molecular mechanisms of action of psychotropic drugs.

Brian Dean research seeks to understand the causes of psychiatric disorders as a basis of advancing the approaches used to manage the treatment of people with such disorders. Hence, among over 235 peer reviewed papers he has published there are significant bodies of work contributing to an understanding the role of muscarinic receptors in the aetiologies and treatment of schizophrenia and mood disorders, the role of cytokine-regulated pathways in the aetiologies of schizophrenia and mood disorders and on the neurobiology of suicide. In addition, his laboratory is making a significant effort to develop useful diagnostic or theranostic test that will assist in the clinical management of psychiatric disorders.

Brian Dean is a Fellow of the Royal Society of Biology and the CINP as well as being a Chartered Biologist. He has received a number of honours including presenting the University of Melbourne Beattie Smith Lecture and the ASPR Lilly Oration as well as being presented with the University of Melbourne Medal.

Brian Dean contributes to the advancement of his field of research, particularly in the Asian region, by being the Treasurer of the CINP, a Councillor of the Asian College of Schizophrenia Research (ACSR) and a Board Member and Chairman of the SAC of the Rebecca Cooper Medical Research Foundation. He was the Inaugural President of Biological Psychiatry Australia and has been Secretary of the ASCR, a Board member of the Asian College of Neuropsychopharmacology and President of the Melbourne Chapter of the Society for Neuroscience. He currently serves on 6 Editorial Boards and provides Ad Hoc Reviewer for 25 Journals.

Aubrey Lewis Award Lecture: Development of Memory and Motivation

Dr Jee Kim, Developmental Psychobiology Laboratory, Florey Institute of Neuroscience and Mental Health, University of Melbourne

Monday, 30th Oct, 9:00 – 10:00 am

Dr Jee Hyun Kim graduated from the University of New South Wales (UNSW) in Australia with the prestigious University Medal in Psychology. In 2008 she completed her PhD at UNSW on the development of memory using rodent models, and was awarded the Australian Psychological Society Award for Excellent PhD Thesis in Psychology. After a postdoctoral fellowship at Michigan University (Ann Arbor, USA), she became the Head of Developmental Psychobiology laboratory at the Florey Institute of Neuroscience and Mental Health/University of Melbourne in 2013. She has received numerous international and national awards including International Society for Developmental Psychobiology Kucharski Young Investigator Award, and Australian Psychological Society Early Career Research Award, The International College of Neuropsychopharmacology Rafaelson Young Investigator Award. She has 52 publications and 1300+ citations. Her team works on memory and forgetting across one's lifetime, demonstrating that emotional memories are regulated differently depending on one's age. This work has major implications for anxiety and addiction treatments, especially early in life. She has been invited to give a TEDxMelbourne talk on this topic, which has now reached +650,000 views (https://www.youtube.com/watch?v=W_t9O5MgisM).

Isaac Schweitzer Award Lecture: From Clinical to Pre-Clinical Research – Using Animal Models to Understand the Neurobiology of Schizophrenia.

Prof. Pat Michie, Emeritus Professor of Psychology, University of Newcastle, Australia.

Tuesday, 31st Oct, 9:00 – 10:00 am

Dr. Pat Michie is currently Emeritus Professor of Psychology at the University of Newcastle, Australia. She previously held professorial positions at UWA and Macquarie University. She is an experimental psychologist whose research has focused on the neural basis of normal and abnormal cognition. She is a Fellow of the Academy of Social Sciences of Australia and is the 2016 recipient of the Australian Psychological Society's Distinguished Contribution to Psychological Science Award. Her research has been characterised by application of theories and methodologies from basic research in cognition and cognitive neuroscience to understand the nature of cognitive deficits and their neural basis in individuals diagnosed with schizophrenia and those at risk. Her research spans auditory processing deficits, impaired inhibitory control and cognitive control more generally and uses both psychophysical methods to assess performance as well as functional brain imaging methods such as event-related potentials (ERPs) of the brain. She was a key member of the Australian group who were the first to demonstrate that individuals with schizophrenia exhibit impaired automatic change detection in a background of auditory regularities, an ERP-derived observation replicated many times and one of the most robust findings in the schizophrenia literature. Her current research is focused on animal models of schizophrenia.

Pat currently chairs the Research Committee of Orygen, the National Centre of Excellence in Youth Mental Health, and the National Committee of Brain and Mind (NCBM) of the Academy of Sciences of Australia. She is past chair of the Australian Brain Alliance, an initiative of the NCBM and the Academy. The Alliance, which is supported by the Australian Psychological Society, the Psychology Foundation and the Australasian Neuroscience Society and major research organisations, aims to secure investment in Australian brain research comparable to other international initiatives.

Symposium 1: Therapeutic potential of cannabidiol treatment for psychiatric illness.

Monday, 30th October, 11:00am – 12:30pm

Speakers: Dr. Katrina Weston-Green, University of Wollongong; Prof Nadia Solowij, University of Wollongong; Prof Paul Amminger, Orygen and University of Melbourne.

Chair: Prof Nadia Solowij, University of Wollongong
Discussant: Prof Patrick McGorry, Orygen and University of Melbourne

Description: Cannabidiol (CBD) is a non-intoxicating compound derived from the cannabis plant that has caused a recent spark of interest for its potential as a novel therapeutic in psychiatric illness/psychological disorders. This symposium will highlight some exciting developments in Australian clinical and preclinical trials with CBD, including: 1) a preclinical investigation of the efficacy of CBD in treating the cognitive deficits and social withdrawal symptoms of schizophrenia in a poly I:C model, with early insight into the potential neurochemical mechanisms underlying these benefits; 2) a pragmatic trial of prolonged CBD treatment in chronic cannabis users, examining potential beneficial effects on cognition, symptoms and brain neurochemistry; and 3) clinical trials examining the efficacy of CBD in treating anxiety disorders in youth, as well as safety (toxicology) considerations. Professor Pat McGorry will discuss the findings from these studies in the context of the growing field of youth mental health, other studies of CBD around the world and the potential for CBD as a medication or adjunct treatment transdiagnostically in psychiatry.

1. Dr. Katrina Weston-Green, University of Wollongong

Cannabidiol treatment in a poly I:C model of schizophrenia: cognitive behavioural improvements and altered neurotransmission. Cognitive impairment is a core symptom domain of schizophrenia. Antipsychotic drugs have minimal benefits in treating cognition and can cause serious side-effects. Therefore, novel therapeutic approaches are required. Cannabidiol (CBD), from the cannabis plant, improves memory and learning in numerous pathological states, and has antipsychotic and neuroprotective properties. We examined the effects of CBD on cognition and neurochemical signalling in a rodent (poly I:C prenatal infection) model of schizophrenia. Pregnant dams were administered (GD15) poly I:C (4mg/kg) or saline (control). Post-pubertal (PND56) offspring were administered CBD (10mg/kg) or vehicle (control) for 3 weeks (n=12/group). Offspring (PND70) underwent behavioural testing: novel object recognition (recognition memory), T maze (working memory) and social interaction (behavioural phenotype for negative symptoms). Post-mortem brain analysis is ongoing. We have examined muscarinic M1 (M1R) and glutamatergic NMDA receptors (NMDAR) in regions of the brain implicated in cognition. Poly I:C impaired recognition and working memory, and reduced social interaction, while CBD restored deficits to control-like levels. Poly I:C down-regulated M1R (cingulate cortex, CPu, hippocampus) and NMDAR (PFC, cingulate cortex, CPu) binding densities, while CBD returned levels to normal. Interestingly, CBD reduced M1R and NMDAR binding in healthy offspring. Our findings demonstrate that chronic CBD treatment reduces cognitive and social interaction deficits caused by prenatal poly I:C infection and suggest a role for muscarinic and glutamatergic signalling in the underlying mechanisms; further investigation is required. Overall, these results present interesting implications for treating cognitive deficits in schizophrenia.

2. Prof Nadia Solowij, University of Wollongong

Prolonged administration of cannabidiol to chronic cannabis users: a pragmatic trial and its cognitive and symptomatic outcomes. Heavy cannabis use is associated with impaired cognition and structural and functional brain alterations, including psychosis at the extreme. Significant interest has emerged in understanding interactions between the two primary constituents of cannabis plant matter: THC which is associated with worse outcomes and cannabidiol (CBD) which may ameliorate adverse effects of THC and has neuroprotective and antipsychotic properties. We showed that exposure to CBD may protect against THC-related hippocampal harms, and that prolonged abstinence may result in recovery of these harms, but many chronic cannabis users have difficulty stopping using. Current treatments for cannabis dependence are inadequate and there is interest in the potential for CBD to be used as an adjunct treatment. We conducted a pragmatic open-label trial (ISRCTN89498802) of prolonged administration of CBD (200mg daily for 10 weeks) to 20 cannabis users who continued using cannabis throughout the trial. Our primary aim was to examine effects on cognition, psychological symptoms and a range of brain functional and structural measures. Effects on cannabis use patterns were also of interest. After 10 weeks of CBD treatment, with no adverse effects, participants showed better memory and attention switching performance, and reported significantly fewer depressive and psychotic-like symptoms than at baseline. Plasma CBD levels correlated with better attention switching performance. This study is the first to examine CBD treatment in current cannabis users, and despite the lack of a placebo control group, the results suggest promising beneficial effects of CBD on psychological symptoms and cognition, in the context of ongoing cannabis use.

3. Prof Paul Amminger, Orygen and University of Melbourne

The cannabidiol youth anxiety pilot study (CAPS): a 12-week open-label pilot study of cannabidiol for anxiety disorders. Anxiety disorders are among the most prevalent psychiatric conditions in adolescents. Current evidence-based treatments include cognitive behaviour therapy (CBT) and/or medication. However, treatment resistance is a significant problem. Only around 50% of children and adolescents remit from their anxiety disorders with CBT or pharmacological intervention. Therefore, there is a clear need to develop and explore novel therapeutic agents for the management of anxiety disorders in this age group. The aim of the present study is to test the feasibility, safety, tolerability and therapeutic effects of 12-week treatment with cannabidiol (CBD) to reduce anxiety severity in young people who do not respond to standard treatment. This is a single-centre (headspace), 12-week open label trial (ANZCTR identifier: ACTRN12617000825358p) of CBD in 30 patients aged 12-25 who do not respond to evidence-based standard treatment for anxiety disorders. Patients will receive CBD on a fixed-flexible schedule, beginning with 200mg of CBD per day (adjusted up to 800mg/day). A background intervention of bi-weekly CBT sessions will be offered. The primary outcome is anxiety severity, measured with the Overall Anxiety Severity and Impact Scale at week 12. Secondary outcomes will include absence of an anxiety disorder diagnosis, depressive symptoms, social and occupational functioning, plasma levels of CBD and its metabolites and study withdrawal due to adverse events. Data from this study will provide the first evidence of the potential safety, tolerability and efficacy of CBD for anxiety disorders in youth. Results will be used to inform further evaluations of CBD for anxiety disorders in larger studies.

Symposium 2: Epigenetic mediators of brain dysfunction and psychiatric disorders.

Monday, 30th October, 2:30pm – 4:00pm

Speakers: Dr Terence Pang, Florey Institute of Neuroscience and Mental Health; Dr Irina Voineagu, University of New South Wales; Dr Xiang Li, Queensland Brain Institute, University of Queensland

Chair/Discussant: Prof Anthony Hannan, Florey Institute of Neuroscience and Mental Health

Description: We are in the midst of a number of major biomedical revolutions. The genomic revolution is delivering unprecedented new insights into genetic predisposition for a wide range of behavioural and cognitive traits, as well as psychiatric and neurological disorders. However, brain function and dysfunction is the result of complex combinations of genetic and environmental factors, and epigenetics is crucial in understanding how 'nature and nurture' combine. The epigenetic revolution provides an added layer of complexity overlaid on genetics and incorporates a nexus of gene-environment interactions. This symposium will address the role of epigenetics in mediating brain function and dysfunction in psychiatric disorders. It will cover a range of epigenetic modifications, including DNA methylation, histone modifications and the regulatory roles of noncoding RNAs. The symposium will incorporate national experts in this field of biological psychiatry. Epigenetic mechanisms mediating key behavioural and cognitive processes, including learning and memory, will be addressed. Furthermore, epigenetics is crucial to our understanding of brain development and healthy function, which will be covered in this symposium. The speakers will also discuss the relevance of epigenetic dysregulation to major psychiatric disorders.
This topic will be of broad interest to a wide range of Biological Psychiatry Australia members, and other attendees of the Annual Scientific Conference. Whether the primary focus of these scientists is molecular, cellular, behavioural, cognitive or clinical, epigenetics impacts on multiple levels of neurobiology and biological psychiatry. Furthermore, the symposium will address both basic and clinical neuroscience, and is likely to engage the diverse BPA audience.

1. Dr Terence Pang, Florey Institute of Neuroscience and Mental Health
Paternal Environmental Exposures Induce Transgenerational Epigenetic Effects on Offspring Brain Function and Psychiatric Endophenotypes. It is now becoming evident that a male's lifestyle prior to conception can significantly alter the health outcomes of his children. Examples of these potentially impactful factors include traumatic stress, a high-fat diet, and exposure to drugs of abuse. Epidemiological evidence traced along the paternal lineage indicates that ancestral exposure to traumatic events elicits negative transgenerational response in subsequent generations. Studies of animal models of traumatic stress (maternal separation, chronic social defeat) have also found long-term impacts on offspring anxiety and stress response. To study the impact of non-traumatic stress (arguably more relevant to the wider population), we developed and demonstrated in a mouse model of low-dose chronic corticosterone supplementation that this led to elevated anxiety in the male F1 offspring (Short et al., 2016). I will discuss how the transgenerational response is modulated by environmental enrichment (increased cognitive stimulation and physical activity) and exercise. This extends on our previously demonstrated benefits of environmental enrichment in various models of neurological conditions, in part by rescuing anxiety and depressive phenotypes (Pang et al., 2009; Du et al., 2012; Pang et al., 2013). I will also discuss our gene expression profiling studies of the offspring hippocampus, where we have examined various molecular mediators associated with anxiety pathology. Our work suggests that paternal preconception conditions

indirectly result in differential regulation of gene expression in offspring brains which could underlie their behavioural phenotypes and modulate their response to environmental cues.

2. Dr Irina Voineagu, University of New South Wales

The Role of the RBFOX1 Splicing Factor and Circular RNAs in Autism Spectrum Disorders. Autism Spectrum Disorders (ASD) are neurodevelopmental conditions that are highly heritable but also genetically very heterogeneous. Current genetic data estimates that over 1000 loci contribute to the genetic landscape of ASD. Despite the genetic heterogeneity of ASD, a replicable molecular signature of ASD brains has been identified by several studies using distinct cohorts (Voineagu et al. Nature 2011, Liu et al. Plos Genetics 2016, Parikshak et al. Nature 2016). One of the genes consistently dysregulated in the brain of ASD patients is the neuronal and muscle specific splicing factor RBFOX1. Several lines of evidence indicate that, RBFOX1 has an effect on transcript abundance. Here we investigate the hypothesis that RBFOX1 might affect transcript abundance by regulating the formation of circular RNA molecules. Circular RNAs (circRNAs) result from non-canonical back-splicing. To investigate the effect of RBFOX1 on circRNA biogenesis, we overexpressed the neuronal isoform of RBFOX1 in human primary astrocytes. We performed RNA-seq on triplicate RBFOX1 overexpression and control samples, with and without RNaseR treatment, to enrich for circular RNA molecules. We observed a strong increase in circRNA expression in cells stably expressing RBFOX1. We also found a significant overlap between RBFOX1-dependent circRNAs and circRNAs previously shown (Zhang et al. Cell.Rep. 2016) to be induced upon neuronal differentiation. These data bring initial evidence for the role of RBFOX1 in regulating the formation of circRNAs in the human brain, a mechanism potentially contributing to its role in ASD.

3. Dr Xiang Li, Queensland Brain Institute, University of Queensland

The devil is in the detail: why studying individual differences in addiction matters... The Formation of Fear Extinction Memory Requires the Accumulation of N6-methyl-2'-deoxyadenosine in DNA. We have discovered that the DNA modification N6-methyl-2'-deoxyadenosine (m6dA) is dynamically regulated in post-mitotic neurons and accumulates genome-wide in the adult brain of C57Bl6 mice in response to fear extinction learning. The deposition of m6dA drives activity induced gene expression and is necessary for the formation of fear extinction memory. In stimulated primary cortical neurons in vitro, m6dA accumulates within the P4 promoter of the gene encoding brain-derived neurotrophic factor (BDNF) and creates an active chromatin state and the recruitment of the activating transcription factor Yin-Yang 1 and RNA polymerase II, which lead to increased BDNF exon IV mRNA expression. The effects are mediated by the activity of a putative adenine methyltransferase (N6amt1), the knockdown of which prevents m6dA deposition and related recruitment of chromatin and transcriptional machinery at the BDNF P4 locus. In the adult infralimbic prefrontal cortex, N6amt1-mediated accumulation of m6dA promotes the expression of BDNF exon IV, which is required for the formation of fear extinction memory. We propose a model in which the experience dependent accumulation of m6dA at specific GATC sites along gene promoters creates an epigenetic state that is permissive for gene activation, and plays a key role in the expression of genes associated with the formation of memory. These findings dramatically expand the scope of DNA modification and its adaptive role in the epigenetic regulation of gene expression in the adult brain, which has implications for understanding the pathogenesis of psychiatric disorders.

Symposium 3: Addicted to addiction – is it lack of love, too much stress, or just your personality (and genes)?

Tuesday 31st October, 11:00am – 12:30pm

Speakers: Prof. Iain McGregor, University of Sydney; Prof. Andrew Lawrence, Florey Institute of Neuroscience and Mental Health; A/Prof. Christopher Dayas, University of Newcaslte

Chair: Dr. Jiamei Lian, University of Wollongong
Discussant: Dr. Jee Hyun Kim, Florey Institute of Neuroscience and Mental Health

Description: Seeking of rewards, such as sex and food, is necessary to promote survival. However, it can manifest as addiction when it interferes with daily functioning. Addiction to drugs of abuse is a chronic brain disorder characterized by compulsive drug seeking and use that persist despite severe adverse consequences, and relapse following treatment is high. It is one of the greatest causes of financial and societal burden in the world. Therefore, understanding the molecular mechanisms underlying drug addiction is clinically important. Our symposium will present the latest findings on different drugs of abuse (alcohol, cocaine, methamphetamine) with significant implications in the field of Biological Psychiatry by leading scientists from Melbourne, Sydney, and Newcastle. The Discussant Dr Jee Kim will first set the scene briefly by raising the hottest questions in addiction and illustrating failures in clinical trials to treat addiction. Professor Iain McGregor will describe his journey in discovering and developing a novel pharmacotherapy exploiting the oxytocin system that may simultaneously cure our substance use disorders and social anxiety. Professor Andrew Lawrence will then highlight that other neuropeptide systems such as relaxin can be manipulated also to cure addiction by reducing stress-induced relapse of alcohol seeking. A/Professor Christopher Dayas will then challenge both their work with his research showing that the key to reducing addiction lies within individual differences in micro-RNA changes in drug-taking, -seeking, and –relapse. Dr Kim will then lead the audience into an exciting discussion into whether we can cure addiction, or at least drink less when stressed.

1. Prof. Iain McGregor, University of Sydney

Serendipity and the Hard Slog: an insiders account of the discovery and development of a novel therapeutic for treating addiction and social deficits. The past few years have seen increasing interest in the neuropeptide oxytocin as a novel and effective intervention for addictive behaviour and for psychiatric disorders that feature social withdrawal as a central feature (e.g. autism). Early studies in laboratory animals showed the capacity of oxytocin to increase prosocial behaviours and to reduce methamphetamine, cocaine and alcohol self-administration and withdrawal symptoms. However, oxytocin itself is unlikely to ever become a mainstream therapeutic due to its poor brain penetration and lack of oral bioavailability. Investigation of non-peptide small molecule oxytocin-like compounds by our group lead to the serendipitous discovery of Synthetic Oxytocin-Like-Compound 1 (SOC-1), a novel compound that stimulates brain oxytocin circuitry and has dramatic prosocial and anti-addiction effects in animal models. SOC-1 reduces intravenous methamphetamine self-administration and reinstatement of methamphetamine seeking behavior in rats, reduces cocaine self-administration in rhesus monkeys, and alcohol self-administration in baboons. SOC-1 shows favourable pharmacokinetics and a very promising toxicity profile, and further testing is being currently undertaken in the USA and Australia to enable fast tracking of Phase 1 human clinical trials. The mode of action of SOC-1 remains something of a mystery: it

stimulates magnocellular oxytocincontaining neurons in the hypothalamus but does not show affinity for more than 100 different receptors and transporters that have been screened, including the oxytocin receptor. Microarray and activity-based proteomic profiling are currently being conducted to better elucidate the actions of SOC-1 on the central nervous system.

2. Prof. Andrew Lawrence, Florey Institute of Neuroscience and Mental Health

Peptide interactions and relapse. Increasing our understanding of the brain circuits and chemicals that regulate alcohol intake and relapse offers the potential for more targeted therapeutic approaches to assist in relapse prevention. Stress is a key precipitant of relapse, and relaxin-3 signalling via RXFP3 modulates both stress responses and alcohol intake. In iP rats, icv microinjection of a selective RXFP3 antagonist prevented yohimbine-induced reinstatement of alcohol-seeking, discrete microinjections implicated dorsal BNST and central amygdala as loci. Relaxin-3 neurons are predominantly located in the CRF-sensitive nucleus incertus (NI). Intra-NI microinjection of a selective CRF1 receptor antagonist attenuated yohimbine-induced reinstatement of alcohol-seeking whereas a CRF2 receptor antagonist had no effect. After long-term voluntary alcohol intake, qPCR revealed that the expression of mRNA encoding both CRF1 and RXFP3 receptors was upregulated in the NI. Furthermore, chronic ethanol intake leads to neuroadaptive changes in CRF and relaxin-3 systems within rat NI. The NI also receives orexinergic innervation, bilateral NI injections of an OX2 receptor antagonist attenuated yohimbine-induced reinstatement of alcohol seeking, while an OX1 receptor antagonist had no effect. Orexin-A depolarized NI neurons recorded in coronal brain slices, sensitive to bath application of TCS-OX2-29, but not SB-334867. These data suggest an excitatory orexinergic input to NI contributes to yohimbine-induced reinstatement of alcohol seeking, predominantly via local OX2 receptor signalling. Collectively, these data implicate CRF and orexin inputs to relaxin-3 neurons of the NI in alcohol-seeking.

3. A/Prof. Christopher Dayas, University of Newcaslte

Non-coding RNA are a level of molecular control that can promote both fine tuning and lasting changes in synaptic plasticity. Micro- RNAs are a form of non-coding RNAs that are short (21-23 nucleotides in length) in length and post-transcriptionally regulate messenger RNA primarily through translational repression or transcript degradation. Key studies have shown that overexpression of specific miRNA with the striatum can profoundly modify drug taking. However, the temporal profile of miRNA dysregulation and contribution to distinct behaviours across the addiction cycle has not been studied. Accordingly, we examined the expression of candidate miRNA in the dorsal and ventral striatum of animals identified as ‘addiction prone’ or resistant either immediately following self-administration training or following extinction and relapse testing. Cocaine self-administration was associated with changes in miRNA expression in a regionally discrete manner within the striatum, with the most marked changes occurring in the nucleus accumbens core. When we examined the miRNA profile of addiction-prone rats following self-administration, we observed increased levels of miR-212 in the dorsomedial striatum. After extinction and relapse testing, addiction-prone rats showed significant increases in the expression of miR-101b, miR-137, miR-212 and miR-132 in NAcSh, and miR-137 in DLS. This study identifies temporally specific changes in miRNA expression consistent with the engagement of distinct striatal subregions across the course of the addiction cycle. Increased dysregulation of miRNA expression in NAcSh and DLS at late stages of the addiction cycle may underlie habitual drug seeking, and may therefore aid in the identification of targets designed to treat addiction.

Special Symposium: Highest rated student abstracts

Tuesday, 31st Oct, 2:30 – 3:10pm

1. The therapeutic potential of cannabidiol (CBD) in a transgenic mouse model of Alzheimer's disease.

Authors: Georgia Watt, Kani Shang, Hongyun Li, Grett Garner and Tim Karl.

Affiliations: Western Sydney University, Neuroscience Research Australia, University of New South Wales, University of Wollongong, Illawarra Health and Medical Research Institute (IHMRI)

Background:
In Alzheimer's disease (AD) pathological brain changes include the accumulation of amyloid-β (Aβ) and tau hyperphosphorylation causing neurodegeneration, neuroinflammation and oxidative stress. Current AD treatments do not stop or reverse the disease progression, highlighting the need for more effective therapeutic alternatives. The non-psychoactive phytocannabinoid cannabidiol (CBD) has demonstrated anti-oxidant, anti-inflammatory and neuroprotective properties. Furthermore, chronic CBD treatment (20 mg/kg) has been shown to reverse social recognition memory deficits in an established mouse model for AD (i.e. APPxPS1 transgenic mice). The current project aimed to determine the effect of 50 mg/kg CBD in APPxPS1 mice.

Methods:
Male APPxPS1 transgenic mice at 12 months of age were treated with CBD (50 mg/kg CBD, daily intraperitoneal injections) starting 3 weeks prior to behavioural testing (WT-VEH n = 10; WT-CBD n = 11; APPxPS1-VEH n = 10; APPxPS1-CBD n = 8). A variety of cognitive domains including object and social recognition memory, spatial memory, and fear-associated memory were evaluated following the initial treatment period. After behavioural test completion, brain tissue was collected and soluble and insoluble Aβ40 and Aβ42 levels were analysed by ELISA as a marker for AD brain pathology.

Results:
Vehicle treated male APPxPS1 mice demonstrated impaired social recognition memory and impaired reversal learning in the cheeseboard task. These deficits were absent in AD mice undergoing CBD treatment. The ELISA results indicated that soluble Aβ42 levels were not affected by CBD treatment. However, there was a trend for CBD to reduce insoluble Aβ40 levels in the hippocampus in APPxPS1 mice.

Conclusions:
This study investigated the therapeutic-like effects of 50 mg/kg CBD on cognition and brain pathology of APPxPS1 transgenic males. Chronic CBD treatment could reverse deficits in social recognition memory and spatial learning in the cheeseboard task. Furthermore, CBD treatment trended to reduce insoluble Aβ40 levels in the hippocampus.

2. Intranasal oxytocin increases amygdala responses to emotional faces in body dysmorphic disorder.

Authors: Sally Grace, Izelle Labuschagne, Matthew Hughes, David Castle and Susan Rossell

Affiliations: Swinburne University of Technology, Australian Catholic University, Melbourne University

Background:
Patients with body dysmorphic disorder (BDD) are impaired at recognising facial emotions and have shown abnormal brain activity in regions involved in face and emotion processing. Past research has demonstrated that the neuropeptide oxytocin increases behavioural performance on face processing tasks, as well as modulates amygdala responses to emotional faces in healthy subjects and those with clinical disorders such as social anxiety and autism.

Methods:
Here, we aimed to assess amygdala responses to emotive faces in a sample of 20 male and female patients with BDD and 22 matched healthy control participants. In a randomized, double-blind placebo-controlled within-subject functional MRI study, we measured group differences in amygdala activation to an emotional face matching task of fearful, angry, disgusted, sad, surprised and happy faces following acute intranasal administration of OXT (24 IU) and placebo.

Results:
Oxytocin elicited differential effects within the left amygdala, with the BDD group showing increased amygdala responses to surprised and threatening faces (anger & fear) following intranasal oxytocin, whereas decreased amygdala responses were observed in the healthy control group.

Conclusions:
Our results provide new evidence that a single a dose of oxytocin has a modulatory effect on amygdala responses to emotive faces in BDD. These observations may reflect oxytocin-induced salience processing of emotive faces and subsequently enhance face emotion processing in male and female BDD patients, which have important clinical implications for the disorder.

3. Altered fetal steroidgenesis and dysregulated placental immune response in a developmental vitamin D deficient rat model of autism.

Authors: Asad Ali, Xiaoying Cui and Darryl Eyles

Affiliations: Queensland Brain Institute, Brisbane

Background:
Emerging evidence suggests that maternal or developmental vitamin D deficiency (DVD-deficiency) is a risk factor for autism. A well-established association has also been found between gestational infection and increased incidence of autism. Postmortem studies have revealed that brains from autistic children have increased inflammatory cytokines. In addition important developmental neurosteroids have been shown to be significantly increased in the amniotic fluid of children who develop autism. Vitamin D has been shown to both promote anti-inflammatory actions in placenta and regulate expression of several steroidogenic enzymes invitro. Here we investigate the effects of DVD-deficiency on fetal steroidogenesis and placental immune functions.

Methods:
DVD-deficiency was induced by feeding vitamin D deficient diet to female Sprague-Dawley rats for the period of 6 weeks before mating. Foetuses were collected at gestational day 18. Male fetuses positioned between two neighbouring males (2M-males) or downstream to a male fetus (1M-males) were selected. The expression of steroidogenic enzymes and certain autism-candidate genes were examined by Real-Time PCR in matching fetal brains and placentas. Baseline levels of cytokines were measured by ELISA. Placental response to the inflammatory agents lipopolysaccharides and polyinosinic-polycytidylic acid (poly I:C) was also examined when placenta was cultured. Data was analysed by multivariate analysis.

Results:
DVD-deficiency reduced aromatase expression in 2M-male brains compared to similar positioned controls ($p=0.031$). The progesterone catabolic enzyme cyp21a1 ($p= 0.04$), foxp2 ($p= 0.023$) and vitamin D activating enzyme cyp27b1 ($p= 0.049$) were all significantly reduced in 2M DVD-deficient brains. In placenta, DVD-deficiency reduced expression of catechol-O-methyltransferase ($p= 0.005$). In contrast to brains, cyp27b1 was up-regulated in DVD-deficient placentas ($p= 0.001$). DVD deficiency did not affect baseline cytokines in brain or placenta. However when activated with poly I:C, DVD-deficient placentas from male fetuses had higher concentration of IL-6 ($p=0.025$) and 1L-1β ($p=0.020$) then control placentas.

Conclusions:
Therefore 3 potential autism-related processes may operate in the DVD-deficient developing brain and placenta. A) The alterations in the aromatase and cyp21a1 expressions may possibly enhance testosterone and progesterone production in DVD-deficient male brains. B) Down-regulation of catechol-O-methyltransferase leads to reduced 2-methoxyestradiol a well-known cause of preeclampsia. C) Increased production of IL-6 and 1L-1β in poly I:C activated DVD-deficient placentas suggests that vitamin D deficiency is sufficient to cause dysregulation of placental immune regulation against viral infections. In conclusion, developmental alterations in steroidogenesis, autism-candidate genes and dysregulated placental immune response provide plausible mechanisms linking DVD-deficiency and autism.

Data Blitz 1

Monday, 30th Oct, 10:00 am – 10:30 am

1. There's something fishy about his behaviour: How does omega-3 status influence aggression and cognitive function and what can be done to ensure a better future?

Authors: Barbara Meyer and Mitchell Byrne

Affiliations: School of Medicine, University of Wollongong; School of Psychology, University of Wollongong

Background:
Diet influences mental health and behaviour. Omega-3 (n-3) fatty acids play a pivotal role in mental health and behavioural self-regulation. The old epithet "you are what you eat" extends beyond physical health and body morphology, with increasing data demonstrating that diet influences both cognitive function and behaviour. This is particularly relevant in offender populations where poor diets combine with higher than average incidence of mental health problems. This presentation outlines the biological plausibility of omega-3 supplementation as an intervention for behavioural disorders (aggression) and mental health difficulties (ADHD).

Methods:
The pilot feasibility study was a double blind cross-sectional study utilising behavioural, psychometric and biological measures. 136 adult male prisoners were recruited from South Coast Correctional Centre (SCCC), NSW Australia. A 7 point categorisation was used to quantify levels of aggressive behaviour (4 weeks) from individual SCCC case notes, whereby higher scores correspond to increasingly aggressive behaviour. Study participants completed the Aggression Questionnaire (AQ) and the Brown's Attention Deficit Disorder Scales (BADDS), provided a blood sample for erythrocyte fatty acid analysis using gas chromatography and the omega-3 index was calculated.

Results:
The baseline omega-3 index ranged from 2.3% to 10.3% with a median of 4.7%, indicating that some participants already had substantial omega-3 intake. Assessment of aggressive and attention deficit behaviour revealed that there were negative correlations between baseline omega-3 index and baseline aggression categorisation scores (r=-0.21, P=0.016); total AQ score (r=-0.234, P=0.011); Anger (r=-0.222 p=0.016); Hostility AQ (r=-0.239, P=0.009); indirect aggression (r=-0.188 p=0.042); total BADDS (r=-0.263, p=0.005); Activation (r=-0.224, p=0.016); Attention (r=-0.192, p=0.043); Effort (r=-0.253, p=0.007); Affect (r=-0.330, p=0.000) and Memory (r=-0.240, p=0.010).

Conclusions:
The study demonstrated that there is a high variability in omega-3 status of a NSW prison population, and inmates with lower omega-3 index were more aggressive and had higher ADD scores. This pilot feasibility study has led to a successful $1.8M NHMRC Partnership Grant that includes a multicentre trial of n-3 and aggressive behaviour in adult male prisoners as well as translation into policy and practice.

2. Vitamin D deficiency reduces hippocampal subfield volume and disrupts right-hippocampal structural connectivity: evidence from mouse and human data.

Authors: Mamun Al-Amin, RK, Sullivan, Nyoman D. Kurniawan, Yeonsil Moon, Seol-Heui Han and THJ Burne.

Affiliations: Queensland Brain Institute, University of Queensland; Centre Advanced Imaging, University of Queensland; Department of Neurology, Konkuk University Medical Centre, Seoul; Australia and Queensland Centre for Mental Health Research.

Background:
Converging evidence from human epidemiological and rodent studies suggest that vitamin D deficiency impairs cognition. Here we examined the impact of adult vitamin D (AVD) deficiency on hippocampal subfield volume and structural connectivity in BALB/c mice. We also analysed previously collected structural and diffusion weighted MRI data of elderly persons having mild cognitive impairment (MCI) to compare with animal findings.

Methods:
Adult male BALB/c mice (10 weeks old) were fed a control diet (1500 IU vitamin D3/kg, n=16) or deficient diet (0 IU vitamin D3/kg, n=16) for a duration of 20 weeks. We used the active place avoidance (APA) test to measure spatial learning and memory formation. We acquired structural and diffusion MRI images of mouse brain using a 16.4T scanner. We used “mrtrix3” and “FSL” for pre-processing of diffusion image. We used “Freesurfer” for motion correction, whole brain and hippocampal subfield segmentation. We also used network based statistics to identify connections and networks that are altered in vitamin D deficiency.

Results:
We observed that AVD-deficient mice had a significantly ($p<0.05$) lower latency to enter the shock zone in APA test. We found a significant ($p<0.05$) reduction of total hippocampal volume in human but not in mouse. Human hippocampal subfield volume analysis showed a significant ($p<0.05$) reduction of CA1, CA3, CA4, subiculum and fimbria volumes. By contrasts, mouse data showed a significant ($p<0.05$) shrinkage of CA1 subfield. Moreover, we found disrupted structural brain connectivity on 29 nodes in mice and 12 brain nodes on the elderly AVD-deficient human. Both species showed that the right-hippocampus is the core hub of the disrupted network.

Conclusions:
Consistent with several previous studies, we found that AVD deficiency impaired spatial learning and memory formation. The affected mouse brain regions are involved in memory, navigation, fear, emotional stimuli processing. In humans, there were reductions in hippocampal subfield volume and disrupted structural connectivity were associated with both memory impairment and AVD deficiency. Our results indicate a vulnerability in hippocampal subfield volume and connectivity associated with vitamin D deficiency in mice and humans.

3. Do sensory integration deficits represent a biomarker for schizophrenia?

Authors: Olivia Carter, Hayley Darke, Christina Damicoucas, Matthew Mitchell, Keri Steenberg and Suresh Sundram.

Affiliations: University of Melbourne, Monash University

Background:
Visual dysfunction is commonplace in schizophrenia and occurs alongside cognitive, psychotic and affective symptoms of the disorder. A substantial body of evidence has repeatedly demonstrated impairments in the integration of "low-level" visual features in patients with schizophrenia. This has led some to suggest that visual integration impairments may serve as a potential biomarker for this disorder. Despite many symptoms of schizophrenia occurring in a range of disorders, visual integration deficits are rarely tested in broader patient populations.

Methods:
The present study assessed patients with a range of psychotic and non-psychotic disorders and healthy controls on a variety of tasks assessing visual contrast detection, visual motion integration, visual contour integration, auditory tone detection, and auditory tone integration. Across the different measures a total of 239 psychiatric inpatients (schizophrenia spectrum disorder n=114; bipolar affective disorder n=44; major depression n=38 and other psychiatric conditions n=33) and 74 healthy controls were assessed.

Results:
Compared with healthy controls and non-psychotic patients, psychotic patients trans-diagnostically were impaired on the sensory integration tasks (visual motion, visual contour and auditory integration) however they were unimpaired in simple visual or auditory detection. Impairment in visual motion integration was correlated with the severity of positive symptoms independent of diagnosis, and could not be accounted for by a reduction in processing speed, inattention or medication effects.

Conclusions:
Our results demonstrate that impaired sensory integration is not specific to schizophrenia, as has previously been assumed. Instead, sensory integration deficits are closely related to the presence of positive symptoms independent of diagnosis. The finding that equivalent integrative sensory processing is impaired in audition is consistent with hypotheses that propose a generalised deficit of neural integration in psychotic disorders.

4. Ketogenic diet normalizes behavioural abnormalities in a chronic neurodevelopmental murine model of schizophrenia

Authors: Ann-Katrin Kraeuter, Zoltan Samyai and Maarten van den Buuse

Affiliations: James Cook University, La Trobe University

Background:
Schizophrenia is a chronic neurodevelopmental disorder effecting around 1% of the world's population. Current medications have poor efficacy with detrimental side effects. Current research associates schizophrenia with a dysfunctioning glucose metabolism. Viral infection during pregnancy activates the maternal immune system, increasing schizophrenia incidences in the offspring through altering brain development. Therefore, we are proposing a metabolic based approach, Ketogenic diet (KD), for the treatment of schizophrenia. KD has been used since 100 years safely for the treatment of childhood refractory epilepsy. We aim to use KD as an alternative fuel source to glucose in a neurodevelopmental mouse model of schizophrenia.

Methods:
Pregnant females were injected i.v. on gestation day 9 with Polyinosinic:polycytidylic acid (Poly I:C) to activate the mothers immune system. Male and female offspring were placed between 5-6 weeks (during adolescence) on Standard diet or KD. Animals remained for 3 weeks on their randomly assigned diets, which was followed by a battery of behavioural assays. Animals were tested behaviourally for locomotor activity (open field), sociability (3 chamber sociability), repetitive behaviour (marble burying) and sensory motor gating (pre pulse inhibition of startle).

Results:
Ketogenic diet normalized locomotor activity and sociability in both genders. Repetitive behaviour was only increased in male Poly I:C animals, which was normalized by the Ketogenic diet. No effect of Poly I:C was found in female animals. In males in combination with 0.25 mg/kg MK-801 a greater sensitivity to the NMDA-receptor antagonist was found within the Poly I:C group, which was normalized by the Ketogenic diet.

Conclusions:
Our findings show that KD was effective in reversing neurodevelopmental changes induced by the maternal immune activation model. However, further research is needed to establish the implications of KD in the maternal immune activation model on cognition. This raises the possibility that a metabolically based approach can be used effectively in the treatment of chronic schizophrenia.

5. The effects of mid-late gestational maternal immune activation in rats on schizophrenia-related behaviour

Authors: Lauren Harms, Ariel Dunn, Anita Gray, Rebecca Tattoli, Patricia T Michie and Deborah M Hodgson

Affiliations: Priority Centre for Brain and Mental Health Research, University of Newcastle

Background:
Prenatal infection is a risk factor for schizophrenia in offspring and is believed to be mediated by maternal immune activation (MIA) in response to an infection. Previous studies in our lab investigating the effect of MIA during mid or late gestation found sensorimotor gating deficits and transient working memory impairments, but did not observe many other behavioural changes consistent with an animal model of schizophrenia. Therefore, the current study aims to determine whether MIA at another gestational time-point leads to significant changes to schizophrenia-related behaviour.

Methods:
Polyinosinic:polycytidylic acid (PolyI:C) was injected to induce MIA in pregnant Wistar rats at gestational day (GD) 14. Control dams were given saline injections. The resulting offspring were raised until adulthood and their behaviours with relevance for schizophrenia and other psychiatric disorders were examined, including the elevated plus maze behaviour, social interaction, sucrose preference, open field activity, sensorimotor gating and locomotor sensitivity to the psychomimetic drugs amphetamine and MK-801.

Results:
MIA-exposed rats were more sensitive to the locomotor-stimulating effects of the psychomimetic amphetamine ($F(1, 29) = 8.00$, $p = .008$) , an effect most pronounced after a high dose (2.5mg/kg) of amphetamine. In addition, MIA-exposed rats exhibited reduced novel object preference in the novel object recognition test of learning and memory ($F(1, 38) = 9.57$, $p = .004$). Both effects were more pronounced in male rats. MIA exposure at GD14 did not affect sensorimotor gating, locomotor responsivity to the psychotomimetic MK-801, social interaction, sucrose preference, elevated plus maze or open field behaviour.

Conclusions:
These findings indicate that the MIA model may be useful for further investigation of schizophrenia-like cognitive deficits and psychotic-like behaviour, but is unlikely to be useful for the further investigation of negative symptom-like behaviour.

Data Blitz 2

Monday, 30th 12:30 – 1:00 pm

1. Raloxifene modulates dopamine-related transcripts in the midbrain in male rats

Authors: Tertia Purves-Tyson, Danny Boerrigter and Cyndi Shannon Weickert

Affiliations: Schizophrenia Research Laboratory, NeuRA; School of Psychiatry, UNSW

Background:
The selective estrogen receptor modulator, raloxifene, improves cognition in schizophrenia and may ameliorate psychosis. Dopamine (DA) dysregulation contributes to cognitive deficits and psychosis in schizophrenia. It is not known if the molecular mechanisms of raloxifene include changes in dopamine regulation at the dopamine cell bodies. We hypothesised that raloxifene modulates DA-related transcripts in the substantia nigra (SN) and ventral tegmental area (VTA) in healthy male rats, and that this may underpin raloxifene-induced changes in DA-related behaviours.

Methods:
Adult male Wistar rats (n=~12/group) were given daily subcutaneous injections of raloxifene (5mg/kg) or vehicle for 4 weeks. DA synthesis enzyme, tyrosine hydroxylase (TH) and dopamine transporter (DAT) mRNAs were assessed by qPCR in the SN and dopamine receptor (DRD2short, DRD2long, DRD1, DRD3) and catabolic enzyme (MAOA, COMT) transcripts in the SN and VTA. Data was analysed with Student's t tests.

Results:
In the SN, there was no change in TH mRNA, but an increase in DAT mRNA with raloxifene treatment. DRD2S, DRD2L and DRD3 transcripts were increased by raloxifene in both the SN and VTA. In contrast, we did not detect a raloxifene-related change in DRD1 mRNA in the midbrain. MAO and COMT mRNAs were increased by raloxifene in both regions.

Conclusions:
Since we have found significant reductions in DAT and DRD2 mRNA in the midbrain of people with schizophrenia, these studies show potential for raloxifene to restore gene expression of molecules that are reduced in the midbrain in schizophrenia. Furthermore, raloxifene also increases catabolic enzyme transcripts that may contribute to reducing extracellular or intracellular dopamine levels. Future studies will investigate DA-related transcripts in striatum and cortex and determine whether raloxifene preserves cognition in a rat model of schizophrenia that exhibits cognitive deficits.

2. Effects of cannabidiol treatment upon hippocampal subfield volumes in current cannabis users.

Authors: Camilla Beale, Samantha Broyd, Yann Chye, Chao Suo, Murat Yucel and Nadia Solowij

Affiliations: School of Psychology, University of Wollongong; Illawarra Health and Medical Research Institute, University of Wollongong; Brain and Mental Health Laboratory, Monash Institute of Cognitive and Clinical Neurosciences, Monash University.

Background:
Chronic cannabis use is associated with neuroanatomical alterations in the hippocampus, a region with a high density of cannabinoid type 1 receptors. Cannabis is comprised of two primary constituents, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). While adverse impacts are generally attributed to THC, there is emerging evidence that CBD is neuroprotective and may ameliorate such harms. We previously found that cannabis users regularly smoking cannabis containing CBD did not show typical hippocampal volumetric loss. The current study examined whether prolonged administration of CBD to regular cannabis users can reverse the characteristic brain harms associated with cannabis use.

Methods:
Eighteen regular cannabis users participated in a 10-week trial of daily administration of 200mg CBD in capsule form, with no change to their ongoing pattern of cannabis use required. Participants underwent structural magnetic resonance imaging (MRI) at baseline and post-treatment, and attended weekly monitoring sessions involving blood sample collection to assay CBD levels in plasma. T1-weighted images were processed using a novel automated longitudinal hippocampal segmentation tool available through FreeSurfer software (version 6.0). Whole hippocampal and twelve subfield volumes were quantified for left and right hemispheres separately. Paired t-tests were conducted to assess volumetric change from baseline to post-treatment.

Results:
No significant change was observed in total left or right hippocampal volume, nor in nine subfields. However, changes were detected in the subicular complex (comprising presubiculum, subiculum and parasubiculum). Left subicular complex volume showed a significant increase ($p=.017$). Heavy and light user groups (median split on cumulative lifetime cannabis exposure; range 140–8700 occasions) were further assessed. Increase in left subicular complex volume was significant in heavy ($p=.005$) but not light users ($p=.37$). In heavy users, greater increase in left subicular complex volume was significantly associated with higher CBD plasma levels during the final week of the trial ($r=.854$, $p=.030$).

Conclusions:
This study reports outcomes from the first trial of prolonged CBD administration to cannabis users. CBD treatment promoted growth in the subicular complex of the left hippocampus, despite ongoing cannabis use. Significant increase in subicular volume in heavy but not light users suggests that CBD treatment may confer greater therapeutic effects to those more heavily engaged in cannabis use. Correlations with CBD plasma levels in this group suggest a CBD treatment-specific effect on subicular growth, a subregion implicated in a range of cognitive processes. These findings support the contention that CBD may facilitate neuroprotection and recovery from cannabis related harms.

3. Decreased hippocampal responsiveness to muscarinic M1 receptor positive allosteric modulation in a sub-group of subjects with schizophrenia.

Authors: Shaun Hopper, Geoffrey Mark Pavey, Madhara Udawela, Andrea Gogos and Brian Dean

Affiliations: The Florey Institute of Neuroscience and Mental Health; Cooperative Research Centre for Mental Health; Centre for Mental Health, Swinburne University

Background:
Cholinergic muscarinic M1 receptor (CHRM1) positive allosteric modulators (PAM) are receptor specific and represent a promising schizophrenia treatment. Our data, using the CHRM1 PAM BQCA, suggest a sub-group of subjects with schizophrenia who have a marked loss of cortical muscarinic receptors (MRDS) will not respond to such treatment. Our mRNA data suggest that CHRM4, not CHRM1, is lower in the hippocampus from subjects with MRDS; we therefore hypothesized that BQCA effectiveness would not be altered in the hippocampus of MRDS subjects. To test this, we developed an auto-radiographic method to measure BQCA effectiveness in subjects with MRDS in the hippocampus.

Methods:
Frozen hippocampal tissue sections (20µm) from 40 subjects (20 MRDS and 20 subjects with schizophrenia and no decrease in cortical muscarinic receptors (non-MRDS)) and 20 matched non-psychiatric control subjects were incubated for 2 hours with [3H]nmethylscopolamine ([3H]NMS; 0.4nM) in the absence (total), and presence (non-specific) of ACh (10mM); specific binding was the difference between total and non-specific binding. We also measured [3H]NMS binding partially displaced by ACh (1mM) in the presence or absence of BQCA (3µM); the difference between these is the BQCA effect (measure of CHRM1 availability).

Results:
[3H]NMS binding was lower in schizophrenia in all sub-fields (dentate gyrus (molecular/granular layers (M/G) and polymorphic layer (PL)); cornu ammonis (CA) 1-3 (alveus layer–pyramidal layer (a-p), lacunosum moleculare–stratum radiatum (lm-r)); and the subiculum (polymorphic/pyramidal layers (PP), molecular layer (ML)); $p<0.01$ all regions) compared to control. BQCA modulation of CHRM1 was significantly lower in M/G dentate gyrus ($p<0.05$) and both layers of the subiculum (PP: $p<0.05$; ML: $p<0.05$) in schizophrenia compared to control. [3H]NMS binding ($p<0.01$ all regions) and the BQCA effect ($p<0.05$ for all regions) were lower in all sub-fields in MRDS, but not non-MRDS, compared to controls.

Conclusions:
We found decreased CHRM1 availability in the hippocampus from subjects with MRDS. These data refute our hypothesis of no decrease in CHRM1 availability in the hippocampus and suggest that the lower [3H]pirenzepine binding we have previously reported in the hippocampus of subjects with schizophrenia included, at least as a component, a decrease in CHRM1 in MRDS. This could have implications for the efficacy of allosteric modulators as treatments for some patients with schizophrenia, highlighting the need for personalised therapeutics.

4. Maternal Fluoxetine treatment alters offspring behaviour and NMDA receptor subunit profile at adolescence

Authors: Samuel J Millard, Jeremey S Lum, Francesca Fernandez, Katrina Weston-Green and Kelly A Newell

Affiliations: School of Medicine, Illawarra Health and Medical Research Institute, University of Wollongong; Australian Catholic University

Background:
8-10% of pregnancies are prescribed antidepressants, most commonly the selective serotonin reuptake inhibitor (SSRI), such as Fluoxetine. Human studies suggest that SSRI treatment during pregnancy may increase offspring risk of developing neurodevelopmental disorders. Human studies are confounded by the difficulty of separating the effects of maternal depression from the effects of SSRI exposure. In the adult brain SSRI treatment has been shown to alter functioning of NMDA receptor and associated scaffolding protein, PSD95; little is known however of the effects of SSRI exposure on the developing brain.

Methods:
The aim of this study was to evaluate the effects of maternal Fluoxetine treatment on offspring behaviours and neurobiology of relevance to neurodevelopmental disorders, using a rodent model of depression. Sprague-Dawley (SD) and Wistar-Kyoto (WKY; depression model) dams were treated with Fluoxetine (10mg/kg/day) or vehicle, from gestational day 0 until postnatal day 14. Once offspring reached adolescence, behaviour was assessed using the elevated plus maze (EPM) and forced swim test (FST) (n=10-14/group), after which brains were collected for western blot analysis.

Results:
Fluoxetine exposed offspring exhibited increased anxiety-like behaviours in the EPM, evident through decreased time spent in open arms (-90%, $p<0.001$). Additionally, Fluoxetine exposed offspring showed increases in depressive-like behaviour, evident through increases in immobility time (+28%, $p<0.05$) in the FST. Immunoblot data revealed that Fluoxetine exposed offspring exhibited reduced relative protein levels of NMDA receptor subunits, NR1 (-12%, $p<0.05$) and NR2A (-13%, $p<0.05$) in the prefrontal cortex and reduced levels of PSD95 in both the PFC (-17%, $p<0.05$) and ventral hippocampus (-18%, $p<0.05$) at adolescence. The effects of maternal fluoxetine treatment on offspring were largely independent of strain.

Conclusions:
Our results demonstrate that maternal SSRI exposure has the potential to alter the neurobiology and behaviour of exposed offspring at adolescence, irrespective of the presence of innate depressive phenotypes. Further studies in various models of maternal depression are required to confirm the findings and establish the effects of Fluoxetine exposure on the developing brain. Given the increasing number of antidepressants prescribed to pregnant women, these findings warrant further investigation.

5. Epigenetic regulation of dopaminergic neuronal differentiation by vitamin D

Authors: Renata Pertile, Xiaoying Cui and Darryl Eyles

Affiliations: Queensland Brain Institute

Background:
Histone modifications are epigenetic marks critical for neuronal development. The histone demethylase JMJD3 removes the H3K27me3 repressive mark from the chromatin of neuronal genes. This acts to promote neurogenesis and dopaminergic neuron differentiation. JMJD3 repression is a key epigenetic mechanism in early neurogenesis, which maintains cells in a stem cell fate until the proper ligand is present. We have shown previously that vitamin D alters the ontogeny of dopaminergic neurons. Intriguingly, vitamin D has been shown to increase levels of the JMJD3 gene. However, there is currently no evidence linking vitamin D with epigenetic marks relevant to dopaminergic neurons.

Methods:
We have evaluated the effect of vitamin D on the epigenetic events occurring during the differentiation of dopaminergic neurons. To this end, we used quantitative PCR to analyse the levels of expression of JMJD3, the vitamin D receptor (VDR) and tyrosine hydroxylase (TH) in our SH-SY5Y cell model in which the VDR is overexpressed. The SH-SY5Y/VDR+ cells were treated with vitamin D or a vehicle control for 48h. The expression of H3K27me3 was analysed using an immunofluorescence technique.

Results:
Our quantitative PCR results show that treatment with vitamin D increases levels of the JMJD3 gene. Furthermore, this increase correlates with increased expression of VDR and TH following the 48h treatment in SH-SY5Y/VDR+ cells. The quantification of mean fluorescence of H3K27me3 suggests that vitamin D does not reduce the overall expression of H3K27me3 in these cells. However, the cells that express high levels of VDR also appear to present lower levels of H3K27me3, as observed by the immunofluorescence intensity.

Conclusions:
These results reveal that vitamin D alters the expression of the histone demethylase JMJD3 in neurons. This further suggests that vitamin D may play a role in altering epigenetic marks in neurons, and it is a potential mechanism by which vitamin D drives the differentiation of dopaminergic neurons. Alongside previous results, these findings lead us to hypothesize that in the absence of vitamin D – in the vitamin D deficient model for instance - JMJD3 gene expression is likely to remain repressed resulting in an impairment of dopaminergic neurons differentiation.

Data Blitz 3

Tuesday, 31 Oct, 10:00 – 10:30 am

1. Withdrawal from the help of friends and family in depression: Links to plasma cortisol and oxytocin levels

Authors: Susan J Thomas and Theresa L Larkin

Affiliations: School of Medicine, Faculty of Science, Medicine and Health and the Illawarra Health and Medical Research Institute, University of Wollongong

Background:
Background: Depressed individuals often refuse or withdraw from help, a phenomenon termed help-negation, which is a risk factor for poor outcomes and suicide. Most previous research has investigated psychosocial factors including stigma as causes of help-negation, however these do not adequately explain the problem. Because help-negation worsens with symptom severity, we hypothesised that it might be linked to neurobiological changes associated with depression itself. We investigated the relative contributions of cortisol, a stress hormone linked to depression, and oxytocin, a pro-social hormone, alongside psychosocial factors, to help-seeking intentions in participants with major depressive disorder (MDD) and healthy controls.

Methods:
Methods: We quantified morning plasma cortisol and oxytocin levels, severity of psychopathology, help seeking intentions, suicidal ideation and perceived social support in 59 untreated adults meeting DSM 5 criteria for MDD, and 60 healthy controls. Cortisol and oxytocin were quantified using a Milliplex fluorescence magnetic bead immunosorbent assay. Between-group analyses of variance, correlational and hierarchical multiple regression analyses were employed.

Results:
Results: Help-seeking intentions were lower in depressed than healthy participants, negatively correlated to cortisol and symptom severity and positively correlated to oxytocin. Cortisol negatively, and oxytocin positively, predicted informal, but not formal, help-seeking intentions, after controlling for symptom severity and psychosocial factors.

Conclusions:
Conclusions: Neuroendocrine changes associated with the progression of depression may contribute to the widespread help-negation observed in MDD, particularly from informal sources such as friends and family. Approaches which incorporate biological as well as psychosocial factors may allow for novel, targeted and more effective early interventions.

2. Deficits in somatostatin and SSTR2 mRNAs in orbitofrontal cortex in schizophrenia

Authors: Tasnim Rahman, Tertia Purves-Tyson and Cyndi Shannon Weickert

Affiliations: Neuroscience Research Australia

Background:
Increased inflammatory markers are found in the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (dlPFC) in a subset of people with schizophrenia. Somatostatin mRNA is reduced in OFC and dlPFC in schizophrenia. In dlPFC, reductions of somatostatin mRNA are exacerbated in cases classified as having high inflammation. Somatostatin inhibits neurotransmission via somatostatin receptors (SSTRs) and SSTR2 mRNA is reduced in layers V and VI of dlPFC in schizophrenia. We hypothesized that schizophrenia cases will have lower SSTR2 mRNA in layers V and VI, and that cases with high inflammatory status will have exacerbated changes in somatostatin and SSTR2 mRNA.

Methods:
Previous two-step clustering of pro-inflammatory cytokine gene expression in OFC cohort yielded the following groups: low inflammation controls (control; 33 cases), low inflammation schizophrenia (SCZ-low; 27 cases), and high inflammation schizophrenia (SCZ-high; 11 cases). Somatostatin and SSTR2 mRNAs were detected by in situ hybridisation autoradiography. Laminar density values derived from the films were compared using repeated-measure ANCOVAs (covariates used: post-mortem interval, age of death, RIN).

Results:
In OFC, somatostatin mRNA was reduced in both schizophrenia groups compared to control ($F(2,59)=21.78$, $p<0.001$), where SCZ-high had less somatostatin mRNA than SCZ-low ($p<0.05$). Somatostatin mRNA was reduced in Layers I and VI of SCZ-high compared to both SCZ-low and control ($p<0.05$; lamina x group interaction effect: $F(7.13,210.17)=24.11$). Layers II-IV also had less somatostatin mRNA in both schizophrenia groups compared to control ($p<0.05$). In Layer V, somatostatin mRNA was reduced in both schizophrenia groups, however, was lower in the SCZ-high compared to SCZ-low ($p<0.05$). SSTR2 mRNA was reduced in both schizophrenia groups compared to control ($p<0.01$; $F(2,67)=8.40$) across all lamina.

Conclusions:
This study indicates that reductions in somatostatin mRNA are more likely to occur in deep cortical lamina in high inflammatory schizophrenia cases, but that reductions in somatostatin mRNA in superficial lamina are found in people with schizophrenia regardless of inflammatory status. SSTR2 mRNA reductions extend to the OFC, however they do not appear to be exaggerated in schizophrenia cases that have elevated inflammatory markers. We conclude that people with schizophrenia may have reduced somatostatin-mediated inhibitory neurotransmission in the OFC regardless of the current state of neuroinflammation, and that increased inflammation may exacerbate this deficit by decreasing somatostatin gene expression.

3. Maternal vitamin D treatment reverses maternal immune activation induced alterations in mesencephalic neurogenesis

Authors: Wei Luan, Luke A Hammond, Urs Meyer and Darryl W Eyles

Affiliations: Queensland Brain Institute, University of Queensland; Institute of Pharmacology and Toxicology, University of Zurich-Vetsuisse, Zurich.

Background:
Dopamine dysregulation is a feature present in the majority of patients with schizophrenia. We propose the aberrant ontogeny of mesencephalic dopamine (mesDA) systems as a common causal pathway for the pathogenesis of schizophrenia. We aim to test whether maternal administration of vitamin D could rescue the aberrant dopamine neurodevelopment induced by maternal immune activation (MIA) using double-strand viral mimic RNA (polyinosinic : polycytidylic acid, poly (I:C)).

Methods:
We administrated poly (I:C) or saline, and the active hormone form of vitamin D (1,25OHD) or its vehicle (corn oil) to pregnant C57BL/6 mouse dams at gestational day (GD) 9. Two days later, GD11, we assessed mesDA neurodevelopment using immunochemistry and automated image analysis of CellProfiler software. Four mesDA factors were employed for immunohistochemical analysis, including LIM homeobox transcription factor 1 alpha (Lmx1a), SRY-related HMG-box2 (Sox2), nuclear receptor related 1 protein (Nurr1), and tyrosine hydroxylase (TH). Four subgroups of early mesDA cells were therefore analyzed: mesDA progenitors, post-mitotic mesDA neurons, immature and mature mesDA neurons.

Results:
The results revealed that MIA and 1,25OHD treatment reduced mesDA progenitors (Lmx1a+Sox2+), however, 1,25OHD treatment increased mature mesDA neurons (Nurr1+TH+). Single-cell quantification showed that 1,25OHD treatment increased the expression of Lmx1a, Nurr1 and TH in individual mesDA cells, but not of Sox2. MIA treatment instead had no obvious effects on the expression of these factors.

Conclusions: In conclusion, our data demonstrates the neuroprotective effects of 1,25OHD on early mesDA neurogenesis possibly via its upregulation of mesDA factors, counteracting against the acute negative effects of MIA treatment.

4. Network-based cortical thinning in treatment resistant schizophrenia

Authors: Cassandra Wannan, Cali Bartholomeusz, Vanessa Cropley, Chad Bousman, Eleni Ganella, Ian Everall, Christos Pantellis and Andrew Zalesky

Affiliations: Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health; Orygen, the National Centre of Excellence in Youth Mental Health; the Centre for Youth Mental Health, University of Melbourne; Brain and Psychological Sciences Research centre, Swinburne University; The University of Melbourne, Department of General Practice; the Cooperative Research Centre (CRC) for Mental Health; Florey Institute for Neurosciences and Mental Health; Centre for Neural Engineering, University of Melbourne.

Background:
Evidence suggests that that brain regions with the most extensive cortical thinning in schizophrenia are strongly connected. However, unlike early and established schizophrenia, few studies have examined cortical thickness in TRS, and none have examined this from a network perspective. The current study aimed to (i) characterise cortical thinning in TRS, and (ii) examine whether the strength of cortico-cortical connections was greater between brain regions showing significant cortical thinning in individuals with TRS.

Methods:
Cortical thickness was compared in 148 brain regions between 47 individuals with TRS and 54 healthy controls. The average structural connectivity strength between pairs of regions with significant cortical thinning in patients was computed and then compared with the average structural connectivity in 5000 groups of randomly chosen regions in patients and controls. Corticocortical connectivity in regions of reduced thickness was then compared between TRS patients and healthy controls.

Results:
Cortical thickness was reduced in 106 out of 148 brain regions in TRS patients, with the greatest reductions observed in frontal, temporal, cingulate, and insular regions (false discovery rate-corrected $p < .05$). Both TRS patients and healthy control subjects showed significantly greater structural covariance in cortical regions that were thinner in TRS patients, compared to randomly selected regions ($p < .00001$). TRS patients also had significantly stronger structural covariance than healthy control subjects in regions of reduced thickness ($p < .00001$).

Conclusions:
These findings support the notion of network-based cortical thinning in the disorder, with regions of reduced thickness demonstrating greater structural connectivity not only in TRS individuals, but also in healthy people.

5. Changes in peripheral immune cell trafficking molecules in schizophrenia

Authors: Helen Q Cai, Thomas W. Weickert, Vibeke S. Catts, Maryanne O'Donnell, Cherrie Galletly, Dennis Liu and Cynthia Shannon Weickert

Affiliations: Schizophrenia Research Laboratory, Neuroscience Research Australia; School of Psychiatry, University of New South Wales; Discipline of Psychiatry, School of Medicine, University of Adelaide; Northern Adelaide Local Health Network.

Background:
Irregular inflammatory processes such as endothelial dysfunction have been implicated in the pathophysiology of schizophrenia. Intercellular adhesion molecule (ICAM1), a marker of endothelial dysfunction with a role in immune cell trafficking, is upregulated in post-mortem brains of schizophrenia patients. However, less is known about the expression of ICAM1's cognate ligands, lymphocyte function-associated antigen-1 (LFA1) and macrophage-associated antigen-1 (MAC1), which are expressed on white blood cells, in schizophrenia.

Methods:
White blood cell mRNA expression of ICAM1, LFA1 and integrin alpha M (ITGAM), which encodes a crucial subunit of MAC1, were measured with quantitative PCR using Fluidigm Biomark HD™ in 86 patients with schizophrenia and 77 healthy controls. Soluble ICAM1 was also measured in plasma from 78 patients with schizophrenia and 73 healthy controls using a Luminex immunoassay. Further, white blood cell counts available from patients were used to determine any associations between the ligands and specific white blood cell populations.

Results:
LFA1 mRNA was reduced by 11.4% in patients with schizophrenia ($t(155) = 3.396$, $p < 0.01$), whereas ITGAM mRNA was elevated by 13.5% in patients with schizophrenia compared to controls ($t(153) = -3.287$, $p < 0.01$). ICAM1 mRNA was unchanged ($t(156) = -1.526$, $p = 0.129$), however sICAM1 protein was higher in plasma of patients with schizophrenia by 29.2% ($t(140) = -3.988$, $p < 0.01$). Neutrophil counts were positively correlated with ITGAM ($r = 0.58$, $p < 0.01$) and negatively correlated with LFA1 ($r = -0.46$, $p < 0.01$) in patients.

Conclusions:
No change in ICAM-1 mRNA expression in WBC, but increased sICAM-1 protein in plasma may suggest increased shedding of sICAM-1 from cells as part of immune response regulation. Different immune cell populations may be trafficked into tissue as the ICAM1 ligands ITGAM and LFA1 expressions are changed in opposite directions in schizophrenia. Schizophrenia may be associated with altered immune cell trafficking.

Poster Session 1

Monday, 30th Oct, 1:30 – 2:30 pm

P1. The effect of oestrogenic compounds on psychosis-like behaviour in female Long Evans rats

Authors: Alyssa Sbisa, Maarten van den Buuse and Andrea Gogos

Affiliations: Florey Institute of Neuroscience and Mental Health; La Trobe University

Background:
17β−estradiol (17β) treatment has shown benefit for schizophrenia symptoms, however long-term use may be associated with negative side effects. Selective estrogen receptor modulators (SERMs), such as raloxifene (RAL) and tamoxifen (TAM), have been proposed as suitable alternatives to 17β. An isomer of 17β, 17α-estradiol (17α), is considered less carcinogenic, and non-feminising in males, however little is known about its potential as a treatment for schizophrenia. However, the mechanism underlying the therapeutic action of SERMs and 17α remains unclear. We aimed to investigate the ability of these estrogenic compounds to attenuate acute pharmacological models of psychosis.

Methods:
We measured two widely used behaviours: psychotomimetic drug-induced hyperlocomotion and disruption of prepulse inhibition (PPI). Female Long Evans rats were either intact SHAM, ovariectomised (OVX), or OVX and chronically treated with 17β, 17α, RAL or TAM.

Results:
Only 17β treatment attenuated locomotor hyperactivity induced by methamphetamine. 17β -treated rats were also protected against methamphetamine- and apomorphine-induced disruption of PPI. The other estrogenic compounds had mixed or lesser effects. TAM-treated rats were protected against methamphetamine- and apomorphine-induced PPI disruption, however RAL-treated rats were only protected against apomorphine-induced disruption. Baseline PPI was significantly reduced following OVX, and this deficit was reversed by all estrogenic compounds. Further, PPI in OVX rats was increased following administration of apomorphine.

Conclusions:
This study confirms a protective effect of 17β in two psychosis-like behaviours in rats, while TAM showed beneficial effects against PPI disruption. In contrast, 17α and RAL showed little effect on attenuating dopaminergic-induced psychosis-like behaviours.

P3. Maternal fluoxetine treatment increases mGluR5 expression in the amygdala of adolescent offspring

Authors: Kimarnie Baskerville, Samuel J Millard, Jeremy S Lum and Kelly A Newell

Affiliations: School of Medicine, University of Wollongong; Illawarra Health and Medical Research Institute

Background:
Approximately 10% of pregnant woman are prescribed antidepressant drugs such as the selective serotonin reuptake inhibitor (SSRI), Fluoxetine (Prozac), for the treatment of depression. Emerging evidence suggests maternal fluoxetine treatment increases the risk of neurodevelopmental disorders in offspring, however the neurobiological underpinnings remain unclear. We have previously found evidence of an increase in anxiety-related behaviour in fluoxetine-exposed offspring, using a rodent model. Due to the role of mGluR5 signalling in the amygdala in modulating fear and anxiety, this study aimed to assess whether mGluR5 protein expression in the amygdala is altered following prenatal fluoxetine exposure.

Methods:
Wistar-Kyoto (established model of depression) and Sprague-Dawley (healthy model) rodent dams were treated with 10mg/kg/day fluoxetine from gestational day 0 to postnatal day 14. Brains of male offspring were collected at adolescence (postnatal day 42) and the amygdala dissected. Relative mGluR5 protein levels were measured via immunoblotting under non-reducing conditions to promote mGluR5 dimer integrity. Raw values were normalized to β-actin and a pooled sample to account for gel-gel variability.

Results:
Immunoblots revealed 3 distinct bands for mGluR5 dimer (250-260kDa), and one distinct band for both mGluR5 monomer (150kDa) and β-actin (37-50kDa). Maternal fluoxetine treatment increased mGluR5 dimer (+13.5%; $p=0.009$) and monomer (+31.4%; $p=0.053$) in the amygdala of adolescent offspring compared to vehicle exposed offspring. There were however no effects of rat strain on mGluR5 and no strain x treatment interactions.

Conclusions:
These findings suggest that antidepressant treatment during pregnancy alters glutamatergic proteins in the amygdala of adolescent offspring. Considering the role of mGluR5 in the amygdala, these changes may contribute to the anxiety-like phenotype observed in fluoxetine-exposed offspring.

P5. Maternal immune activation induces changes in microglia IBA1+ immunoreactivity in the white matter of the corpus callosum of adult rats

Authors: Ryan Duchatel, Crystal Meehan, Lauren Harms, Patricia Michie, Mark Bigland, Doug Smith, Rohan Walker, Phillip Jobling, Deborah Hodgson and Paul Tooney

Affiliations: University of Newcastle

Background:
Prenatal immune challenge is an environmental risk factor for the development of psychiatric illnesses including schizophrenia. Modelling this epidemiological link in animals shows that maternal immune activation (MIA) is capable of inducing long-lasting deficits in brain structure, function and behaviour in the offspring. Microglia activation and cytokine upregulation have been proposed to play key roles in the neuropathology of schizophrenia. We hypothesised that MIA induces changes in microglia and cytokines in the brains of the adult offspring.

Methods:
MIA was produced by injecting PolyI:C into pregnant Wistar rats on GD 10 or GD19; brain tissue from the offspring was collected 12 weeks of age. Iba1, Gfap, TNF-α and IL-1β mRNA levels in the cingulate cortex were determined by quantitative RT-PCR from fresh frozen tissue of adult offspring of GD10 and GD19 PolyI:C dams compared to controls. Microglia IBA1+ immunoreactive material (IBA1+-IRM) / astrocyte GFAP+-IRM was measured in offspring of GD10 or GD19 PolyI:C dams compared to pooled controls in the cingulate cortex (C-CTX) and white matter of the corpus callosum (CC) using immunohistochemistry and cumulative threshold analysis.

Results:
There was no change in Iba1, Gfap, IL-1β and TNF-α mRNA levels in the C-CTX in offspring exposed to MIA. Whilst MIA had no effect on IBA1+-IRM in C-CTX, a significant main effect on IBA1+-IRM was observed in the CC, with post-hoc analyses identifying a significant increase in IBA1+-IRM at GD19 ($p = 0.017$), but not GD10. MIA had a significant main effect on GFAP+-IRM in the CCTX, with post-hoc analyses identifying a strong trend towards increased GFAP+-IRM in the offspring of GD19 PolyI:C ($p = 0.054$), but not GD10 PolyI:C dams. No change in GFAP+-IRM was observed in the CC.

Conclusions:
These findings suggest that late gestation MIA is capable of causing subtle alterations to microglia and astrocytes. How these findings relate to the pathophysiology of schizophrenia requires further investigation.

P7. Early antipsychotic treatment in juvenile rats elicits long-term alterations to the adult serotonin receptors

Authors: Michael De Santis, Xu-Feng Huang and Chao Deng

Affiliations: Illawarra Health and Medical Research Institute; School of Medicine, University of Wollongong

Background:
Antipsychotic drug prescription and use in children has increased significantly over the past decade. This is despite a lack of insight into potential long-term effects of treatment during this critical neurodevelopmental time period on adult brain functioning. Whilst initial studies have uncovered long-term alterations to adult behaviours following early antipsychotic treatment, further investigations into potential changes to neurotransmitter systems are necessary. The current investigation utilised an established animal model for early antipsychotic treatment with aripiprazole, olanzapine and risperidone in male and female juvenile rats, to investigate potential long-term changes to the adult serotonin (5-HT) neurotransmitter system.

Methods:
Male and female juvenile rats (n=6/group) were treated with aripiprazole, olanzapine and risperidone from postnatal day (PD) 22-50 equating to the human childhood-adolescent time period. Adult animals were then sacrificed on PD106. Levels of 5-HT1A, 5-HT2A and 5-HT2C receptors were measured in the prefrontal cortex (PFC), caudate putamen (CPu), nucleus accumbens (NAc) and hippocampus via western blot and receptor autoradiography.

Results:
In the male cohort, aripiprazole decreased 5-HT2A levels in the PFC and hippocampus, whilst 5-HT2C was decreased in the PFC, and increased in hippocampus. Olanzapine decreased 5-HT2A levels in the hippocampus and 5-HT2C levels in the PFC, whilst risperidone decreased 5-HT1A levels in the PFC and NAc and 5-HT2A levels in the PFC and hippocampus, whilst increased 5-HT2C levels in the hippocampus. Analysis of the female cohort uncovered lesser effects, with decreased 5-HT1A levels following aripiprazole treatment in the NAc and 5-HT2A levels in the hippocampus following olanzapine treatment, whilst early risperidone treatment decreased 5-HT2A levels in the hippocampus.

Conclusions:
These results suggest that early treatment of various antipsychotics in juvenile rats may cause gender and brain regional specific changes in 5-HT2A and 5-HT2C receptors in the adult brain.

P9. Variation in laboratory housing conditions impacts on drug-induced locomotion in rats

Authors: Suzy Alexander, Emilia Lefevre, Darry Eyles and Thomas H.J. Burne

Affiliations: Queensland Brain Institute, University of Queensland

Background:
Variations in housing conditions are known to impact on rodent behaviour. In particular, the use of MK-801 to elicit a locomotor response is particularly sensitive to environmental conditions, with alterations in response induced by stress, novelty, dietary manipulations, prior handling, arena size and prior exposure to some anaesthetic agents. With so many environmental variables altering the response of MK-801 induced locomotion our aim was to identify the impact of exposure to unexpected laboratory conditions during repeated testing in adult rats.

Methods:
We used adult Sprague Dawley rats tested in 2 different sized open fields and collected locomotor data using Ethovision video tracking during 1) habituation to a novel field (45cm x 45cm) and after saline or MK-801, or 2) immediately following administration of saline or MK-801, in a 60cm x 60cm open field. We retrospectively coded data for different laboratory conditions. These conditions included exposure to other rat injection procedures prior to testing and a refurbishment event in the animal facility.

Results:
For Experiment 1, rats exposed to other rats receiving IP injections prior to testing led to an increase in MK-801 induced locomotion, compared to non-exposed rats from the same group, on the day of exposure and again 24 hours later. This exposure had no effect on saline-treated rats or on the initial 30-minute habituation to the open field on either day.
For Experiment 2, female rats exposed to the refurbishment of an adjacent room in the animal facility had decreased MK-801 induced locomotor responses compared to their non-exposed equivalents, while male rats treated with saline had decreased locomotor responses compared with their performance 14 days prior to commencement of refurbishment.

Discussion:
Reporting housing conditions has become more standardised in rodent behaviour but additional laboratory variables can have a large impact on behaviour. These results suggest that both baseline performance and drug-induced locomotion is susceptible to environmental laboratory conditions.
If possible, minimising alterations in environmental laboratory conditions would be ideal but is sometimes unavoidable. Minimising administering rat injection procedures around other rats or avoiding testing during refurbishment events would be highly recommended. However, even using control animals matched for time of day may underestimate the effect of unforeseen conditions on behavioural outcomes. We conclude that clear documentation and consideration of any change in environmental conditions may account for, or help reduce the variability in behavioural data.

P11. The effect of chronic antidepressant treatment on NMDA, AMPA and Group I mGlu receptors in the cingulate cortex

Authors: Emily Szafranek*, Rebecca Webby*, Jeremy Lum, Nicholas Storr, Jessica Nealon and Kelly A Newell
*: Equal contribution

Affiliations: School of Medicine, University of Wollongong; Illawarra Health and Medical Research Institute

Background:
Antidepressant drugs (ADD) target monoaminergic neurotransmitter systems, but typically require 3-4 weeks for therapeutic response. Emerging evidence suggests downstream effects on the glutamatergic system, particularly the NMDA, AMPA and Group I metabotropic (mGluR1, mGluR5) glutamate receptors, could be central to the antidepressant effects. In line with this, antagonists or negative allosteric modulators (NAMs) of mGluR5 have shown promise for the rapid treatment of depression in animal models. This study aimed to determine whether chronic antidepressant drug treatment influences mGluR5, NMDA and AMPA protein expression and how this compares to an mGluR5 NAM.

Methods:
Adult female Sprague-Dawley rats were treated with the ADDs fluoxetine (10mg/kg; a selective serotonin reuptake inhibitor), imipramine (10mg/kg; a tricyclic antidepressant), MPEP (3mg/kg; an mGluR5 NAM) or vehicle (saline) for 5 weeks. Their brains were collected and cingulate cortex dissected. Immunoblot analyses were performed to determine the level of expression of mGluR1, mGluR5, NR1 (the obligatory NMDA subunit) and the AMPA GluA1 subunit (n=6/group).

Results:
Fluoxetine and Imipramine treatment both caused an increase in mGluR1 monomers compared to control treated rats (+63% and +37% respectively; $p<0.05$) and a reduction in mGluR1 dimers (-33% and -30% respectively; $p<0.05$) following 5 weeks of treatment, while MPEP treated rats showed no change in mGluR1 protein. Fluoxetine treatment additionally increased mGluR5 monomers (+220%; $p<0.0\%$), but not dimers, compared to control treated rats. There were no effects of fluoxetine, imipramine or MPEP treatment on NR1 or GluA1 protein expression in the cingulate cortex.

Conclusions:
These results reveal that the ADDs fluoxetine and imipramine both alter the expression of mGluR1 in the cingulate cortex, after a period of chronic treatment and suggest that traditional antidepressant drugs may mediate their effects via changes to Group 1 mGluRs in this region. Further investigation into how these molecular changes relate to depressive-like behaviours and whether these changes extend to other relevant brain regions such as the hippocampus will be important to characterise their mechanism of action and define more effective and rapid treatment targets for depression.

P13. Stress induced behavioural deficits ameliorated by ganaxolone therapy in male guinea pig offspring

Authors: Gabrielle K. Crombie, Hannah K. Palliser, Julia C. Shaw, Debra M. Hodgson, David W. Walker and Jonathon J. Hirst

Affiliations: School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle; Hunter Medical Research Institute, Mothers and Babies Research Centre; School of Psychology, University of Newcastle; School of Health and Biomedical Science, RMIT University.

Background:
Neurosteroids promote neuronal survival and myelination in the developing brain. Perinatal stress, and associated neurosteroid disruption, is known to impair neurodevelopment and lead to behavioural disorders. Human studies have shown a relationship between early life stress and attention deficit hyperactivity disorder (ADHD) in offspring. ADHD is characterised by symptoms of inattention, hyperactivity and impulsivity. We propose that disturbances in the maturation of the GABAergic system, through perinatal stress, may promote excitation which can have damaging effects on the immature brain and lead to these disorders. Additionally, we propose that replacement of neurosteroids in early life will reduce these adverse outcomes.

Methods:
Guinea pig pups were exposed to prenatal stress (maternal strobe light exposure for 2hrs a day on GA50, 55, 60 and 65; term 71days), postnatal stress (maternal separation for 2hrs on postnatal days 2-8) or a combination of both stressors (dual stress). Pups were administered ganaxolone, a synthetic allopregnanolone analogue, twice daily (5mg/kg) on days 2-8. Pups underwent open field and elevated plus maze behavioural assessment on day 9, to assess for hyperactive behaviour. Brains were collected on day 30 for quantification of GABAA subunit receptor mRNA expression by real time PCR and mature myelin by MBP immunostaining.

Results:
Male guinea pigs exposed to perinatal stress displayed an increase in hyperactive behaviour at 9 days of age. This hyperactive behaviour was observed as increased speed travelled, and increased entries into, and distance travelled, in the inner zone of the open field arena. These males also displayed increased locomotion in the open field and elevated plus maze behavioural test. Ganaxolone administration in the first week of life returned behavioural parameters of the dual stress group toward that of control guinea pigs. GABAAR subunit mRNA expression was increased and mature myelination decreased in the hippocampus of males exposed to prenatal stress.

Conclusions:
Perinatal stress leads to changes in GABAergic pathways that may contribute to reduced myelination, altered GABAA subunit expression and behavioural deficits in the exposed offspring. Neurosteroid supplementation using ganaxolone treatment following dual stress ameliorates later hyperactive behaviour in male offspring.

P15. The effects of handling techniques on the behavioural phenotype of a genetic mouse model for schizophrenia

Authors: Stefan Guerra, Cynthia Shannon Weickert and Tim Karl

Affiliations: School of Medicine, Western Sydney University; School of Psychiatry, University of New South Wales; NeuRA, Randwick, Australia.

Background:
Handling of laboratory mice has a noticeable effect on both the wellbeing of the test animal and the reliability of experimental test results. So far, handling studies have been limited to common strains of laboratory mice. However, it is of utmost importance to assess handling effects in genetic mouse models for human diseases. Here, we determined the impact of two types of handling (e.g. tail versus tube handling) on the face validity of a newly established transgenic mouse model for the schizophrenia risk gene neuregulin 1 (i.e. type III Nrg1 overexpressing mice; Nrg1 III tg).

Methods:
Nrg1 III tg and wild type-like littermate control mice of both sexes are initially assigned to either handling group, those being the standard tail handling method or the use of a PVC tunnel. Animals are exposed to tail / PVC handling for 10 days before behavioural testing commences. A comprehensive battery of test paradigms with relevance to schizophrenia is applied: open field, elevated plus maze, social preference, prepulse inhibition and fear conditioning tests. Mice are also handled with their assigned method between test days as so the effects does not diminish over the full test period.

Results:
This project is currently ongoing and testing will be completed by early October.

Conclusions:
Results will have been analysed by mid-October.

P17. The time-dependent effects of olanzapine treatment on the gluco-metabolic disorders and hepatic AKT/GSK3β/PPARα pathway in rats

Authors: Jiamei Lian, Xu-Feng Huang and Chao Deng

Affiliations: School of Medicine, University of Wollongong; Illawarra Health and Medical Research Institute

Background
Olanzapine is effectively to treat schizophrenia and other mental disorders. However, it is associated with gluco-metabolic side-effects; however the underlying pathogenesis mechanisms are still largely unknown. The peroxisome proliferator-activated receptor (PPAR) is associated with the type II diabetes and metabolic symptoms including obesity and insulin resistance. PPARα is believed to participate in fatty acid uptake, balancing glucose homeostasis, mainly in the liver. The glycogen synthase kinase 3β (GSK-3β) activity is attenuated after phosphorylation by AKT, which contributes to the insulin stimulated glucagon synthesis. Therefore, the aim of this study was to investigate the time-dependent effects of olanzapine on gluco-metabolic side effects and hepatic mechanisms in a rat model.

Methods
Female Sprague Dawley rats (201-225g) were administered with olanzapine (2 mg/kg， t.i.d.) for 2,3,4,5,7,9 weeks. Plasma was taken for insulin, glucose and lipid analysis by ELISA or a KoneLab analyser. Protein levels were examined by Western Blot.

Results
Olanzapine significantly increased body weight gain, food intake, liver weight, white fat pad. Olanzapine significantly altered the plasma glucose, insulin, cholesterol, non-esterified fatty acid levels compared to controls in a time-dependent manner. Furthermore, the activation of hepatic PPARα, AKT and GSK-3β phosphorylation were also observed by olanzapine administration, with time-dependent difference.

Conclusions
Therefore, this study suggested that olanzapine induced gluco-metabolic disorders, at least partially attributed to the hepatic AKT/GSK/PPARα signalling pathway.

P19. Manipulation of developing dopamine neurons in mice with targeted SiRNA transfection

Authors: James P. Kesby, Wei Luan and Darryl W. Eyles

Affiliations: Queensland Brain Institute, The University of Queensland, Queensland Centre for Mental Health Research, The Park Centre for Mental Health.

Background:
Schizophrenia is a chronic psychiatric disorder with a poorly understood aetiology. Dopamine is a neurotransmitter that has been implicated in the cause and treatment of schizophrenia. Thus, understanding the consequences of altered dopamine neuron development represents a core developmental drug target in schizophrenia. We are using in utero electroporation for the transfection of siRNA into developing dopamine neurons in mice.

Methods:
Pregnant mice were anaesthetised and the uterine horns exposed. A reporter plasmid encoding a yellow fluorescent protein (pCAGeYFP, 1.5 ug) and siRNA targeted against dopamine specification/differentiation factors was injected into the mesencephalic ventricle of E11 mice embryos. Electroporation was accomplished using a triple electrode configuration. Five electrical pulses (amplitude, 30 V; duration, 50 ms; intervals, 950 ms) were administered. Embryos were harvested at E13 and expression of target factors were determined using quantitative immunofluorescence.

Results:
Our data demonstrates the feasibility of this technique to target dopamine progenitors in the ventral mesencephalon. Moreover, we will present evidence demonstrating the specific downregulation of dopamine target factors by transfection of siRNA into dopamine progenitors.

Conclusions:
These data suggest that the transient manipulation of factors at early stages of dopamine neuron development is possible with the use of in utero electroporation. This work will allow us to gain a better insight into the role of specific differentiation factors in dopamine neuron development.

P21. Modelling an autism risk factor in rats, the impact of perinatal immune challenges on gastrointenstinal inflammation and integrity

Authors: Sharon Hollins, Luke Brock, Rafael Barreto, Patricia Michie and Deborah M. Hodgson

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Background:
Autism Spectrum Disorder (ASD) often presents with numerous comorbidities correlated to its severity, including immune system and gastrointestinal (GI) disorders. Research suggests these abnormalities may be involved in the aetiology, pathogenesis and pathophysiology of ASD, however, the biological pathways involved are unknown Given that animal models of maternal immune activation (MIA) have demonstrated ASD-like peripheral and neural findings, if analogous GI integrity and immune phenotypes were also demonstrated, the model presents itself as a potential tool to investigate the etiology, pathogenesis and pathophysiology of ASD gut-brain interactions, potentially presenting the GI tract as a target for novel psychiatric treatment options.

Methods:
Pregnant rats were exposed to PolyI:C (MIA) at gestational day (GD) 10 and 19. A segment of colon was extracted from offspring on postnatal days (P) 7 and 84 and tissue was examined for expression of tight junction protein and proinflammatory cytokine mRNA. A segment of the jejunum and distal ileum was removed from P7 offspring for histological studies. Cross-sections were selected and embedded in paraffin. Full- thickness sections of 5 µm were obtained at different levels and stained with haematoxylin and eosin. The histological damage was evaluated by a pathologist observer, who was blinded to the experimental groups.

Results:
P7 MIA offspring exhibited alterations in tight junction proteins as well as proinflammatory immune markers. P84 offspring exhibited subtle alterations in tight junction proteins however no alterations in inflammatory markers were observed. Specifically, MIA offspring exhibited significantly reduced expression of the proinflammatory immune marker Interleukin 6 (IL-6) at P7 but not P84. Increased expression of tight junction proteins Tight Junction Protein 1 (TJP1), Tight Junction Protein (TJP2) and Occludin (OCLN) were observed at P7, while decreased expression of TJP2 was observed at P84. Histological evaluation showed no architectural damage or signs of inflammation in P7 MIA offspring.

Conclusions:
We found that MIA alters the expression of pro-inflammatory cytokines and GI tight junction proteins during early development, with alterations diminishing throughout adulthood. These findings suggest that perinatal immune challenge can have a significant impact on neonatal GI inflammation and integrity. Changes in expression of intestinal tight junction protein and IL-6 mRNA at P7 suggest MIA may lead to early changes in brain-gut signalling. Although histological evaluation showed no signs of architectural damage or inflammation, our results suggest this animal model may provide a useful tool to investigate gut-brain axis deficits underlying the GI and immune aberrations seen in ASD.

P23. Olanzapine decreased hypothalamic POMC expression via H1R and 5-HT2CR antagonism

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Background:
olanzapine decreases energy expenditure and increases food intake while the mechanism is not fully understood. Hypothalamic POMC plays an important role regulating both energy expenditure and intake. Using hypothalamic POMC-GFP neurons, this study investigated the effect of olanzapine on POMC expression with/without H1R and 5-HT2CR agonists.

Methods:
Methods: We have used hypothalamic POMC-GFP cell line in this study. First, we tested the effect of 50 µM olanzapine in inhibition of POMC expression. We tested the effect of olanzapine under the condition of no, low and high glucose treatment. Then the cells were treated with olanzapine+FMPH, olanzapine + lorcaserin and controls including FMPH and lorcaserin only. After 6 hours of various concentrations of treatments, cells were collected and analysed by flowcytometry and flexstantion.

Results:
Results: (1) We found that 50 µM olanzapine reduced POMC expression by 30% in 6 hours. No difference of POMC expression was detected under various glucose concentrations. (2) Secondly, we found that olanzapine can decrease 50% of POMC expression. (3) Thirdly, FMPH (a H1R agonist) and lorcaserin (a 5 HT2CR agonist) increased POMC expression by 30% and 70%, respectively. (4) Furthermore, olanzapine-induced inhibitory effect on POMC can be reversed by FMPH and lorcaserin.

Conclusions:
Conclusions: This study indicated that olanzapine reduced hypothalamic POMC expression via both H1R and 5-HT2CR antagonism. Either H1R or 5-HT2CR agonist could partially reverse the inhibitory effect of olanzapine-induced down-regulation of hypothalamic POMC expression.

P25. D2 Receptor hyperactivity increases D2R-DISC1 interaction and impairs neurite growth in the prefrontal cortex

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Background:
D2 receptor (D2R) hyperactivity and DISC1 dysfunction are associated with psychosis and neuronal development. Although both in vivo and in vitro studies connected DISC1 to the dopaminergic system, the actual role of DISC1 in mediating D2R signalling was not elucidated. This study was to investigate if the D2R-DISC1 complex formation induced by D2R over-activation has morphological effects in cortical neurons.

Methods:
(1) We cultured primary prefrontal cortical neurons from DISC1 locus impairment (LI) mice and wild type mice (WT) at postnatal day 0; (2) After 7 days of culturing, the neurons were treated with D2R agonist (quinpirole, 100uM) or pre-treated with partial agonist (aripiprazole, 10 uM) or antagonist (haloperidol, 10 uM); (3) Fluorescence resonance energy transfer (FRET) was applied to examine protein interaction; (4) Western blot was used to quantify protein expression. (5) HEK 293 cells transfected with D2R-EGFP and DISC1-mCherry plasmids were used to study DISC1 interaction.

Results:
This study showed that (1) Over activation of D2R by high dosage of quinpirole inhibited neurite growth of primary prefrontal neurons of DISC1 LI and WT mice; (3) GSK3β phosphorylation was decreased in the prefrontal cortical neurons of DISC1 LI mice, while quinpirole further reduced it; (4) D2R agonist quinpirole induced increasing interaction of D2R and DISC1 in prefrontal cortical neurons; (5) Haloperidol and aripiprazole were unable to reverse neurite impairment induced by quinpirole in DISC1 LI mice in which D2R-DISC1 complex was fully abolished; (6) Quinpirole increased DISC1-mCherry aggregation and promoted the transfer of aggregates in HEK 293 cells.

Conclusions:
In this study, over-activation of D2R increased D2R-DISC1 complex formation and inhibited neurite growth in the prefrontal cortical neurons. Further, D2R-DISC1 complex is involved in the therapeutic effects of antipsychotic drug haloperidol and aripiprazole on neurite growth and GSK3β phosphorylation. This study suggests that DISC1 aggregation induced by D2R over-activation may be related to neuronal development. Thus, manipulation of D2R and DISC1 complex formation might be a novel therapeutic target for improving neuronal connection.

P27. Elevated Peripheral C-reactive Protein Levels in People with Schizophrenia

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Background:
There is increasing evidence implicating a pathogenic role of inflammation in schizophrenia: a severe psychiatric disorder for which no biomarkers currently exist. An elevated level of C-reactive protein (CRP) in the blood serum and plasma is commonly used as a marker for systemic inflammation. While most studies of peripheral CRP in schizophrenia report increased levels, there are conflicting results in the field. We analysed CRP levels in two distinct cohorts and hypothesized that CRP would be elevated in people with schizophrenia compared to healthy controls within both cohorts.

Methods:
Blood was collected from patients and controls in two different cohorts. In the "CASSI" cohort plasma was collected from the blood of healthy controls (n=97) and patients with schizophrenia and schizoaffective disorder (n=87) from Sydney and Adelaide. In a separate cohort, the "ASRB" cohort, serum from healthy controls (n=644) and people with schizophrenia (n=374), schizoaffective disorder (n=58) or atypical psychosis (n=44) was received from the Australian Schizophrenia Research Bank (ASRB). CRP levels were quantified using CRP High-Sensitivity ELISA from IBL International and analysed in IBM SPSS Version 24.

Results:
In the CASSI cohort, CRP levels in plasma were significantly higher in people with schizophrenia compared to controls (Mann- Whitney U=1439, $p<0.0001$; means schizophrenia 3.41 mg/L, control 1.79 mg/L). Serum CRP levels were also significantly higher in people with schizophrenia compared to controls in the ASRB cohort (Mann-Whitney U=104889.5, $p<0.0001$; means schizophrenia 3.33 mg/L, controls 1.80 mg/L). Within both schizophrenia and control groups from the ASRB cohort, CRP levels were significantly higher in females than males. Findings of increased CRP in the schizophrenia group remained significant when we co-varied for gender.

Conclusions:
Our findings support the growing literature demonstrating a strong link between inflammation and schizophrenia. The data suggests that CRP levels may be used as a potential biomarker for people with schizophrenia and suggests future investigations into the benefits of adjunctive anti-inflammatory treatments.

P29. The association between systolic blood pressure variability with depression, cognitive decline and white matter hyperintensities: the 3C Dijon MRI study

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Background:
Accumulating evidence links blood pressure variability (BPV) with white matter hyperintensities (WMH) and stroke. The longitudinal association between BPV with late onset depression and cognitive decline remains unexplored.

Methods:
Prospective cohort study of 2812 participant's age ≥ 65 years (median age 72 years, 63.6% female) without dementia or stroke. Serial clinic visits assessed blood pressure, cognitive function, depression disorder, and depressive symptoms. A brain magnetic resonance imaging (MRI) substudy was performed in 1275 persons to examine possible associations with WMH.

Results:
The interaction between symptomatic late onset depression and systolic BPV was associated with cognitive decline on the Isaac Set Test (β -4.45; 95% CI -8.92 to -.16, p = .04), Benton Visual Retention Test (β -.89; 95% CI -1.77 to -.01, p = .049), Mini Mental State Examination (β - 1.08; 95% CI -1.86 to -.30, p = .007) and Finger Tapping Test (β -7.53; 95% CI -13.71 to -1.34, p = .017) . The MRI substudy demonstrated that systolic BPV was associated with cognitive decline via interactions with depression and total WMH volume.

Conclusions:
The findings show that the interaction between systolic BPV with symptomatic depression and WMH increases cognitive decline in persons ≥ 65 years of age. Future work could extend these findings by examining systolic BPV in relation to cognitive decline and WMH in older populations with depression.

P31. Cortisol and oxytocin are differentially correlated with specific psychopathology symptom profiles

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Background:
The stress-associated hormones cortisol and oxytocin are both implicated in psychological health and disease, but with contrasting effects. In particular, dysregulation of the hypothalamic–pituitary-adrenal (HPA) axis is a major contributor to depression. The HPA axis is activated during stress, with consequent increased cortisol secretion. Oxytocin is secreted in response to high cortisol levels to attenuate the HPA stress response. Accordingly, cortisol is associated with psychopathologies including stress and hostility, while oxytocin is inversely correlated with anxiety. We aimed to determine whether cortisol and oxytocin are differentially correlated with distinct symptom profiles of psychopathology in depressed and non-depressed individuals.

Methods:
Plasma cortisol and oxytocin concentrations were quantified in healthy participants and participants meeting DSM 5 criteria for major depressive disorder. Blood was sampled between 9 and 11 am to account for diurnal variations in cortisol secretion. Cortisol and oxytocin were quantified simultaneously in plasma using a fluorescence magnetic bead immunosorbent assay (Milliplex). Participants completed the Brief Symptom Inventory (BSI), a 53-item self-report measure of most major forms of psychopathology with nine domains (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, Psychoticism) and three global indices. Pearson's correlations and Student's t-tests were performed.

Results:
Data were collected for 60 non-depressed participants (58% female; mean age 31.8 ± 11.0 years) and 63 depressed participants (56% female; mean age 31.9 ± 14.5 years). Oxytocin was significantly lower (158 ± 140 versus 262 ± 159 pg/mL) and cortisol was significantly higher (252 ± 103 versus 107 ± 65 ng/mL) among depressed versus non-depressed participants with no gender difference. Cortisol was significantly correlated with all subscales of the BSI. Oxytocin was significantly but inversely correlated with Depression, Paranoid ideation and Psychoticism. Oxytocin was more variable than cortisol (co-efficient of variation: 89% versus 33%).

Conclusions:
These results provide further insight into the differential associations of cortisol and oxytocin with psychiatric symptom subtypes. Evidence of HPA axis dysregulation and a role of oxytocin were apparent in depression, with depressed participants having more than double the plasma cortisol concentration and approximately half the plasma oxytocin concentration levels of controls. Cortisol was a more consistent biomarker across a broad range of psychopathologies. The oxytocin results are in line with emerging research that suggests oxytocin is implicated in psychopathologies related to social discomfort, including depression and psychoses, and with growing interest in using synthetic oxytocin as an adjunct therapy.

P33. Allostatic load and depressive symptoms in patients with major depressive disorder

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Background:
Activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent sensitisation of neuroendocrine, immune and oxidative pathways are thought to contribute to the pathophysiology of mood disorders. Previous studies indicated that allostatic load (AL) may be elevated in late-life depression and indicative of future depressive episodes in population-based studies but it is unclear if allostatic load is elevated in major depressive disorder (MDD).

Methods:
We assessed AL in inpatients with MDD (n=31) and healthy controls (n=28). Biomarkers for the AL index were selected based on (1) representation of several physiological systems including the cardiovascular, neuroendocrine, immune, and metabolic systems, (2) use in previous AL research, and (3) associations with disease risk. We adopted a scaled AL algorithm whereby each marker proportionally contributes to the overall AL index. Unadjusted and adjusted differences between patients with MDD and controls in AL were tested with ANCOVA and partial correlations were used to test associations of AL with psychometric variables.

Results:
Unadjusted between-group comparison of patients with MDD and healthy controls showed higher AL in patients relative to controls (3.92 ± 1.30 vs. 2.59 ± 1.42, $p<0.001$). However, this difference became non-significant when age and smoking were entered as covariates ($F(1,55)=2.153$, $p=0.15$). We tested if AL was correlated with psychometric variables using partial correlations and found that AL at baseline was not associated with HAMD scores (adjusted $R=-0.217$, $p=0.27$) or GAF scores (adjusted $R=0.010$, $p=0.96$).

Conclusions:
Multisystem dysregulation, measured as AL, is not increased in hospitalised patients with MDD compared to controls when age and lifestyle factors are taken into account. These findings contrast with previous studies that found elevated AL in late life depression. AL may be associated with depression only in older populations or the association may be mediated by health behaviours.

P35. Increased circulating glucocorticoid receptor cofactor FKBP5 mRNA in schizophrenia

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Background:
A decrease of the glucocorticoid receptor and an increase in its co-factor FKBP5 has been found in several brain regions involved with cognition in people with schizophrenia. A number of single nucleotide polymorphisms within the FKBP5 gene have been associated with poorer cognitive performance in stress related disorders, such as major depressive disorder and schizophrenia. We sought to determine the extent to which peripheral FKBP5 mRNA levels are increased in people with schizophrenia and whether FKBP5 rs4613916 impacts peripheral mRNA levels in controls and people with schizophrenia. We also tested the extent to which FKBP5 rs4613916 predicts cognitive ability.

Methods:
Peripheral FKBP5 mRNA levels and genotype for FKBP5 rs4713916 were determined in 77 healthy controls and 93 people with schizophrenia, using Taqman mRNA expression assay (hs01561006_m1) and Taqman SNP genotyping assay, respectively. Cognitive assessment scores were adjusted for age, converted into z scores, and grouped into five cognitive domains: verbal memory, working memory, language, processing speed, and perceptual organization.

Results:
Significant elevation in peripheral FKBP5 mRNA was found in people with schizophrenia compared to healthy controls, $t(156) = -2.97$, $p < 0.01$. There was no statistically significant main effect of genotype or interaction between FKBP5 rs4613916 genotype and diagnosis on peripheral FKBP5 mRNA levels, $F(2,143) = 0.94$, $p = 0.39$. There was a significant genotype effect on language in healthy controls, $F(2,74) = 4.90$, $p = 0.01$, such that risk allele AA homozygotes (n=11) performed significantly worse than GG homozygotes (n=35) ($p=0.02$).

Conclusions:
The increase in peripheral FKBP5 mRNA levels identified in people with schizophrenia, may be suggestive of an overactive stress response pathway and blunted negative feedback ability. The one single nucleotide polymorphism examined in the FKBP5 gene may not be a major determinant for the level of FKBP5 mRNA levels in the blood of healthy controls and people with schizophrenia. However, genetic variation in FKBP5 appears to relate to language ability in healthy adults.

P37. Dysregulated adult neurogenesis and gliogenesis in the human subependymal zone in psychiatric disease

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Background:
The human subependymal zone (SEZ, also subventricular zone) adjacent to the caudate nucleus is the largest reservoir of newly born inhibitory interneurons and glial cells in the adult brain. Precursor cells can be recruited for brain repair hence impaired neurogenesis in the SEZ may account for deficits in inhibitory interneurons in psychiatric diseases. We hypothesized that adult neurogenesis and gliogenesis would be reduced in the human SEZ in schizophrenia and bipolar disorder compared to controls.

Methods:
Post-mortem tissue was obtained from 33 schizophrenia, 32 bipolar disorder and 33 control cases from the Stanley Medical Research Institute. SEZ tissue was dissected from 60 µm thick sections for RNA isolation and cDNA synthesis. Gene expression was measured by quantitative polymerase chain reaction and included markers of neural stem cells (GFAPδ), transit amplifying progenitors (Ki67), neuronal precursors (ASCL1), immature neurons (DCX), astrocytes (VIM, pan-GFAP), oligodendrocytes (OLIG2) and microglia (IBA1).

Results:
GFAPδ, ASCL1 and pan-GFAP mRNAs were decreased in schizophrenia (24%, $p=0.03$; 20%, $p<0.0001$ and 32%, $p=0.007$, respectively) and bipolar disorder (24%, $p=0.009$; 32%, $p=0.004$ and 22%, $p=0.01$, respectively) compared to controls. Ki67 and IBA1 mRNAs were decreased in bipolar disorder compared to controls (23%, $p=0.02$ and 26%, $p=0.007$). No significant differences in DCX, VIM and OLIG2 mRNAs were detected between diagnostic groups (all $p> 0.14$).

Conclusion:
Schizophrenia and bipolar disorder shared deficits in neural stem cell, neuronal precursor and mature astrocyte expression suggesting that the production of new cells may be impaired across psychiatric diseases. Bipolar disorder showed unique deficits in cell proliferation and microglia indicating disease-specific alterations in the adult SEZ. Impaired neurogenesis and gliogenesis may contribute to the neuropathology of psychiatric diseases and provide a potential target for the development of new therapeutic treatments. Future work will determine protein levels of cell-type specific markers and examine the expression of factors that regulate cell proliferation and fate determination in the human SEZ.

P39. Glial excitatory amino acid transporter 1 (EAAT1) mRNA is increased in the prefrontal cortex of subjects with schizophrenia

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Affiliations: Molecular Psychiatry Laboratories, The Florey Institute of Neuroscience and Mental Health; The CRC for Mental Health; The Centre for Mental Health, Swinburne University

Background:
Astrocyte dysfunction has been implicated in a range of psychiatric illnesses, including major depressive disorder and schizophrenia. Using an Affymetrix™ microarray, we observed a 36% increase in expression of the predominantly astrocytic glutamate transporter Excitatory Amino Acid Transporter 1 (EAAT1) in the prefrontal cortex (Brodmann's area (BA) 9) from subjects with schizophrenia (Scarr et al, 2017). The aim of the current study is to determine whether changes in EAAT1 mRNA levels are present within other cortical regions from subjects with schizophrenia.

Methods:
The human CNS tissue used in this study was obtained from the Victorian Brain Bank Network. cDNA was synthesized from RNA that was extracted postmortem from BA44 of subjects with schizophrenia (n=27) and healthy controls (n=29). EAAT1 mRNA levels were measured using the Bio-Rad iQ5 qPCR Detection System with SYBR Green 1 dye technology. Reactions were measured in triplicate with results normalised to the geometric mean of three stably expressed reference genes – glyceraldehyde 3-phosphate dehydrogenase (GAPDH), transcription factor B1, mitochondrial (TFB1M) and S-phase kinase-associated protein 1A (SKP1A).

Results:
Normalised levels of EAAT1 mRNA were significantly higher in BA44 from subjects with schizophrenia compared to age and sex matched controls (Mann Whitney test, $p = 0.0004$). EAAT1 mRNA levels were not related to sex, suicide completion, duration of illness, type or dose of medication.

Conclusions:
Our data suggests that a widespread increase in EAAT1 mRNA in the prefrontal cortex may be involved in the pathophysiology of schizophrenia. These findings are important as they support a role for astrocytes in glutamatergic dysfunction in schizophrenia and may have important implications for the treatment of the disorder.

P41. Peripheral microRNA-mRNA interactions in individuals with schizophrenia

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Background:
Schizophrenia is a severe neuropsychiatric disorder, characterised by positive and negative symptoms, and cognitive deficits. High throughput technologies including microarrays, and more recently next-generation sequencing have identified numerous genetic variants and transcriptional signatures associated with schizophrenia. In particular, microRNAs (miRNAs) have been found differentially expressed in both peripheral and post-mortem grey matter tissue in schizophrenia, and one of the most significant schizophrenia-associated variants occurs within the MIR137 genetic locus. These small, non-coding RNAs are potent regulators of translation, can target a wide variety of transcripts, and are thus of particular interest in polygenic disorders such as schizophrenia.

Methods:
We obtained peripheral blood mononuclear cell (PBMC) samples from 36 individuals with schizophrenia and 15 healthy controls. After isolating total RNA from these samples, we utilised RNA sequencing to examine both the miRNA and mRNA expression profiles. Raw reads were aligned to the human genome (hg38), annotated, counted and analysed for differential expression using an open source software pipeline. Correlations between miRNA and mRNA expression were found and matched to predicted TargetScan miRNA-mRNA interactions using the miRComb R package.

Results:
16 miRNAs and 25 genes were differentially expressed (adjusted $p<0.05$); most miRNAs (13 out of 16) were downregulated, while the vast majority of mRNAs (21 out of 25) were upregulated. When males and females were analysed separately, we found 38 miRNAs and 90 genes differentially expressed in males, while females only showed 1 differentially expressed gene (no miRNAs reached significance). Several miRNAs in males were found to significantly correlate with differentially expressed genes. Furthermore, many differentially expressed genes and miRNAs have previously been linked to schizophrenia and neuronal function.

Conclusions:
These results contribute to a growing body of evidence that suggest peripheral miRNA and mRNA expression is altered in schizophrenia. We identify a general downregulation of miRNAs and upregulation of mRNAs in peripheral tissue in schizophrenia. Several significant correlations between miRNAs and mRNAs previously linked to schizophrenia and brain function suggest potential miRNA-mRNA interactions that may be significant for disease pathophysiology.

P43. Development of and EGFP knock-in human dopaminergic cell model using CRISPR-CAS9 system

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Background:
It is hypothesized that alterations in the development of the dopaminergic system are central to schizophrenia. Animal models of schizophrenia, including developmental vitamin D deficiency, have shown delayed or diminished dopamine system development. Furthermore, the addition of vitamin D promotes the differentiation of dopamine neurons. To determine the effect of vitamin D on the functional and electrophysiological properties of dopaminergic neurons, we generated a genomic knock-in cell model. This was achieved by fusing green fluorescent protein (GFP) into the endogenous tyrosine hydroxylase (TH, dopamine neuronal marker) sequence using the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 (Cas9) system.

Methods: The guide (g)RNAs against TH terminals were designed using the Zhang lab website (http://crispr.mit.edu/). The donor vector was constructed from the EGFP gene flanked by short homology arms (1kb each) to insert the EGFP gene after the TH sequence. This produced EGFP fused in-frame with TH protein. The pU6Cas9-mCherry and TH-EGFP donor plasmids were transfected into human neuroblastoma cells SHSY5Y using electroporation. mCherry-positive cells were sorted using flow cytometry. The incorporation of EGFP in genome was assessed by PCR and cells were differentiated with retinoic acid (RA, 10µM).

Results:
PCR amplification of the junction between the TH sequence and EGFP was detected from genomic DNA. This indicates that Cas9 mediates double strand break-induced homology-direct repair (HDR) with the targeted plasmid sequence. Seven days after RA-induced differentiation, EGFP-expressing cells were observed. Immunofluorescence was used to further confirm that these EGFP cells were TH-positive. This finding indicates the successful fusion of EGFP with the endogenous TH protein.

Conclusions:
We demonstrated that a targeted knock-in method could be used in human dopaminergic cells to induce the fusion of EGFP with endogenous TH. This cell model could be used for many purposes including 1) tracing the differentiation and maturation of dopaminergic neurons; 2) examining the functional or electrophysiological properties of these dopaminergic neurons, and 3) assessing the effect of neuromodulators such as vitamin D specifically within dopaminergic neurons. These de novo targeted knock-in constructs could be also applied in human IPS cells to further explore the development of dopamine cells.

P45. Structural networks characterise methylphenidate response in youth with ADHD

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Background:
While MPH is largely successful in treating the symptoms and cognitive impairments associated with ADHD, in approximately 30%of cases it is either ineffective or causes intolerable side-effects. The exact biological reasons for this individual variability in response to methylphenidate are unclear. Here we used graph theory to determine whether whole-brain white matter connectivity differed in MPH responders versus non-responders.

Methods:
Thirty-six children and adolescents with ADHD completed baseline brain imaging in a 6 week MPH trial (international Study to Predict Optimized Treatment Response in ADHD; iSPOT-A). Treatment response was defined as >25% improvement from baseline on the ADHD-Rating Scale. An 84x84 structural connectivity matrix for each individual was constructed from DTI tractography between 84 parcellated cortical and sub cortical regions. Graph theory was used to compute metrics that characterize both the global organization of anatomical networks (characteristic path length, clustering coefficient and global efficiency) and the participation (degree) of local nodes within the network.

Results:
MPH responders (R, n=20) exhibited increased pre-treatment global efficiency relative to non-responders (NR, n=16). Locally, NR had higher participation of the right superior temporal and supramarginal regions, while R had greater participation of the left caudate and amygdala. Lower right Supramarginal and higher left caudate participation was associated with greater reduction of inattentive symptoms (r=.447, p=.006; r=-.423,p=.01), while higher amygdala nodal degree was associated with greater hyperactivity symptom reduction (r=-.574, p<.001).

Conclusions:
In ADHD, patterns of striatal organization and connectivity may be useful for distinguishing those who are unlikely to respond to MPH. Structural covariance provides a novel method for examining the neurobiological basis for MPH response in ADHD.

P47. Regional brain network organization distinguishes the combined and inattentive subtypes of Attention Deficit Hyperactivity Disorder

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Background:
Attention Deficit Hyperactivity Disorder (ADHD) is characterized clinically by hyperactive/impulsive and/or inattentive symptoms which determine diagnostic subtypes as Predominantly Hyperactive-Impulsive (ADHD-HI), Predominantly Inattentive (ADHD-I), and Combined (ADHD-C). Neuroanatomically though we do not yet know if these clinical subtypes reflect distinct aberrations in underlying brain organization.

Methods:
We imaged 34 ADHD participants defined using DSM-IV criteria as ADHD-I (n= 16) or as ADHD-C (n=18) and 28 matched typically developing controls, aged 8-17 years, using high-resolution T1 MRI. To quantify neuroanatomical organization we used graph theoretical analysis to assess properties of structural covariance between ADHD subtypes and controls (global network measures: path length, clustering coefficient, and regional network measures: nodal degree). As a context for interpreting network organization differences, we also quantified gray matter volume using voxel-based morphometry.

Results:
Each ADHD subtype was distinguished by a different organizational profile of the degree to which specific regions were anatomically connected with other regions (i.e., in "nodal degree"). For ADHD-I (compared to both ADHD-C and controls) the nodal degree was higher in the hippocampus. ADHD-I also had a higher nodal degree in the supramarginal gyrus, calcarine sulcus, and superior occipital cortex compared to ADHD-C and in the amygdala compared to controls. By contrast, the nodal degree was higher in the cerebellum for ADHD-C compared to ADHD-I and in the anterior cingulate, middle frontal gyrus and putamen compared to controls.

Conclusions:
ADHD-C also had reduced nodal degree in the rolandic operculum and middle temporal pole compared to controls. These regional profiles were observed in the context of no differences in gray matter volume or global network organization. Our results suggest that the clinical distinction between the Inattentive and Combined subtypes of ADHD may also be reflected in distinct aberrations in underlying brain organization.

P49. The effects of cannabis molecule, cannabidiol (CBD), on dopaminergic signalling: A systematic review of the literature

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Background:
Cannabidiol (CBD) is one of the major constituents of the cannabis plant. Recent studies have demonstrated a wide range of therapeutic benefits of cannabidiol (CBD), including antipsychotic, and pro-cognitive effects. Indeed, we recently showed that CBD attenuates negative and cognitive symptoms in a poly I:C model of schizophrenia; however, the underlying mechanisms are unknown. Dopamine (DA) plays a pivotal role in normal brain function and the pathophysiology of schizophrenia. This study aimed to examine the effects of CBD on dopamine signaling in the brain.

Methods:
We conducted a systematic review of the literature in accordance with PRISMA guidelines using studies dating from the commencement of records to August 2017. Major electronic databases (Scopus, Medline and Pubmed) were searched using the keywords, 'dopamine' AND 'cannabidiol', in the title, abstract and keywords. The exclusion criteria was studies that were (i) not fully published articles and (ii) studies that administered impure treatments (eg CBD+THC or botanic extracts) without a CBD-only control group.

Results:
Eighteen studies were included for qualitative synthesis (cell (n=3), healthy rodents (n=11), Parkinson's disease models (PD) (n=3), amphetamine-sensitized rodents (n=1)). CBD increases DA uptake in synaptosomes in a dose-dependent manner. In healthy rodents, CBD increased DA levels (nucleus accumbens (NAc)) and decreased DA precursor/metabolites (L-DOPA, DOPAC, HVA) (NAc, pre-frontal cortex, striatum). Conversely, acute maternal CBD decreases hypothalamic DA in adult offspring. In PD, CBD restores DA and tyrosine hydroxylase (TH) levels (CPu), but not levels of TH (in substantia nigra) or DOPAC (CPu). CBD prevents amphetamine-increased DA neuronal firing (VTA) but decreases firing in healthy rats.

Conclusions:
Overall, CBD does exert actions on the dopamine signaling pathways in the brain. CBD tends to increase DA, possibly by increasing DA uptake and reducing DA turnover in the healthy brain. Maternal (acute) CBD exposure can induce long-term DA changes in the adult offspring brain. CBD restores some DA imbalances in PD and protects against amphetamine treatment. This review can be used to aid identification of gaps in knowledge, which will help guide future mechanistic studies on the therapeutic benefits of CBD.

Poster Session 2

Tuesday, 31st Oct, 1:30 – 2:30 pm

P2. Behavioural effects of high fat diet in early adulthood in Nrg1 transmembrane domain mutant mice

Authors: Jerzy Zieba, Margaret J Morris and Tim Karl

Affiliations: Neuroscience Research Australia; Schizophrenia Research Institute; School of Medical Sciences, University of New South Wales; School of Medicine, Western Sydney University.

Background:
Schizophrenia patients are often obese or overweight. Poor dietary choices are a factor in this phenomenon. Poor diet has complex consequences for the mental state of patients. Furthermore, female adult mice of an established model for the schizophrenia risk gene neuregulin 1 (transmembrane domain Nrg1: Nrg1 TM HET) show a behavioural response to high fat diet (HFD), including attenuation of cognitive deficits. As sex effects are described for Nrg1 mutant mouse models and adolescence is a period of increased sensitivity to environmental risk factors, we investigated whether HFD provided early in life to both sexes modulates schizophrenia-relevant behaviours.

Methods:
Male and female Nrg1 TM HET and control littermates were exposed to either HFD or a standard chow diet (CHOW) (N=12-16) for 8 weeks starting in late adolescence. After this initial period, mice were kept on the respective dietary conditions and tested in behavioural domains relevant to schizophrenia including locomotion and exploration in open field (OF) social preference and sociability behaviours, sensorimotor gating (i.e. prepulse inhibition (PPI), and associative learning in the fear conditioning task (FC).

Results:
All mice on HFD weighed significantly more compared to CHOW mice regardless of genotype. In OF, Nrg1 TM HET mice of both sexes exhibited increased locomotion and reduced anxiety. In females, there was a significant 'habituation' by 'diet' interaction with HFD increasing the locomotor habituation in the OF. In PPI, Nrg1 TM HET males and females displayed a reduced acoustic startle response. In FC, a strong trend for a 'diet' by 'genotype' interaction was detected for freezing in males with HFD impairing associative memory for the cue in Nrg1 mutants. There were no 'genotype' or 'diet' effects on social behaviours.

Conclusions:
In the current study, male and female Nrg1 TM HET mice displayed increased explorative behaviours and locomotion confirming previous findings. Additionally, Nrg1 mutants exhibited a lower response to an acoustic startle stimulus compared to control animals. HFD had a moderately stronger negative impact on fear-associated memory in Nrg1 TM HET males. Adolescent HFD did not augment the majority of behaviours assessed. This resilience of late adolescent Nrg1 mutant mice, who are susceptible to HFD effects in adulthood, is similar to what has been found in previous studies evaluating the effects of cannabis exposure across development.

P4. Increased TH in the dorsal striatum: A new animal model of schizophrenia

Authors: Alice Petty, Xiaoying Cui and Darryl Eyles

Affiliations: Queensland Brain Institute, Queensland Centre for Mental Health Research

Background:
Increased dopamine synthesis and release in the dorsal striatum is one of the strongest neurochemical findings in patients with schizophrenia. This finding has been reliably documented through PET studies. Intriguingly, this abnormality is also found prior to schizophrenia proper, in the 'prodromal' period, though to a lesser extent. Thus the progressive nature of this abnormality suggests there may be a window of opportunity for therapeutic intervention. In order to develop interventions however, greater understanding of the transition from the prodrome to schizophrenia is necessary. We have therefore developed an animal model of this prodromal abnormality.

Methods:
We used an adeno-associated viral (AAV) vector to insert a genetic construct into the substantia nigra pars compacta (SNpc) of adolescent rats. The construct contains tyrosine hydroxylase (TH) and GTP cyclohydrolase 1 (GCH1); rate limiting factors in dopamine synthesis. The control vector is GCH1 alone. The SNpc innervates the dorsal striatum. Six weeks after the injection (in adolescence - P35), animals were tested for amphetamine-induced locomotion (0.6mg/kg AMPH), pre-pulse inhibition (PPI) and "negative" symptom tests. Neurochemistry of the dorsal striatum (medial and lateral portions), nucleus accumbens (NAc) and prefrontal cortex (PFC) was analysed with HPLC and rtPCR.

Results:
Animals injected with the TH+GCH1 vector showed increased amphetamine-induced hyperlocomotion, and decreased %PPI compared to controls. These animals also failed to show normal social novelty preference, but showed typical open field locomotion, sucrose preference, and spontaneous alternation behaviour. Neurochemical analysis revealed that, as expected, virally-generated huTH was found primarily in the dorsal striatum (68%) compared to the NAc (32%). This indicates preferential infection of the SNpc compared to the VTA in the midbrain. This treatment had no effect on basal levels of dopamine or its metabolites. The expression of a range of dopamine-related genes was also unchanged.

Conclusions:
We have generated a model of increased expression of the TH enzyme preferentially in the dorsal striatum. This treatment resulted in abnormal amphetamine-induced locomotion and PPI; behaviours clearly reflecting the "positive" symptoms of schizophrenia. These animals also exhibited deficient social novelty preference, representing a "negative" symptom of schizophrenia. Further experiments are undergoing to examine the exact nature of the changes induced by the addition of the TH enzyme to the dorsal striatum. We now have a model to potentially understand how the most robust neurochemical finding in schizophrenia may result in its key "positive" symptoms.

P6. Brain derived neurotrophic factor reverses dopamine mediated deficits in prepulse inhibition in early life stress models of schizophrenia`

Authors: Emily J. Jaehne, Elaine Mei San Chong and Maarten van den Buuse

Affiliations: School of Psychology and Public Health, La Trobe University, Melbourne

Background:
Schizophrenia is a devastating mental illness caused by genetic and environmental factors. Levels of Brain-Derived Neurotrophic Factor (BDNF) have been shown to be reduced in post-mortem brain tissue from patients with schizophrenia. BDNF may therefore be a potential therapeutic target for schizophrenia; however the mechanisms by which it affects behavioural changes relevant to schizophrenia, remain unclear. We used two developmental animal models of schizophrenia, maternal immune stimulation and social isolation rearing, to investigate the role of BDNF in the regulation of prepulse inhibition (PPI), a model of sensorimotor gating which is reduced in schizophrenia.

Methods:
Pregnant Long-Evans rats were treated with the viral mimetic, poly I:C, and male offspring were compared in adulthood to control offspring. PPI testing included the BDNF receptor agonist, 7,8-dihydroxyflavone (7,8-DHF, 10 mg/kg), as well as the dopamine receptor-stimulating drug, apomorphine (APO, 1 mg/kg), or the dopamine releasing drug, methamphetamine (METH, 2 mg/kg) to induce a schizophrenia-like PPI disruption. A second cohort of rats were reared in social isolation from weaning to adulthood and compared to group-housed controls.

Results:
Acute administration of APO caused a significant reduction of PPI which was not significantly altered in poly I:C rats. However, in poly I:C offspring only, 7,8-DHF significantly reversed the effect of APO on PPI (Control baseline 54 ± 2%, APO 20 ± 4%, APO+DHF 16 ± 2%; poly I:C baseline 54 ± 3%, APO 16 ± 3%, APO+DHF 35 ± 3%; $p < 0.05$). A similar trend was observed after treatment with METH as well as in social isolation rats.

Conclusions:
These findings suggest that 7,8-DHF has the ability to reverse dopamine-mediated deficits in PPI in early life stress models of schizophrenia. This highlights the therapeutic potential of targeting BDNF signalling for the treatment of schizophrenia.

P8. Using mouse operant tasks to investigate the neural mechanisms underlying reward, motivation and choice in schizophrenia

Authors: Kyna-Anne Conn, Thomas HJ Burne and James P Kesby

Affiliations: Queensland Brain Institute, The University of Queensland

Background:
The negative symptoms of schizophrenia include impaired motivation and cognition deficits, and one of the most robust pathophysiological findings is aberrant striatal dopamine function. The striatum is involved with the coordination of motor- and action-planning, decision-making, reinforcement and reward perception. By unpicking specific pathways in this region and assessing their contribution to motivational and cognitive dysfunction, we can better target interventions to improve daily functioning. Therefore, the aim of my PhD project is to use operant tasks that permit the exploration of reward, motivation and choice, and, the detection of differences due to striatal dopamine dysfunction in mice.

Methods:
By combining two existing operant tasks in mice, the Outcome-specific Devaluation Task (ODT) and the Progressive Ratio Breakpoint Task (PRBT), we can dissect motivational and cognitive performance in ~50 days of training and testing. Using 16 adult male C57BL/6J mice, the amalgamated tasks have been established to detect individual variations in reward valuation (value testing), goal-directed action selection (choice testing) and incentive motivation (breakpoint testing). We can also assess a reversal learning component in the ODT to examine cognitive flexibility. Mice are also tested with amphetamine to determine the sensitivity to detect changes in systemic dopamine on the PRBT.

Results:
We were able to separate reward valuation, goal-directed action selection and incentive motivation in a single throughput test battery. Detecting differences due to changes in systemic dopamine are also examined in this study validating the future aims to manipulate major dopaminergic striatal pathways that have been implicated in schizophrenia. With the prospective application of the chemogenetic tool Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) used to modulate receptor activity in vivo, in the meso-limbic and nigrostriatal pathways in particular, we will be able to dissect the role of these circuits in motivation, reward valuation, cognitive flexibility and goal-directed action.

Conclusions:
My project will contribute significantly to understanding the overlap between the negative (lack of motivation) and cognitive (impaired decision making) symptoms seen in patients with schizophrenia. The interactions between these symptoms are poorly understood, are known to contribute to functional impairments and reduced quality of life, and there are currently no efficacious treatments. In addition, the ODT and PBRT have identical task equivalents in humans, making this behavioural test battery highly relevant for crossspecies translational studies. This work will also increase our knowledge about brain mechanisms that are involved with complex behaviours, such as motivation and decision-making.

P10. Rationale and methods of the role of estrogen in modulating executive function in the rat

Authors: Kara Jaeschkea, Anrea Gogos and Thomas H.J. Burne

Affiliations: Queensland Brain Institute, University of Queensland; Florey Institute of Neuroscience and Mental Health, University of Melbourne

Background:
Numerous studies have suggested that estrogen is neuroprotective against cognitive dysfunction in both the male and female brain. Cognitive deficits, particularly executive deficits, are key drivers of adverse functional outcomes in neuropsychiatric disorders. However, they remain currently unresolved by pharmacological and behavioural intervention. While several models have been developed to assess executive functioning, most are non-automated and labour intensive. Thus, this study aims to develop an automated operant task in rodents that mimics the human intra-/extra-dimensional (ID/ED) task to look at the role of sex and estrogen in neurobiological components of executive function.

Methods:
Two dissociable components of executive function will be measured in this task: reversal learning and set-shifting within the same dimension (intra-dimensional) or between different dimensions (extra-dimensional). During this task, rats will be trained during ~5 daily sessions and then tested over ~10 daily sessions. Two dimensions will be used in this task and stimuli can be simple or compound. Performance on this task will be used to determine the effects of sex (male versus female Sprague Dawley (SD) rats) and estrogen (ovariectomised or sham-operated with 17β-estradiol (25mg) or vehicle via a silastic implant in female SD rats) on executive deficits.

Results:
This task will be used to explore the role of sex and estrogen in executive function. The main outcome variables are intra-dimensional and extra-dimensional set-shifting and reversal learning ability. This task aims to provide the possibility to test the effects of various neural, pharmacological and behavioural manipulations on discrete measures of executive function, including accuracy, perseverative responses and response latencies.

Conclusions:
The neural circuits underlying behaviour during reversal learning and set-shifting are highly conserved across humans, nonhuman primates and rodents. Thus, this operant task aims to provide face, construct and predictive validity for executive deficits present in neuropsychiatric disorders. It aims to address limitations of existing tasks by reducing extensive training periods and omission rates, and controlling body position by using central nose poke to self-initiate a trial. This task has the potential to be used by a variety of fields to assess cognitive phenotypes and specific differences (i.e. sex) or treatments (i.e. estrogen) in animal models relevant to neuropsychiatric disorders.

P12. Baseline phenotypeof Immp2l knockout-mice: A model for Tourette syndrome

Authors: Fabian Kreilaus, Rose Chesworth, Valsamma Eapen, Raymond Clarke and Tim Karl

Affiliations: School of Medicine, Western Sydney University; School of Psychiatry, Faculty of Medicine and Ingham Institute University of New South Wales; Neuroscience Research Australia

Background:
Tourette Syndrome (TS) is a neurodevelopmental disorder, characterised by motor and vocal tics. TS is often co-morbid with other conditions including obsessive compulsive disorder and possibly autism spectrum disorder. The genetic factors relevant to the development of TS are yet to be fully understood. A targeted gene association study in TS patients has identified an association between TS and a mutation in the inner mitochondrial membrane peptidase subunit 2 (IMMP2L) gene. Germline knockout (KO) of Immp2l in mice results in mitochondrial dysfunction, increase ischemic brain damage and infertility. The impact of Immp2l on behaviour is unknown.

Methods:
In this study, we aimed to characterise the behavioural consequences of Immp2l deletion in both male and female adult mice (C57/BL6 background). Heterozygous and homozygous Immp2l KO mice were compared to control littermates in a battery of behavioural tests relevant to TS including open field (OF), social interaction (SI), novel object recognition (NOR), marble burying (MB) and prepulse inhibition (PPI). The effect of acute dexamphetamine (5 mg/kg) on open field behaviour was also investigated.

Results:
Under baseline conditions, the time spent in the centre zone of the OF was significantly longer in male homozygous KO mice compared to control males indicating an anxiolytic-like phenotype. Total distance travelled was not significantly different across genotypes but homozygous KO mice showed a faster recovery from the dexamphetamine-induced locomotor stimulation compared to heterozygous KO and control mice. The NOR test indicated a deficit in male heterozygous and homozygous males to explore a novel object when compared to control mice. These behavioural changes were not detected in female mice. Further tests including PPI, SI and MB are currently being analysed.

Conclusions:
Deficiency in Immp2l decreased the anxiety response of male homozygous KO mice, compromised their object recognition memory, and modulated the locomotor response to dexamphetamine. The effects of Immp2l deficiency appeared gene-dose and sex dependent. The modulated response to dexamphetamine in homozygous KO mice suggests a potential role of Immp2l in controlling dopamine-related brain metabolism. These preliminary results indicate that this model may possess partial face validity for preclinical research into TS pathophysiology and therapy.

P14. Effect of environmental risk factors on electrophysiological features related to schizophrenia

Authors: Ariel Dunn, Lauren Harms, Juanita Todd, Ross Fulham, Aarong Wong, Deborah Hodgson, Ulrich Schall and Patricia Michie

Affiliations: School of Psychology, University of Newcastle; Priority Research Centre for Brain and Mental Health Research, University of Newcastle; School of Medicine and Public Health, University of Newcastle

Background:
Maternal immune activation (MIA) in response to gestational infection is a risk factor for the development of schizophrenia in offspring. Previous studies have shown that MIA in rats and mice, induced by the non-infectious viral mimic Poly(I:C), produces a variety of schizophrenia-like behavioural, cognitive and morphological alterations. However, it was unknown if MIA altered electrophysiology in rats. The current study therefore investigated the impact of MIA on two electrophysiological features altered in schizophrenia, gamma activity and mismatch negativity (MMN). Furthermore, our study investigated these features in both male and female rats.

Methods:
Pregnant Wistar rats were exposed to either Poly(I:C) (MIA) or saline during late gestation (gestation day 19). Offspring underwent surgery in adulthood to implant skull electrodes which were used to assess the neurophysiological phenotypes of gamma activity and MMN. Gamma activity was measured using an auditory steady state response (ASSR) task, while MMN was measured via an oddball and many-standards control paradigm.

Results:
MIA rats had reduced gamma power ($p = .018$) and phase-locking ($p = .020$) between 30 and 50 Hz. No sex effects were found for gamma activity. MMN-like responses were found and female animals had higher overall responses than males early in the MMN waveform, a novel finding ($p = .029$). No significant treatment effects were found for any MMN component.

Conclusions:
A multiple hit model of MIA, or a two-hit model of a variety of risk factors will be implemented in the future to investigate more reliable and robust electrophysiological alterations, as well as behavioural and cognitive alterations. Our findings of sex differences suggest that animal research should consistently include both sexes to improve the validity of current models of schizophrenia.

P16. Postnatal development of the endocannabinoid system in transmembrane domain neuregulin 1 mutant mice, a genetic mouse model of schizophrenia

Authors: Rose Chesworth, Leonora Long, Cyndi Shannon Weickert and Tim Karl

Affiliations: School of Medicine, Western Sydney University; Neuroscience Research Australia

Background:
Cannabis use is a well-established component risk factor for schizophrenia, particularly in individuals with genetic predisposition for the disorder. Alterations to the endocannabinoid system have been found in post-mortem brain tissue of schizophrenia patients. Thus, we assessed whether molecular alterations in the development of the endocannabinoid signalling pathway were associated with genetic mutations which increase risk for schizophrenia

Methods:
We analysed transcripts encoding key molecules of the endocannabinoid system in a genetic mouse model for schizophrenia known to have increased sensitivity to cannabis exposure (heterozygous transmembrane domain Neuregulin 1 mice: Nrg1 TM HET). Tissue from the prelimbic cortex and hippocampus of Nrg1 TM HET mice and wild type-like littermates (n = 8-12 /genotype /age) was collected at postnatal days 7, 10, 14, 21, 28, 35 and 161. Quantitative polymerase chain reaction was conducted to assess mRNA levels of cannabinoid receptor 1 (CB1), and enzymes for the synthesis and break down of the endocannabinoid 2-arachidonoylglycerol (2-AG).

Results:
Hippocampal and cortical mRNA expression of diacylglycerol lipase alpha (DAGLα), monoglyceride lipase (MGLL) and α/β-hydrolase domain-containing 6 (ABHD6) was dynamic across postnatal development, with only minor changes in CB1mRNA found across postnatal development in the hippocampus. Nrg1 TM HET mRNA expression was not different from control mice for any endocannabinoid marker investigated.

Conclusions:
Here, we provide a detailed developmental trajectory of key endocannabinoid system transcripts in the mouse brain. Nrg1 TM HET mutation did not alter the developmental trajectory of the endocannabinoid markers assessed, suggesting other mechanisms may be responsible for cannabinoid susceptibility in these mice.

P18. Maternal immune activation adversely affects the ontogeny of dopamine neurons: Is vitamin D neuroprotective?

Authors: Suhailah Ali, Leon Luan and Darryl Eyles

Affiliations: Queensland Brain Institute; Queensland Centre for Mental Health Research

Background:
Dopamine dysregulation is one of the major hypotheses underlying the pathophysiology and treatment of schizophrenia, which may result from early alterations in dopamine ontogeny. Two well-established animal models – maternal immune activation (MIA) using Poly(I:C) treatment, and developmental vitamin D deficiency (DVD) – both show an initial reduction in factors crucial for dopaminergic development. This suggests a convergent aetiological mechanism, which is supported by our recent evidence showing that vitamin D can ameliorate schizophrenia-related behavioural phenotypes in the Poly(I:C) model. We therefore want to investigate whether vitamin D is acting to correct the abnormal dopaminergic development induced by Poly(I:C).

Methods:
Pregnant mice were co-administered the active vitamin D hormone simultaneously with Poly(I:C) at gestational day 9 and embryos were collected at two developmental time-points, E11 and E14. In order to examine dopamine ontogeny, we used immunohistochemistry to analyse the expression of four dopamine lineage markers – Lmx1a, Sox2, Nurr1 and TH – which can be used to distinguish dopamine progenitors, immature neurons and mature neurons. Using spinning-disk confocal microscopy coupled with an optimised CellProfiler analysis pipeline, we were able to identify individual dopaminergic cells and quantify the expression of these markers, alongside cell number, shape, size and spatial position.

Results:
We have so far obtained preliminary results for the expression of Lmx1a and Sox2 in E11 embryos. Our interpretations are currently limited as we remain blind to treatment groups until the Nurr1 and TH images have been analysed. Poly(I:C) had a significant effect on the number and nuclear shape of progenitors (Lmx1a+ Sox2+), while vitamin D had a significant effect on the expression of Lmx1a in progenitors and the lateral position of postmitotic cells (Lmx1a+ Sox2-). No interactions between Poly(I:C) and vitamin D were observed.

Conclusions:
Poly(I:C) and vitamin D appear to be having independent effects on dopaminergic development at E11. However, we have yet to analyse Nurr1 and TH in the E11 embryos, which will allow us to distinguish between immature and mature neurons. We are also currently processing the E14 embryos, which represents a time-point when dopamine neurogenesis is almost complete. We hope to use these findings to better understand how different environmental risk factors for schizophrenia converge on developing dopaminergic systems.

P20. Post-weaning social isolation impairs fear extinction recall in adolescence

Authors: Katherine Drummond and Jee Hyun Kim

Affiliations: The Florey Institute of Neuroscience and Mental Health

Background:
Early life chronic stress may increase an individual's vulnerability to develop anxiety disorders and may reduce the efficacy of treatment by subsequent behavioural therapies. Social isolation stress during puberty is a relevant model of adolescent chronic stress. This study aims to investigate in rats the effects on post-weaning social isolation on adolescent fear extinction behaviour.

Methods:
At 21 days of age male and female Sprague Dawley rats were housed in 3's or in isolation for three weeks. Then all rats received a 6 white noise (10s)–foot shock (1s,1mA) pairings. The next day, all rats received 60 presentations of the noise without shock (i.e. extinction). On day three, extinction recall was tested with rodents presented with the a noise-alone trial (2 mins) in the extinction context.

Results:
Isolation housing had no effects on conditioning and extinction acquisition compared to group housing. However, at extinction recall test, both female and male isolation-housed rats froze higher than group housed rats (*post-hoc tests following interaction, $p< 0.05$; **t-test $p<0.05$).

Conclusions:
This demonstrates that social isolation stress can impair fear extinction recall in adolescence. Better understanding of the mechanisms that underlie this impairment may lead to novel treatments to assist in prevention and treatment of anxiety disorders.

P22. Elevated immune cell markers in the neurogenic subependymal zone in schizophrenia

Authors: Hayley North, Christin Weissleder, Maree Webster and Cynthia Shannon Weickert

Affiliations: Schizophrenia Research Laboratory; Neuroscience Research Australia; School of Psychiatry, University of New South Wales; Laboratory of Brain Research, Stanley Medical Research Institute

Background:
Research indicates a dysregulation of adult neurogenesis and a pathogenic role of neuroinflammation in schizophrenia and bipolar disorder. The greatest extent of post-natal neurogenesis occurs in the subependymal zone (SEZ; also termed subventricular zone). Immune cells trafficked to the brain can release molecules that impact neurogenesis; and we hypothesized that molecular indicators of immune cell levels in the SEZ would be increased in psychiatric disorders. If immune cells infiltrate the SEZ in schizophrenia and bipolar disorder, this may be associated with reduced markers for neural stem cells (GFAPδ) and neuronal precursor cells (ASCL1) found in the SEZ in these disorders.

Methods:
Post-mortem caudate tissue was obtained from 32 schizophrenia, 29 bipolar disorder and 32 control cases from the Stanley Medical Research Institute. SEZ tissue was dissected from 60 µm thick sections ~2 mm deep to the lateral ventricle surface for RNA isolation and cDNA synthesis. We tested for diagnostic differences in gene expression of immune cell markers CD14 (monocytes), CD163 (perivascular macrophages) and FCGR3A (natural killer cells) with quantitative polymerase chain reactions using Fluidigm Biomark HDTM.

Results:
CD163 was increased in schizophrenia compared to controls (161%, p=0.01) and bipolar disorder (158%, p=0.01). FCGR3A and CD14 were not significantly different across diagnostic groups (p=0.10 and p=0.49), but planned contrasts showed increased FCGR3A in schizophrenia compared to controls (47%, p=0.05). In schizophrenia, CD163 correlated positively with GFAPδ (r= 0.55, p= 0.001) and negatively with ASCL1 (r= 0.40, p= 0.03); and FCGR3A correlated positively with GFAPδ (r= 0.57, p= 0.001) but not ASCL1. In bipolar disorder, CD163 was not significantly correlated with GFAPδ or ASCL1; whereas FCGR3A correlated positively with GFAPδ (r= 0.636, p <0.001) but not ASCL1.

Conclusions:
We find the first evidence of increased markers of perivascular macrophages and natural killer cells in the SEZ in schizophrenia, which we plan to further explore with immunohistochemistry. No changes in immune cell markers were found in the SEZ in bipolar disorder despite previous findings of neuroinflammation in other regions. Our data is consistent with increased neuroinflammation in schizophrenia and the correlations between markers for immune cells and neurogenesis in the SEZ may have implications for the dysregulation of neurogenesis in schizophrenia.

P24. An assessment of presynaptic markers, vGluT1 and synaptophysin, in the nucleus accumbens in schizophrenia

Authors: Samara Brown, Jeremy S Lum and Kelly A Newell

Affiliations: School of Medicine, University of Wollongong; Illawarra Health and Medical Research Institute

Background:
The nucleus accumbens (NAc) is implicated in the pathology of schizophrenia however there has been little direct investigation of this region in schizophrenia subjects. The NAc receives inputs from multiple regions of the brain, including the prefrontal cortex and hippocampus, with emerging evidence suggesting altered projections onto the NAc in schizophrenia, particularly glutamatergic projections. The purpose of this study was to use a large postmortem cohort to measure the presynaptic markers, vGluT1 (a marker of presynaptic glutamatergic terminals) and synaptophysin (a marker of pre-synaptic density), in the NAc in schizophrenia.

Methods:
Postmortem NAc samples from 30 schizophrenia and 30 control subjects, matched for age at death, postmortem interval and brain pH, were obtained from the NSW Brain Tissue Resource Centre. The relative protein levels of vGluT1 and synaptophysin were assessed via western blot and normalised to GAPDH. T-tests and ANCOVA were used to compare between schizophrenia and control subjects. Correlation analyses were used to determine any associations between vGluT1 and synaptophysin and clinical variables including estimated lifetime antipsychotic drug dose and duration of illness.

Results:
Protein levels of vGluT1 and synaptophysin in the NAc were not significantly different between control and schizophrenia subjects. As expected however, vGluT1 and synaptophysin were positively associated in the NAc in both control ($r=0.875$ $p<0.001$) and schizophrenia subjects ($r=0.610$; $p<0.001$). There was no association between vGluT1 or synaptophysin and estimated lifetime antipsychotic drug intake or duration of illness.

Conclusions:
The present study does not provide evidence for presynaptic glutamatergic abnormalities in the NAc of schizophrenia subjects. The lack of change in VGluT1 suggests there are no changes in cortical and hippocampal glutamatergic projections to NAc in schizophrenia, however we cannot rule out changes to specific subdivisions of the NAc (ie core v shell) or in other presynaptic glutamatergic markers (e.g. vGluT2).

P26. Increase in Prefrontal Cortex and Decrease in Striatum of Dopamine Transporter have the Possibility of Supporting Dopamine Hypothesis in Schizophrenia

Authors: Hirotaka Sekiguchi, Geoff Pavey and Brian Dean

Affiliations: The Florey Institute of Neuroscience and Mental Health

Background:
The dopamine hypothesis in schizophrenia has been discussed for several decades. It has been proposed that in schizophrenia there is a hypodopaminergic state in the prefrontal cortex and a hyperdopaminergic state in the striatum; the hyperdopaminergic state in the striatum due to synaptic dopamine elevation, particularly in the dorsal striatum. The dopamine transporter (DAT), which is a regulator of dopamine concentration through the reuptake of dopamine from the synaptic cleft by the pre-synaptic neuron, is one of the molecules that may be involved in the dopaminergic pathophysiology of schizophrenia. Therefore, we measured levels of DAT in the cortex and striatum.

Methods:
Levels of DAT were measured in the gray matter from frontal pole (Brodmann's area (BA) 10) and striatum from 15 subjects with schizophrenia and 15 controls using in situ radioligand binding of [3H]mazindol (15 nM) displaced by mazindol (1 µM) quantified using autoradiography. Klüver-Barrera stained sections were referred in order to detect the boundary between the gray matter and the white one within BA10. Approval to collect human tissue was obtained from the Ethics Committee of the Victorian Institute of Forensic Medicine.

Results:
Levels of [3H]mazindol were higher in BA10 from subjects with schizophrenia ($t=3.11$; $df=19.77$; $p=0.0055$; Cohen's $d=1.14$) but lower in the dorsal striatum from those with the disorder ($t=3.61$; $df=25$; $p=0.0013$; Cohen's $d=1.40$).

Conclusions:
The changes in levels of [3H]mazindol imply that levels of DAT are that higher in BA 10 but lower in the striatum from subjects with schizophrenia. We hypothesis that higher levels of DAT in BA10 could be contributing to low synaptic dopamine whereas lower levels of striatal DAT in the striatum could be contributing to a hyperdopaminergic state in that CNS regions.

P28. Increased CypA expression in the anterior cingulate cortex of subjects with major depressive disorder

Authors: Kate McPherson, Andrew Gibbons, Andrea Gogos and Brian Dean

Affiliations: The Florey Institute of Neuroscience and Mental Health

Background:
A growing body of evidence suggests that inflammatory protein levels are altered in the CNS of patients with mood disorders. Cyclophilin A (CypA), a major immunosuppressant drug target, regulates the expression of several key inflammatory proteins. Furthermore, drugs that bind to CypA can induce depressive side effects in patients with inflammatory disorders. However, it is unclear whether CypA is involved in the pathophysiology of mood disorders. We investigated whether CypA mRNA expression is altered in subjects with major depressive disorder (MDD) or bipolar disorder (BD), compared to controls in BA24, a brain region that is important in controlling mood.

Methods:
Human post-mortem brain tissue was obtained from the Victorian Brain Bank Network. RNA was extracted from BA24 (anterior cingulate cortex) tissue, obtained post-mortem from subjects with MDD (n = 20), BD (n = 18), and non-psychiatric controls (n = 20). The RNA was reverse transcribed and expression levels were quantified using qPCR with SYBR green chemistry in a Bio-Rad iQ5 Real-Time PCR Detection System. Reactions were performed in triplicate, and relative quantities of CypA mRNA expression were normalized to the geometric mean quantities of two stably expressed reference genes; GAPDH and SKP1.

Results:
CypA mRNA expression was increased in BA24 from MDD subjects compared to controls ($p < 0.0001$). There was no significant difference in CypA mRNA expression in BD compared to controls. Furthermore, there was no significant variation in age, post-mortem interval, and sex across diagnostic cohorts. Brain pH was higher in the MDD cohort compared to the control and BD cohorts ($p = 0.0005$). However, CypA mRNA expression did not correlate with pH. Therefore, this is not likely to impact interpretation of the data across diagnoses. There was no relationship between CypA mRNA expression and suicide completion or antidepressant use.

Conclusions:
We have shown that the level of CypA mRNA expression is increased in BA24 from subjects with MDD but not subjects with BD. These findings indicate that increased expression of CypA could contribute to the pathophysiology of MDD. The diagnostic specificity of these findings has implications for understanding the biochemical differences underlying MDD and BD.

P30. Regulation of the D2R-DISC1 complex formation and the neurite outgrowth by antipsychotic drugs

Authors: Minmin Hu, Peng Zheng, Yuanyi Xie, Zehra Boz, Hongqin Wang, Yinghua Yu and Xu-Feng Huang

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Background:
Schizophrenia is a chronic mental illness, which is characterized by episodes of psychotic symptoms, cognitive impairments and social behavior disorders. Dopamine D2 receptor (D2R) is the main target of antipsychotic drugs. Haloperidol is a D2R antagonist and aripiprazole is D2R partial agonist. D2R belongs to the G-protein-coupled receptor family. Recently, it has been shown that D2R can form a protein complex with Disrupted in schizophrenia (DICS1), which regulates the glycogen syntheses kinase3 (GSK3) signaling pathway. However, the role of the D2R-mediated signaling events in the actions of antipsychotics remains unclear.

Methods:
(1) Design and construct the fusion protein of D2R-GFP, D2R mut-GFP and DISC1-mCherry; (2) Transfection of plasmids intoHEK293 cells; (3) Fluorescence microscopy and Western blot to confirm the protein expression; (4) Fluorescence resonance energy transfer (FRET) analysis to investigate the effect of Haloperidol and Aripiprazole on the interaction between D2R and DISC1 in HEK 293 cells; and (5) Detect the effect of Haloperidol and Aripiprazole on Retinoic Acid-induced neurite outgrowth in SHSY5Y cells.

Results:
Establishment of D2R-GFP, DISC1-mCherry, D2R-GFP+DISC1-mCherry, D2R mut-GFP +DISC1-mCherry in HEK293 cells; (2) D2R agonist quinpirole overstimulation induced a significant increase of D2R/DISC1 complex formation; (3) D2R antagonist Haloperidol and Aripiprazole prevented D2R/DISC1 complex formation; (4) Haloperidol decreased the neurite outgrowth of the SHSY5Y cells.

Conclusions:
Antipsychotics drugs, Haloperidol and Aripiprazole, can block the complex formation between D2R and DISC1. Also, Haloperidol inhibited the neurite outgrowth of SHSY5Y Cells.

P32. Multidimensional analysis of gene expression in differentiated human neuroblasts after whole cell depolarisation

Authors: Dylan Kiltschewskil and Murray Cairns

Affiliations: School of Biomedical Sciences and Pharmacy, Faculty of Health, The University of Newcastle; Priority Research Centre for Brain and Mental Health Research, Hunter Medical Research Institute; Schizophrenia Research Australia

Background:
Dysregulation of the signaling associated with neuronal excitation and connectivity is a common feature of psychiatric disorders including schizophrenia, addiction and autism spectrum disorders. While these processes involve spatially and temporally restricted patterns of mRNA translation, the posttranscriptional regulatory mechanisms that facilitate this are poorly understood. To gain further insight, we explored the translational dynamics of depolarisation in a differentiated human neuroblast culture system using high throughput ribosome profiling and reconciled this with associated changes in mRNA abundance and miRNA expression.

Methods:
SH-SY5Y neuroblastoma cultures were differentiated with all-trans retinoic acid (0.1µM) for 7 days. Membrane excitation was induced by incubation with Hank's Balanced Salt Solution, supplemented with depolarising concentrations of KCl (100mM). After a total of 4 stimulus – rest cycles, cells were harvested 1 hour following the final stimulus in the presence of the translational inhibitor cycloheximide. Changes in mRNA abundance and translation were determined by sequencing both mRNA and ribosome protected total RNA fragments. These were then compared with miRNA expression examined through small-RNA sequencing. All libraries were produced and sequenced (NextSeq500) according to the manufacturer's instructions (Illumina).

Results:
Ribosome profiling revealed over 1230 genes were subject to a significant ($p < 0.05$, $q < 0.1$), excitation associated change in translational activity after depolarization. Interestingly, integrative analysis with mRNA steady-state expression data indicated the majority of differentially translated genes (85%) were primarily regulated at the translational level. The analysis of miRNA expression suggested the majority of significant miRNA:mRNA interactions affected steady mRNA levels rather than translation directly. hsamiR-1271-5p and hsa-miR-125b-5p were identified as major regulators of depolarisation associated translation, which correlated with subsets of mRNAs at both the transcriptional and translational levels.

Conclusions:
These results provide compelling insights into dynamic regulation of excitation-associated neuronal gene expression. Translational activity 1 hour after membrane excitation appears to be highly regulated, however with minimal influence from mRNA abundance and miRNA expression. We suspect changes in translational activity may show stronger correlation with interactions between mRNA and the RNA induced silencing complex, with correlation analysis suggesting miRNA primarily influence mRNA abundance at the whole-cell level at this time-point post-depolarisation. These insights into the regulation of neural activity-associated translation and the role of posttranscriptional gene regulation are to understand the changes in this system observed in psychiatric disorders.

P34. Olanzapine inhibits mitophagy and upregulates ROS in NPY-expressing hypothalamic neuronal cells

Authors: Zehra Boz, Yinghua Yu and Xu-Feng Huang

Affiliations: Illawarra Health and Medical Research Institute, University of Wollongong

Background:
Olanzapine is a commonly prescribed second-generation antipsychotic. However a major side-effect associated to olanzapine are metabolic disorders such as; extreme weight-gain and diabetes. The mechanism underlying antipsychotic-induced metabolic dysfunction remains unknown. Mitophagy is an intra-cellular mechanism activated upon cellular stress such as nutrient deprivation or oxidative stress. This mechanism moderates stress via "recycling" damaged or prolonged mitochondria for energy replenishment while retaining the integrity of the cell. This study aimed to investigate the effects of olanzapine on hypothalamic mitochondria and particularly mitophagy.

Methods:
Hypothalamic NPY-expressing mHypOA-59 neuronal cells were cultured at 37°C in a CO2 incubator with DMEM 5796, supplemented with 1% penicillin/streptomycin and 10% fetal bovine serum. Cells were seeded in 6-well plates overnight, at 70% confluency cells were treated with various doses of olanzapine in serum-free DMEM for 24hrs. Cells were washed with PBS and stained with either Mitotracker Green FM (200nM) for 30 minutes or Mitosox red (5µM) for 20 minutes. Plates were then imaged for fluorescence using the incucyte ZOOM or DMi8 fluorescent microscope and then trypsinized for flow cytometry analysis.

Results:
Our results demonstrate that olanzapine significantly increased mitochondrial mass with Mitotracker Green in mHypOA-59 cells after a 24hr treatment in a dose-dependent manner; 50µM ($p < 0.001$), 100µM ($p < 0.001$), 150µM ($p < 0.001$) compared to the control group. We also found a significant increase in superoxide anion (O2-) with Mitosox red in a dose-dependent manner, 50µM ($p<0.05$), 100µM ($p < 0.01$), 150µM ($p < 0.05$); an indicator of mitochondrial reactive oxygen species (ROS) and oxidative stress.

Conclusions:
Increased mitochondrial mass or number as a results of olanzapine treatment suggests an impairment in mitochondrial clearance or mitophagy. Mitochondria are the main source of ROS production in a cell and the most undesirable form of ROS is the superoxide anion (O2-). Therefore, olanzapine causes mitochondrial stress to the cell, which may inhibit mitophagy ultimately lead to apoptosis - cell death. Chronic hypothalamic ROS release is involved type 2 diabetes and other neurodegenerative diseases. Hence, our findings imply that olanzapine causes detrimental effects in the metabolic regulation of hypothalamic neurons.

P36. Decreased 5-HT2cR and GHSR1a dimerization by olanzapine contributes to increased hypothalamic NPY and obesity side-effects

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Affiliations: Jiangsu Key Laboratory of Immunity and Metabolism, Department of Pathogen Biology and Immunology, Xuzhou Medical University, Xuzhou, Chine; Illawarra Health and Medical Research Institute; School of Medicine, University of Wollongong; Department of Endocrinology, Zhongnan Hospital of Wuhan University, Wuhan, China

Background:
Both antagonism of serotonin 2c receptors (5-HT2cR) and activation of ghrelin receptor type 1a (GHSR1a) signalling have been identified as a main cause of second generation antipsychotic (SGA) induced obesity. Recently, the 5-HT2cR was reported to regulate GHSR1a signalling via a 5-HT2cR and GHSR1a interaction. This study investigated whether the obesogenic SGA olanzapine alters this 5-HT2cR/GHSR1a interaction, affecting orexigenic neuropeptide signaling in the hypothalamus.

Methods:
Primary hypothalamic neurons, mHypoA-59 and mHypoA-NPY/GFP cells were treated with olanzapine (25 and 50μM), 5HT2cR antagonist (SB242084, 10, 50 and 100μM) and olanzapine (50μM) + 5HT2cR agonist (lorcaserin, 10 and 50μM). We used immunofluorescence and confocal Fluorescence Energy Transfer (FRET) technology to characterize the interaction of 5-HT2cR and GHSR1a in hypothalamic neurons. FRET efficiencies for the sensitized emission (SE) were calculated and analysed by FRET-SE Wizard Software. The GHSR1a signaling molecules, pAMPK, FOXO1, UCP2 and pCREB were measured by Western blot. The orexigenic neuropeptide Y (NPY) expression levels were quantified following olanzapine and/or lorcaserin treatments by the FlexStation.

Results:
We found that the 5-HT2cR dimerized with the GHSR1a in primary hypothalamic neurons using FRET technology, which enables measurement of receptor dimerization at a single cell level. Olanzapine and the 5-HT2cR antagonist, SB242084, decreased the interaction between 5-HT2cR and GHSR1a, in turn activating GHSR1a signalling (pAMPK-UCP2-FOXO1/pCREB) in hypothalamic neurons. The 5-HT2cR agonist, lorcaserin, counteracted the reduced interaction between 5-HT2cR and GHSR1a caused by olanzapine. Furthermore, lorcaserin prevented olanzapine's activation of GHSR1a signalling and orexigenic NPY levels in hypothalamic neurons.

Conclusions:
Taken together, these findings suggest that the inhibitory effect of olanzapine on 5-HT2cR and GHSR1a dimerization could be prevented by a 5-HT2cR agonist, which restores hypothalamic NPY to normal levels. These results may have broader implications for the use of a 5-HT2cR agonist in clinical trials to counteract the obesity side-effects of SGAs with strong 5-HT2cR antagonistic profiles.

P38. The effects of electrical stimulation and conductive polymer on hypothalamic neurons in psychiatric disorders

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Affiliations: Intelligent Polymer Research Institute, Illawarra Health and Medical Research Institute, University of Wollongong; ARC Centre for Excellence for Electromaterials Science; Centre for Translational Neuroscience; Department of Surgery, St Vincents Hospital, University of Melbourne

Background:
The unique mechanical, electrical and chemical properties of conducting polymers (CPs), such as polypyrrole (Ppy), make these materials attractive for biomedical applications. A previous study has shown amelioration of schizophrenia (Sz) deficits with in vitro electrical stimulation (ES) mediated by CP. However, the mechanisms elicited by ES at the cellular and molecular level remain unclear. Given the role of hypothalamus in the pathogenesis and treatment of psychiatric disorders, including the therapeutic effects of deep brain stimulation or transcranial direct current stimulation, we have studied the effect of ES and CP in an in vitro phencyclidine (PCP) model of Sz.

Methods:
PCP-treated and untreated adult mouse hypothalamic neurons were seeded onto Ppy films doped with dodecylbenzenesulfonate (DBS) and electrically stimulated for 8 hours/day over three days at 0.25 mA/cm2 current density and 250 Hz frequency. Phenotypical assessment was performed using immunocytochemistry and neuronal markers were quantified with quantitative realtime polymerase chain reaction and flow cytometry.

Results:
Immunostaining showed that ES increased neurite outgrowth of the adult hypothalamic neurons, compared to non-ES controls. The mRNA expression of MAP2 and Dlg4, along with protein expression of MAP2, were increased in ES cells ($P<0.05$). PCP treatment significantly reduced the mRNA expression of MAP2 in cells cultured on standard tissue culture plastic, however the PCP treatment along with PCP+ES treatment increased the neuronal mRNA and protein markers in cells cultured on Ppy-DBS.

Conclusions:
ES via Ppy-DBS enhances neurite outgrowth of hypothalamic neurons. Interestingly, Ppy-DBS alone and in combination with ES, reversed the effect of PCP on the cells. This is consistent with reports of CPs ameliorating reduced neurite outgrowths in Sz knockout models. This study confirms the effectiveness of ES and suggests the promising capability of CPs in alleviating neural deficits in Sz models.

P40. Symptom profiles, hormones, and quality of life in major depressive disorder

Authors: Tang Ai Ling (Claire), Susan J Thomas and Theresa Larkin

Affiliations: School of Psychology, Faculty of Social Sciences, University of Wollongong; School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong

Background:
Quality of life (QoL) is emerging as a better indicator of health than symptom measures alone. Depression is a heterogeneous condition involving physical and psychological symptoms, and substantial impairment in QoL. However, little research has examined which symptom types have greatest impacts on QoL. Additionally, there is a lack of understanding about the roles biological factors play in QoL in depression. This study aimed to examine relationships between depressive symptoms and QoL. Additionally, the interplay between cortisol, oxytocin and QoL was investigated in depression. It was hypothesised that key hormones linked to depression would differentially predict QoL levels.

Methods:
Firstly, 570 community members completed the World Health Organization Quality of Life-BREF questionnaire, encompassing Physical, Psychological, Social and Environmental domains; and the Beck Depression Inventory II, measuring psychological and physical symptom profiles. Secondly, 60 adults meeting DSM-5 criteria for major depressive disorder (MDD) and 60 healthy controls provided morning plasma samples and completed questionnaires. Cortisol and oxytocin were quantified using a Milliplex fluorescence magnetic bead immunosorbent assay. Symptom profiles were correlated with QoL-domains. Between-group ANOVAs compared depressed with healthy participants. QoL domain scores were correlated with cortisol and oxytocin levels. Multiple regression analyses were performed to examine relationships between variables.

Results:
In the community study, as hypothesised, relationships were found between QoL and symptomatic profiles, and different symptom profiles were found to predict specific domains in QoL. In the biological study, as expected, participants with MDD had lower QoL than healthy controls. Additionally, cortisol and oxytocin levels were differentially associated with specific QoL domains. Oxytocin was positively correlated with the QoL domains of Psychological health and Social relationships. Cortisol was negatively correlated with all domains of QoL. Both oxytocin and cortisol uniquely predicted variance in QoL after controlling for symptom severity and demographic variables.

Conclusions:
These findings provide new information about the relationships between specific types of depressive symptoms on QoL. Additionally, this study confirms previous findings of lower QoL in MDD, and provides novel evidence for neuroendocrine pathways linked to QoL which may be affected in MDD. These pathways may help to explain the large burden of MDD and its effects on QoL. In conclusion, multifaceted approaches to QoL in mental health may lead to greater understanding of the underlying mechanisms, and in turn, to improved and tailored preventions and treatments. Further, limitations and suggestions for future research are discussed.

P42. Problematic eating behaviours and weight gain in major depressive disorder: The role of leptin

Authors: Jessica Mills, Susan J Thomas, Theresa A Larkin, Chao Deng and Nagesh B Pai

Affiliations: School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong; Illawarra Health and Medical Research Institute

Background:
Appetite and weight changes are core symptoms of major depressive disorder (MDD), and those with MDD are at an increased risk of obesity, cardiovascular disease and metabolic disorders. Understanding the mechanisms of appetite dysregulation and overeating may allow for improved interventions aimed at preventing weight gain and chronic diseases in at-risk individuals. Leptin promotes hunger satiety, and is associated with mood. Leptin dysregulation and resistance are noted in obesity; however the role of leptin in weight changes in MDD is not established. This study investigates relationships between leptin, depressive symptom profiles, appetite, problematic eating behaviours and weight changes in MDD.

Methods:
Plasma leptin levels, psychopathology and biometrics were compared between participants meeting DSM-5 diagnostic criteria for MDD (n = 63) and healthy controls (n = 60). MDD participants were sub-categorised by their symptoms into those with increased, decreased or unchanged appetite and/or weight. Eating behaviour styles and food addiction measures were examined in a subset of participants with MDD, using the Dutch Eating Behaviours Questionnaire and the Yale Food Addiction Scale.

Results:
Participants with MDD had significantly higher leptin levels than controls, and females overall had significantly higher leptin levels than males. Participants with MDD with increased appetite/weight had significantly higher leptin levels than those with decreased or unchanged appetite/weight. Leptin levels were positively correlated with BMI and waist circumference. Leptin levels were also positively correlated with Emotional and Restrained eating subscales of the Dutch Eating Behaviours Questionnaire, and the Increased food intake subscale of the Yale Food Addiction Scale. One quarter of the depressed subset met the Yale criteria for food addiction. Further, females reported more comfort eating behaviours than males.

Conclusions:
The current study provides new information regarding relationships between leptin and symptom profiles in MDD. Additionally, novel links were identified between leptin, problematic eating behaviours and food addiction. The results indicate that leptin is associated with increased weight, appetite and anthropometric risk factors for cardiovascular disease and metabolic syndrome in MDD, particularly in females. The relationships observed in the current study indicate promising areas of future research investigating risk factors for weight gain and potential early interventions aimed at preventing weight gain in those at risk due to MDD.

P44. Altered functional segregation of insula cortex in patients with treatment resistant schizophrenia

Authors: Ye Tian, Chad Bousman, Christos Pantellis and Andrew Zalesky

Affiliations: Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne; The Cooperative Research Centre (CRC) for Mental Health; Centre for Neural Engineering, Department of Electrical and Electronic Engineering, University of Melbourne

Background:
Using resting-state functional MRI (fMRI), insula cortex can be subdivided into spatially contiguous sub-regions that are characterized by distinct patterns of functional connectivity with the cortex. While early studies indicate a bipartite subdivision comprising posterior and anterior sub-regions, recent studies provide evidence of a tripartite clustering in which anterior insula is further subdivided into dorsal and ventral components. Given that insula is associated with psychological processes in perception, self-awareness and cognitive function, which is severely disturbed in patients with treatment-resistant schizophrenia (TRS). We aimed to test whether insula would demonstrate altered or absent functional segregation in this cohort.

Methods:
Resting-state fMRI was acquired in 50 TRS patients and 52 matched controls. A connectional fingerprint was mapped for each insula voxel by correlating its resting-state activity with all other cortical voxels. Hierarchical clustering based on Ward's linkage was then used to delineate clusters individually. Clusters comprised voxels that were functionally connected to common cortical targets, representing putative insula sub-regions. The optimal number of clusters was found with Silhouette criterion. To define consensus group-level clustering, Newman's spectral community detection algorithm was employed to map probabilistic segmentations. Between-group differences in the functional connectivity of sub-regions were tested using variance and cluster-based statistics.

Results:
Cluster analysis indicated that the left and right insula each comprise two sub-regions in patients and controls; an anterior subregion that is functionally connected to the fronto-temporal cortex and a posterior sub-region characterized by parieto-occipital connections. This bipartite subdivision exhibited significantly less consensus across patients than controls (right: $P=0.0038$, left: $P=0.002$), suggesting altered insula segregation in schizophrenia. In patients, the anterior insula was significantly more strongly
connected to sensory-motor and occipital cortex, while the posterior insula showed more extensive connectivity to prefrontal cortex ($P_{FWE}<0.025$). The dysconnectivity between anterior insula and anterior cingulate cortex was correlated with emotional withdrawal ($r=-0.51$, $P<0.001$).

Conclusions:
TRS patients have impaired functional coupling between anterior and posterior subdivisions and other large-scale brain networks, including default mode network, central executive network, sensory-motor network as well as language/auditory processing related brain regions. These disturbances were widespread within and across hemispheres associated with perceptual, emotional and cognitive systems, suggesting a crucial role of the insula in the psychopathology of TRS.

P46. Assessment of multiple classes of rare genetic variants in extended families with bipolar disorder implicate postsynaptic density genes

Authors: Claudio Toma, Alex D Shaw, Richard JN Allcock, Anna Heath, Kerrie D Pierce, Philip B Mitchell, Peter R Schofield and Janice M Fullerton

Affiliations: Neuroscience Research Australia and Schizophrenia Research Institute, Randwick, NSW; School of Pathology and Laboratory Medicine, University of Western Australia; Black Dog Institute, Prince of Wales Hospital, Sydney

Background:
Bipolar disorder (BD) is a complex psychiatric condition with high heritability, the genetic architecture of which likely comprises both common variants of small effect and rare variants of higher penetrance. Multiplex families with high density of illness provide an opportunity to map novel risk genes or consolidate evidence for existing candidates, by identifying genes carrying pathogenic rare variants.

Methods:
We performed whole exome sequencing (WES) in 15 BD families (117 subjects: 72 affected, 28 unaffected relatives), augmented with copy number variant (CNV) microarray data, to examine contributions of: i) predicted pathogenic SNVs and likely-gene disruptive variants shared in affected versus unaffected relatives; ii) genome-wide burden of likely-gene-disruptive variants; iii) de novo variants; iv) rare CNVs; and v) rare highly penetrant variants under family-specific linkage peaks. Linkage analysis and haplotype reconstruction using WES-derived genotypes enabled elimination of false-positive SNVs, CNV inheritance, and candidate gene prioritisation.

Results:
Rare predicted pathogenic variants shared amongst ≥3 affected relatives were over-represented in postsynaptic density (PSD) genes (P=0.002, PBonf=0.024), with no enrichment in unaffected relatives. Burden of likely-gene-disruptive variants was no different in affected versus unaffected relatives (P=0.24), but correlated significantly with age of BD onset (P=0.017). The number of de novo variants in affected versus unaffected offspring was no different (P=0.23). We identified novel BD candidate genes: the X-linked IRS4 with a stop mutation in all 5 affected siblings which mapped within a family-specific linkage peak, and deletions across the protocadherin family of genes, which act to mediate neuronal connectivity.

Conclusions:
Genetic approaches that combine WES, CNV and linkage analyses in extended families is an effective method for detection of potential pathogenic variation, pinpointing genes and pathways that may contribute to the pathophysiology of BD. We observed heterogeneity within and between families, with alleles of modest effect and reduced penetrance being the most likely genetic model. A high burden of brain-expressed loss-of-function variants may expedite symptom onset in BD individuals, and further investigation of this relationship with other measures of BD severity are warranted.

P48. Sex-specific associations of androgen receptor polyglutamine repeat length with testosterone and stress symptoms in schizophrenia

Authors: Samantha Owens, Tertia D Purves-Tyson, Thomas W Weickert and Cynthia Shannon Weickert

Affiliations: Schizophrenia Research Laboratory, Neuroscience Research Australia; School of Psychiatry, Faculty of Medicine, University of New South Wales.

Background:
Shorter androgen receptor (AR) polyglutamine (CAG) repeat length confers more efficient AR function and is associated with lower circulating testosterone and more depressive symptoms in males. In men with schizophrenia, testosterone is associated with negative symptoms and impaired emotion processing, suggesting that androgen signalling may be involved. We hypothesised that the relationship between circulating testosterone and CAG repeat length would be disrupted in schizophrenia and shorter CAG repeat length would be associated with more negative and emotional symptoms in schizophrenia patients.

Methods:
Serum testosterone was measured in 97 (59 male/38 female) schizophrenia patients and 87 (46 male/41 female) healthy controls. CAG repeat length was determined from genomic DNA using capillary electrophoresis. Symptom severity was assessed using the Positive and Negative Syndrome Scale and negative emotional states were evaluated using the Depression and Anxiety Stress Scale (DASS). Spearman's correlations were performed between CAG repeat length and peripheral testosterone levels. Symptom and emotional state ratings were analysed by CAG repeat length group (short $\leq$21/long >21) and sex using multivariate analysis of variance.

Results:
Circulating testosterone levels and CAG repeat length were significantly and positively correlated in male controls (ρ=0.429, p=0.008) and female patients (ρ=0.429, p=0.01), but were not correlated in female controls (ρ=-0.163, p=0.322) or male patients (ρ=0.101, p=0.454). There was a trend for a CAG repeat length x sex interaction on DASS subscale scores [V= 0.078, F(3,88)=2.491, p=0.065]. Stress scores were significantly higher in male patients with short compared to long CAG repeat lengths [t(55)=2.436, p=0.018].

Conclusions:
Sex-specific alterations of the relationship between CAG repeat length and testosterone were found in schizophrenia patients and may indicate that abnormal androgen signalling contributes to disease pathogenesis. Sex steroid modulating therapies may be beneficial for stress symptoms in a subset of male schizophrenia patients with more robust AR signalling.

P50. Decreased serum acid levels after treatment in drug naive bipolar patients during a manic episode

Authors: Jing-Xu Chen, Li-Gang Zhang, Hong-Mei Chen, Yun-Long Tan, Fu-De Yang and Xu-Feng Huang

Affiliations: Beijing Hui-Long-Guan Hospital, Peking University, China; School of Medicine, Illawarra Health and Medical Research Institute, University of Wollongong

Background:
Evidence suggests that UA levels may contribute to the pathophysiology and therapeutics of bipolar disorder(BPD). The aim of this study was to evaluate whether uric acid(UA) levels were associated with clinical properties and the changes in UA levels after treatment in BPD during the manic episode.

Methods:
Drug-naive, first-episode manic patients (34 men,43 women) and 76 ages- and gender- matched healthy subjects were enrolled. Young Mania Rating Scale (YMRS) and serum UA levels were evaluated at baseline and at the end of 8-week treatment with quetiapine and sodium valproate in patients.

Results:
UA levels in manic phase were higher than those in remitted phase but all of them had higher UA levels compared to controls (378.55±99.08, 323.57±73.53, 290.89±72.18umol/L, respectively). No significant relation was found between YMRS scores and UA level either at baseline or at the endpoint. While there was a significant correlation between the decrease in UA levels and that in YMRS scores in these patients (r = 0.250).

Conclusions:
Our results suggest that serum UA levels might not only be a state marker of severity of mania but also be a trait marker in bipolar patients and it may be an important target for developing improved therapeutics.

Maps

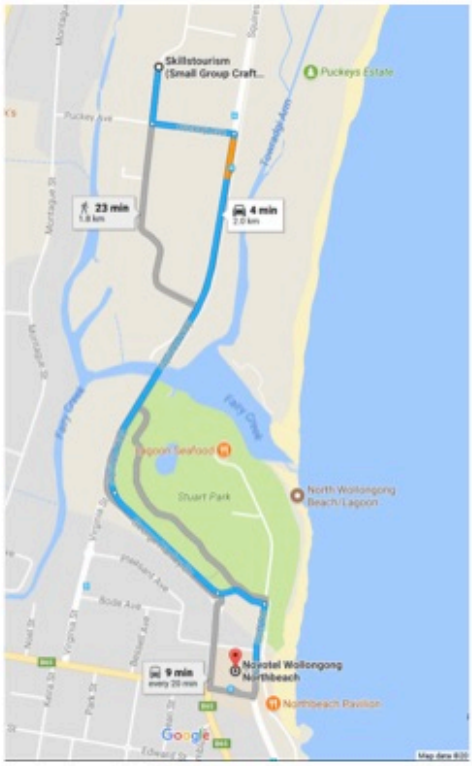
Sunday 29th October:

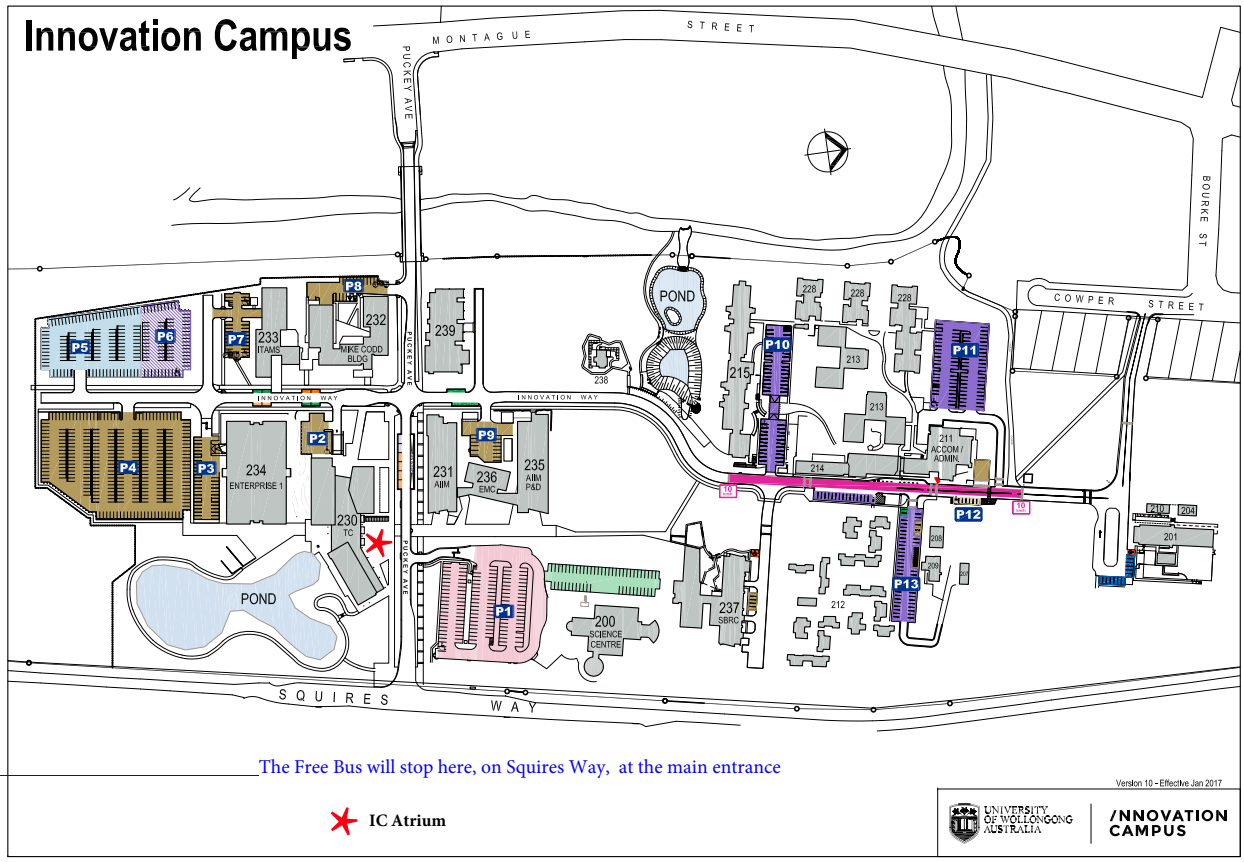
IC Atrium, Innovation Campus

Free Bus (recommended): Get on the 55A free shuttle bus at the bus stop (buses come every 20 mins), across the road on the western side of the Novotel. Depart at the next stop located on Squires Way, opposite the main entrance to the Innovation Campus. (5 mins)

Walk: A cycleway is located on the eastern side of the Novotel. Follow the cycleway north until you reach the Innovation Campus (20-30 mins).

The IC Atrium is located in the first building on your left as you enter Innovation Campus.

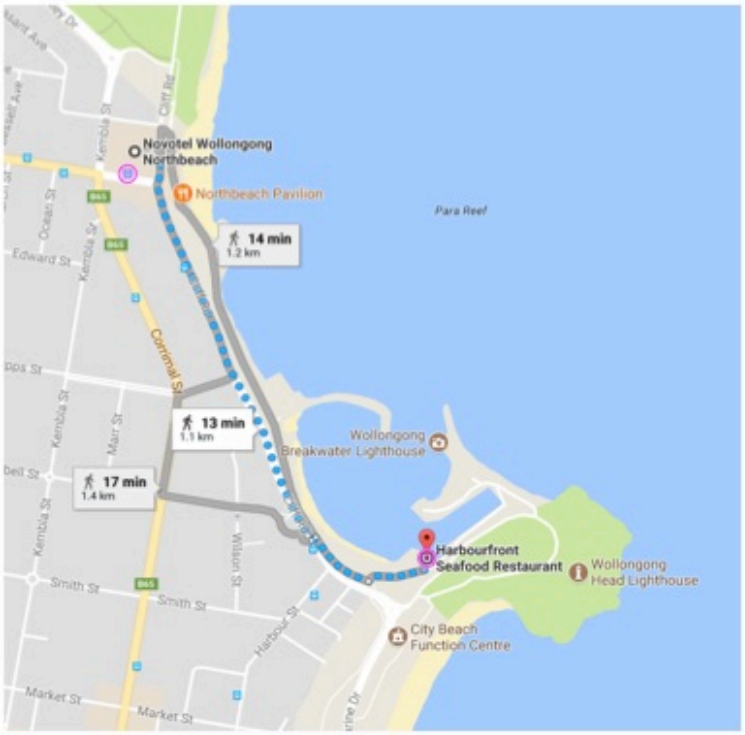




Monday 30th October Social Function:
Level One @ Harbourfront

Free Bus: Get on the 55C free shuttle bus at the bus stop (buses come every 20 mins), located at the front of the southern side of the Novotel (highlighted in pink). Get off at the 2nd stop located at Wollongong Harbour. Level One function centre is located on the bottom level of the building in the southern corner of the harbour (5 mins).

Walk (recommended): A cycleway is located on the eastern side of the Novotel. Follow the cycleway south until you reach the harbour (15 mins).



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