ANS 2019 Symposium Abstracts

TUESDAY 3 DECEMBER 2019

SYMPOSIUM 1

10:00am – 12:00pm, City Rooms 1&2

New insights in Motor Neuron Disease pathogenesis, therapeutics and biomarkers

Chairs: Mary-Louise Rogers (Flinders University) & Bradley Turner (Florey Institute of Neuroscience and Mental Health)

10:00am **Don Cleveland** (Ludwig Institute, University of California)
Premature polyadenylation and loss of the neuronal stathmin-2 inhibits axonal regeneration in TDP-43-dependent neurodegeneration

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are associated with loss of nuclear TDP-43. We have identified TDP-43 to regulate stathmin-2, a neuronal growth factor essential for axon stability and regeneration. Reduction of TDP-43 suppresses stathmin-2 levels by uncovering a premature polyadenylation site in the first intron of stathmin-2 pre-mRNA, producing a truncated non-functional mRNA. Reduction of stathmin-2 mRNA is found in neurons trans-differentiated from patient fibroblasts expressing an ALS-causing TDP-43 mutation, in iPSC-derived motor neurons depleted of TDP-43, and in motor cortex and spinal motor neurons isolated from familial ALS patients with GGGGCC expansion in C9orf72, but not those with mutant SOD1. Reduced stathmin-2 is consistently found in sporadic ALS. Loss of TDP-43 from iPSC-derived motor neurons is shown to block axonal regeneration. Remarkably, rescuing stathmin-2 levels in TDP-43 depleted neurons is sufficient to restore axonal regeneration capacity. These findings establish that premature polyadenylationmediated reduction in stathmin-2 is a hallmark of ALS that functionally links TDP-43 proteinopathy to enhanced neuronal vulnerability. A therapeutic approach for sporadic ALS will now be development of antisense oligonucleotides to block premature polyadenylation of stathmin-2 pre-mRNA, thereby maintaining stathmin-2 expression levels despite the reduction in nuclear TDP-43 found in sporadic and C9orf72-mediated ALS.

10:30am **Avinda Nath** (National Institute of Neurological Disorders and Stroke)
Endogenous Retroviral Elements in ALS and other neurodegenerative diseases

Endogenous Retroviral Elements in ALS and other neurodegenerative diseases" To date all genetic studies have focused on only one percent of the human genome. Whereas 40% of the human genome consists of transposable elements and 8% is retroviral sequences. Most of these are repeat sequences and have been termed junk DNA. Many of these genes are specific to humans. Their role in mediating neurodegenerative disorders has only recently been considered. We found that the envelope protein of a human endogenous retrovirus-K (HERV-K/ HML-2) was expressed at a critical stage of embryonic development and was important for mediating stemness by triggering secondary signaling pathways important for cell division and survival. The virus was very tightly regulated during neurodevelopment

and silenced in neurons. Forced expression of HERV-K in terminally differentiated neurons resulted in cell death. We found increased expression of HERV-K in the brains of nearly one third of the patients with ALS. Mice in which HERV-K envelope was expressed in cortical neurons developed an ALS like phenotype that could be blocked by an sh-RNA to the HERV-K env. We also tested a panel of antiretroviral drugs for their efficacy against HERV-K in vitro and also in the context of the "Lighthouse study". The significance of these findings will be discussed in the context of findings by other groups showing dysregulation of other transposable elements in ALS and Alzheimer's disease.

11:00am **Andreas Malaspina** (Blizard, Institute of Cell and Molecular Medicine, Barts & the London School of Medicine & Dentistry, London)
Pathogenesis and Molecular Mechanisms that inform ALS/MND biomarkers

The pathogenesis of amyotrophic lateral sclerosis (ALS) and the molecular mechanisms behind its clinical heterogeneity are a major focus of research. The lack of a full understanding of the molecular changes driving the disease progression limits our ability to develop novel therapeutic strategies. It does also affect the rate of success of clinical trials, where lack of biomarkers of treatment response and of knowledge of the most effective therapeutic targets has conditioned the failure of more than 200 studies. The work presented is about the dissection of molecular mechanisms involved in inflammation, metabolism, senescence and relevant to cytoskeletal integrity, which have been identified as major drivers of disease progression in ALS. Novel biomarkers of disease progression as well as therapeutic strategies have been formulated on the basis of proteomic experiments which have looked at the tissue/fluid interface in individuals with a significant difference in prognosis and survival at different time points in the disease progression. Along with neurofilaments which have already been used for disease stratification, other makers involved in the humoral response to axonal proteins and in axonal regeneration hold promise as biomarkers and therapeutic targets for ALS.

11:30am **Shyuan Ngo** (Australian Institute for Bioengineering and Nanotechnology)
Insights into metabolic dysfunction in motor neuron disease

Metabolic perturbations occur in motor neuron disease (MND) patients and in mouse models of the disease; both at the systemic and cellular level. Clinically, an increase in resting energy expenditure and decline in body mass index is linked to worse outcome. It is therefore possible that the therapeutic targeting of metabolic perturbations could improve patient outcomes. However, to develop effective treatment strategies, it is first necessary to understand the mechanisms of dysregulated metabolism and their impact on the disease process. In this talk, I will present our research into altered energy balance in MND and discuss our recent work that has led to the identification of possible therapeutics that could improve metabolic imbalance and modify the course of MND

SYMPOSIUM 2

10:00am – 12:00pm, City Rooms 3&4

New perspectives in neural circuits modelling

Chair: Gary Egan (ARC Centre of Excellence for Integrative Brain Function)

10:00am **Pulin Gong** (The University of Sydney)
An integrated model linking structural and dynamical properties of local cortical circuits

Experimental studies have begun revealing essential properties of the structural connectivity and the spatiotemporal activity dynamics of cortical circuits. To integrate these properties from anatomy and physiology, and to elucidate the mechanistic links between them, we develop a novel cortical circuit model that captures a range of realistic features of synaptic connectivity. We show that the model accounts for the emergence of higher-order connectivity structures, including highly connected hub neurons that form an interconnected rich-club. The circuit model exhibits a rich repertoire of dynamical activity states, ranging from asynchronous to localized and global propagating wave states. We find that around the transition between asynchronous and localized propagating wave states, our model quantitatively reproduces a great variety of major empirical findings regarding neural spatiotemporal dynamics, which otherwise remain disjointed in existing studies. These dynamics include diverse coupling (correlation) between spiking activity of individual neurons and the population, dynamical wave patterns with variable speeds and precise temporal structures of neural spikes. We further illustrate how these neural dynamics are related to the connectivity properties by analysing structural contributions to variable spiking dynamics and by showing that the rich-club structure is related to the diverse population coupling. These findings establish an integrated account of structural connectivity and activity dynamics of local cortical circuits, and provide novel experimentally testable predictions.

10:30am **Anthony Burkitt** (The University of Melbourne)
Real-time temporal alignment of neural activity in neural circuits

The real-time temporal alignment hypothesis postulates that information of sensory signals is transmitted through neural pathways in a manner that compensates for neural transmission delays at each stage of the pathway. These neural transmission delays result from both synaptic delays and the time required for action potential conduction via axons. For sensory inputs that change in a predictable fashion, their representation at higher levels of the processing hierarchy remain aligned with the stimulus. Neural information that is fed backwards from higher to lower levels of the hierarchy is realigned in time through a synaptic plasticity mechanism based upon nonlinear Hebbian learning and normalization at each level of the hierarchically structured network. These predictions from the higher levels of the pathway are thereby able to be fed backwards without becoming increasingly misaligned over time with the incoming sensory input. Examples from visual motion processing indicate that such neural processing is plausible and is consistent with the psychophysically observed results of several known motion-position illusions.

11:00am **Tatiana Kameneva** (Swinburne University of Technology & The University of Melbourne)
Mechanisms of combined electrical and optogenetic costimulation

Neuroprosthetic devices are reaching a level of maturity and have benefited many people who suffer from neurological conditions such as deafness and blindness. However, the perception outcome that they provide is significantly less than normal function. In part, this is due to the current spread, neural adaptation and inability to selectively activate different classes of neurons when using electrical stimulation. Optogenetic neural stimulation may provide an alternative to conventional electrical pulse stimulation by delivering more targeted stimulation with higher spatial resolution. A novel way to stimulate neurons is to combine conventional electrical stimulation with targeted optogenetic stimulation. The mechanisms of neural activation in response to the combined electrical and optogenetic costimulation are not clear.

To investigate the mechanisms of neural activation in response to electrical and optogenetic costimulation, we used computer simulations in the NEURON environment. We simulated single compartment neurons and used Hodgkin-Huxley type formalism to study how costimulation and a combination of ionic channels affect the neuronal response. To simulate an optogenetically modified neuron, we combined voltage-activated currents with a model of channelrodopsin-2 ion channel responsive to voltage, temperature and light. We systematically applied different levels of intracellular current pulse stimulation and optical stimulation to bring the membrane potential close to firing threshold. We also applied mock-electrical current stimulation that approximates the response of neurons to optical-alone stimulation and studied the activation of ionic channels in this case. To isolate the mechanisms during costimulation, the maximum sodium conductance in the NEURON model was set to zero, simulating total blockage of sodium channels.

Our results showed that the membrane is initially depolarised by a small inward channelrhodopsin current during the optical stimulation, followed by a rapid sodium current following the electrical trigger. During costimulation, the channelrhodopsin current transiently reduced during the action potential due to its voltage sensitivity. This result matched modelling and experimental data reported by Williams et al. (2013) in cardiomyocytes. Our results support the interpretation of a costimulation mechanism involving two separate families of ion channels. Our results may have implications for the development of stimulation strategies in novel neurosprosthetic devices that have electrical and optogenetic stimulation capabilities.

11:30am **Geoffrey Goodhill** (The University of Queensland)
Separating spontaneous and evoked activity with a latent factor model of calcium imaging data

The pattern of neural activity evoked by a stimulus can be substantially affected by ongoing spontaneous activity. For calcium imaging data there is currently a lack of statistically principled methods for estimating the relative contributions of evoked and spontaneous activity at each moment, making it difficult to, for instance, accurately estimate neural tuning curves. I will present a probabilistic latent variable model that decouples the components of calcium imaging data that are due to evoked activity from those driven by low dimensional spontaneous activity. We use variational inference to compute an approximate posterior distribution over latent sources of shared variability, identifying low dimensional structure underlying spontaneous activity and allowing for the estimation of stimulus tuning properties that take this variability into account. Applying this model to 2-photon recordings

from the mouse cortex and the zebrafish optic tectum reveals the extent to which neurons are driven by visual stimuli, latent sources of spontaneous activity, and their interaction. This model is broadly applicable to calcium imaging data, brings new insight into population-level neural activity, and can refine our understanding of the role of spontaneous activity in neural computation.

SYMPOSIUM 3

10:00am – 12:00pm, Riverbank Room 7

Diagnostics and Theranostics in Psychiatry: Using advanced biological, bioinformatics and computational tools to improve clinical outcomes

Chair: Thomas Burne (Queensland Brain Institute)

10:00am **Elizabeth Thomas** (The Scripps Research Institute)
DNA methylation biomarkers as early predictors of psychiatric disorders

Substantial experimental and epidemiological evidence suggests that stressful events and environmental exposures early in life can lead to psychiatric disorders later in life, and these events occur via epigenetic mechanisms. Accordingly, alterations in DNA methylation in the brain are associated with several psychiatric disorders, however, these data have been limited to postmortem samples. In this study, we utilize saliva to examine the associations between genome-wide DNA methylation profiles and prodromal symptoms in n= 816 kids 12 years old and younger who are part of the Family Life Project. DNA methylation patterns were analyzed using Ilumina Methylation EPIC BeadChips. DNA methylation signals from epithelial, fibroblast and immune cell populations, were estimated. To identify differentially methylated CpG sites, we performed an association analysis adjusting for age, estimates of cell proportions, and considering different groups of subjects. We specifically focus on prodromal symptoms using several clinical metrics. We further investigated the DNA methylation age (epigenetic age) using the 353-CpG based Horvath clock and whether clinical characteristics impact these patterns. Overall, our goals are to identify peripheral DNA methylation markers that may be used to identify individuals at high risk for developing psychiatric disease later in life and may be candidates for early interventions.

10:30am **Brian Dean** (Florey Institute of Neuroscience and Mental Health)
From Brain Transcriptomics to Blood Tests: Fact or Fantasy

Psychiatric disorders occur in individuals with a genetic predisposition who encounter a deleterious environmental factor that triggers biochemical changes in the CNS leading to symptom onset. It is postulated that changes in gene expression brought about by the inheritance of risk genes and the impact of environmental factors on epigenetic mechanism are the foundation for changes in the activity of biochemical pathways that underly the onset of symptoms. This has led to the use of high-throughput transcriptomics to identify changes in gene expression in post-mortem CNS from subjects with psychiatric disorder, particularly in the cortex as a

dysfunctional cortex is common to disorders such as schizophrenia, major depression and bipolar disorder.

In this presentation, the outcome of such studies using cortex from schizophrenia, bipolar disorder and major depressive disorder held in the Melbourne Psychiatric Brain Bank will be summarised after analyses using established approaches. In addition, data from a novel analysis using the full richness of data from studying the human transcriptome will be presented to argue that such an approach could lead to diagnostic and theragnostic tests for psychiatric disorders. The presentation will end with a summary of the challenges in translating this technology from CNS to blood, a step vital to create a clinical useful tool.

11:00am **Rachel Hill** (Monash University)
A National data linkage platform to identify predictors of mental illness

Most severe psychiatric disorders, such as schizophrenia, bipolar disorder and major depression, have neurodevelopmental origins. They first appear as subtle cognitive deficits in childhood. However, they are not identified until they have progressively worsened to manifest as psychiatric symptoms in late adolescence / early adulthood. There is no accurate way of identifying those with subtle changes before they become acutely unwell. In the absence of this information it is not possible to effectively prevent these disorders or to develop disease modifying interventions.

This large scale, data linkage project will provide the critical information required to predict cognitive trajectories that are associated with increased risk of mental illness. Our approach is to link NAPLAN performance to mental health outcomes later in life to identify predictors of mental illness. In collaboration with data linkage experts from the population health research network and Australian Centre for Family Studies with the department of psychiatry at Monash University this symposium presentation will describe a preliminary cohort of individuals born between 1995-2001 and currently diagnosed with a psychiatric disorder that have been linked to their NAPLAN educational performance outcomes. I will describe here trajectories of performance that increase risk for mental illness.

11:30am **Scott Clark** (University of Adelaide)
Multimodal Machine Learning for Prediction of the First Psychotic Episode

Psychotic illness has major personal and social impacts. Evidence suggests that early intervention improves outcomes however, clinical criteria for those at ultra-high risk of a first psychotic episode are not specific. Only around 30% of individuals identified as high risk go on to a first psychotic episode, while many of those that do not transition have poor long-term functional outcomes. Multimodal biological markers show potential to improve accuracy, however there have been problems with replication across cohorts. Models require test and training data sets which may be divided from the same sample. Potentially, the unintentional transference of information from the test data set to the training data set causes "data leakage" providing overly optimistic

estimates of model accuracy, limiting generalisability outside the study sample. The use of robust cross validation techniques embedded in a machine learning pipeline reduces the risk of data leakage. To illustrate the impact of rigorous cross validation we contrast results from methods implemented with and without a robust machine learning pipeline used in the analysis of prediction of transition to psychosis using baseline clinical, and biological data for cohort of patients identified as Ultra-high risk of psychosis.

SYMPOSIUM 4

10:00am – 12:00pm, Riverbank Room 8

Through the looking glass: Observing real time changes in brain circuitry

Chairs: Alison Canty (Wicking Dementia Research and Education Centre, University of Tasmania)

10:00am **Vincenzo De Paola** (Imperial College London)
Illuminating cortical circuit development and dysfunction in humanised models

Proper assembly of cortical circuitry is a critical step in brain development and maturation of high-order cognitive abilities. Despite their pivotal role, we do not yet have a clear understanding of how human cortical circuits develop in vivo, and why this process can fail leading to cognitive disturbances in neurodevelopmental conditions such as Down syndrome (DS). We recently established a new approach to study in real-time the assembly of human cortical circuits using transplanted donor-derived induced pluripotent stem cells and intravital longitudinal imaging. We found that human axons grew as bundles along vessels towards their cortical and subcortical targets, and remodelled mainly via branch-specific retraction and via the turnover of synaptic specializations. Axon and synaptic remodelling were accompanied by widespread oscillatory population activity. Finally, we demonstrated this approach by modelling DS, the most common chromosome abnormality in humans caused by trisomy of chromosome 21 (T21). Unexpectedly, we found that the early stages of developmental human axon pruning were unaffected in transplants from two individuals with DS, while dendritic spines were more stable and tended to be more abundant in T21 circuits compared to controls. We also discovered a reduction in oscillatory network activity in T21, demonstrating the potential of in vivo imaging in human tissue grafts for subject-specific modelling of cortical development and physiology.

10:30am **Catherine Blizzard** (University of Tasmania)
Do regional spine dynamics contribute to the vulnerability of brain regions to neurodegenerative disease such as Amyotrophic Lateral Sclerosis an Frontotemporal Dementia?

Neurodegenerative diseases produce an array of behavioural phenotypes, relating to the region of the brain affected. Why various brain regions are specifically

vulnerable to degeneration remains undefined. In an additional layer of complexity, diseases affecting specific regions (such as Amyotrophic Lateral Sclerosis (ALS) that affects the motor cortex and frontotemporal dementia (FTD), that affects the frontal and temporal lobes) frequently have different risk profiles between males and females. Using cranial windows we have mapped Layer V pyramidal dendrite spine turnover and stability over a 48 hour time-course (three imaging sessions) in adult Thy1-YFP mice at postnatal day (P) 60 and 90. Our studies indicate that male mice show a higher rate of spine turnover in the motor cortex in comparison to the somatosensory cortex in the juvenile mouse at P60 ($n=12$, $p<0.05$). This change is not mirrored in females. To investigate if these differences effect vulnerability to disease, spine turnover was investigated in the TDP-43A315T mouse model of ALS-FTD. At the pre-symptomatic time point of 60, the male TDP-43A315T motor cortex displayed a significant reduction in overall turnover of dendritic spines compared to controls, specifically in regards to mature spine types ($n=10$, $p<0.01$). These spine changes occur pre-symptomatically in the cortical region most susceptible to disease insults in ALS-FTD, and highlights the vulnerability of males to TDP-43-mediated alterations at the dendritic spine. This research provides insights into early disease events that can be utilised to understand region specific, activity-dependent disease pathology for future research and therapeutics to mitigate neurodegenerative diseases.

11:00am **Lucy Palmer** (Florey Institute of Neuroscience and Mental Health)
Imaging neural dynamics during goal-directed behaviour

Goal-directed behaviour is crucial for survival in dynamic environments. It typically involves the encoding and integration of sensory information from different modalities that leads to specific rewarded behaviours. However, how neurons integrate information from multiple sensory pathways and to what extent this influences behaviour is largely unknown. Here, we report how activation of auditory input influences coding in somatosensory cortex as well as somatosensory goal-directed behaviour. Using two-photon calcium imaging of mice previously injected with the calcium indicator GCaMP, calcium activity in layer 2/3 pyramidal neurons in the primary somatosensory cortex was assessed through a chronic window during goal-directed behaviour. We show that monosynaptic input from auditory cortex enhances distal dendritic $Ca2+$ responses and somatic action potential output in the somatosensory cortex. This effect was restricted to layer 2/3, but not layer 5, pyramidal neurons and was associated with enhanced performance during a sensory association task. Taken together, these results indicate that the distal dendrites of cortical layer 2/3 pyramidal neurons represent a site where multi-sensory information is encoded, leading to enhanced neuronal output and performance during processing of auditory and somatosensory input.

11:30am **Ethan Scott** (University of Queensland)
Sensory processing in larval zebrafish: perspectives from whole-brain calcium imaging

Traditionally, neural activity has been monitored in great detail for one or a few cells (as in electrophysiology) or brain-wide by methods that do not provide single-

cell resolution (such as functional MRI). The gap between these techniques has made it difficult to observe activity across large populations of neurons while regarding them as individual units. Because the nervous system is, ultimately, a highly interconnected network of neurons, this represents a major blind spot in our ability to describe the functioning brain.

Ethan Scott's group is interested in the neural mechanisms by which sensory stimuli are encoded and interpreted, and in how inputs from different sensory modalities are integrated in the brain. To address the problem described above, they have adopted optogenetic and microscopic techniques that allow calcium imaging across the entire zebrafish larval brain at single-cell resolution. In the work presented here, they have applied sensory stimuli to intact, alert larvae while observing the genetically-encoded calcium indicator GCaMP6. With house-built selective plane illumination microscopes (SPIM), they have observed large populations of neurons representing nearly the entire brain.

This presentation will provide an overview of this approach, including its strengths and limitations. Examples of recent work will include descriptions of the neural processing underlying vision, audition, vestibular perception, and water-flow detection, as well as the neural integration of stimuli across these modalities. It will also include the Scott lab's preliminary work using this approach to study sensory processing in models of psychiatric disease, using fmr1 mutant zebrafish as an example.

SYMPOSIUM 5

10:00am – 12:00pm, Hall L

Presidential Symposium: Synaptic mechanisms of plasticity and memory

Chair: Cliff Abraham (Australasian Neuroscience Society, Brain Research New Zealand and University of Otago)

10:00am **Haruhiko Bito** (University of Tokyo)
Regulation of Long-term memory via inverse synaptic tagging of activity-induced Arc

Deciphering the intricate and interactive relationship between the information encoded in the genome and the ongoing synaptic activity is critical for understanding the molecular and cellular signaling underlying long-term memory formation and maintenance. To systematically dissect this question, we have investigated the molecular basis of the signaling from synapses to the nucleus and from the nucleus to the synapses, which crucially determines the persistence of synaptic plasticity. Activity-induced Arc/Arg3.1 expression has been proposed to regulate surface expression of AMPA receptors (AMPA-Rs), although the mechanisms involved remain unclear. We previously found an inverse synaptic tagging rule by which Arc preferentially targeted weaker, rather than stronger,

synapses. Whether this critically affected the temporal dynamics of spine AMPA-R turnover, however, remained unexplored. To address this issue, we analyzed subunit-specific AMPA-R lateral diffusion during structural plasticity in wildtype and Arc-knockout hippocampal neurons. Long-term potentiation (LTP) of surface GluA1/GluA2 in expanded spines was normal both in wildtype and Arc-KO neurons. However, removal of surface GluA1/GluA2 from non-expanded spines was slow but significant in wildtype neurons, during the late phase of plasticity. This late-phase heterosynaptic depression was disrupted in Arc-KO neurons, consistent with inverse synaptic tagging. Thus, activity-dependent Arc expression may regulate dynamics of distinct AMPA-R complexes during multiple phases of LTP in an input-regulated manner.

10:30am **Graham Collingridge** (University of Toronto)
Calcium permeable AMPARs and synaptic plasticity in the hippocampus

In synaptic plasticity, the role of NMDARs was first identified and has been best characterized at synapses made between CA3 and CA1 pyramidal neurons in the hippocampus. Calcium-permeable (CP) AMPARs have been implicated in synaptic plasticity at these synapses but their roles are poorly understood. We have studied long-term potentiation (LTP) at these synapses in slices from adult rats and mice in response to various patterns of theta burst stimulation (TBS). We have found that CP-AMPARs are required for the PKA- and protein synthesis-dependent component of LTP that is induced when a spaced TBS induction protocol is used (inter-episode interval of 10 min). For a short time window following induction, CP-AMPARs are present at the synapse resulting in inward rectification and an increase in single channel conductance. CP-AMPARs are also expressed at neighbouring synapses (i.e, a control pathway not receiving TBS) where they serve as a synaptic tag to enable a weak input to generate protein synthesis-dependent LTP. The results demonstrate a role for CP-AMPARs in a form of hippocampal heterosynaptic metaplasticity.

11:00am **Johanna Montgomery** (University of Auckland)
The role of plasticity in disorders of the central and peripheral nervous systems

Synaptic plasticity is an activity-dependent change in synaptic strength. Two major forms of plasticity have been well defined, longterm potentiation (LTP) and longterm depression (LTD), which represent an increase or decrease in synaptic strength respectively. Synaptic plasticity underpins cognitive, motor, and sensory behaviours, and changes in the ability to induce, express, or maintain plasticity occur with neurodevelopmental and neurodegenerative diseases. In Autism Spectrum Disorders (ASD), deficits in excitatory synaptic function occur as a result of ASD-associated mutations in the Shank family of synaptic structural proteins (Arons et al., 2012). Recently we have observed that these changes can be reversed by zinc supplementation (Arons et al., 2016). Moreover, zinc supplementation can reverse ASD-associated behavioural deficits in social interaction, repetitive behaviours, and anxiety (Fourie et al., 2018). These data provide promise for zinc-related therapies in ASD. In other plasticity-related research, we have also sought to examine plasticity outside the brain, in the peripheral nervous system where "little brains" are located on the heart surface. These neurons are critical for neural control of heart rhythm.

Our data show that plasticity also occurs in the neurons of the little brains of the heart with pathological changes in heart function, particularly in spontaneous activity and synaptic protein expression. Together these data show that plasticity is critical in normal and pathological conditions, and harnessing plasticity mechanisms is critical for understanding and treating disorders of the nervous system.

11:30am **Joanna Williams** (University of Otago)
Bilateral regulation of histone deacetylase activity and gene expression is associated with an intermediate form long-term potentiation *in vivo*

Long-term potentiation (LTP) is a synaptic plasticity mechanism critical to long-term memory. LTP induced in vivo is associated with rapid upregulation and subsequent downregulation of gene expression. This temporal shift in gene expression is predicted to be partly mediated by histone deacetylases (HDACs), epigenetic inhibitors of gene expression. Further, pharmacological inhibition of HDACs has previously been shown to enhance LTP persistence in vitro and been proposed as a therapeutic intervention to alleviate memory impairments. To explore the contribution of HDACs to the persistence of LTP, we examined HDAC1 and HDAC2 activity over a 24 h period following unilateral LTP induction in vivo in the rat dentate gyrus. We found changes in HDAC1 and HDAC2 activity in both the stimulated and unstimulated hemispheres, with the largest increase in activity occurring 20 min post-HFS. During these timepoints of heighted activity, Chromatin immunoprecipitation showed that HDAC1 and HDAC2 are enriched at distinct sets of genes in both hemispheres. Further, we found the HDAC inhibitor Trichostatin A enhanced LTP2 an intermediate, protein synthesis dependent form which has not previously associated with alterations in transcription. The inhibitor had no effect on the persistence of LTP3. This suggests that mechanisms which have previously been attributed to long-term plasticity may instead only be involved in the intermediate stages of LTP maintenance.

SYMPOSIUM 6

1:45pm – 3:45pm, City Rooms 1&2

Technical developments at the frontier of neuroscience

Chair: Timothy Bredy (The University of Queensland)

1:45pm **Dan Ohtan Wang** (Kyoto University)
Dynamic localization of RNA molecules and techniques to visualize them

mRNA localization and regulated translation provide a means of spatially restricting gene expression within each of the thousands of subcellular compartments made by a neuron, thereby vastly increasing the information coding capacity of a neuronal transcriptome. To understand how dynamic our gene expression regulation can be in three dimensions, cutting-edge technologies have been developed to visualize RNA molecules in living cells and living brains. We have focused on using hybridization-sensitive fluorescent probes to visualize abundant RNA species in living cells, brain slices, and now in intact brain. I will discuss the insights the new

technologies have helped reveal. Not only will the techniques be presented, but their advantages and disadvantages will also be thoroughly discussed toward developing innovative RNA detection technologies.

2:15pm **Ryan Lister** (The University of Western Australia)
Editing the epigenome

Covalent modifications of DNA and histones play critical roles in the regulation of gene expression, cell activity, development, and disease. DNA methylation is a critical layer of the vertebrate epigenome, however despite several decades of investigation, the precise roles of DNA methylation in the control of genome and cell activity are still not clearly understood. A major obstacle in deciphering the mechanistic roles of epigenomic modifications has been the inability to precisely control and change the modification states in the genome. However, genome editing technologies are now rapidly being repurposed to achieve editing of epigenomic modifications where desired in the genome, in order to elucidate the causal relationships between these modifications and genome regulation, and as artificial regulatory tools to control cell activity and identity. We employed a broadly active artificial epigenome modifying protein to achieve genome-wide anipulation of promoter DNA methylation, enabling comprehensive assessment of its effects upon transcription and histone modifications, and the stability of artificially induced methylation. Furthermore, we have developed new CRISPR-Cas9 based tools that enable highly specific addition or removal of DNA methylation at desired locations in the genome in a controlled fashion. In addition to optimizing the efficacy and specificity of these functional epigenomics tools, we have utilized them to explore the sensitivity of DNA binding proteins to DNA methylation state. Overall, recent developments in epigenome editing tools are providing new insights into the role of covalent genome modifications in regulating gene expression, and new platforms for the manipulation of cell activity and identity.

2:45pm **Phillipa Taberlay** (University of Tasmania)
geNOMeC maps of neuronal epigenetic changes in Alzheimer's disease

The epigenome is comprised of multiple regulatory layers including the physical positioning of nucleosomes, DNA methylation and histone modifications. These mechanisms act in concert and their combinations create an intricate epigenetic pattern along the DNA. Precise epigenetic layering ensures that the gene expression program of a cell is tightly controlled and facilitates appropriate cell behaviour and function. Thus, every cell type has a unique epigenetic pattern that is subject to changes during ageing and across progression in disease contexts. Indeed, the brain is highly complex and comprised of multiple cell types including neurons and glia, which can exhibit vastly divergent epigenetic signatures in disease states. Recent research highlights the importance of isolating different cell types for epigenetic analyses rather than using whole brain homogenate. The neuroscience and epigenetics fields are both moving towards cell type specific investigations and while

we can isolate neuronal nuclei from human brain tissue, these samples are a precious resource. We are developing an assay that can measure three epigenetic layers simultaneously across individual DNA molecules, called 'geNOMeC' (genome-wide nucleosome occupancy, methylation and ChIP-sequencing) to both address this limitation and to improve our current methods. The key advantage of geNOMeC is that we will be able to obtain a readout of three epigenetic layers directly, thus avoiding any association bias that is a caveat of epigenetic data integration. Our goal is to develop a technique that is broadly applicable to almost any organism and disease state and to apply this to neurons obtained from a 'healthy' aged cohort and those with Alzheimer's pathology.

3:15pm **John Lin** (University of Tasmania)
New optogenetic tools for the modulation of membrane excitability, synaptic plasticity and learning

In this talk, I will describe some recent works from my laboratory on the development of new optogenetic tools to modulate membrane excitability and intracellular signalling. We have developed a channelrhodopsin with 3 stable photocycle states from our mutagenesis screen of ReaChR, which may be useful in the modulating membrane excitability of neurons. We also initiated a mutagenesis screen of the anion-conducting channelrhodopsin ZipACR with some mutants showing interesting spectral and kinetic properties. In addition to modulating membrane excitability, we are also working on optogenetic modulation of intracellular signalling. For intracellular signalling, we have developed optogenetic tools to activate BDNF/TrkB signalling, inhibit Gq signalling and modulate calcineurin signalling. With the optogenetic BDNF/TrkB system, we can detect the membrane upregulation of AMPA-type glutamate receptors after illumination, indicative change in synaptic plasticity. With light-mediated inhibition of Gq signalling, we can suppress learning of mating behaviour in drosophila. Optogenetic inhibition of calcineurin signalling and Gq signalling can also alter behaviour of C. elegans. These tools will be made available for the neuroscientific community to study neuronal signalling and neurocircuitry.

SYMPOSIUM 7

1:45pm – 3:45pm, City Rooms 3&4

Glia in neurotransmission

Chair: Kimberley Pitman (University of Tasmania)

1:45pm **Raphael Ricci** (University of Tasmania)
Kainate receptor signalling in Multiple Sclerosis and Schizophrenia

Recent studies have identified genes that are associated with Multiple Sclerosis (MS). However, failed to explain the central nervous system (CNS) degeneration that continues to occur, even in the absence of immune infiltrates. This neurodegeneration typically involves oligodendrocyte death, myelin loss, and axon

disruption and retraction, leading to cognitive impairment and loss of motor and sensory function. In addition, people with MS usually experience schizophrenic symptoms and have high risk of developing schizophrenia. A family study carried out at University of Tasmania by Dr. Jac Charlesworth identified GRIK4 gene as high genetic risk associated with MS development. The same gene was previously described as associated with susceptibility to develop schizophrenia. GRIK4 encodes for a kainate receptor subunit, an ionotropic glutamate receptor. Oligodendrocyte progenitor cells (OPCs) express a variety of cell surface receptors, including glutamate receptors. Therefore, the kainate receptor mutation could be affecting oligodendrocyte lineage cells behaviour contributing to MS and Schizophrenia pathology. RNA sequencing data indicates GRIK4 is highly expressed in the brain, principally by OPCs. We performed a western blot analysis of mouse tissue and it showed Gluk4 expression occurs in the brain and spinal cord but not in the thymus and spleen. Itsuggests GRIK4 mutation is potentially affecting cells of the CNS and not immune cells. Furthermore, DNA sequencing analysis was used to prove that Grik4 can be successfully knock out from the mouse brain. The major aim of my project is to understand the pathological signals influencing oligodendrocyte death and myelin loss observed in MS, as well as the physiological signals that promote oligodendrocyte generation and myelin repair. Therefore, kainate receptor dysfunction could be affecting oligodendrocyte lineage cells behaviour and contributing to MS pathology onset and progression.

2:15pm **Nicola Allen** (Salk Institute for Biological Studies)
Astrocyte regulation of neuronal synapses

Our work investigates how neuronal synapses are regulated throughout life: from the formation of synapses during development, to the remodelling of synapses in the adult in response to experience, to the loss of synapses in aging. We approach this not just by studying neurons, but by asking how non-neuronal glial cells, specifically astrocytes, regulate synapse number and synaptic function. I will present our recent work identifying proteins secreted by developing astrocytes that are sufficient to induce immature synapses to form, and a second signal secreted by older astrocytes that induces synapse maturation and limits synaptic plasticity. Further, I will present our work examining how astrocyte properties change in the aging brain, producing an environment that will allow synapse loss and potentially predispose the brain to the development of neurodegenerative disorders.

2:45pm **Yasuyuki Osanai** (Monash University)
Length of myelin internodes of oligodendrocytes is controlled by microenvironment influenced by axonal activity in sensory deprived mouse models

Oligodendrocytes myelinate the axons of neurons in a tightly regulated manner during postnatal development and substantially increase the velocity of neuronal impulse conduction in the central nervous system. Neuronal axons projecting from multiple brain regions fasciculate as they transit through regions of white matter; however, it is unclear whether oligodendrocytes selectively ensheath a particular set of axons or do so randomly within the mammalian brain. We developed a novel method

to visualise oligodendrocyteaxon interactions in mouse white matter by combinatorial injection of attenuated rabies virus and adeno-associated virus. We found that some populations of callosal and chiasmal oligodendrocytes predominantly ensheathed axons derived from a specific brain region, while others did not discriminate between axons of different origin, suggesting heterogeneity in axon-selectivity of oligodendrocytes. We further examined the effects of sensory deprivation on myelination by unilateral eyelid suturing or whisker cauterisation. Oligodendrocytes did not discriminate between axons derived from control regions or inputdeprived regions in unilaterally sensory deprived mice. Importantly, the average length of the myelin sheath formed by individual oligodendrocytes changed as a function of the relative abundance of control versus sensory-input deprived axons, indicating that an abundance of deprived axons near an oligodendrocyte influences the myelination program of a single oligodendrocyte.

3:15pm **Junhua Xiao** (Florey Institute of Neuroscience and Mental Health)
Neurotransmission in myelin-forming glial cells and function

Increasing evidence suggests that neuron-glia signal transmission is critical to CNS function in both health and disease. However, little is known in the roles that neuron-oligodendrocyte synaptic transmission play in myelination. Precisely understanding how neurotransmission regulates myelination is not only important to the biology of human demyelinating diseases such as multiple sclerosis but other neurodegenerative diseases where demyelination is a primary or secondary neural pathology. In this talk, I will present our latest and unpublished findings that the neurotrophin receptor TrkB is a novel neuronal signal that regulates synaptic transmission (e.g. glutamatergic neurotransmission) from neurons to oligodendrocyte progenitor cells (OPCs), highlighting the importance of a pre-synaptic mechanism of action in driving the myelinating process. Together, our findings are highly significant and will provide new insights into the mechanisms underpinning CNS function and plasticity in both health and diseases.

SYMPOSIUM 8

1:45pm – 3:45pm, Riverbank Room 7

Mechanisms of Pain: From the periphery to the brain

Chair: Andrea Harrington (University of Adelaide)

1:45pm **Stuart Brierley** (Flinders University)

Peripheral targets for treating chronic visceral pain: From tarantula toxins to itchy colons

This presentation will describe critical components of peripheral sensation. This includes signalling from enterochromaffin cells, and sensory afferents that contribute to the neuroplasticity within visceral nociceptive pathways in response to inflammation of the gut and following recovery of inflammation. These studies provide evidence for the role of specific ion channels and receptors whose expression and function are altered by inflammation and contribute to chronic abdominal pain. In particular the presentation will focus on a) new insights into the coupling between GPCRs and ion channels in rodent and human DRG neurons in disease states, b) highlight the adaptation of pruritogenic signalling mechanisms to provide novel signalling pathways in the viscera, and c) describe how these findings can be translated into the clinic to provide novel peripherally restricted treatments of visceral pain.

2:15pm **Yves De Koninck** (Université Laval & CERVO Research Centre)
Spinal inhibition in health and disease

Prof. Yves De Koninck Yves De Koninck is Professor of Psychiatry & Neuroscience at Université Laval, Scientific Director of the CERVO Brain Research Centre and Director of Research of the Quebec Integrated University Health and Social Services Centre, Fellow of the Canadian Academy of Health Sciences and of the Royal Society of Canada. While he dedicated his career to understanding the mechanisms underlying chronic pain, he has been a strong proponent of transdisciplinarity, leading efforts to bridge across disciplines, create collaborative research environments and train young scientists at the interface of research fields. He now leads Sentinel North a global initiative to harness the power of light for the benefit of health, environment and sustainable development in the North. For his transdisciplinary efforts he received the Jacques-Rousseau Prize from Acfas, the 2018 Brockhouse Canada Prize and the 2019 Emily Gray Award from the Biophysical Society.

2:45pm **Brett Graham** (University of Newcastle)
Using optogenetics to link spinal circuits and pain behaviour in mice

The spinal dorsal horn is the primary recipient zone for sensory information from the body including touch, pain, thermal, and itch related signals. This region is also endowed with a large population of interneurons that provide a substrate for substantial processing before refined sensory signals are relayed to higher brain structures by a much smaller population of projection neurons. Despite this general understanding, the precise role of specific interneuron populations, connectivity in microcircuits, and contribution to sensory experience remains to be fully resolved. This presentation will describe how our group has combined optogenetic approaches with reduced in vitro preparations, deeply anaesthetised and freely behaving mice to study the properties of spinal microcircuits and how they contribute to sensory experience. Experiments will be described with particular focus on technical details for each preparation. The data described will be used to propose novel roles for a specific excitatory interneuron population that expresses the calcium binding protein

calretinin, unmasking an amplification circuit capable of sustaining spinal excitation and generating a distinct pain response profile.

3:15pm **Elena Bagley** (The University of Sydney)
Central sensitization of the spino-parabrachial-amygdala pathway that outlasts a brief nociceptive stimulus

Chronic pain is disabling because sufferers form negative associations between pain and activities, such as work, leading to the sufferer limiting these activities. Pain information arriving in the amygdala is responsible for forming these associations and contributes to us feeling bad when we are in pain. Ongoing injuries enhance the delivery of pain information to the amygdala. If we want to understand why chronic pain can continue without ongoing injury, it is important to know whether this facilitation continues once the injury has healed. In this talk, I will describe our work investigating how peripheral noxious stimulus alone, without ongoing injury, is able to enhance exaggerated and persistent pain information input into the amygdala. I will describe a range of approaches we use to establish that this information pathway can be primed so that subsequent injuries may feel even worse and the associative learning that results in pain-related avoidance may be promoted. I will also discuss the optogenetic approaches we use to selectively activate key synapses to establish the pharmacology mediating persistent amygdala activation.

SYMPOSIUM 9

1:45pm – 3:45pm, Riverbank Room 8

Deconstructing the synapse: How pre- and post-synaptic proteins come together to fine tune synaptic strength in health and disease

Chairs: Nela Durisic (The University of Queensland) & Ramón Martínez-Mármol (The University of Queensland)

1:45pm **Subhojit Roy** (The University of California)
Gene-editing in sporadic Neurodegenerative diseases

CRISPR/Cas9 therapeutics is poised to transform the future of medicine. However, application to neurodegenerative diseases has been limited, and there is scepticism regarding the utility of gene-editing in these incurable illnesses. While some apprehension stems from a reluctance in questioning traditional paradigms like small molecules – that have been generally disappointing – a more legitimate concern is that conventional gene-editing strategies would only be applicable to the small number of patients who have inherited disease. Gene delivery to brain has also traditionally been a limiting factor in the past. This talk will focus on new gene-editing strategies that 'tweak' endogenous proteins to render then pathologically silent; while preserving physiologic activity. These strategies can be potentially applied to all

Alzheimer's disease, and we will also highlight recent advances in delivering genetic material into the brain using viral vectors and nanoparticles.

2:15pm **Frederic Meunier** (The University of Queensland)
Nanoscale organisation of the exocytic machinery

Communication between cells relies on regulated exocytosis, a multi-step process that involves the docking, priming and fusion of vesicles with the plasma membrane, culminating in the release of neurotransmitters and hormones. Key proteins and lipids involved in exocytosis are subjected to Brownian movement and constantly switch between distinct motion states which are governed by short-lived molecular interactions. Critical biochemical reactions between exocytic proteins that occur in the confinement of nanodomains underpin the precise sequence of priming steps which leads to the fusion of vesicles. The advent of super-resolution microscopy techniques has provided the means to visualize individual molecules on the plasma membrane with high spatiotemporal resolution in live cells. These techniques are revealing a highly dynamic nature of the nanoscale organization of the exocytic machinery. In this talk, I will focus on soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) syntaxin-1, which mediates vesicular fusion and reflect on recent studies which have revealed the mechanisms regulating syntaxin-1 nanoclustering on the plasma membrane.

2:45pm **Sarah Gordon** (Florey Institute of Neuroscience and Mental Health)
Neurodevelopmental synaptopathies: Presynaptic dysfunction in intellectual disability

Neurodevelopmental disorders (including intellectual disability, autism spectrum disorder and movement disorders) affect 2-5% of children worldwide. The cause of neurological impairment in the vast majority of individuals with these brain disorders remains unknown. However, advances in gene technology is now enabling the identification of novel substrates underlying neuronal dysfunction. This provides a new starting point for understanding the relationships between specific genetic mutations, brain function, neurodevelopment and cognition. Moreover, this provides a novel avenue for uncovering the molecular mechanisms underlying normal protein function.

Importantly, mutations in proteins involved in neurotransmitter release and synaptic vesicle cycling have been identified in a range of neurodevelopmental disorders, including intellectual disability, epilepsy, and autism spectrum disorders. Alterations to the efficiency with which exocytosis or endocytosis occurs have adverse effects on neurotransmitter release, and therefore on all coordinated neuronal activity.

Newly identified mutations in key presynaptic proteins including synaptotagmin-1 and synaptophysin have been found in children with intellectual disability. Model systems were used to examine the effect on these mutant proteins on presynaptic function,

revealing mutation-specific effects on exocytosis, endocytosis and protein trafficking. These findings provide a framework for unravelling how disruption to synaptic vesicle dynamics and neurotransmitter release produces overlapping and distinct clinical phenotypes.

3:15pm **Patricio Opazo Olavarria** (The University of Queensland)
Compensating and recovering from dendritic spine loss in spinopathologies

Brain disorders as diverse as schizophrenia (SCZ), autism spectrum disorders (ASD), depression (D) and Alzheimer's disease (AD) specifically target dendritic spines, small dendritic protrusions that accommodate most excitatory synapses in the brain. In particular, most of these brain disorders are characterized by a striking reduction in the number of dendritic spines. Although these "spinopathologies" have different molecular etiologies and impact different brain regions, several studies suggest that neurons implement the same strategies to compensate for the loss of dendritic spine and the subsequent loss in neuronal connectivity. In this talk, I will introduce an optogenetic tool we have recently developed for the artificial elimination of dendritic spines using light as a way to model "spinopathologies". We have taken advantage of this optical probe to eliminate dendritic spines with a high spatiotemporal control and have examined the emergence of compensatory mechanisms over time. Using this optical tool we hope to uncover the molecular mechanisms underlying synaptic compensation with the ultimate goal of boosting them in the fight against spinopathologies.

SYMPOSIUM 10

1:45pm – 3:45pm, Hall L

The Stressed Brain: Translating Preclinical Concepts into Therapeutic Realities

Chair: Anand Gururajan (University of Sydney)

1:45pm **Olivia O'Leary** (University College Cork)
An emerging therapeutic target for stress-related psychiatric disorders

FK506 binding protein 51 (FKBP51) is a co-chaperone protein of the glucorticoid receptor (GR) that regulates GR's translocation from the cytoplasm to the nucleus. GR-mediated negative feedback of the Hypothalamic-Pituitary-Adrenal axis is frequently disrupted in the stress-related psychiatric disorder, depression, and has been implicated in treatment-resistant depression. Thus, regulators of GR activity are attractive targets for antidepressant drug development. Emerging evidence from clinical and preclinidal studies suggest that dis-inhibition of FKBP51 is associated with susceptibility to phenotypes associated with stress-related pychiatric disoders, while inhibition of FKBP51 may increase stress resilience and may have antidepressant-like effects. Dr Olivia O'Leary will present unpublished data on the effects of FKBP51 inhibition on depression-, anxiety- and antidepressant-like behaviour in a mouse model of chronic psychosocial stress, as well as the effects of FKBP51 inhibition on

hippocampal neurogenesis and neurite outgrowth, mechanisms previously implicated in anatidepressant action.

2:15pm **Christopher Dayas** (University of Newcastle)
Channel Rhodopsin (ChR2)-assisted circuit mapping of novel stress control pathways

My group has been investigating how specific cell groups within the hypothalamus such as corticotrophin-releasing hormone (CRH)-expressing hypothalamus (PVN) are recruited by imminent threats. We are interested in the circuitry controlling innate behaviours to threat, with a prediction that long lasting dysregulation of these pathways contribute to maladaptive stress coping and neuroendocrine function – cardinal features of stress-related disorders such as depression and anxiety. Using a combination of techniques including optogenetics, CLARITY and electrophysiology we have recently identified a previously uncharacterised glutamatergic pathway originating from medial amygdala (MeA) neurons that express single-minded 1 (Sim1) and directly target CRH cells in the PVN that controls neuroendocrine and behavioural responses to threat. These findings will be discussed in the context of stress-related illness and PTSD.

2:45pm **Anthony Hannan** (University of Melbourne)
Neurobiological effects of stress and associated glucocorticoids in mouse models of brain disorders

We have been investigating how various environmental manipulations selectively alter gene expression, cellular plasticity and associated cognitive processes and behaviours. Huntington's disease (HD) is one of over 40 tandem repeat disorders and involves a triad of psychiatric, cognitive and motor symptoms. In a transgenic mouse model of HD we have demonstrated that environmental enrichment and exercise can delay onset of the affective (depressive-like), cognitive and motor endophenotypes. These findings have been extended to included stress and stress hormone (glucocorticoid) manipulation in HD mice and mouse models of psychiatric disorders, including depression and anxiety disorders. These approaches may also facilitate the development of 'enviromimetics' for a variety of brain disorders known to be modulated by environmental stimuli. We have also explored the transgenerational effects of paternal environmental exposures. Our findings reveal significant experience-dependent effects on offspring via transgenerational epigenetic inheritance, which occurs via epigenetic modifications in the sperm of the fathers. We are exploring the impact of specific environmental and pharmacological factors, including stress hormone elevation, and the relevance of these discoveries in mice to human transgenerational epigenetics. Our findings, and their relevance to the proposed transgenerational inheritance of increased predisposition to various brain disorders, have major public health implications.

3:15pm **Dagmar Koethe** (University of Sydney)
Endocannabinoids and Neuropeptides in CSF and serum from borderline personality disorder and PTSD patients

Due to its neuromodulatory potential, its role in emotion regulation and in extinction of aversive memory, the endocannabinoid system might be another potential candidate system in both, posttraumatic stress disorder (PTSD) and/or borderline personality disorder (BPD). We addressed this question by analyzing serum and cerebrospinal fluid (CSF) levels of the endocannabinoids anandamide and 2-arachidonoyl-sn-glycerol (2-AG) and related endogenous lipids oleoylethanolamide and palmitoyletnanolamide. Using HPLC-MS/MS we analyzed human serum samples from patients suffering from BPD or PTSD as well as matched healthy controls. In addition, we measured these and the neuropeptides oxytocin and vasopression in CSF and serum samples in an independent cohort of BPD patients and matched controls. Serum levels of anandamide and 2-AG were significantly elevated in BPD, while oleoylethanolamide was significantly elevated in PTSD when compared to controls. In CSF, levels of anandamide as well as oleoylethanolamide and palmitoyletnanolamide were significantly decreased in BPD, while 2-AG was not affected. This was not correlated to decreased CSF but not serum OXT levels or VPA levels. Our data suggests that the endocannabinoid system may play an independent functional role in the pathophysiology of BPD and PTSD, warranting further investigation of this contribution.

WEDNESDAY 4 DECEMBER 2019

SYMPOSIUM 11

10:00am – 12:00pm, City Rooms 1&2

Vision, information processing and cognition

Chair: Ehsan Arabzadeh (Australian National University)

10:00am **Karin Nordstrom** (Flinders University)
Target detection in the hoverfly visual system

Despite being equipped with low-resolution eyes and tiny brains, many insects are able to rapidly detect and use visual information. For example, many insects, including hoverflies, are amazingly good at pursuing small moving targets even in highly complex surrounds. Subsequently, animals whose survival depends on target detection are often equipped with sharply tuned visual systems. Supporting their high-speed pursuits, which are amazing considering the relatively poor optical input, the optic lobes harbor sharply tuned neurons as well as neurons that are tuned to self-generated optic flow. Target tuned neurons in the hoverfly and dragonfly brain continue to respond robustly to target motion even when displayed against syn-directional background clutter. Importantly, in diptera, the encoding of visual information by the descending neurons, which are more directly involved in

generating the behavioral output, has received less attention. To redress this deficiency we have identified target selective descending neurons in the hoverfly ventral nerve cord. As opposed to the target tuned neurons in the optic lobes, we find that dipteran target-selective descending neurons (dTSDNs) only respond to target motion if the background is stationary or moving slowly, moves in the opposite direction, or has unnaturalistic spatial characteristics. In contrast, optic flow sensitive neurons in the hoverfly ventral nerve cord give stronger responses when stimulated with background images with naturalistic spatial statistics. As the descending neurons are close to behavioral output, it is important to understand more about their neurophysiology, as these findings affect our interpretation of target-tracking behaviors.

10:30am **Stephen Williams** (Queensland Brain Institute)
N/A

11:00am **Paul Martin** (University of Sydney)
New Insights into Ancient Visual Pathways

High-acuity vision in humans and other diurnal primates depends on two main nerve pathways (called Parvocellular [P] and Magnocellular [M]) which densely innervate the central retina at the fovea, and deliver spatially precise nerve signals to the brain. But in addition to P and M cells there are about 20 other pathways, which send a variety of low spatial resolution messages to the brain. I will show some new insights we have gained about the physiology and anatomical connections of these evolutionary ancient pathways.

11:30am **Jason Mattingley** (Queensland Brain Institute)
Understanding the role of prediction in sensory encoding

At any given moment the brain receives more sensory information than it can use to guide adaptive behaviour, creating the need for mechanisms that promote efficient processing of incoming sensory signals. One way in which the brain might reduce its sensory processing load is to encode successive presentations of the same stimulus in a more efficient form, a process known as neural adaptation. Conversely, when a stimulus violates an expected pattern, it should evoke an enhanced neural response. Such a scheme for sensory encoding has been formalised in predictive coding theories, which propose that recent experience establishes expectations in the brain that generate prediction errors when violated. In this talk I will present findings from experiments in humans and mice in which we asked whether the encoding of elementary visual features is modulated when otherwise identical stimuli are expected or unexpected based upon the history of stimulus presentation. In human participants we employed electroencephalography to measure neural activity evoked by gratings of different orientations, and used multivariate forward modelling to determine how orientation selectivity is affected for expected versus unexpected stimuli. Using an analogous visual paradigm in awake head-fixed mice, we used two-photon calcium imaging to quantify orientation tuning of individual neurons in the primary visual cortex to expected and unexpected gratings. Results revealed enhanced orientation tuning to unexpected visual stimuli, both at the level

of whole-brain responses and for individual visual cortex neurons. I will discuss the implications of these findings for predictive coding theories of sensory encoding.

SYMPOSIUM 12

10:00am – 12:00pm, City Rooms 3&4

Parkinson's disease: from pathogenesis to regeneration

Chair: Lachlan Thompson (Florey Institute of Neuroscience and Mental Health)

10:00am **Glenda Halliday** (University of Sydney)
The role of a-synuclein in dopamine neuron degeneration in Parkinson's disease

Intracellular a-synuclein (a-syn)-rich protein aggregates called Lewy pathology (LP) and neuronal death are commonly found in the brains of patients with clinical Parkinson disease (cPD). It is widely believed that LP appears early in the disease and spreads in synaptically coupled brain networks, driving neuronal dysfunction and death. However, post-mortem analysis of human brains and connectome-mapping studies show that the pattern of LP in cPD is not consistent with this simple model, arguing that, if LP propagates in cPD, it must be gated by cell- or region-autonomous mechanisms. Moreover, the correlation between LP and neuronal death is weak. This presentation will discuss the evidence for and against the spreading LP model, as well as evidence that cell-autonomous factors govern both a-syn pathology and neuronal death.

10:30am **Clare Parish** (Florey Institute of Neuroscience and Mental Health)
Advancing stem cell and gene therapy for Parkinson's disease

The derivation of neurotransmitter and region-specific neuronal populations from human pluripotent stem cells (hPSC) provides impetus for advancing cell therapies into the clinic. At the forefront is our ability to generate midbrain dopaminergic progenitors, suitable for transplantation in Parkinson's disease. However pre-clinical studies have highlighted the relatively low proportions of dopamine neurons within these grafts and their inferior plasticity, particularly in comparison to human fetal grafts. Utilising novel reporter lines we have recently demonstrated the benefit of (FACS) isolation of ventral midbrain progenitors prior to transplantation – resulting in smaller grafts, enriched with dopamine neurons that are capable of reversing Parkinsonian motor deficits in rats. Furthermore, we have examined the potential of modifying the host environment, through the viral delivery of a developmentally critical molecule, glial cell-line derived neurotrophic factor (GDNF), to influence the survival, integration and function of transplants. We tracked the response of dopaminergic progenitors implanted into either a GDNF-rich environment or following delayed exposure to the neurotrophin. We demonstrate that timing of exposure to GDNF had differing effects on survival, plasticity, dopamine metabolism and overall motor function. These results highlight the potential of combined cell-

sorting and targeted neurotrophic gene therapeutic strategies to improve cell transplantation outcomes for PD.

11:00am **Deniz Kirik** (University of Lund)
Gene therapy for Parkinson's disease: GDNF and □-synuclein lowering approaches

Gene transfer is a promising drug delivery method of advanced therapeutic entities for Parkinson's disease. One advantage over conventional therapies, such as peripheral delivery of the dopamine pre-cursor l-DOPA, is site-specific expression of proteins with regenerative, disease-modifying and potentially neuroprotective capacity. Several clinical trials have been performed to test the capacity of glial-cell line derived neurotrophic factor and neurturin to rescue degenerating dopaminergic neurons in the substantia nigra and their axon terminals in the striatum by delivery of these neurotrophic factors either as purified protein or by means of viral vector mediated gene delivery to the brain. Although gene therapy approaches tested so far have been shown to be safe, none met their primary endpoints in phase II clinical trials designed and powered to test the efficacy of the intervention. Here I discuss the state-of-the-art in the field, how different technical parameters were translated from pre-clinical studies in non-human primates to clinical trials, and what these trials taught us regarding important factors that may pave the way to the success of gene therapy for the treatment of Parkinson's disease.

11:30am **Cedric Bardy** (Flinders University)
Genetic predispositions of Parkinson's disease revealed in patient-derived brain cells

Modelling central nervous system diseases in vitro with human induced pluripotent stem cells (iPSC) is still in its debut, yet translation is urgently needed, and we need to anticipate the next steps of this exciting experimental approach to bridge translational gaps. Parkinson disease (PD), being the second most prevalent neurological disorder and still lacking a cure, has been the focus of intense investigations. I will discuss the interplay between genetic predispositions and brain cell functions in people living with Parkinson's. I will present a metadata analysis of 287 hiPSC-derived neuronal lines from 51 recent independent original research articles, which pointed towards specific impairments of neurons from Parkinson's patients. Despite the heterogenous nature of the disease, this recent work reveals the potential for converging molecular pathways prior to neurodegeneration in familial and sporadic Parkinson's disease.

SYMPOSIUM 13

10:00am – 12:00pm, Riverbank Room 7

Computational Psychiatry

Chairs: Marta Garrido (Queensland Brain Institute, The University of Queensland) & Carsten Murawski (The University of Melbourne)

10:00am **Bernard Balleine** (University of New South Wales)
Hierarchical and network models of decision-making and specific psychopathology

Goal-directed control depends on constructing a model of the world that maps actions onto specific outcomes, allowing choice to remain adaptive when outcome values change. Such actions are, therefore, highly adaptive but computationally expensive and subject to disturbance from brain changes associated with psychiatric conditions. In such cases the flexibility of goal-directed control is lost and behaviour often becomes rigid or habitual and so subject to errors of various kinds. Understanding the nature of habits and their neural bases is therefore of some value as is the ability to generate and model behavioural tests sensitive to the transition from goal-directed to habitual control. Here I consider recent models of habit, the data on which they are based and the neural structures implicated in their control. Such approaches have been relatively successful in characterising deficits in psychiatric populations, however the specific assumptions about learning processes that they make can cause them to underfit observed behaviours. I consider an alternative method using recurrent neural networks to model the complex learning and decision-making strategies of humans and demonstrate the benefits of this latter approach based on the performance of patients with unipolar or bipolar depression making decisions on a two-armed bandit task.

10:30am **Shinsuke Suzuki** (University of Melbourne)
Obsessive-compulsive traits impair reinforcement learning through the change of exploration strategies

Learning from reward experience, called reinforcement learning, is indispensable for appropriate decision-making. Yet, little is known about HOW reinforcement learning is deterred by psychiatric symptoms. To address this issue, we conducted a large-scale online experiment. In the experiment, participants were first engaged in a conventional three-armed bandit task (reinforcement-learning task), and then asked to complete questionnaires about schizotypal personality, obsessive compulsivity, depression, anxiety, impulsivity and socioeconomic status. First, applying a factor analysis to the questionnaire data, we show evidence for two dissociable factors underlying the psychiatric symptoms: the first one is associated with obsessive-compulsive traits and the second one is associated with anxious and depressive traits. Next, we found that the first factor, but not the second factor, was significantly correlated with overall performance in the bandit task, suggesting that obsessive-compulsive traits impairs reinforcement learning. Finally, computational modeling combined with mediation analysis demonstrates that the negative effect of obsessive-compulsive traits on the learning performance was mediated by decrease in the uncertainty-driven exploration and increase in the random exploration. These

findings together imply that obsessive-compulsive traits impair reinforcement learning through the change of exploration strategies, and may potentially contribute to deeper understanding of obsessive-compulsive disorder.

11:00am **Roshini Randeniya** (The University of Queensland)
Bayesian models of atypical sensory perception in Autism Spectrum

A general consensus persists that sensory-perceptual disruptions in Autism Spectrum Disorder (ASD), such as hypersensitivities to light or sound, result from a strong reliance on new sensory observations. However, conflicting Bayesian theories remain unresolved as to whether such disruptions are caused by overly precise sensory information or reduced precision on prior beliefs (or model) of the sensory environment. Here, I will discuss an experimental approach to differentiate between Bayesian models of perception in ASD using a visual decision-making task with fMRI. We provide empirical evidence for the neural underpinnings of sensory learning and decision-making associated with Autism traits and sensory sensitivities in a neurotypical population.

11:30am **Xiaosi Gu** (Icahn School of Medicine at Mount Sinai)
The Anatomy of Beliefs: Insights from Computational Psychiatry Research on Addiction

For centuries, artists, philosophers, and scientists have inquired about the nature of human beliefs. Recent advances in computational psychiatry and neuroscience have started to shed light on the neural underpinnings of the human belief system. Yet little is known about how beliefs impact biophysically described processes in the presence of neuroactive drugs, which presents a profound challenge to the understanding of the mechanisms and treatments of mental illnesses. Here I will describe a set of empirical findings from humans that demonstrate how beliefs about nicotine modulate neuro-computationally defined learning signals and subjective craving in cigarette smokers. Using functional magnetic resonance imaging (fMRI) and computational modeling, we showed that beliefs can override the effect of nicotine, a potent neuroactive drug, on the human brain. Furthermore, I will present a Bayesian model of beliefs that offers a neurocomputational account for these findings. Taken together, this work not only highlights the significance of having a mechanistic understanding of beliefs in mental health research, but also indicates the importance of managing patients' beliefs in clinical settings.

SYMPOSIUM 14

10:00am – 12:00pm, Riverbank Room 8

Illuminating neural circuits of emotional and motivational behaviour

Chairs: Asheeta Prasad (University of New South Wales) & Zoran Boskovic (Queensland Brain Institute)

10:00am **Mazen Kheirbek** (University of California)
Memory codes in the dentate gyrus

A central goal of neuroscience is to understand how sensory stimuli are encoded within ensembles of neurons, and how these representations are modified by learning. The hippocampus (HPC) has a well-documented function in encoding spatial information, however, it also encodes non-spatial information crucial for memory formation. Granule cells (GCs) in the dentate gyrus (DG) have been implicated in memory generalization, a process impaired in individuals with anxiety disorders such as post-traumatic stress. DG GCs receive input from the lateral entorhinal cortex, which is known to process non-spatial olfactory information. Thus, we leveraged the use of odor stimuli to understand general principles of stimulus encoding and memory formation in DG GCs. In this talk, I will present recent data using in vivo 2-photon calcium imaging combined with behavior to determine the mechanisms by which DG GCs represent odor information and how fear learning alters these representations. I will discuss our findings revealing that odor identity is robustly encoded within the DG, and that fear learning stabilizes these representations providing evidence for olfactory memory traces in the dentate gyrus and mechanisms for stimulus generalization and discrimination.

10:30am **Robyn Brown** (Florey Institute of Neuroscience and Mental Health)
Why do women overeat? Characterizing a model of 'emotional' binge eating in female mice

Overeating of highly palatable food is a major contributing factor to obesity and related health complications. For women in particular, negative emotions such as stress, frustration, anxiety, and loneliness have been shown to strongly influence eating behaviour and bingeing episodes. Despite this knowledge there is a paucity of research investigating the neurobiology underlying emotional and stress related bingeing, particularly in female subjects. This is primarily due to a lack of suitable animal models and the historical focus of neuroscientific studies on male subjects. Dr Brown will describe a model of emotional stress-induced binge eating she has developed in mice that does not depend on caloric restriction, a behaviour that she has observed specifically in female mice. This behaviour is not oestrogen-dependent as it is not impacted by ovariectomy. Dr Brown will describe the neural correlates and putative networks driving this behaviour which has been investigated using a multidisciplinary approach.

11:00am **Roger Marek** (Queensland Brain Institute)
Neural function and connectivity to drive emotional learning

Fear conditioning is an established Pavlovian learning paradigm. The amygdala, medial prefrontal cortex (mPFC) and hippocampus, three structures with extensive inter-connectivity, are key elements of the circuits that mediate emotional learning. While fear learning and extinction, both learning processes linked to negative emotions, are initiated in the amygdala, expression of fear and its extinction also engage the hippocampus, and mPFC. In rodents, the prelimbic (PL) and infralimbic (IL) sub-regions of the mPFC have been implicated in regulating different stages of fear learning, with the PL implicated in fear expression and the IL in fear extinction.

We have recently identified the precise neural circuits in the mPFC that mediate contextual information from the hippocampus to the PFC. The findings revealed that the hippocampus sends a dominant projection to parvalbumin-positive interneurons in the IL that shunts IL activity to allow the relapse of fear. I will summarise our recent findings and discuss the role of the PFC and hippocampus for the expression of fear-related behaviours, and will allude to future studies that are necessary in order to comprehend prefrontal functionn to regulate emotional learning.

11:30am **Dhanisha Jhaveri** (The University of Queensland)
Targeting adult-born hippocampal neurons to regulatelocal circuitry and anxiety- related behaviour

A mechanistic understanding of how emotions are represented in the brain and lead to physiological changes that impact behaviour has been a major quest in neuroscience. Adult neurogenesis, the production and integration of new neurons in the hippocampus, has emerged as a key mechanism regulating the hippocampal circuitry and a vital player in the modulation of cognition and emotion. However, precise roles of adult-born neurons in regulating the local circuitry and mediating behavioural responses to stress and antidepressants are not fully understood. In this talk, I will present our recent data showing that genetic ablation of adultborn neurons during a critical window of neuronal maturation prevents chronic stress-induced anxiety. I will further discuss our ex vivo electrophysiology findings combined with morphological analyses that demonstrate selective alterations in membrane properties, maturation status and local connectivity of these adult-born neurons in stressed animals and show that these changes are reversible by treatment with select clinical antidepressants. These results provide evidence for an instructive role of adult-born, immature hippocampal neurons in regulating the local hippocampal circuitry and anxiety-related behaviour during stress and suggest that interventions that target the properties of these adult-born neurons may prove useful for treating anxiety in various neuropsychiatric conditions.

SYMPOSIUM 15

10:00am – 12:00pm, Hall L

When gut meets brain: their impact on food intake control

Chair: Denovan Begg (University of New South Wales)

10:00am **Damien Keating** (Flinders University)
Understanding interactions between the gut microbiome, enteroendocrine cells and the nervous system

Gut-brain interactions are emerging as a new area of frontier science with direct implications for human health. However we understand little about mechanisms governing these signalling pathways. Our research has demonstrated bi-directional

signalling occurs between the microbiome and hormone-secreting host cells lining the gut wall, called enteroendocrine (EE) cells. We have defined that EEcell secretion modulates the activity of extrinsic and intrinsic nerves to have both local and CNS effects. These effects include the alteration of gastrointestinal motility and peristalsis by serotonin-secreting cells in the gut, the density of which arecontrolled by the gut microbiome and in human health disorders such as obesity. Several gut hormones have major metabolic effects on blood glucose and body weight via various mechanisms including modulating central feeding behaviour. Our unpublished data defines one such hormone as being central to the modulation of host metabolism by the gut microbiome. Not only does the microbiome effect host physiology, but we find that specific EE cell populations modulate the gut microbiome, as does the extrinsic innervation of the gut, and these interactions underpin unrecognised regulatory pathways within the host.

10:30am **Zhi Yi Ong** (University of New South Wales)
Hindbrain control of feeding behaviours

Mechanisms underlying food intake controlare complex owing to the contribution of avariety of peripheral and central factors.Theunderstanding ofhow peripheral and central signals interact to control food intakerequires investigations into the function ofneurons in hindbrain nucleus of the solitary tract (NTS). NTS neuronsreceive visceral inputs arising from gastrointestinal tract,project to and receive inputs from brain regions important in feeding behaviours. Thus, NTS neurons are importantfor theintegration of peripheral gut signalsand central signals in food intake control. We and others showedthat appetite suppressing peptides such asleptin, glucagon-like peptide-1 and oxytocin reducefood intake via interaction with NTS satiation signal processing. These peptides are thought to act viaNTS noradrenergic neurons. Werecently showed that selective activation of NTS noradrenergic neurons suppresses food intake as well as the appetitive and motivational aspects of feeding behaviours, suggesting a critical role of these neurons in food intake control. This line of workhighlights the NTS as an important neural substrate in food intake controlandis one step towards disentangling the complexityof feeding behavioursand a better understanding of eating disorders.

11:00am **Amanda Page** (The University of Adelaide)
Gastric vagal afferent satiety signalling in health and disease

In animals, the acquisition of life-sustaining nutrients requires the intake of food, which is finely regulated by a well-integrated multilevel system. The gut-brain axis is an important component of thissystem relaying information on the arrival, amount, and nutrient composition, of food consumed. These inputs are then integrated to regulate subsequent food intake and energy balance. Initially it was thought that the primary source of feedback was from intestinal vagal afferents. However, it is now clear from our work, and that of others, that the stomach also has a pivotal role and gastric vagal afferent nerves transmit information relating to the amount of food consumed to the hindbrain. We have shown that gastric vagal afferent responsiveness is modified by circadian cues, nutrients, gastric hormones and adipokines. Further, we have demonstrated that the nature of the response of gastric vagal afferents to meal related stimuli may be profoundly altered by

nutritional status. Thus, gastric vagal afferent function demonstrates plasticity in order to finely control the amount of food consumed. Disruption of this axis can have profound effects for food related disorders, such as obesity.

11:30am **Ivan de Araujo** (Icahn School of Medicine at Mount Sinai)
The Gut-brain Axis and Reward

The presentation will discuss recent evidence supporting a role for the gut-brain axis in controlling brain circuits involved in reward, emotion and motivation. It will be argued in particular that gut-innervating vagal sensory neurons function as reward neurons. Via asymmetric ascending pathways of vagal origin, gut signals reach brain reward regions via dedicated visceral nuclei in pons. More generally, a topographic sensory organization for food reward appears to exist throughout the striatum, with gastrointestinal vs. orosensory rewarding signals causing dopamine release into different striatal sectors. The extent to which these findings relate to human neuroimaging findings will be also discussed. In sum, the gut-innervating vagal neurons have sensory-specific control over dopamine reward neurons, and may constitute a novel target for stimulation therapies for eating and affective disorders.

THURSDAY 5 DECEMBER 2019

SYMPOSIUM 16

9:00am – 11:00am, City Rooms 1&2

How altered lipid metabolism and myelin structure causes neurodegeneration

Chair: Junhua Xiao (The University of Melbourne)

9:00am **John Kwok** (The University of Sydney)
Mutations in white matter disease genes are causal of frontotemporal dementias and their impact on neuroimaging and peripheral lipid biomarkers

Frontotemporal dementia (FTD), a common cause of presenile dementia, is characterised by behavioural and/or language changes and cognitive deficits. An established FTD gene, GRN, has significant impact on white matter (WM) tracks. We hypothesise that mutations in WM disease genes would also be causal of FTD. 208 FTD patients (recruited via FRONTIER research clinic) underwent whole-exome or whole-genome sequencing. 35 patients were identified with deleterious mutations in 20 WM disease genes including ARSA and FA2H. Blood-based lipids were assayed by mass-spectrometry [Kim WS et al. Frontiers in Neurology 2018; 9:104] in 40 sporadic FTD cases, 18 mutation carriers and 22 neurological controls. Univariate analyses identified simple glycosphinglipids (hexosyl ceramides) as significantly different between groups ($p = 0.00027$). Brain diffusion tensor imaging with fractional anisotropy was examined as a measure of WM integrity between $N = 7$ mutation carriers and age, sex and education matched neurological controls. Significant (corrected $p < 0.05$) widespread loss of white matter integrity was found bilaterally in both cerebral and cerebellar regions of the mutation carriers compared with

controls. These data suggest that mutations in genes causal of WM disease contribute to FTD via direct or indirect dysregulation of lipid metabolism.

9:30am **Karen Mather** (The University of New South Wales)
Investigating lipidomics from an ageing perspective and as potential biomarkers of early Alzheimer's disease

Lipidomic changes have been investigated in relation to age-related disorders including neurodegenerative diseases, such as Alzheimer's disease (AD). However, before investigating pathological changes to the lipidome it is important to understand lipidome variation in healthy individuals in regard to ageing and other variables, such as sex. Since blood is a convenient and easily accessible sample for human studies, we investigated the relationships between age/sex and a broad range of lipids. Using cognitively healthy individuals aged 56-103 years, inverse associations with various lipids and age were observed and sex differences were also found.

Biomarkers to facilitate early AD detection may facilitate interventions to delay the onset or treat the disease at the preclinical stage. Lipidomic markers show promise as early biomarkers of AD, given the brain's relatively high lipid content and altered lipid metabolism in early AD. For example, one class of lipids, the sphingolipids, is enriched in myelin and is altered in AD. In our study examining conversion from normal cognition to mild cognitive impairment or AD 8 years later, there were significant differences observed for certain lipid classes measured at baseline. These results suggest that lipidomics may be useful in identifying individuals at early stages of AD.

10:00am **Maria Fuller** (Women's and Children's Hospital)
The brain lipidome as a therapeutic target for inherited neurodegenerative disorders

Inherited neurodegenerative disorders encompass a large heterogenous group of diseases that result from genetic defects. Neurocognitive regression is the clinical hallmark and their complex pathophysiology renders treatment difficult. A common pathobiological phenomenon may be deregulated lipid metabolism as neurons contain vast amounts of surface membranes, of which lipids are the major constituent, due to their elaborate axons and dendritic spines, the latter being the anatomical substrate of memory learning. Interrogation of the brain lipidome (>600 individual species of sphingolipids and phospholipids) in two disparate inherited disorders, Gaucher disease and Sanfilippo syndrome, arising due to deficiencies in lysosomal hydrolases required for proper sphingolipid and carbohydrate degradation, was undertaken to inform on mechanistic links with observed neuronal pathology and identify potential therapeutic targets. Common to both disorders was the accumulation of gangliosides - complex glycosphingolipids defined by the presence of sialic acid – in particular the simple gangliosides of the a and b series. Patterns of ganglioside expression are tightly regulated during neurodevelopment and the presence of these, largely embryonic, gangliosides suggest retarded neurodevelopment. Of the phospholipids, congruent alterations in lipid mediators were evident consistent with neuroinflammation drawing attention to a plausible

concept that interfering with phospholipid metabolism may indeed attenuate these cascades.

10:30am **Anthony Don** (The University of Sydney)
Restoring neuroprotective lipid signalling in Alzheimer's Disease

Genetic risk factors clearly implicate altered lipid homeostasis in the pathogenesis of Alzheimer's disease (AD) and other dementias, however it is not known how altered lipid metabolism promotes neurodegeneration. My research has begun to elucidate the changes to lipid metabolism, particularly myelin lipid metabolism, that occur in the early pre-clinical development of AD. We have shown pronounced loss of the neuroprotective signalling lipid sphingosine 1-phosphate (S1P) in pre-clinical AD pathogenesis [1], and as a function of increasing age in the hippocampus of cognitively normal females [4]. I will present our very recent work establishing that S1P maintains oligodendrocyte health and myelination. Loss of S1P in the brain, through deletion of sphingosine kinase 2, enhanced hippocampal volume loss, cognitive deficits, and myelin loss in an amyloid β-producing mouse model, despite a significant reduction in amyloid β load. This is attributed to greatly enhanced sensitivity of oligodendrocytes to amyloid β toxicity in the absence of protective S1P, suggesting that loss of neuroprotective signalling is a more important driver of neurodegeneration than gross amyloid β concentration or plaque density. The S1P receptor agonist Fingolimod is a first-line therapy for multiple sclerosis. Our research suggests that S1P receptor agonists may prove effective for dementia.

SYMPOSIUM 17

9:00am – 11:00am, City Rooms 3&4

Pathway to success: paving the way for translational stroke research

Chairs**:** Michelle Rank (The University of Melbourne) & Kirsten Coupland (University of Newcastle)

9:00am **Steven Zuryn** (Queensland Brain Institute)
Discovery of molecules and molecular mechanisms that protect neurons from stress

Withlifeexpectanciesincreasingaroundtheworld,stroke,neurodegenerativedisorders,andotherlate-onsetinflictionsrepresentanenormousdiseaseburden.Acellularhallmarkofmanyofthesediseasesisalossofmitochondrialfunction.Mitochondriaaretheorganelleswithinourcellsthatconvertthecaloriesweeatandtheoxygenwebreathintotheprimaryenergysubstrateofthecell,ATP.Lossofoxygensupplytothebrainduringstrokewillultimatelyinhibitmitochondrialrespiration,starvingneuronsoftheenergytheyrequiretofunctionandsurvive.Inaddition,theseorganellesharbourtheirowngenome(mtDNA),whichisessentialformitochondrialfunctionbutpronetomutationandmolecularlesion.AgradualbuildofmtDNAdamageoverlifehasbeenproposedtocontributetotheprogressiveriskoflate-onsetdiseases,andcandirectlycausestroke-likesymptoms.Hisgrouphasusedsimplemodelorganismstoscreenforandcharacterisem

oleculardpathwaysthatprotectneuronsfromstressesassociatedwithstrokeandneurodegeneration,includingmitochondrialDNAinjury.Hewillpresentthegroup'slatestfindingsanddescribehowtheyaretestingthemoleculeswehaveuncoveredinhumancells:afirststeponthetranslationpathway

9:30am **Nicole Jones** (University of New South Wales)
Hypoxia inducible-1 (HIF-1) as a target for brain repair

Dr Jones is a Senior Lecturer in Pharmacology at UNSW Sydney. Her broad research interests are aimed at understanding the cellular and molecular pathways which are involved in protecting the brain and promoting functional recovery and plasticity after an acute brain insult such as a stroke or birth asphyxia. In particular, she is interested in studying roles for the transcription factor hypoxia-inducible factor-1 (HIF-1) in mediating brain repair processes after acute brain injuries. She has received funding from NHMRC and UNSW to support this ongoing work. In recent years, she has been involved in commercial and academic collaborations to explore the HIF-1 pathway as a potential therapeutic strategy in rodent models of stroke and perinatal asphyxia. Herstudies have shown that mild hypoxia and drugs that enhance the HIF-1 can reduce injury and enhance functional recovery rodent injury models, with 12 published articles in this research area. Hertranslational research has informed recent clinical studies that have shown success using mild hypoxia to enhance recovery in spinal cord injured patients.Additionally,the iron chelator deferrioxamine, which can increase HIF-1,is being tested in clinical trials for intracerebral haemorrhage.

10:00am **Michael O'Sullivan** (University of Queensland Centre and Royal Brisbane and Women's Hospital)
What, if anything, have experimental lesions in models taught us about cognitive function after brain injury in humans?

Animal models have been used in the search for new treatments to ameliorate the damage of human stroke. However, to date, almost all attempts to translate promising interventions to humans have failed. Studying the effect of experimental lesions on behaviour has also been a mainstay in exploring cognitive systems in the brain. Have these studies contributed to our understanding of the effects of naturally-occurring injury, or do they also fail to translate tohumans? Advances in neuroimaging now make it possible to test hypotheses generated in models in clinical studies of brain injury. This talk will describe progress to date, focussing on key examples such as lesions in the extended hippocampal system, experimental frontal lobe injury in rodentsand models of disconnection in monkeys and their application to human conditions such as stroke and traumatic brain injury.

10:30am **Michael Tymianski** (Krembil Research Institute, Toronto Western Hospital, University of Toronto)
Development of PSD95 inhibitors for acute ischemic stroke: From target discovery to Phase 3 trials

Prof.Tymianskiis a neurosurgeon andSenior Scientist, a Professorin theDept of Surgeryat the University of Toronto, and a Canada Research Chair in Translational Stroke Research. His most advanced contribution isthe development of PSD95

inhibitors, beginning with the discovery that PSD95, an abundant synaptic protein,is a therapeutic target for neurodegeneration (Sattler et al., Science, 1999). By 2002, he developed NA-1, a drug that inhibits PSD95 and reduces ischemic brain damage in rats (Aarts et al., Science,2002). Over the next decade, theTymianskilab focused on translating NA-1 to the point of clinical utility through extensive target validation (Cui et al, JNeurosci,2007), testing in rodent models (Sun et al., Stroke, 2008) and, ultimately, in primate models of stroke (Cook et al., Nature,2012; Cook et al., Sci Transl Med, 2012). In 2012,Tymianskiand his team published the first clinical trial supportive of neuroprotection by NA-1 in humans (Hill et al., Lancet Neurology, 2012). His team are currently conducting two phase 3 trials of NA-1, namely FRONTIER (NCT02315443) and ESCAPE-NA1 (NCT02930018), with the latter recruiting 1120 subjects globally.Prof Tymanski will speak about his group's journey from discovery to translation.

SYMPOSIUM 18

9:00am – 11:00am, Riverbank Room 7

Wiring the brain: the development of cortical neurons and networks

Chair: Geoffrey Goodhill (University of Queensland)

9:00am **Nathalie Dehorter** (Australian National University)
Molecular control of cortical interneuron development in the mouse embryo

The developing brain undergoes fundamental modifications in molecular composition which enableneurons to construct functional neuronal circuits. The Er81 transcription factor controls cell excitabil-ity in adult interneurons of the cortex (Dehorter et al. 2015). It is also expressed in the birthplaceof the cortical interneurons, suggesting that it can play a crucial role in interneuron developmentand early specification. However, nothing is known on the role that Er81 plays on progenitor andpost-mitotic cells. For the first time, we reveal that Er81 is fundamental for the development of themedial ganglionic eminence-derived interneurons and their identity at embryonic stages. Our studydemonstrates how this process critically impacts on cortical physiology and behaviour. We show thatthe expression of the activity-dependent Er81 transcription factor is modified at early stages of devel-opment in a mouse model of autism, revealing a new marker of pathology. Our results significantlyimprove our knowledge of cortical development by identifying a crucial mechanism underlying theremarkable flexibility of neurons during a critical period of brain maturation.

9:30am **Michael Crair** (Yale University)
Self-organization in the developing nervous system

Increasing evidence suggests that most of the complex brain circuitry responsible for our ability toperceive the world with precision actually develops in the womb, before sensory experience is evenpossible. For instance, visual circuits responsible for

our ability to perceive depth and see shapesand colors are already well formed at birth, however visual deprivation later in life leads to permanentblindness. Similarly, children are born with the ability to perceive a full complement of sounds but it isonly later in life that they lose the ability to distinguish sounds that are unfamiliar in their native tongue.This implies that intrinsic mechanisms working in the womb, apart from sensory experience, are re-sponsible for wiring the complex brain circuits mediating basic perception. In this presentation, wewill examine the limits and links between genetic mechanisms and spontaneous or intrinsic neuronalactivity in wiring the brain during development. The work described employs a broad array of experi-mental approaches, from advanced gene sequencing to sophisticated optical imaging and stimulationin living organisms to study the properties, role and mechanisms of spontaneous neuronal activityin guiding neural circuit development. The research suggests that the remarkable development ofcomplex brain circuitry that occurs in the womb is due, in part, to the generation of complex andpatterned spontaneous activity in the peripheral nervous system that then spreads into and throughthe brain, wiring it along the way. Disruption of this ongoing activity may play an important role inneurodevelopmental disorders such as amblyopia and autism.

10:00am **Linda Richards** (University of Queensland)
Emergence of activity patterns in the developing cerebral cortex

Spontaneous activity arises in the cortex in early development and may be the precursor to bothresting state activity and brain states during sleep. It may also play a role in the establishment ofconnections and neural networks in the developing brain. However, exactly how spontaneous activityarises in the cortex and what specific circuit properties control how the circuit develops into a func-tional network are unknown. We have been investigating the emergence of spontaneous activity inthe developing marsupial, the fat-tailed dunnart,Sminthopsis crassicaudata. Cortical development indunnarts closely resembles that of placental mammals, making this an ideal model for studying earlymammalian brain development. For example, access to developing joeys in the pouch allows imagingof spontaneous activity using the sensitive calcium indicator GCaMP6S at much earlier stages thancan be achievedin vivoin placental mammals. We have identified the emergence of various patternsof activity including: a) asynchronous bursts, b) synchronous bursts, c) travelling waves and d) long-lasting events. In addition, we are identifying how these patterns first emerge and what principlesguide circuit formation and function. This work may have implications for understanding how func-tioning circuits develop in humans, and what alterations may occur in disorders leading to intellectualand learning disabilities as well as autism.

10:30am **James Bourne** (Monash University)
The role of the thalamic nuclei in development of cortical anatomy and function

Expansion of the neocortex in primates, including humans, has occurred alongside a concomitantincrease in the size of the underlying thalamus, comprising additional nuclei and connections. Tha-lamic nuclei act as hubs relaying information from, for example, sense organs (e.g. the eye) to theneocortex, and also between cortical

areas (e.g. visual to frontal cortex) to enable complex cognitionand behaviour. Although there have been significant advances in mapping the afferent and efferent connections of the thalamus, it is only in recent years that we have started to clarify an intricate rolefor the thalamus in regulating the development, function and plasticity of the neocortex. For example,my group provided the first evidence that a primate-specific thalamic nucleus, the inferior pulvinar(medial subdivision), is crucial for: i) the normal development of the visual cortex and perception; ii)the re-routing of visual information from the eye and preservation of vision following early-life damageto the primary visual cortex; and iii) the development of reaching and grasping behaviours, a skill thatdistinguishes primates from other mammals. Collectively, my discoveries demonstrate that thalam-ocortical connections are less hardwired at birth and more plastic than initially thought and play acrucial role in regulating the anatomy and function of the neocortex.

SYMPOSIUM 19

9:00am – 11:00am, Riverbank Room 8

Neurobiological Mechanisms of Drug addiction

Chair: Andrew Lawrence (Florey Institute of Neuroscience and Mental Health)

9:00am **Michael Bowen** (University of Sydney)
Rebalancing the addicted brain: prosocial compounds for treating substance use disorders

One of the most debilitating aspects of substance-use disorders is the profound social withdrawal that so often co-occurs. Considerable potential benefit might therefore be derived from developing pharmacological interventions for addiction that serve to enhance social motivation. There has been growing interest in exploring the anti-addictive effects of the so-called social neuropeptide, oxytocin. Despite promising preclinical findings, pharmacokinetic issues will likely prevent oxytocin itself from unlocking the full potential of targeting the social brain to treat substance use disorders. Through a phenotypic drug discovery program we discovered a novel small-molecule, KNX100, with powerful prosocial and anti-addictive effects in preclinical models. KNX100 has excellent oral bioavailability, readily enters the brain and a long half-life, overcoming the substantial pharmacokinetic challenges presented by oxytocin. Peripherally administered KNX100 increased social preference and social interaction in rats and restored normal social behaviour in a mouse model of autism. Across rodent and non-human primate models KNX100 has shown considerable promise for treating opioid, nicotine, alcohol and stimulant use disorders. Importantly, KNX100 itself does not appear to have abuse liability. In initial preclinical safety studies KNX100 was well-tolerated with a wide therapeutic window. KNX100 is now being developed by a University of Sydney spinout company, Kinoxis Therapeutics.

9:30am **Jennifer Cornish** (Macquarie University)
Methamphetamine addiction circuitry: the effect of oxytocin treatment

Methamphetamine (METH or "ice") abuse and addiction are significant problems worldwide, with current treatments (pharmacological or psychological) inadequate for curing addiction and the associated mental health disorders that develop with repeated METH abuse (psychoses, depression, anxiety). Our aim, using rodent models, is to discover the neurobiological underpinnings of METH abuse and addiction to develop effective pharmacotherapies. The neuropeptide oxytocin is showing promise as a pharmacotherapy for reducing METH abuse and addiction. Using the model of intravenous METH self-administration in rats we have demonstrated that either the acute or chronic systemic administration of oxytocin significantly reduced the relapse potential of re-exposure to METH (1mg/kg, i.p.) or cues associated with METH use. We have also shown that the direct administration of oxytocin into reward-related brain areas, such as the nucleus accumbens (NA) or subthalamic nucleus (STh), significantly reduced METH-seeking behaviour, however the effect is mediated by Vasopressin V1A receptors. Our most recent work has investigated the neural circuitry involved in METH addiction and how oxytocin treatment alters this circuit. This symposium presentation will explore the neurobiological mechanisms and how they may be engaged by oxytocin to reduce METH abuse and addiction.

10:00am **Arnauld Belmer** (Queensland University of Technology)
Serotonin neuron signalling and plasticity in chronic alcohol consumption and withdrawal

Alcoholism is a chronic relapsing disease, with abstinence leading to mood and emotional deficits such as depression and anxiety, which in turn, increase the risks of relapse. Alterations in the serotonin (5-HT) system has been linked to various psychiatric disorders including anxiety, depression, impulsivity and addiction. However, the serotonin system is complex with numerous receptors involved, and its role in alcohol drinking behaviour is not fully understood. Using a long-term model of chronic ethanol exposure in mice, we identified the serotonin receptors 5-HT1A as playing a pivotal role in alcohol binge drinking behaviour, with selective partial agonists both reducing alcohol intake and preventing withdrawal-induced anxiety. We further observed that alcohol-induced changes in serotonin innervation and neurogenic deficits in the hippocampus are totally reversed by chronic tandospirone treatment. This effect is highly specific to alcohol, as it was not observed in sucrose-consuming control mice. Since 5-HT1A receptors are located both pre- and postsynaptically, we have started to dissect the contribution of each 5-HT1A receptor subtype and the circuitry involved in alcohol drinking behaviour and associated emotional and neurogenic deficits. Our findings suggest that drugs targeting the serotonin 1A receptors represent a promising treatment strategy to reboot the alcoholic brain and reduce the emotional alterations that drive the relapse to alcohol consumption

10:30am **Asheeta Prasad** (The University of New South Wales)
Complementary roles for ventral pallidum cell types and their projections in relapse

A fundamental theoretical and clinical problem is understanding why relapse is so common for individuals with alcohol use disorders, who are frequently highly motivated to abstain from drinking. To better understand relapse behaviour we applied a well validated animal behavior model of two d ifferent forms of relapse to alcohol seeking in combination with a multidisciplinary technical approach including in vitro electrophysiology, RNAscope, projection-specific optogenetics, and cell-type specific chemogenetics in transgenic rats. We make the discovery that different forms of relapse are assembled from different ventral pallidal cell types (Gad1 and parvalbumin) and their different projections to the lateral hypothalamus and ventral tegmental area. Although we use a model of alcohol abuse, the differences we have discovered are likely to apply to other problems of motivation that require behaviour change to achieve positive outcomes. Such problems include over-eating and gambling. Finally, current pharmacotherapies for alcohol abuse are only modestly effective and have low levels of patient compliance. Our discovery that different ventral pallidal cell types and their projections assemble different forms of relapse raise the possibility of personalized treatments targeting these different pathways for different forms of relapse.

SYMPOSIUM 20

9:00am – 11:00am, Hall L

EMBL Australia scientific symposium on neural circuitry and cellular integrity in health and disease

Chair: Ville-Petteri Makinen (South Australian Health and Medical Research Institute)

9:00am **Cornelius Gross** (European Molecular Biology Laboratory)
Primal Fear - the neural circuitry of instinctive defence

Prof Cornelius Gross is Group Leader, Senior Scientist, and Deputy Head of Unit at the Epigenetics & Neurobiology Unit of EMBL Rome since 2003, and he also holds Adjunct Professorship at Monash University Melbourne. He works to understand the neural circuit mechanisms controlling instinctive behaviours, with a focus on fear and anxiety. Prof Gross received undergraduate training in biophysics at the University of California, Berkeley and pursued doctoral research at Yale University studying transcriptional regulation by homeodomain factors with William McGinnis. He did his postdoc with René Hen at Columbia University where he discovered a developmental role for serotonin in determining life-long anxiety-related behaviour and identified the serotonin receptor responsible for the therapeutic effects of antidepressants. At EMBL, he showed how deficits in serotonin autoregulation can cause sudden infant death syndrome and how serotonin moderates the impact of maternal care on anxiety traits in adulthood. Recently, his laboratory has focused on characterizing hypothalamic and brainstem circuits that regulate social and predator fear and understanding the role of microglia in the proper wiring of behavioural circuits during development. In 2013 he was awarded an Advanced Grant from the European Research Council to study social and predator fear circuits in the brain.

9:30am **Yann Gambin** (University of New South Wales)
Protein-protein interactions, Parkinson's disease and biomarkers in blood

Dr Yann Gambin is an EMBL Australia Group Leader in Single Molecule Science at the University of New South Wales, Sydney, and investigates the mechanisms that underlie aggregated proteins that are associated with Parkinson's and other neuro-degenerative diseases. He did his PhD at École Normale Supérieure in Paris, and joined the EMBL Australia Partnership Network in 2015. He and his collaborators have developed new aggregation analyses by single molecule techniques including a hybrid method of "pure" single-molecule spectroscopy (only pM concentrations required) and fluorescence correlation spectroscopy to enable rapid and precise determination of the size of oligomers and quantification of large, but rare, aggregates. By combining cell-free protein synthesis and genetically encoded fluorophores such as GFP or Cherry, single molecule measurements can performed directly in the translation mixture without purification and labelling steps that could disturb oligomers and aggregates. The techniques are opening new opportunities to identify which proteins can co-aggregate and decipher the order in which these aggregates are formed under disease conditions. Dr Gambin also aims to elucidate the triggers to the misfolding of synuclein (a Parkinson's hallmark), and his work on prion-like behaviour of innate immunity may shed light on the etiological connections between dementia and the immune response.

10:00am **Pirjo Apaja** (South Australian Health and Medical Research Institute)
Regulation of proteostasis during astrocyte stress responses

Astrocytes have multilevel supporting functions in the central nervous system from synaptogenesis to maintaining movement of ions and water. Astrocytes are extremely responsive and adaptive to changing conditions, and in stress respond to injury or disease by swelling and becoming reactive. Astrocyte reactivity at the molecular level is still poorly understood, and even less is known of adaptive stress mechanisms. We have identified a specific protein complex which is responsive to astrocyte volume/shape changes, and how this complex and functional location is regulated by the endomembrane trafficking. Recently, we have discovered a completely new layer of complexity connected to the astrocyte volume/shape regulation by identifying an adaptive functional protein network that regulates proteostasis status of astrocytes through autophagy and ubiquitin signalling during the induced stress. In this talk, I will describe the molecular mechanisms of our discovery and discuss the implications to stress responses and astrocyte reactivity.

10:30am **Leon Teo** (Monash University)
Unravelling the identity and reactivity of astrocytes in primates after injury

Glial scarring and reactive astrogliosis after CNS injuries (from trauma and strokes) are major impediments to neuro-regeneration. While reactive astrocytes can exacerbate

secondary neuronal degeneration, evidence suggests they also play crucial neuroprotective roles in the early stages post-injury. These include limiting neuronal apoptosis, suppressing inflammatory responses, maintaining homeostatic balance and providing trophic support to surviving neurones. The prevailing thought is that these neuroprotective roles are underpinned by a high level of plasticity that can induce phenotypic changes on reactive astrocytes to confer neuroprotective functions, especially in the early stages after CNS injury. Due to the vast differences in astrocyte transcription between traditional rodent models compared to human, a clinically translatable nonhuman primate (NHP) marmoset model was used. Single-cell transcriptional profiling of marmoset astrocyte after injury revealed considerable heterogeneity in reactive astrocyte subpopulations post-injury. We identified an anti-inflammatory subpopulation of reactive astrocytes that contributes to infiltrating macrophage corralling through the NogoA/ LILRB2 signalling pathway. In addition, we determined that reactive astrocyte phenotypes can be altered to a more neuroprotective state through the re-introduction ephrin-A1 signalling, an early-life regulator of astrocyte reactivity. These results highlight the functional heterogeneity of reactive astrocytes which can be harnessed to promote neuroprotection after CNS injuries.