ANS 2023

AUSTRALASIAN NEUROSCIENCE SOCIETY
41ST ANNUAL SCIENTIFIC MEETING

4–7 December 2023 | W, Brisbane, Queensland

EXCITING THE NETWORK

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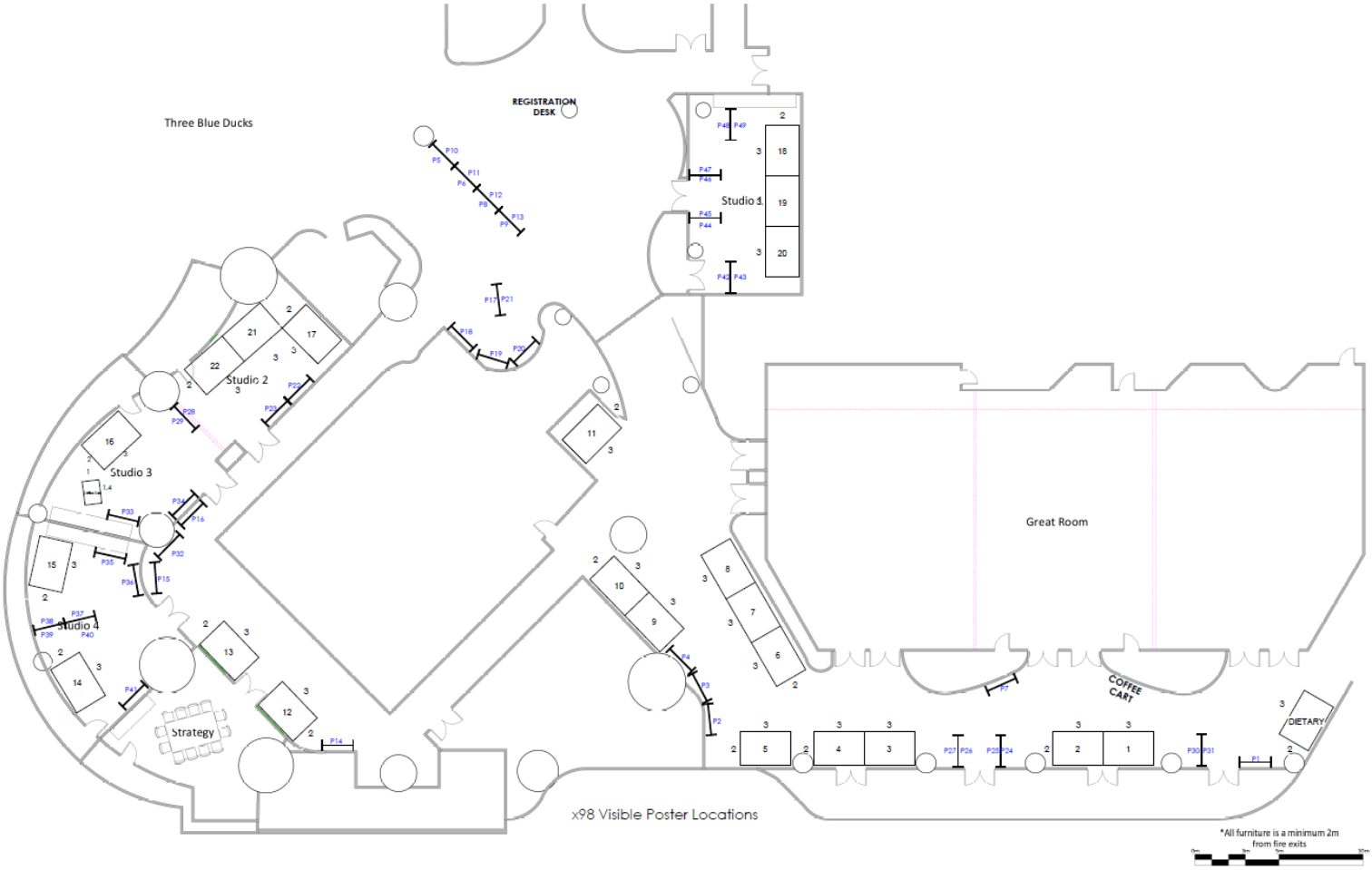
SCALE 1 : 200

NOTE: Floorplan subject to venue approval



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CLINICAL SCIENCE

HB

Monday 4/12/2023

06:00 PM-07:00 PM
Social

ANS Welcome Drinks
Foyer/Studio 1/2/3/4

Tuesday 5/12/2023

08:45 AM-09:00 AM
Welcome to Country, Conference Open
Great Room 1/2/3

09:00 AM-10:00 AM
Marcello Rosa
Elspeth McLachlan Plenary Lecture
Great Room 1/2/3

10:00 AM-10:30 AM
Break
Morning Tea, Exhibition and Poster Display

10:30 AM-12:30 PM
Timothy Bredy
Symposium 1: Unexpected mechanisms of experience-dependent plasticity across the lifespan
Great room 1

Timothy Bredy 1, Shaam Al Abed 2, Jocelyn Widagdo 3, Coleen Murphy 4, Paul Marshall 2
1. University of Queensland, St Lucia, QUEENSLAND, A4ustralia
2. ANU, Canberra
3. QBI, Brisbane
4. Princeton University, New Jersey, USA

Despite more than 100 years of effort, we still do not know how the brain encodes and stores information in the form of long-term memory. Most neuroscientists have focused on circuit-mediated mechanisms and, at the molecular level, a great deal of effort has been placed on understanding protein metabolism in the context of neural plasticity. These efforts have been commendable; however, we haven't really moved the needle much in terms of the precise regulatory mechanisms underlying cognition and memory. In recent times, several new players have emerged from the shadows and, with the advent of new technologies, their importance as key molecular processes underlying memory is ready for prime time. In this symposium we will discuss four newly discovered features of experience-dependent plasticity that are both surprising and thought provoking as they shed new light on the brains most complex abilities. Dr. Al Abed will lead off with the identification of new histone variants involved in memory, and followed by Dr. Widagdo who will tell us about RNA modifications in the brain and how they impact brain and behaviour across the lifespan. Prof Murphy will describe an unexpected retrotransposon-derived mechanism of transgenerational memory in worms, and we will conclude with Dr. Marshall discussing dynamic non-canonical DNA structures states and their role in memory.

10:30 AM-10:55 AM
Renee Seto
The role of the Cer1 transposon in horizontal transfer of transgenerational memory

Caenorhabditis elegans must distinguish pathogens from nutritious food sources among the many bacteria to which it is exposed in its environment. We found that a single exposure to purified small RNAs isolated from pathogenic Pseudomonas aeruginosa (PA14) is sufficient to induce pathogen avoidance in the treated worms and in four sequent generations of progeny. The RNA interference (RNAi) and PIWI-interacting RNA (piRNA) pathways, the germline and the ASI neuron are all required for avoidance behaviour induced by bacterial small RNAs, and for the transgenerational inheritance of this behavior. A single P. aeruginosa non-coding RNA, P11, is both necessary and sufficient to convey learned avoidance of PA14, and its C.elegans target, maco-1, is required for avoidance. Finally, we found that the Cer1 retrotransposon is necessary not only for intracellular communication, but also for inter-individual horizontal transfer of learned information. Our results suggest that this noncoding-RNA-dependent mechanism evolved to survey the microbial environment of the worm, use this information to make appropriate behavioral decisions and pass this information on to its progeny, using a surprising retrotransposon-based mechanism.

10:55 AM-11:20 AM
Shaam Al Abed
H2A.B: A new epigenetic player that controls the consolidation of long-term memory

Despite intensive research, the neuronal mechanisms underlying long-term storage of information remain elusive. It is however well-established that memory consolidation requires a highly coordinated pattern of gene expression, which is stabilised by epigenetic-based mechanisms. We have discovered a new epigenetic component in mammals, the

H2A histone variant H2A.B. Different to other histones, H2A.Bdisplays a tissue-specific expression pattern, being expressed in the brain and specifically, in the hippocampus and prefrontal cortex, both critical for learning and memory. Excitingly, we have found thatH2A.B knockout mice exhibited impaired consolidation of hippocampus-dependent memory. This memory profile was associated with reduced excitability and altered long-term potentiation of CA1pyramidal neurons in H2A.B knockout mice. Interestingly, H2A.B is targeted to the transcription start site and the intron–exon boundaries of genes concurrent with their transcriptional activation. Revealing the importance of these genomic locations, H2A.B knockout mice display major changes in the hippocampus transcriptome. Taken together, our work shows that H2A.B deposition is a novel mechanism that controls the fine-tuning of hippocampal neurons, from genes to electrical properties, and the stability of long-term memory. This new understanding of the molecular basis of cognitive function reveal H2A.B as a potential therapeutic target for memory disorders.

Tuesday 11:20 AM-11:45 AM
Jocelyn Widagdo
Understanding the m6A-epitranscriptomic regulation in neuronal functions and dysfunctions

The post-transcriptional modification by N6-methyladenosine (m6A) is a prevalent epitranscriptomic mark in eukaryotic RNAs, from yeast to humans. Modifications of m6A in mRNAs and non-coding RNAs affect various aspects of RNA metabolism at multiple stages of the RNA life cycle. In the central nervous system, the dynamic and reversible nature of m6A offers a desirable mechanism for tuning neuronal response to signals and environmental stimuli. Indeed, our earlier work has demonstrated the dynamic landscape of m6A in the mouse brain following behavioural training. In our recent work, we investigated the changes in the m6A-transcriptomic landscape during normal ageing. In parallel, we also providedevidence for how this age-dependent regulation is perturbed in pathology in the brain of Alzheimer's disease. We propose that m6A acts as an essential homeostatic mechanism in the brain that tunes multiple neural signalling pathways during activity and perturbation. Therefore, understanding the molecular mechanisms by which this is achieved is our current research focus.

11:45 AM-12:10 PM
Paul Marshall
DNA G-quadruplex is a transcriptional control device that regulates memory

The conformational state of DNA fine-tunes the transcriptional rate and abundance of RNA. Here we report that DNA G-quadruplex (G4-DNA) accumulates in neurons in an experience-dependent manner, and that this is required for the transient silencing and activation of genes that are critically involved in learning and memory. In addition, site-specific resolution of G4-DNA by dCas9-mediated deposition of the helicase DHX36 impairs fear extinction memory. Dynamic DNA structure states therefore represent a key molecular mechanism underlying memory consolidation.

12:10 PM-12:15 PM
Xiaoying Cui
Data Blitz: Epitranscriptomic regulation of striatal function: a new biology of schizophrenia?

Xiaoying Cui1, 2, Alice Petty3, Ning Wang1, Darryl Eyles1, 2
1. Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia
2. Queensland Centre for Mental Health Research, Wacol, QLD, Australia
3. Imperial College London, United Kindom
We have developed the Enhanced Dopamine in Prodromal Schizophrenia (EDiPS) animal model, replicating increased dopamine synthesis and release in the dorsal striatum observed in schizophrenia. EDiPS animals exhibit schizophrenia-relevant behavioural phenotypes and show enhanced dopamine release in response to amphetamine. RNA methylation, N6-methyladenosine (m6A), modulating RNA processing and protein translation, influences dopamine-mediated behaviours and has been implicated in schizophrenia pathology. We employed the EDiPS model to investigate how elevated dopamine synthesis and release impact the striatal epitranscriptome.
To create EDiPS animals, we overexpressed human tyrosine hydroxylase and GTP cyclohydrolase I in the nigro-striatal pathway during adolescence. sequent m6A-immunoprecipitation sequencing identified 119 differentially methylated transcripts in the adult EDiPS striatum, with over 80% showing hypermethylation, consistent with our recent finding of increased m6A methyltransferase Mett14 expression. Notably, 13 m6A-marked transcripts were closely associated with schizophrenia, as revealed by GeneCard analysis.
To assess the causative role of m6A accumulation in schizophrenia-related transcripts, we developed a Crispr-inspired m6A-RNA editing system (CIRTS) that, in cultured neurons, effectively removed m6A from phospholipase (PLC)-β1 RNA, which was hypermethylated in the EDiPS striatum. Future investigations will determine whether removing m6A from PLC-β1 RNA in the EDiPS striatum using this technology will mitigate schizophrenia-relevant behavioural phenotypes.
Hyper-dopaminergia in the dorsal striatum is a promising neurochemical target for schizophrenia prophylaxis. The crucial role of RNA methylation in striatal function indicates that understanding the impact of m6A accumulation on schizophrenia-related transcripts will provide etiological insights and unveil potential novel treatment targets for schizophrenia.

Tuesday 12:15 PM-12:20 PM
Paul Lockhart
Data Blitz: NEW TOOLS FOR DIAGNOSIS AND DISCOVERY OF PATHOGENIC REPEAT EXPANSIONS CAUSING ATAXIA

Haloom Rafehi1, 2, Justin Read3, 4, David J Szmulewicz5, 6, Kayli C Davies3, 4, Penny Snell3, Liam G Fearnley3, 1, 2, Genevieve Thompson3, 4, Liam Scott1, Mark F Bennett1, 2, 7, Martin B Delatycki3, 4, 8, Melanie Bahlo1, 2, Paul J Lockhart3, 4
1. Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia
2. Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia
3. Murdoch Childrens Research Institute, Melbourne, VICTORIA, Australia
4. University of Melbourne, Parkville, Victoria, Australia
5. Cerebellar Ataxia Clinic, Eye and Ear Hospital, Melbourne, Victoria, Australia
6. The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia
7. Epilepsy Research Centre, Austin Health, Heidelberg, Victoria, Australia
8. Victorian Clinical Genetics Services, Melbourne, Victoria, Australia
Next Generation Sequencing technologies are revolutionizing diagnostics and clinical medicine. However, these approaches have previously proven inefficient at identifying pathogenic repeat expansions (RE), which underlie at least 50 conditions including cerebellar ataxia. Traditionally, molecular testing for RE has utilised single-gene PCR-based methods, however these approaches tend to be low throughput and expensive. Standard diagnosis in Australia screens six of sixteen REs known to cause ataxia, with diagnostic rates of 10%.
Methodological advances have made detection of known and novel pathogenic RE with whole genome sequencing (WGS) feasible. Using these tools, we recently identified the novel RE that causes CANVAS (1). In our current study we have performed short-read WGS on 120 Australian individuals with ataxia and a negative diagnostic test outcome. Discovery analysis for novel RE identified a GAA repeat in FGF14 underlying ~20% of cases, representing the most common genetic cause of ataxia yet identified (2). While analysis is ongoing, to date we have achieved a genetic diagnosis in 33% of individuals. Thirty cases have pathogenic RE in genes that are not assessed by current diagnostic methodology, with an additional ten individuals carrying non-RE pathogenic variants e.g. point mutations in genes associated with ataxia.
This research provides considerable evidence that implementation of WGS as a frontline test for cerebellar ataxia will significantly increase diagnostic yield and fundamentally alter patient experience and clinical pathways for these disorders. More broadly, similar outcomes are anticipated for the >30 other RE disorders, many of which also lack a diagnostic testing pathway in Australia.

12:20 PM-12:25 PM
Abdulhameed Bosakhar
Data Blitz: Can SS3T-CSD be Used to Detect Neuropathology Relevant for Preterm Brain Injury?

Abdulhameed Bosakhar1, Sebastian Quezada1, Claire Kelly2, 3, Mikaela Barresi1, Thijs Dhollander2, David Walker1, 4, Mary Tolcos1
1. School of Health and Biomedical Science , RMIT University, Melbourne, VICTORIA, Australia
2. Murdoch Children's Research Institute , Melbourne, VICTORIA, Australia
3. Turner Institute for Brain and Mental Health, School of Psychological Sciences , Monash University, Melbourne, Victoria, Australia
4. The Ritchie Centre, Hudson Institute of Medical Research , Monash University , Melbourne, VICTORIA, Australia
The brain changes rapidly during development making correlating pathology with neuroimaging in preterm infants challenging. Single-Shell 3-Tissue Constrained Spherical Deconvolution (SS3T-CSD), a diffusion magnetic resonance imaging technique, shows promise in linking brain abnormalities to adverse neurodevelopmental outcomes in preterm children. However, the microstructural changes contributing to these abnormalities remain unknown. Here we determine whether SS3T-CSD-derived white matter-like (TW), grey matter-like (TG), and cerebrospinal fluid-like (TC) tissue signal fractions correspond to cellular and microstructural features in the developing fetal sheep brain. Fetal sheep brains (gestational ages [Ga] 70, 80, 90, 110 days; n=5/age)were imaged ex vivo (Bruker Avance IIIHD system, ParaVision 6.0.1software). Images were processed via MRtrix3, MRtrix3tissue, and FSL software packages; TW, TG and TC were calculated from white matter, grey matter, and cerebrospinal fluid compartment images. Brains were immunostained to assess axons, myelinated fibers, and microglia. Multivariate analysis compared tissue signal fractions between gyri and sulci at different developmental stages. At Ga80, sulci exhibited increased TC (P0.001), and at Ga90 gyri displayed increased TW(P0.001). At Ga110,sulci showed increased TW and decreased TC (P0.001),while gyri exhibited the opposite (P0.001). Preliminary analysis revealed axonal and myelinated fibre staining correlated with TW, while microglial staining correlated with TG and TC. Importantly, no differences observed between sulci and gyri before gyrification (Ga70). Co-registering SS3T-CSD with histology enhances our understanding of microstructural changes during brain development. SS3T-CSD holds potential for identifying neuropathology arising from hypoxic injury, inflammation, or infection in the perinatal brain.

Tuesday 12:25 PM-12:30 PM
Bao Ngoc Tran
Data Blitz: Discovering the influence of an enriched environment on neuronal epigenome ageing as a potential strategy for treating age-related diseases.

Bao Ngoc Tran1, Brandon Signal2, Duncan Sinclair1, James Vickers1, Phillippa Taberlay2, Adele Woodhouse1
1. Wicking Dementia Research and Education Centre, University of Tasmania, Hobart, Tasmania, Australia
2. School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
Epigenetic alterations across the course of ageing have a strong association with age-related diseases. A high-quality condition for living, called environmental enrichment (EE), can rescue aberrant epigenetic changes in whole brain homogenate and purified neurons, resulting in the reduction of pathological risk during ageing. As different neuron types have different epigenetic signatures, we aimed to generate the first genome-wide data investigating epigenetic signatures in excitatory neurons from aged EE-exposed and standard housing (SD) mice. Male C57/BL6 wild-type mice were aged in SD and EE housing to 12, 18 and 24 months of age (n=10 per housing/age, total n=60) and were cognitively tested (open field, Y maze, Barnes maze). A novel FACS protocol was used to purify excitatory neuronal nuclei, then nucleosome occupancy and DNA methylation sequencing (NOMe-seq) was performed. Differentially hyper- and hypo-methylated regions (DMRs) were detected in excitatory neurons from EE compared to SD mice at all timepoints (p0.01). The highest number of DMRs were detected in excitatory neurons at 12-month-old EE mice, correlating with improved long-term memory of EE versus SD 12-month-old mice. DMRs in EE compared to SD excitatory neurons were more frequently located at promoters at all ages, less frequently present in intergenic regions at all ages, and less frequently observed at enhancers at 12 months and at exons at 24 months of age (p0.05). DMRs were mapped to predominantly neurodevelopmental biological processes. The comprehensive picture of age-environment interactions in animal models may aid in reinstating learning and memory function in ageing and neurodegenerative conditions.

Tuesday 10:30 AM-12:30 PM
Laura Jacobson, Matilde Balbi

Symposium 2: Navigating the neuro-vascular interactions in health and disease

Great room 2

Navigating the neuro-vascular interactions in health and disease
Phoebe Mayne1
1. Queensland Brain Institute , University of Queensland, Brisbane , QLD, Australia
The central nervous system relies on an extensive and complex vasculature to function optimally. In response to brain activation, complex interactions between neurons, glia and endothelial cells, pericytes and fibroblasts of the vascular unit act synergistically to increase cerebral blood flow, a phenomenon termed Neuro-Vascular Coupling (NVC). The resultant functional hyperemia ensures that the neuronal energy demands are satisfied by the timely delivery of nutrients and the removal of metabolic waste. Normal NVC is critical for maintaining cognitive health and the integrity of the blood-brain barrier. Compelling evidence obtained both in elderly patients and rodent models shows that aging significantly impairs NVC responses, increasing the risk of stroke and dementia. Moreover, NVC is significantly affected in several neurodegenerative and neurovascular diseases.
The importance of vascular contributions to the brain in health and disease cannot be overemphasized and the age- and disease-related mechanisms that contribute to neurovascular un-coupling are likely multifaceted. In this symposium, we highlight critical research that explores various aspects of the interactions between the vascular system and neural parenchyma that coordinate NVC responses. A primary focus of the symposium will be how the cells of the neurovascular unit communicate and how breakdown in this communication may contribute to vascular dysfunction and disease pathogenesis. A secondary focus of the symposium will highlight various endogenous and therapeutic mechanisms that may help restore functional revascularisation following NVC impairment across several disease models. While there will be a predominant focus on experiments using rodent models with advanced in vivo microscopy methods, some speakers will also include clinical findings from human post-mortem studies.
This symposium is highly relevant to ANS attendees, as NVC is a critical homeostatic process which underscores healthy brain functions such as learning and memory and is impacted in normal aging and in neurodegenerative and neurovascular diseases. A comprehensive characterization of how NVC is regulated will not only improve our understanding of this biological process, but potentially guide new therapeutic interventions in conditions characterized by cerebrovascular dysfunction.

10:30 AM-10:55 AM
Brad Sutherland
Microglia interactions with pericytes, implications for cerebral blood flow in health and disease

Recently, a -population of microglia, the brain's resident immune cells, have been identified to reside in close proximity to cerebral blood vessels implying an important function in cerebral blood flow regulation. Pericytes are embedded within capillaries with critical functions including regulating cerebral blood flow and maintaining blood-brain barrier integrity. Using in vivo two-photon microscopy in mice, we uncover new spatial associations between microglia and pericytes; their associations are dynamic and can influence blood flow, as vessel diameter is increased at locations where pericytes or microglia reside. Following an inflammatory stimulus, microglia rapidly migrate towards blood vessels increasing the number of pericyte-associated microglia. Using the Cortical MM^3 database, we identify examples of direct contact between microglia and pericytes next to capillaries. Studies in human post-mortem brain samples also reveal a population of microglia that is closely associated with pericytes. Interestingly, in an Alzheimer's disease cohort, the numbers of microglia residing on blood vessels and associated with pericytes are reduced. These findings suggest a novel association between microglia and pericytes is important for maintaining the brain's vasculature, and that a breakdown in this association may contribute to vascular dysfunction and pathogenesis in Alzheimer's disease.

10:55 AM-11:20 AM
Louis-Philippe Bernier
Brain pericytes and perivascular fibroblasts are stromal progenitors with dual functions in cerebrovascular regeneration after stroke

Functional revascularization is key to stroke recovery and requires remodeling of blood vessels, around which is located the brain's only stromal compartment. Stromal progenitor cells (SPC) form a functional grouping of cells critical for tissue regeneration following injury in many organs, yet their identity in the brain remains elusive despite implications in neovascularization and scar formation. Here we show that the perivascular niche of brain SPCs includes pericytes, venular smooth muscle cells and a distinct population of perivascular fibroblasts, that together help regenerate the cerebral microvasculature following stroke. The ischemic injury triggers amplification of pericytes and perivascular fibroblasts in the infarct region where they associate with endothelial cells inside a reactive astrocyte border. Fate-tracking of Hic1+ SPCs uncovers a transient functional and transcriptional phenotype of stroke-activated pericytes and perivascular fibroblasts, where both populations remain segregated, displaying dichotomous angiogenic

and fibrogenic profiles. In the adult brain, pericytes and perivascular fibroblasts are therefore distinct populations of stromal progenitors that coordinate revascularization and scar formation after injury.

Tuesday 11:20 AM-11:45 AM
Phoebe Mayne
Longitudinal monitoring of mesoscale calcium activity and hippocampal electrophysiological recordings in a mouse model of small vessel disease

Small vessel disease (SVD) is characterized by sporadic occlusions of small vessels in brain microvasculature. This results in impaired blood flow, increased blood brain barrier permeability and neuronal cell death. While SVD is the leading cause of vascular dementia, the underlying mechanisms remain elusive, limiting treatment options. Growing evidence indicates SVD is significantly associated with altered communication between the vascular system and neural parenchyma, impairing cerebrovascular communication. A recent notion is that evoked visual stimulation can enhance neuronal activity, leading to remodelling of the cerebrovascular architecture. Here, we visualised neuronal activity and cerebrovascular haemodynamics using wide-field calcium imaging in awake head-fixed GCaMP6 mice. Baseline mesoscopic calcium activity and hippocampal electrophysiological recordings were recorded prior to an endovascular injection of fluorescent microspheres into the internal carotid artery, which caused microinfarcts in the brain microvasculature. The microsphere occlusions were quantified along with changes in calcium activity, cerebral blood flow and electrophysiological recordings. Behavioral outcomes were assessed by the neuro-deficit score and the novel object recognition test. We assessed immunohistochemistry markers of reactive astrogliosis and neuronal cell loss. Our results indicate that visually evoked stimulation impacts revascularisation following microinfarct injury, ameliorating behavioural and motor functions as well as reducing reactive astrogliosis and neuronal cell loss.

11:45 AM-12:10 PM
Virginie LAM
Plasmalogen supplementation attenuates doxorubicin-induced cognitive impairment and neurodegenerative changes in mice

Chemotherapy-Induced Cognitive Impairment (CICI), termed chemobrain', is a debilitating neurocognitive side effect of chemotherapy that impacts ~70% of cancer survivors. Pre-clinical evidence suggests CICI-induced neurotoxicity and cognitive dysfunction are resultant of neurovascular breakdown. Here, we explored the efficacy of plasmalogens, neuroprotective glycerophospholipids, in preventing CICI. To induce chemobrain, adult C57BL/6J mice were administered with doxorubicin (DOX), a widely used chemotherapeutic agent. Cognitive function and changes in cerebral blood flow, volumetry and white matter anomalies were assessed by in vivo magnetic resonance imaging (MRI). We performed ex vivo confocal immunomicroscopy to assess cortical and hippocampal blood-brain barrier permeability, neuroinflammation, oxidative stress and neuronal death. DOX-treated mice developed significant spatial learning and memory impairments, coinciding with a reduced cerebral blood flow, hippocampal atrophy, heightened neuroinflammation, oxidative stress, pronounced blood-brain barrier (BBB) permeability, and stantive neuronal loss. Co-provision of plasmalogens in DOX-treated mice restored cognitive function in alignment with increased hippocampal blood flow and restoration' of brain volumes in specific regions of interest, comparable to controls. Restoration of cognitive function was associated with a marked reduction in BBB permeability, astrocyte and microglial activation, and oxidative stress. Our findings identify plasmalogens as an effective therapeutic agent for preventing and/or reversing CICI via a vascular-mediated axis, enabling a potential translational clinical strategy.

12:10 PM-12:15 PM
Gerhard Leinenga
Data Blitz: Scanning ultrasound improves memory and connectivity in an Alzheimer's disease mouse model without reducing amyloid-beta

Gerhard Leinenga1, 2, Xuan Vinh To1, 3, Liviu Bodea1, 2, Fatima Nasrallah1, 3, Jürgen Götz1, 2
1. Queensland Brain Institute, Brisbane, QUEENSLAND, Australia
2. Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
3. Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia
Our objective was to determine if ultrasound stimulation of the brain can improve memory function in an Alzheimer's disease mouse model (APP23 mice) and whether amyloid-β (Aβ) removal occurs. We found that repeated scanning ultrasound (SUS) treatment at 1 MHz frequency can ameliorate memory deficits in APP23 mice without reducing Aβ and without opening the blood-brain barrier (BBB). Quantitative proteomics and functional magnetic resonance imaging revealed that ultrasound induced long-lasting functional changes that correlated with the improvement in memory. The treatment was more effective at improving memory when a higher frequency (1MHz) was used, rather than at a lower frequency (286 kHz) and this was reflected in the changes to the proteome and brain connectivity. Together, our data suggest frequency-dependent bio-effects of ultrasound and a dissociation of cognitive improvement and Aβ clearance, with implications for the design of trials for AD therapies.

Tuesday 12:15 PM-12:20 PM
Elizabeth Kalotay
Data Blitz: Novel mouse models for proof-of-concept of rAAV-mediated gene therapy for the leukodystrophy HBSL

Elizabeth Kalotay1, Elena Venuti1, Gary Housley1, Matthias Klugmann1, Dominik Fröhlich1
1. University of New South Wales, Sydney
Leukodystrophies are a diverse group of over 50 genetic diseases affecting myelination of the central nervous system (CNS), most of which are currently incurable. In addition to its essential function in facilitating saltatory conduction, myelin provides critical metabolic support to neurons and plays an important role in CNS neuroplasticity. Pathological disruptions to CNS myelination can consequently lead to severe neurological dysfunction, lifelong disability, and premature mortality. Biallelic mutations in the DARS1 gene, which encodes the cytosolic aspartyl-tRNA synthetase, cause a leukodystrophy known as Hypomyelination with Brainstem and Spinal cord involvement and Leg spasticity (HBSL). Presently, there is limited understanding of the underlying pathophysiology, and no available treatment. To address this, our group has generated two novel transgenic mouse models of HBSL pathology through conditional knockout of Dars1 expression in neurons (Dars1NeuroKO) and oligodendrocytes (Dars1OligoKO), using the Cre-loxP system. These models have demonstrated that loss of Dars1 is not tolerated in either of these cell populations, with both Dars1NeuroKO and Dars1OligoKOmice exhibiting pronounced neurodegeneration, motor deficits, and reduced lifespan. Further characterisation of these models will inform on the specific contributions of neuronal and oligodendroglial dysfunction to HBSL pathology, guiding selection of an appropriate therapeutic target. Additionally, we have developed recombinant adeno-associated viral vectors (rAAVs) that drive expression of an optimised human DARS1 coding sequence in the CNS. Systemic rAAV-mediated DARS1 delivery has shown great efficacy in ameliorating the phenotype of our most severe Dars1NeuroKOmodel, providing the first proof-of-concept of DARS1 gene replacement therapy for the treatment of HBSL.

12:20 PM-12:25 PM
Emily Willis
Data Blitz: ¬Intravenous immunoglobulin (IVIG) promotes brain repair and improves cognitive outcomes after traumatic brain injury in a FcγRIIB receptor-dependent manner

Emily Willis1, Ellen R Gillespie2, Kristen Guse3, Adrian W Zuercher3, Fabian Käsermann3, Marc J Ruitenberg1, Jana Vukovic4, 1
1. School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia
2. The University of Queensland, Annerley, QLD, Australia
3. CSL Biologics Research Centre, CSL Behring, Research, Bern, Switzerland
4. Queensland Brain Institute, Brisbane, QLD, Australia
Intravenous immunoglobulin (IVIG) is a promising immune-modulatory therapy for limiting harmful inflammation and associated secondary tissue loss in neurotrauma. Here we show that IVIG therapy attenuates hippocampal-dependent spatial learning and memory deficits following a controlled cortical impact mouse model of traumatic brain injury (TBI). These improvements in cognitive outcomes were associated with the support of hippocampal neurogenesis, increasing the survival of immature hippocampal neurons and the activity of intermediate neuronal progenitors after TBI. High-resolution 16.4T magnetic resolution and diffusion tensor imaging demonstrated IVIG treatment led to an overall reduction in brain tissue loss and a greater preservation of neural connectivity. We also demonstrate that IVIG therapy reduces neuroinflammation, reducing the presence of neutrophils and attenuating activation of microglia and astrocytes that occurs following TBI. Mechanistically, we demonstrate that the neuroprotective benefits of IVIG therapy are reliant upon the presence of the main inhibitory IgG receptor Fc γRIIB receptor after TBI, and our results also highlight the role of this receptor in reducing secondary damage arising from brain injury. Taken together, these findings demonstrate that IVIG treatment acts in a manner dependent upon the presence of the inhibitory Fc γRIIB receptor to alleviate the cognitive deficits and mitigate secondary neurodegeneration that otherwise occurs after TBI.

Tuesday 10:30 AM-12:30 PM

Selected Orals 1: Neurodevelopment

Great room 3

10:30 AM-10:45 AM
Jingqi Wang

Organelle mapping in dendrites of human iPSC-derived neurons reveals dynamic functional dendritic Golgi structures

Jingqi Wang1, Marlene Hao2, Maciej Daniszewski2, Alice Pébay2, 3, Lou Fourriere1, Paul Gleeson1
1. Department of Biochemistry and Pharmacology, University of Melbourne, Parkville, VICTORIA, Australia
2. Department of Anatomy and Physiology, University of Melbourne, Parkville, Victoria, Australia
3. Department of Surgery, University of Melbourne, Parkville, Victoria, Australia

Neurons have a very large surface area and the transport of newly synthesised proteins from the cell body to distal synapses represents a significant challenge. Unique secretory pathways within dendrites of neurons have been proposed following the identification of dendritic Golgi (also called Golgi outpost) structures and other dendritic secretory organelles for local protein transport, which are independent of the central machinery in the soma and could overcome this transport challenge 2,3. However, little is known about the dynamics and behaviour of the dendritic organelles during the neuronal development of human neurons. Here, we quantified the spatial and dynamic behaviour of dendritic Golgi and endosomes during the differentiation of human neurons generated from induced pluripotent stem cells (iPSCs) using a range of imaging techniques including long-term live imaging 1. In early neuronal development when neurons are highly mobile, the entire Golgi was observed to transiently translocate from the soma into one dendrite. Later, in mature neurons, dynamic Golgi elements, containing cis and trans-Golgi cisternae, were transported from the soma along dendrites, in an actin/ROCK-dependent process. Dendritic Golgi outposts in human neurons are dynamic and display bidirectional movement with similar structures observed in cerebral organoids. Using the retention using selective hooks (RUSH) system, Golgi resident proteins were shown to be efficiently transported into Golgi outposts from the endoplasmic reticulum. This study has revealed unique features associated with the secretory pathway in human neurons and provides a foundation to investigate local protein trafficking in the dendrites of human neurons.

10:45 AM-11:00 AM
Gabriela Bodea

Mobile DNA activity enriches neuronal transcriptome diversity

Gabriela O. Bodea1, Juan Manuel Botto1, Maria Eugenia Ferreiro1, Jose de Los Rios Barreda1, Darwin Da Costa Guevara2, 1, Geoffrey J. Faulkner2, 1
1. Queensland Brain Institute, University of Queensland, St Lucia, QLD, Australia
2. Mater Research Institute-University of Queensland, Woolloongabba, QLD, Australia

The mammalian brain's complexity arises from diverse neuronal cell types. Neuronal diversity can be defined by variations in intrinsic properties such as transcriptome signatures and extrinsic properties related to extracellular factors. Many aspects of this diversity remain poorly understood.
Single-cell genomics technology advancements helped unveil the uniqueness of each neuron's DNA. Mobile DNA is one of the significant contributors to variations in the neuronal genome. Long Interspersed Element 1 (L1), a class of mobile DNA, was shown to be active in human neurons. L1 can mobilise or jump from one place in the genome to another via an RNA intermediate. L1 insertions can impact gene expression through various mechanisms, including changes in chromatin structure, transcription, and pre-mRNA processing. Prior research shows that neuronal differentiation provides an opportunity for L1 mobilisation. However, it remains unclear whether: 1) L1 activity prefers specific neuronal lineages and 2) the relevance of L1 insertions in neuronal biology.
Here, we show that L1 mobilisation is stimulated by SRY-box transcription factor 6 (SOX6), a key player in the transcriptional program of parvalbumin-expressing (PV+) interneuron development. We found that PV+ neurons harbour unmethylated L1 promoters, express higher levels of L1 mRNA and protein than other neurons, and support L1 transgene mobilisation in vivo. Using long-read nanopore DNA sequencing, we identified unmethylated L1 promoter loci in PV+ genes that can drive the expression of novel transcript isoforms relevant to neuronal biology. Our findings reveal a remarkable capacity of mobile DNA activity to enhance regulatory gene networks, expanding neuronal transcriptomes.

11:00 AM-11:15 AM
Lincon Stamp

Stem cell therapy for Hirschsprung disease

Juan Molero1, 2, Cameron Adams2, Enie Lei2, Hui Yu1, Lilith Caballero Aguilar3, Marlene Hao1, David Nisbet3, John Furness1, 2, Lincon Stamp1, 2
1. Anatomy and Physiology, University of Melbourne, Parkville, Victoria, Australia
2. The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia

3. The Graeme Clark Institute, University of Melbourne, Parkville, Victoria, Australia
Objective: Hirschsprung disease is an archetypal neurocristopathy characterized by the congenital absence of enteric neurons in variable lengths of the distal bowel. Current surgical interventions, while lifesaving, frequently result in chronic, debilitating, and life-threatening complications. Using a novel rat model of Hirschsprung disease, we aim to assess the efficacy of stem cell therapy together with an enhanced implantation microenvironment to regenerate the enteric nervous system in the aganglionic bowel.
Methods: Enteric neural precursor cells were derived by directed differentiation of human induced pluripotent stem cells. These enteric neural precursors were sequently transplanted, in the presence or absence of bespoke peptide hydrogels, into the distal colon of cyclosporin immunosuppressed Ednrb-/- rats, a commonly used genetic model of Hirschsprung disease.
Results: As Ednrb-/- rats die during early postnatal development due to their Hirschsprung phenotype, a colostomy was first developed for these rats to prolong their survival. Surgically rescued Ednrb-/- rats survived months beyond the time that they would have died. Human induced pluripotent stem cell-derived enteric neural precursors were implanted as either cell suspensions or cell aggregates in a range of laminin pentapeptide hydrogels, by microelectrode injections. We found that human enteric neural precursors survived and gave rise to mature neurons in the colon of wildtype and Ednrb-/- rats. The newly generated neurons consisted of a range of neurochemical phenotypes, with axon-like projections. The presence of peptide hydrogels supported the survival and neurogenesis of transplanted enteric precursors. Stem cell therapy together with microenvironment enrichment provides a novel potential treatment for Hirschsprung disease.

Tuesday 11:15 AM-11:30 AM
Ryan Keable
Deficiency in NCAM2 results in reduced BACE1 activity, affects axonal organization in the hippocampus and leads to behavioral deficits

Ryan Keable1, Saroj Sah1, Shangfeng Hu1, Grant Pfundstein1, Irina Kozlova1, Feifei Su1, Kelly J Clemens1, Denovan Begg1, Ximing Du1, Hongyuan Yang1, Jenny Gunnersen2, Melitta Schachner3, Iryna Leshchyns'ka1, Vladimir Sytnyk1
1. University of New South Wales, Kingsford, NSW, Australia
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Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), also known as β-secretase, is an aspartic protease. The sorting of this enzyme into recycling endosomes, which transport BACE1 to axons and presynaptic boutons, regulates the BACE1-mediated cleavage of its strates. However, the mechanisms underlying this targeting remain poorly understood. We demonstrate that BACE1 cleaves its strate neural cell adhesion molecule 2 (NCAM2) in the dendrites of hippocampal neurons. BACE1 remains associated with the transmembrane cleavage product of NCAM2, which targets BACE1 to Rab11-positive recycling endosomes and delivers BACE1 to axons and synaptic boutons. NCAM2 deficiency results in BACE1 retention in clusters at the surface of dendrites, while the axonal levels of BACE1 are reduced in hippocampal mossy fiber projections, and the infrapyramidal bundle of these projections is shortened. This abnormal axonal organization correlates with impaired short-term spatial memory and cognitive flexibility in NCAM2-deficient male and female mice. Self-grooming, rearing, digging and olfactory acuity are increased in NCAM2-deficient male mice, when compared to littermate wild-type mice of the same sex. NCAM2-deficient female mice also show increased self-grooming, but are reduced in rearing, and do not differ from female wild-type mice in olfactory acuity and digging behavior. Our results indicate that errors in axonal guidance and organization caused by impaired BACE1 function can underlie the manifestation of neurodevelopmental disorders, including autism as found in humans with deletions of the NCAM2 gene.

11:30 AM-11:45 AM
Evan Bailey
ventricular zone cells lack competency to produce neurons in a developing marsupial cortex

Evan J Bailey1, 2, Peter Kozulin2, Annalisa Paolino2, Elizabeth Haines1, 2, Dylan Black2, Rodrigo Suarez1, 2, Laura Fenlon1, 2
1. Queensland Brain Institute, St. Lucia, QLD, Australia
2. School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland, Australia
The evolutionary expansion of the ventricular zone during development is thought to underly enlargement of the neocortex in primates. In particular, a type of progenitors that detach from the surface of the ventricle and divide in the ventricular zone is present in all placental mammals studied to date and contributes to cortical expansion through additional amplification of cell numbers during corticogenesis. However, the existence of these ventricular zone progenitors in marsupials remains unclear despite similarly sized and laminated cortices to placental mammals. Here we present unpublished work showing that a mouse-sized marsupial species, the fat-tailed dunnart, lacks progenitor cells in the ventricular zone of the developing neocortex and instead relies solely on neurogenesis from the pool of progenitors that line the lateral ventricles. To explore the mechanisms by which corticogenesis diverges between mice

and dunnarts, we probed the dynamics of cell-cycle progression via dual-pulse birthdating and single-nuclei RNA-seq, revealing differences in the temporal and transcriptional dynamics of cell-cycle in ventricular progenitors. We further examined how neurogenesis is coupled to specific cellular processes by manipulating cell-cycle phase length, forcing delamination of ventricular progenitors, and disrupting the mitotic cleavage angle. Despite these cellular processes increasing the frequency of ventricular progenitors in mice during development, they were insufficient to produce ventricular progenitors in dunnart, suggesting that dunnart ventricular zone cells lack the capacity for neurogenesis. Overall, this work reveals key evolutionary divergences in corticogenesis between mammals and provides insight into alternative mechanisms by which mammals may produce similarly-sized brains.

Tuesday 11:45 AM-12:00 PM
Alexandre Cristino
An introgressed neanderthal genetic variant within the MIR137HG locus impairs human cell migration and neuron differentiation.

Alex Sykes1, Caio Damski1, Daniel Russell1, Jamila Iqbal1, Alexandre S. Cristino1
1. Griffith University, Nathan, QLD, Australia
Schizophrenia is a complex psychiatric disorder influenced by several genetic variants with small effects contributing to disease risk, many of which lie within non-coding regulatory regions of the genome. Whilst many loci have been consistently identified by several genome-wide association studies, understanding the functional consequences of these genetic variations in non-coding regions remains a significant challenge for the field. One of the most relevant locus is MIR137HG, which encodes a long non-coding RNA and two microRNAs, namely miR-137 and miR-2682. Common variants associated with schizophrenia within this locus have been associated with reduced expression of miR-137 in the brain. In this study, we delve into the functional implications of a single nucleotide variation (SNV) in the mature sequence of miR-2682-3p, originating from Neanderthal/Denisovan humans and also conserved in all primates. Our investigation reveals that this modern human SNV results in an elevated expression of miR-2682 mature sequences compared to its ancestral counterpart. Furthermore, we have uncovered distinct differences in the target networks of modern and ancestral miR-2682, impacting the regulation of several genes associated with crucial processes like cell migration and neuron differentiation. The overarching objective of our research is to shed light on disease-associated pathways that could be potentially restored by manipulating microRNAs. By identifying and understanding the functional roles of these genetic variations in small regulatory RNAs, we aim to explore novel therapeutic avenues for schizophrenia. Our findings offer promising insights into the potential use of microRNA as innovative therapeutic strategies for this debilitating mental disorder.

12:00 PM-12:15 PM
Lara Rogerson-Wood
Enrichment drives targeted microglial-engulfment of mis-mapped retinal inputs in a narrow postnatal time-window.

Lara Rogerson-Wood1, Claire Goldsbury1, Atomu Sawatari1, Catherine Leamey1
1. The University of Sydney, Sydney, NSW, Australia
Due to loss of an early axonal guidance cue, Ten-m3 knock-out mice display a pronounced and stereotyped visuo-topic mis-mapping of ipsilateral retinal inputs to the visual thalamus1,2. We have previously shown environmental enrichment (EE) from ~ birth -but not weaning (P21) or adulthood (>3 months-old)- for 6 weeks drives corrective' pruning of the most mis-mapped inputs3, along with improved visually-mediated behaviour (usually defective)4. The process was later shown as in-progress' at postnatal-day (P)25 5. Importantly though, an EE-driven activated' microglial profile was concurrently observed specifically at the corrective pruning site5, suggesting microglial involvement. A comprehensive time-course of this latter effect (of EE on microglia) and clarification of cellular mechanism were still lacking, however. Here we show, via immunofluorescence labelling of microglia and anterograde tracing of retinal inputs, that this effect hasn't commenced at P18, is apparent at P21 ($p=0.010$), at higher levels at P25 ($p=0.002$) and ceased by P30. This further correlated with an absence of pruning following EE until P18 but significant corrective pruning by P30 (p0.001). Most notably though, through 3D reconstruction of high-resolution confocal images, EE until P25 was also shown to increase microglial-engulfment of mis-mapped inputs at the corrective pruning site ($p=0.009$) but not control site - no changes in this measure were noted at P18. Collectively these findings identify targeted microglial-engulfment as a likely mechanism via which EE drives corrective' pruning of mis-mapped retinal inputs in Ten-m3 KO mice. This may have important therapeutic implications for neurodevelopmental conditions involving genetically-caused connectivity defects.

12:15 PM-12:30 PM
Dhanisha Jhaveri
Tapping into mechanisms of resilience in the treatment of stress-induced anxiety disorder

Dhanisha Jhaveri2, 1
1. Queensland Brain Institute, The University of Queensland, Brisbane
2. Mater Research Institute, The University of Queensland, Brisbane

Chronic stress is a major risk factor for anxiety and depression and has been designated by the World Health Organization as the defining health epidemic of this century. Although progress has been made in mapping the brain circuitry associated with these stress-induced neuropsychiatric conditions, their treatment remains a challenge because we do not yet have a clear understanding of the cellular and molecular mechanisms. The hippocampal circuit has unique developmental, physiological and circuit properties that contribute to emotional processing, including anxiety and depressive behaviours. We have found that chronic stress exposure alters the structural and functional development of adult-born neurons in the mouse hippocampus. Using selective ablation and optogenetic strategies combined with behaviour we provide evidence for a causal role for immature adult-born hippocampal neurons in suppressing stress-induced anxiety-like behaviour. Furthermore, we show that resilience-promoting effects of a clinical antidepressant is associated with the prevention of stress-induced structural, physiological, and transcriptional changes in adult-born neurons. Collectively, our findings provide a new framework to understand the role of immature hippocampal neurons in mood regulation and pave the way towards novel resilience-enhancing therapeutics.

Tuesday 12:30 PM-01:30 PM

Break

Lunch, Exhibition and Poster Display

Foyer/Studio 1/2/3/4

12:30 PM-01:30 PM

Brain Bee Final

Great room 1

Tuesday 01:30 PM-03:30 PM
Matthew Kiernan

Symposium 3: Toxicity and axonal degeneration: Mechanisms and biomarkers

Great room 1

Susanna B Park1, Andrea Loreto 2, Irina Vetter3, Anna King4, Matthew Kiernan1
1. University of Sydney, Camperdown, NSW, Australia
2. Cambridge Neuroscience, University of Cambridge, Cambridge, UK
3. Institute of Molecular Bioscience, The University of Queensland, St Lucia, QLD, Australia
4. Wicking Dementia Research and Education Centre , University of Tasmania, Hobart, Tasmania, Australia

Axonal degeneration is a common pathophysiological event, and axonal loss is linked to disability in neurological disorders. There are a diverse range of triggers which can precipitate axonal degeneration, leading to a systematic molecular cascade resulting in axon loss. Improved understanding of the contributors to this active and controlled process will assist in developing effective therapeutic strategies to prevent neurological disease.
However, in the context of neurodegenerative disease, the onset and triggers of degeneration remain ill-defined and may occur decades prior to clinical onset. In contrast, toxicity-induced degeneration often occurs in response to toxic exposure to a known agent within a defined timeframe, enabling more focal examination of the mechanisms underlying degeneration. This symposium will address our understanding of molecular and neuroimmune pathways important in producing neurotoxicity and axonal degeneration, bringing together leading researchers from multiple fields including neurodegeneration, axon biology, sensory neuropharmacology and clinical neuroscience.

01:30 PM-01:55 PM
Anna King
Understanding axon pathology and degeneration in neurodegenerative disease

To provide context for a comparative understanding of axonal degeneration, Professor King (University of Tasmania) will present insights into the mechanisms of axon loss in neurodegenerative disease, providing evidence for a disease and cell-type specific approach to axon protection strategies. This work harnesses axon self-destruction pathways common across neurodegenerative disease and toxic axonopathy, such as Wallerian degeneration, to understand how axon pathology and loss is instigated by neuronal insults such as excitotoxicity. This will provide the basis for understanding common mechanisms of axon degeneration following neurotoxic insults and in neurodegenerative disease.

01:55 PM-02:20 PM
Andrea Loreto
A druggable pathway of programmed axon death as a driver of environmental neurotoxicity and toxic neuropathies

Next, Dr Loreto (Cambridge University) will provide recent evidence of the relevance of NAD+ synthesis pathways and the sterile-α and Toll/interleukin 1 receptor (TIR) motif containing protein 1 (SARM1) enzyme pathways in controlling axonal degeneration following neurotoxic insults. Loreto will discuss the SARM1 axon death pathway in relation to environmental neurotoxins, providing findings of relevance to pathways across neurotoxic triggers and experimental evidence of pharmacological interventions to prevent axonal degeneration.

02:20 PM-02:45 PM
Irina Vetter
Macrophage-derived interleukin-1ß is both necessary and sufficient for vincristine-induced peripheral neuropathy

Professor Vetter (University of Queensland) will address the role of neuroinflammation as a key mediator of axonal damage in chemotherapy-induced peripheral neurotoxicity (CIPN), a prominent cause of toxic axonopathy. Neuroinflammation, glial activation and cytokine modulation have been linked to CIPN and sequent degeneration in experimental models, and are also relevant across neurodegenerative disorders. This presentation will examine the role of macrophages in neurotoxicity following treatment with the chemotherapy vincristine, providing a potential therapeutic strategy to prevent neurotoxicity development.

02:45 PM-03:10 PM
Susanna Park
Axonal degeneration in paclitaxel-induced peripheral neuropathy: genetic, neurophysiological and serum biomarkers

A/Professor Park (University of Sydney) will provide clinical evidence of the importance of axonal degeneration pathways in paclitaxel-induced neurotoxicity, including genetic predisposition to axonal degeneration and evidence

that the serum biomarker of axonal damage, neurofilament light chain, provides an early indicator of clinical neurotoxicity that is linked to axonal excitability disruption in vivo.
These pre-clinical and clinical insights into mechanisms of axonal degeneration in toxic neuropathies will provide important information regarding the development and progression of axonal dysfunction more broadly. The aim of this symposium is to bring together novel multidisciplinary research into axonal degeneration to assist in the development of successful interventions for axonopathy and other neurodegenerative disorders.

Tuesday 03:10 PM-03:15 PM
Kushan Gandhi
Data Blitz: Transcranial Focused Ultrasound-mediated Ropinirole Release from Liposomes in a Hemiparkinsonian Rat Model

Kushan Gandhi2, 1, Jason Gray2, 1, John N.J. Reynolds2, 1
1. The Brain Health Research Centre, University of Otago, Dunedin, Otago, New Zealand
2. Department of Anatomy, University of Otago, Dunedin, Otago, New Zealand
Pharmacological strategies for Parkinson's disease aim to alleviate disabling symptoms by dopamine supplementation using the prodrug (levodopa) or receptor agonist (e.g. ropinirole). However, oral delivery of these drugs results in non-physiological stimulation of dopamine receptors in the striatum and off-target effects. To circumvent these issues, we present a novel, ultrasound-mediated system capable of phasic releasing of ropinirole from packaged liposomes (ropinisomes) in targeted areas.
We prepared a hemiparkinsonian rat model by injecting the neurotoxin 6-OHDA into the left medial forebrain bundle. The efficacy of ropinirole release from intravenously-delivered ropinisomes was assessed by measuring contralateral rotational motor responses following application of transcranial ultrasound, applied to the skull overlying the striatum. Mean contralateral turns per minute (tpm) were assessed at baseline, after isolated ultrasound application, following ropinisome administration, and after ultrasound application in the presence of ropinisomes. Additionally, we exposed rats to single and repeat (20 over 28-days) ultrasound applications to histologically assess ultrasound safety.
Significant ultrasound-mediated ropinirole release was observed in 80% of trials (1.08 tpm; p 0.0001). No turning was observed at baseline or after isolated ultrasound application, and only a trend observed due to spontaneous release after ropinisome administration (0.14 tpm; p = 0.775). Single and repeat applications of ultrasound did not induce blood-brain barrier disruption, nor any haemorrhagic, parenchymal, gliotic or apoptotic change.
Thus, we demonstrate in vivo the feasibility and safety of transcranial focused-ultrasound to mediate ropinirole release from ropinisomes. Successful translation requires improvement in ropinisome stability, and scale-up to humans via a large-animal model.

03:15 PM-03:20 PM
Neha Satish Kumar
Data Blitz: New Insights into the Cellular Kinetics of Microglial Cell Cycle Dynamics During Development and Demyelination

Neha Satish Kumar1, Samuel Mills1, David Gonsalvez1, 2, Aaron Andres1, David Homewood2
1. Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia
2. Department of Anatomy and Physiology, University of Melbourne, Melbourne, VIC, Australia
Microglia are crucial to proper CNS function. However, we are yet to address key questions about how microglia adapt their cellular kinetics to enable the dynamic changes in cell production required for development and disease pathogenesis. We address these using cell cycle assays, design-based stereology and mathematical modelling to demonstrate for the first time that:
Microglia have a fast ~14-hour (SD =4.3) cell cycle length during embryonic development. 1289 cells (SD=317.9, n=6) colonizing yolk sac microglia at E10.5 expand to 8722 (SD= 733.2, n =6) cells by E15.5, and reach 1,404,605 (SD=189,789, n=6) cells by P15. However, our data finds virtually no excess cell production during this growth, which is a striking contrast to what is reported for neuronal production and oligodendrocyte production where cells are produced at almost 50% excess.
This is the first account of in vivo microglial production dynamics. We show a model of cellular expansion that is distinct to neuroectodermal-derived cells in the CNS. In response to 3 weeks of demyelinating injury, microglia take longer to complete cell division than in embryonic development, with a cell cycle length of ~30 hours (SD= 15). Furthermore, microglia in the corpus callosum increased from ~10,000 to ~120,000 cells.
This study gives insight into the cell cycle dynamics of embryonic microglia and fills the gap in the literature regarding microglial proliferation during development, and in acute white matter injury.

03:20 PM-03:25 PM
Montana Samantzis
Data Blitz: Effects of non-invasive brain stimulation on neural and behavioural changes following photothrombotic ischemic stroke

Montana Samantzis1, Georgie Moore1, Phoebe Mayne1, Matilde Balbi1

1. Queensland Brain Institute, Brisbane, QLD, Australia
Stroke is a major cause of long-term disability worldwide, however, current therapeutics are limited. Previous research in mice has demonstrated that optogenetic stimulation in the gamma frequency range, specifically at 40Hz, is beneficial for recovery post-stroke. However, this treatment option is not easily translated to human patients. Thus, our project is investigating whether delivering non-invasive electrical brain stimulation at 40Hz could be a potential therapeutic to restore neuronal dynamics and improve behaviour. In this study we investigated neural and behavioural changes in mice following a photothrombotic stroke in the area between the primary motor cortex and somatosensory cortex in awake mice. We performed mesoscale cortex-wide imaging and electrophysiology recordings of mice over a baseline period and within the 30 days following stroke. Motor behaviour and cognitive performance were also assessed over the post-stroke period. Our results demonstrate that following gamma frequency stimulation, we see increases in blood flow, including oxygenated haemoglobin levels. Using mesoscale imaging we could see alterations to neuronal activity and connectivity, as well as identifying the effects of the stimulation on specific neuronal populations using electrophysiology. We also found changes to the performance of mice on motor tasks, that may indicate a protective effect of our stimulation. Together, our results suggest that non-invasive electrical stimulation can affect neuronal activity and motor behaviour of mice following stroke.

Tuesday 03:25 PM-03:30 PM
Aishwarya Johnson
Data Blitz: Spleen Tyrosine Kinase activation drives inflammasome activation and synuclein pathology in Parkinson's disease

Aishwarya Mary Johnson1, Katherine Z. Hanton1, Natalia J.GROVES1, Eduardo A.Albornoz2, John O'Sullivan2, Nanthini Jayabalan1, Richard Gordon1
1. QUT, BRISBANE, ACT, Australia
2. UQ, Brisbane
Parkinson's Disease (PD) is a slow progressive neurodegenerative condition with debilitating motor and non-motor symptoms. To date there are no effective treatments available beyond the symptom management, signalling a growing socio-economic impact. Emerging as a central driver of neuropathology in PD and other diseases, there is a growing recognition of the role played by chronic immune and NLRP3 inflammasome activation, triggered by synuclein aggregates. Several small molecule NLRP3 inhibitors are now being developed as promising disease-modifying therapeutics for PD and other CNS indications where persistent NLRP3 activation has been shown. Since oligomerisation, assembly and activation of the NLRP3 inflammasome is tightly orchestrated by kinases and phosphatases, we explored the kinases which are involved in NLRP3 activation in PD. We observed that Spleen Tyrosine Kinase (Syk) was highly activated in the CNS at the sites of neurodegeneration in human PD patients. Syk pathway activation was also evident in the nigrostriatal system in PD models, and this occurred at the peak of NLRP3 inflammasome activation, alongside dopaminergic neuron loss. Exposure to synuclein fibrils in primary microglia also triggered activation of the Syk (pSyk Tyr 525). Syk inhibition with R778, an FDA approved Syk inhibitor, blocked NLRP3 activation in microglia by multiple triggers. In animal studies, our preliminary findings suggest that an orally active and CNS-permeable inhibitor of Syk kinase prevents dopaminergic neuron loss in the CNS and the accumulation of pathological synuclein aggregates (pS129-Syn).Together, our studies identify Syk kinase inhibition in the CNS as a novel druggable therapeutic strategy for PD.

Tuesday 01:30 PM-03:30 PM
Lincon Stamp; Marlene Hao

Symposium 4: Following your guts: Advances in enteric nervous system research

Great room 2

Marlene M Hao1, Lincon A Stamp1, Faranak Fattahi2, Nick J Spencer3, Nikhil Thapar4, Shanti Diwakarla1
1. Department of Anatomy and Physiology, University of Melbourne, Parkville, VIC, Australia
2. Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California, USA
3. College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia
4. Gastroenterology, Hepatology and Liver Transplant, Queensland Children's Hospital, Brisbane, QLD, Australia

Correct control of digestive function is vital to the survival of all organisms. The breakdown of food and its movement through the gastrointestinal tract are essential for extracting the necessary nutrients and eliminating waste. Affectionately called the second brain, the enteric nervous system (ENS) is a complex network of neurons and glia that plays a vital role in the control of gastrointestinal function. Located within the wall of the gut, the ENS co-ordinates the movement of food through the entire gastrointestinal tract, and regulates secretion into the gut lumen. Dysfunctions of the ENS can lead to a variety of digestive disorders, such as Hirschsprung Disease, irritable bowel syndrome, achalasia, gastroparesis and many more. Understanding the role of the ENS in digestion and motility is crucial for developing effective treatments for these disorders and improving overall digestive health.
The speakers in this symposium represent an ideal cross-section of recognised senior and young investigators in enteric neuroscience, stem cell technology and clinical neurogastroenterology. This symposium will present new results investigating function of the human ENS and paediatric gut motility, the use of animal models in the investigation of optogenetic control of the ENS, and neurodegenerative disease, as well as the synthesis of new enteric neurons from iPSCs for disease treatment. This program integrates discovery science in animal models with clinical applications for digestive diseases.
In addition to control of digestive function, the ENS also influences our immune function, and communication along the gut-brain axis highlights the importance of the ENS in regulating our neurophysiology. This symposium will provide fellow neuroscientists with an update of the most recent findings of how enteric neurons are generated, communicate and how their function impacts gut health. Our colleagues will appreciate the tremendous advantages in working on the Enteric Nervous System as an open window to the complexities of the nervous system in health and disease.

01:30 PM-01:55 PM
Faranak Fattahi
hPSC-derived enteric ganglioids for the study of GI motility disorders

The enteric nervous system (ENS) plays a central role in regulating the gut and its cross talk with other organs. The human ENS has remained elusive, highlighting the need for an authentic in vitro model. Here we derived enteric ganglioids from human pluripotent stem cells that model the molecular and functional features of the primary tissue. To demonstrate the power of this system, we comprehensively characterized nitrergic neurons (NO neurons)which are implicated in gut motility disorders. We conducted a screen and identified drugs that modulate NO neurons and promote motility in mouse colonic tissue. We defined the developmental programs in NO neuron specification and discovered that PDGFR inhibition boosts their differentiation. These ganglioids engraft extensively in the colon of NO neuron deficient mice, enabling the development of cell therapies for gut motility disorders. These studies provide a new experimental system for deciphering fundamental features of the human ENS and designing effective therapeutic strategies.

01:55 PM-02:20 PM
Nikhil Thapar
The Enteric Nervous System in disease: how much do we really know?

Enteric neuropathies represent some of the most challenging clinical disorders with a significant burden of disease and very limited potential therapeutic strategies. This remains the case despite considerable advances in our understanding of enteric nervous system (ENS)development, structure and function in experimental models as well as in regenerative medicine as a means of providing curative therapies. The talk will explore our current understanding of the aetiopathogenesis, and pathology of the most severe enteric neuropathies seen in patients, from oesophageal achalasia, an acquired disorder characterised by destruction of the ENS, to intestinal pseudo-obstruction where function alfailure rather than structural disruption of the ENS is the hallmark. It will review the molecular and genetic aspects of ENS disturbance in such disorders as well as potential mechanisms that may lead to such pathology including intestinal dysbiosis and neuropathic microorganisms, immune dysregulation as well as the potential of disordered gut-brain interaction. Finally, it will address potential contemporary and futuristic avenues and tools that scientists and clinicians alike may use in the search for better outcomes for these most devastating of conditions.

02:20 PM-02:45 PM
Shanti Diwakarla
The Gut and Parkinson’s Disease

Parkinson's disease (PD) is a progressive degenerative disorder that effects multiple systems. The disease is characterised by the accumulation of misfolded aggregates of the protein alpha synuclein (asyn) in dopaminergic neurons of the stantia nigra pars compacta (SNpc), which are thought to drive motor symptom onset. Clinical diagnosis predominantly occurs when~50-80% of neurons in the SNpc are lost, leaving the window for therapeutic intervention limited. Clinical studies indicate that GI function is often affected decades before motor symptom onset, and recent evidence suggests GI inflammation and alterations to the gut barrier emerge at early stages of disease. Therefore, using the GI tract to predict disease mayprove beneficial. We have assessed several pre-clinical models of PD to evaluate the role of the GI tract, with particular emphasis on the intestinal barrier, in disease development and progression. Our results have demonstrated that different mouse models of PD display heterogeneity with respect to GI function, and that enteric neuropathy, altered intestinal morphology/gut barrier integrity, and intestinal inflammation are evident. Collectively, our results highlight the prominence of GI dysfunction in mouse models of PD, which may be pertinent to not only the progression of disease but could influence the oral bioavailability of therapeutic interventions.

Tuesday 02:45 PM-03:10 PM
Nick Spencer
Identifying the functional role of intrinsic sensory neurons in the enteric nervous system using neurogenetic technology

Compared with all other internal organs, the gastrointestinal tract is unique, because it contains not only its own intrinsic nervous system (known as the enteric nervous system, ENS), but also its own unique population of sensory neurons, known as intrinsic primary afferent neurons (IPANs). It has been very difficult to determine the functional role of IPANs in the gut wall until recent advances in neurogenetic techniques. RNA sequencing identified that the neuropeptide CGRP-B is highly expressed in IPANs. Therefore, we generated a transgenic mouse expressing inducible cre under the CGRP-beta promotor. CGRP-beta mice were crossbred with Ai9 mice to induce cre-driven expression of the fluorescent reporter protein, td Tomato. Reporter expression was identified in IPAN nerve cell bodies and numerous axons throughout the colonic myenteric plexus. This gave us a priceless opportunity to identify and record from IPANs in intact neural networks. CGRP-beta cre mice were crossbred with Ai32 mice to induce cre-driven expression of channelrhodopin-2. Blue light stimulation of the isolated mouse colonic wall evoked premature contractions along the colon in cre+ but not cre- mice (N=5). Calcium imaging of tdTomato labelled IPANs revealed that these neurons generated regular calcium transients that were time-locked with other interneurons. These calcium transients were blocked by hexamethonium (N=6).Channel rhodopsin-driven activation of IPANs evoke contractions that could propage along the colon. The findings suggest that IPANs generate considerable ongoing activity and in addition to behaving as sensory neurons, also receive prominent fast synaptic inputs from other interneurons.

03:10 PM-03:15 PM
Tanya McDonald
Data Blitz: Glucose dyshomeostasis in the R6/1 mouse model of Huntington’s Disease

Tanya S McDonald1, Titaya Lerskiatiphanich1, Trent M Woodruff1, 2, John D Lee1
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2. Queensland Brain Institute, Univeristy of Queensland, St Lucia, Queensland, Australia
There is increasing evidence linking glucose intolerance and diabetes mellitus with Huntington's disease (HD). However, the mechanisms linking glucose dyhomeostasis to disease progression in HD are not yet understood. Here, we investigated the role of insulin and glucagon signalling in energy dysregulation using the R6/1 HD mouse model. Male transgenic R6/1 mice and their wild-type littermates underwent intraperitoneal glucose/insulin tolerance tests, and plasma glucoregulatory hormone profiles were analysed using ELISAs. Pancreatic islet cell mass and function were assessed by measuring hormone secretion in isolated islets, and pancreatic α- and β-cell immunoreactive areas. We identified that R6/1 mice at the onset of motor symptoms presented with higher blood glucose concentrations in both the fed and fasted states, and this correlated with a loss of circulating plasma insulin concentrations. Additionally, R6/1 mice displayed glucose intolerance following an intraperitoneal injection of glucose, which could be due to a loss of insulin secretion, as glucose-stimulated insulin secretion was reduced both in vivo and in vitro. Taken together, our findings indicate that insulin secretion is disrupted at the early stage of disease, which plays a significant role in the loss of glucose homeostasis. Interestingly, we found that the response to exogenous insulin was similar between R6/1 and wild-type mice, suggesting that downstream insulin signalling remains intact. Overall, our study demonstrates that impaired insulin secretion is a key early factor contributing to glucose dyshomeostasis in R6/1 mice. Therapeutic targeting insulin secretion may be a potential approach to improve glucose homeostasis, and slow disease progression in HD.

Tuesday 03:15 PM-03:20 PM
Wendy Qin

Data Blitz: Investigating the effects of the Huntington's disease gut microbiota on brain and gut function in mice

Wendy Qin1, 2, Bethany Masson2, Thibault Renoir2, Carolina Gubert2, Anthony Hannan1, 2
1. Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, Victoria, Australia
2. Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, Melbourne, Victoria, Australia
Huntington's disease (HD) is a monogenic neurodegenerative disorder that is characterised by psychiatric, motor, and cognitive impairments. HD is caused by an expansion in the CAG trinucleotide in the huntingtin gene, which is expressed throughout the brain and peripheral tissues – including the gastrointestinal system. This fatal disorder has no effective disease-modifying treatments. Previously, research has focused on the brain to explain the motor, cognitive, and psychiatric symptoms of HD whilst the impact on peripheral systems is not yet fully elucidated. A whole-body approach for HD has discovered disruption of the gut microbiota in preclinical and clinical HD. Hence, our lab has begun to explore the gut microbiota as a potential target for therapeutic interventions. We were the first to show that faecal microbiota transplant (FMT) from wild-type (WT) into HD mice positively influences cognitive outcomes. To clarify the role of the gut microbiota in HD, we investigate the opposite FMT direction. We assessed whether FMT from HD into WT mice could modulate behavioural, cognitive, and gastrointestinal outcomes. Antibiotics (ATB) were given to mice prior to FMT to deplete the microbiota, allowing donor bacteria to proliferate in a less competitive environment. To control for the effects of ATB and FMT process, groups of mice were given water and a vehicle FMT. Differences between FMT groups were not significant ($p>0.05$). Our investigation suggests that the gut microbiota alone is not enough to modulate cognitive and gastrointestinal outcomes. This clarifies the development of future clinical interventions HD, which modulate the gut microbiota.

Brendan McCarthy
Data Blitz: Electrical Stimulation of the Dorsolateral Prefrontal Cortex Inhibits Vestibular Signalling and Vestibulosympathetic Reflexes in Humans

Brendan McCarthy1, 2, Donggyu Rim3, Gianni Sesa-Ashton2, Sudipta Datta1, 2, Rebecca Wong1, 2, Lewis S Crawford4, Tye Dawood1, 2, Luke A Henderson4, Vaughan G Macefield1, 2, 3
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Aims: To determine the effects of combining sinusoidal galvanic vestibular stimulation (sGVS) with transcranial alternating current stimulation (tACS) of the dorsolateral prefrontal cortex (dlPFC) on generating vestibular sensations and vestibulosympathetic reflexes, alongside determining the neural pathways between the systems.
Methods: Muscle sympathetic nerve activity (MSNA) was recorded from 11 awake human participants via a microelectrode inserted percutaneously into the right common peroneal nerve near the fibular head. Sinusoidal stimuli (±2 mA, 0.08 Hz, 100 cycles) were applied in a randomised order: (i) tACS of the dlPFC at electroencephalogram site F4, (ii) bilateral sGVS via the mastoid processes, and (iii) tACS and sGVS together. In a separate study, the same areas were stimulated (±2 mA, 0.2 Hz, 60 cycles) in 14 participants while performing fMRI of the brain.
Results: tACS of the dlPFC caused no perceptions of motion when delivered on its own, and abolished all vestibular perceptions of motion (and nausea) when delivered concurrently with sGVS. MSNA cross-correlation analysis revealed that the amplitude and pattern of cyclic modulation produced by combined stimulation was similar to that produced by tACS of the dlPFC alone. Increases in blood-oxygen-level-dependent signal intensity occurred within the insula during sGVS but not when tACS was applied concurrently.
Conclusions: Perceptions of sway and feelings of nausea during sGVS were eliminated with concurrent tACS of the dlPFC, along with activation of core vestibular areas in and around the insula. This, coupled with inhibition of the vestibulosympathetic reflexes, suggests that the dlPFC exerts top-down inhibitory control of vestibular processing.

03:25 PM-03:30 PM
Eduardo Albornoz Balmaceda
Data Blitz: Complement activation drives inflammasome mediated neuropathology in Parkinson's disease

Eduardo Albornoz Balmaceda1, Richard Gordon2, John Lee1, Trent Woodruff1
1. School of biomedical sciences (SBMS), The University of Queensland, Brisbane, QLD, Australia
2. Centre for Microbiome research, Queensland University of Technology , Brisbane, QLD, Australia
The activation of the innate immune system in the CNS is a key trigger of dopaminergic neuronal loss in Parkinson's disease (PD). We previously demonstrated that microglial NLRP3 inflammasome inhibition prevents α-synuclein pathology and dopaminergic neurodegeneration in mice. In this study, we investigated whether complement signaling also underpins the activation of microglial NLPR3 inflammasomes in PD. We demonstrate widespread dysregulation of complement proteins in PD patients and in experimental PD mice models. Genetic deletion of key complement effectors highlighted a critical role for complement C5a receptors (C5aR1) in driving neurodegeneration in response to dopaminergic toxins. Fibrillar α-synuclein aggregates, the predominant protein found in PD brain Lewy bodies, directly activated complement to generate C5a and increased C5aR1 expression in microglia. Oral administration of a brain-

permeable C5aR1 antagonist significantly protected against behavioral motor deficits, microglial activation, and nigrostriatal dopaminergic degeneration in two preclinical PD models. Notably, delaying drug administration until symptom onset remained neuroprotective. Mechanistically, microglial NLRP3 inflammasome activation was impaired in the absence of C5aR1 signaling. Indeed, both mouse and human microglia were unable to secrete IL-1β in response to α-synuclein in the presence of C5aR1 inhibitors. Taken together, our results suggest that complement activation and persistent C5a generation by misfolded protein aggregates in the PD brain can contribute to microglial NLRP3 inflammasome activation, and thereby exacerbate disease pathology. Selective targeting of C5aR1 may therefore be a viable therapeutic strategy to reduce microglial inflammation, and thus slow disease progression in PD.

Tuesday 01:30 PM-03:30 PM

Selected Orals 2: Excitability

Great room 3

01:30 PM-01:45 PM
Sarah Gordon
Alpha-synuclein as a regulator of SNARE protein trafficking

Sarah Gordon1, Elyas Arvell1, Holly Melland1
1. Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
Repeated rounds of exocytosis and endocytosis of neurotransmitter-containing synaptic vesicles play a critical role in the maintenance of neurotransmission. Alpha-synuclein, a protein which has been extensively studied for its role in Parkinson's disease, is a known modulator of the synaptic vesicle cycle. However, its exact function remains unclear. In this study, we reveal a novel function of alpha-synuclein in the control of the trafficking of a key SNARE protein, synaptobrevin. Phosphoproteomic LC-mass spectrometry of resting or depolarised primary hippocampal neuron lysates revealed an activity-dependent increase in phosphorylation at two of four sites examined in alpha-synuclein. We investigated the role of these activity-dependent phosphorylation sites by rescuing alpha-synuclein knockout (KO) hippocampal neuron cultures with phosphomutant variants of alpha-synuclein that mimic (phosphomimetic) or abolish (phosphonull) phosphorylation at these residues. Ablation of one of these phosphorylation sites disrupted the trafficking and activity-dependent retrieval of synaptobrevin 2, a known binding partner of alpha-synuclein that is crucial for synaptic vesicle fusion. These results constitute the first evidence that dynamic, activity-dependent phosphorylation of alpha-synuclein is involved in the modulation of various stages of the synaptic vesicle cycle.

01:45 PM-02:00 PM
Matthew Kenna
Distinct amygdala to prefrontal connectivity drives fear memory consolidation

Matthew Kenna1, Li Xu1, Roger Marek1, Pankaj Sah1
1. Queensland Brain Institute, Brisbane, QLD, Australia
Elucidating the neural circuitry that underpins memory formation is critical to understanding how the brain stores information. In fear memory, the initial learning phase is thought to be governed by the basolateral amygdala (BLA), while the sequent retrieval of the memory is driven principally by the medial prefrontal cortex (mPFC). While it is assumed that a period of consolidation after learning is responsible for the redistribution of the memory trace to the mPFC, a precise mechanism for this process remains unclear. It has been shown previously that direct monosynaptic connections exist between the BLA and mPFC in both directions, forming reciprocal loops of neural activity. Therefore, we posited that this reciprocal connectivity could be driving the consolidation of fear memories. Using activity-dependent labelling in rodents, we have shown that the consolidation of fear memories involves a significant shift in neural activity towards layer 2/3 cells of the mPFC. In addition, we show that a rostro-caudal distribution exists in the connections from the BLA to mPFC, with the rostral BLA preferentially innervating the rostral mPFC and caudal BLA with the caudal mPFC. Furthermore, the consolidated fear engram in the mPFC is predominately driven by rostral BLA engram cells, suggesting that this distinct circuitry pattern may hint at a mechanism for fear memory consolidation. Taken together, these findings indicate that the consolidation of fear memories induces dominant L2/3 activity in the mPFC, which is largely driven by projections from the rostral BLA – perhaps providing a circuitry mechanism for fear memory consolidation.

02:00 PM-02:15 PM
Yee Lian Chew
What makes a memory? Identifying the molecules that boost learning and memory formation.

Aelon Rahmani1, Ericka Allen1, Caitlin Minervini1, Anna McMillen1, Yee Lian Chew1
1. Flinders University, Bedford Park, SA, Australia
Learning is essential to survival. There is strong evidence that memory results from protein-level changes in expression or localization in specific brain regions. Our goal is to map the complete set of protein changes that occur during learning, in distinct cellular compartments, within specific brain cells.
Our strategy is to use proximity labelling to tag protein changes, during learning, within the experimentally accessible Caenorhabditis elegans (nematode worm) brain. C. elegans displays robust associative learning: we use a behavioural paradigm pairing a normally attractive gustatory cue (salt/NaCl) with starvation (a strongly aversive cue). After training, worms change their innate behaviour, and learn to avoid high salt concentrations. We utilize the TurboID biotin-based labelling method to label proteins in C. elegans, by genetically encoding TurboID expression in the worm nervous system. We restrict labelling to the learning phase by adding biotin only during this period. We then identify labelled proteins via mass spectrometry, and compare protein lists from trained and control cohorts.
Our data indicate that this strategy efficiently labels known pathway regulators of learning/memory, including cAMP signalling, synaptic vesicle exocytosis, MAPK signalling and G protein signalling. We have also discovered potentially novel regulators of learning, including ligand-gated ion channels as well as proteins involved in fatty acid metabolism

and protein quality control, currently under investigation. Our future work will use a similar strategy to explore learning regulators at synapses, and within specific brain regions. We conclude that our strategy is functional and can potentially be expanded to other organisms and behaviours.

Tuesday 02:15 PM-02:30 PM
Lachlan Rash
Development of venom peptides for in vivo target validation of acid-sensing ion channel 1 in neurodegenerative diseases.

Lachlan Rash1
1. University of Queensland, St Lucia, QLD, Australia
Acidosis is a hallmark of CNS lesions in multiple sclerosis. Overactivation of acid-sensing ion channel 1a (ASIC1a) is associated with nerve injury in mouse models of MS and in MS patient tissues. Inhibition ASICs shows strong therapeutic potential in the EAE mouse model of MS. Hi1a is a 76 amino acid, double inhibitor cystine knot venom peptide that is the most potent known inhibitor of ASIC1a and has shown promising therapeutic potential in animal models of ischaemic stroke and ischaemic heart damage. We show that the peptide Hi1a decreases the development of muscle paralysis and spinal cord damage in a dose-dependent manner but loses effectiveness at higher doses. We have also labelled the peptide with fluorescent or radioactive probes to facilitate in vivo biodistribution and target engagement studies in naïve mice compared to a mouse model of multiple sclerosis (experimental autoimmune encephalitis- EAE). Peripheral administration of Hi1a (IV injection) and monitoring biodistribution via dynamic PET/CT showed that although the peptide appears to clear from the plasma within 20 minutes, a stantial fraction remains in circulation for longer than 90 mins. We also show that following IV injection, fluorescently labelled Hi1a accumulates in the spinal cord of EAE mice but not in those of naïve mice, consistent with a potent therapeutic effect in this mouse model. These advances in our understanding the structure-activity relationship, biodistribution and target engagement of Hi1a in preclinical mouse models of disease should help guide studies on this promising peptide through further preclinical development.

02:30 PM-02:45 PM
Mitchell St Clair-Glover
Engineering Functional Sensory Neuron Networks through 3D Bioprinting of Neural Crest Cells

Mitchell St Clair-Glover1, 2, 3, 4, 5, Rocio K Finol-Urdaneta1, 2, 4, Sara Miellet1, 2, 4, Zhilian Yue1, 5, Gordon G Wallace1, 2, 5, 6, Mirella Dottori1, 2, 3, 4, 5
1. University of Wollongong, Wollongong, NSW, Australia
2. Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, NSW, Australia
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5. ARC Centre of Excellence for Electromaterials Science, Intelligent Polymer Research Institute, University of Wollongong, Wollongong, NSW, Australia
6. Australian National Fabrication Facility, Materials Node, Wollongong, NSW, Australia
The skin contains diverse sensory neurons (SNs) responsible for touch, temperature, and pain perception. There is growing evidence supporting the role of the peripheral nervous system in cutaneous health and wound healing. Although tissue-engineered skin shows promise for wound repair, restoring somatosensory perception remains a challenge.
To address this, our laboratory developed transgenic human pluripotent stem cell (hPSC) lines that efficiently differentiate into mature SNs by inducing Neurogenin 2 (NGN2) expression. We demonstrated that progenitors derived from these transgenic hPSC lines can be extrusion bioprinted and further differentiated within biocompatible scaffolds, forming functional 3D induced SN (iSN) networks. After 21 days in culture, iSNs exhibited extensive neurite outgrowth and expressed markers consistent with various somatosensory neuron types. Orthogonal sectioning and 3D reconstruction revealed widespread iSN dispersion throughout the bioprinted scaffolds.
Functionally, the generated iSN networks displayed depolarization-induced intracellular calcium ([Ca2+]i) increases, indicating neuronal firing. Brief exposure to KCl transiently increased [Ca2+]i, while responses to the voltage-gated sodium (Nav) channel modulators Tetrodotoxin (TTX) and Veratridine confirmed the involvement of TTX-sensitive Nav channels in the membrane excitability of encapsulated iSNs.
To advance this technology further, we incorporated hPSC-derived iSNs alongside dermal fibroblasts and keratinocytes to develop a 3D bioprinted innervated human skin model. This innovative approach offers insights into the factors behind skin tissue reinnervation, with the potential to enhance future therapeutics and improve wound healing outcomes.

02:45 PM-03:00 PM
Hilary Yong
The microtubule-associated protein Tau controls the homeostasis of NMDA receptors

Xuan Ling Hilary Yong1, Pranesh Padmanabhan1, Kristie Stefanoska2, Andrew Kneynsberg1, Arne Ittner2, Jürgen Götz1, Victor Anggono1
1. Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
2. Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia
Homeostatic synaptic plasticity maintains neuronal excitability by dynamically adjusting the surface expression of ion channels and neurotransmitter receptors to avoid excessive neuronal excitation or quiescence. Failures in maintaining neuronal homeostasis are linked to the pathophysiology of several neurological disorders, including Alzheimer's disease (AD). Using a cellular model of homeostatic plasticity, we show that chronic neuronal silencing induced by tetrodotoxin (TTX) treatment leads to a compensatory increase in the level of GluN2B-containing NMDA receptors (NMDARs) in primary hippocampal neurons. This process depends on the phosphorylation of GluN2B at Tyr-1472 by Fyn kinase. The microtubule-associated Tau protein is required to retain Fyn at the synapse. Accordingly, loss of Tau expression inhibits TTX-induced Tyr-1472 phosphorylation and consequently the synaptic up-scaling of GluN2B-NMDARs. Single particle tracking of GluN2B molecules reveals that Tyr-1472 phosphorylation increases the retention time of GluN2B on the plasma membrane and dendritic spines. Re-expression of wild-type Tau or the phospho-mimetic Y1472E mutant in Tau knockout neurons fully restores TTX-induced synaptic up-scaling of GluN2B-NMDARs. Overall, our study identifies a new physiological role of Tau in regulating the homeostasis and nanoscale organisation of surface NMDARs in mammalian central neurons.

Tuesday 03:00 PM-03:15 PM
Lee Fletcher
Dendritic potassium channels suppress active dendritic integration and quicken action potentials in human frontal and occipital cortical layer 2/3 pyramidal neurons.

Lee N Fletcher1, Barbora Fulopova1, Tobias Bluett1, Arne Brombas1, Stephen R Williams1
1. Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
The asymmetric expansion of the neocortex, particularly in visual and executive function regions, is thought to underly the evolutionary amplification of visual processing and human intelligence. The disproportionate locus of this expansion is within neocortical layer 2/3 (L2/3), notably resulting in diversification of glutamatergic neurons and elaboration of their dendritic arborisations. Our recent work suggests that while biophysical properties are relatively conserved between rodents and humans, the physical expansion of the dendritic arbour of L2/3 pyramidal neurons allows the enhanced expression of dendritic sodium spike mechanisms that define distal dendritic integration in the human temporal association cortex. It remains unclear, however, whether synaptic integration and computational function are stereotyped across the human neocortex. Here, we perform multi-site, whole-cell patch-clamp recordings throughout the dendritic arbour of L2/3 pyramidal neurons in frontal, occipital, and temporal cortices of humans and rats to investigate how neocortical areas differentially process information. Surprisingly, we find stark differences between the human frontal and occipital L2/3 pyramidal neurons and those in temporal cortex and homologous rat cortices. Action potentials (APs) in human frontal and occipital L2/3 pyramidal neurons are significantly faster. Remarkably, dendritic input into the distal apical dendrites of frontal and occipital L2/3 pyramidal neurons fails to drive dendritic spikes and only contributes to axo-somatic integration through -threshold voltage spread. This is driven by strong voltage-gated potassium channel mediated -rectification of depolarising dendritic input, suppressing expression of dendritic sodium spikes. These results suggest divergent optimisation of AP speed and dendritic integration across the human neocortex.

03:15 PM-03:30 PM
Shanley Longfield
Synapsin2a tetramerization selectively controls the presynaptic nanoscale organisation of reserve synaptic vesicles.

Shanley F Sanders1, Rachel S Gormal1, Tristan P Wallis1, Merja Joensuu2, George J Augustine3, Ramon Martinez-Marmol1, Frederic A Meunier1
1. Queensland Brain Institute , Brisbane, Queensland, Australia
2. Australian Institute for Bioengineering and Nanotechnology, Brisbane, QLD, Australia
3. Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
Neurotransmitter release relies on the regulated fusion of synaptic vesicles (SVs) that are tightly packed within the presynapse of neurons. The mechanism by which SVs are anchored at the presynapse while preserving their ability to dynamically recycle thereby supporting neuronal communication remains unknown. Synapsin2a tetramerization was recently suggested to cluster SV in presynapses. Here, we used Dual-pulse -diffractional Tracking of Internalised Molecules (DsdTIM) to simultaneously track SVs from the recycling and reserve pools, in live hippocampal neurons. The reserve pool displays a lower presynaptic mobility compared to the recycling pool and exhibits a more mobile axonal pool. Synapsin1-3 triple knockout (SynTKO) selectively increased the reserve pool mobility. Re-expression of wild-type Synapsin2a, but not the tetramerization-deficient mutant K337Q, fully rescued these effects. Tracking Synapsin2aK337Q-mEos3.2 revealed altered synapsin activity-dependent presynaptic translocation and

nanoclustering. Synapsin2a tetramerization therefore controls its own presynaptic nanoclustering allowing dynamic immobilisation of the reserve pool at the presynapse.

Tuesday 03:30 PM-04:00 PM

Break
Afternoon Tea, Exhibition and Poster Display

04:00 PM-04:25 PM
Plenary
AW Campbell Award Presentation
Great room 1/2/3

04:25 PM-04:50 PM
Plenary
Nina Kondelos Award Presentation
Great room 1/2/3

04:50 PM-05:00 PM
Plenary
Illumina Neurogenomic Award Presentation
Great room 3
Illumina Neurogenomic Award Presentation
The Epigenome of olfactory neural stem cells derived from early-onset schizophrenia Patients
Alexandre Cristino

05:00 PM-05:30 PM
Saul Villeda
International Plenary Lecture
Great Room 1/2/3

Wednesday 6/12/2023

9:00 AM-10:00 AM
Elizabeth Coulson
Laurie Austin Plenary
Great Room 1/2/3

10:00 AM-10:30 AM
Break
Morning Tea, Exhibition and Poster Display

10:30 AM-12:30 PM
John Power; Joanna Yau
Symposium 5: Neuroplasticity in health and disease
Great room 1

John M Power1, Joanna Yau2, Melissa J Sharpe3, 4, Johanna M Montgomery5, Gavan P McNally2, Jai S Polepalli6
1. Translational Neuroscience Facility, School of Biomedical Sciences, UNSW, Sydney, NSW, Australia
2. School of Psychology, UNSW Syndey, Sydney, NSW, Australia
3. Department of Psychology, University of California, Los Angeles , Los Angeles , CA, USA
4. Department of Psychology, University of Sydney, Sydney, NSW, Australia
5. Department of Physiology, University of Auckland, Auckland, New Zealand
6. Department of Anatomy, National University of Singapore, Singapore
Synapses are fundamental to complex cognitive processes including the formation of memory, and the ability to use past experiences to make informed decisions which lead to desirable outcomes. Abnormal synaptic and circuit function caused by aberrations in synaptic proteins results in abnormal behavioural outcomes that are associated with a multitude of neuropsychiatric disorders, including stance-use disorders. This symposium highlights the fundamental understanding of the molecular mechanisms that mediate synaptic and circuit function – how synapses shape neuronal circuits, how these neuronal ensembles mediate learning and memory, and how disorders that arise from aberrant synaptic activity lead to disease pathology associated with a wide variety of neurological and neuropsychiatric diseases.
The four speakers in this symposium emphasise that aberrant and maladaptive learning and memory leads to undesirable behavioural outcomes. Dr Melissa Sharpe (UCLA / University of Sydney) shares her recent work describing the role of a novel circuitry between neurons in the mid-brain and the hypothalamus in model-based' and reinforcement- learning', and how plasticity mechanisms in this circuit potentially mediate behaviours related to stance-use disorders. Professor Gavin McNally (UNSW Sydney) will discuss how alterations in activity of distinct ensembles of reward and aversion coding neurons in the basolateral amygdala underlies instrumental aversive learning. The capacity to withhold actions that may cause harm is essential to healthy choices and is disrupted in a variety of neuropsychiatric conditions including stance use disorders. Dr Jai Polepalli (National University of Singapore) will present recent work on the synaptic and circuit mechanisms underlying long term memory storage and retrieval in the prefrontal cortex, highlighting the necessary role played by a disease -associated, transsynaptic cell adhesion molecule, Cerebellin-4 in mediating this process. Professor Joanna Montgomery from the University of Auckland will present recent work on the synaptic basis of the behavioural abnormalities in animal models of autism spectrum disorders, highlighting the importance of zinc as a synaptic regulator during synaptic plasticity, at least in part ameliorating the synaptic plasticity and behavioural deficits in these disorders. Professor Montgomery will also discuss how aberrant peripheral nervous system plasticity contributes to conditions such as cardiac arrhythmias.
Significance: This symposium is aligned with synaptic transmission and synaptic plasticity theme of ANS. Overall, the four talks in this symposium relate to the synaptic and circuit basis of neurological and neuropsychiatric disorders including autism spectral disorder, schizophrenia, and stance abuse. The talks linking cellular changes to behaviour should have broad appeal. Additionally, this symposium is of significant interest to not only to researchers with shared interests, but also to those Australians who suffer from long-term mental health disorders, their families, employers and the wider society.

10:30 AM-10:55 AM
Gavan McNally
Instrumental aversion coding in the basolateral amygdala

Our capacity to withhold actions that may cause us harm is essential to healthy choices and is profoundly disrupted in a variety of neuropsychiatric conditions including stance use disorders. The basolateral amygdala is essential to this capacity but how activity in basolateral amygdala neurons integrates actions and their aversive consequences to guide our behaviour and choices is unknown. Using complementary calcium imaging approaches in rats and mice we address this. We first show that at a population level, basolateral amygdala projection neurons encode both instrumental actions and their aversive consequences. Aversive instrumental learning depends on a reversible

transformation of actions so that they evoke punisher-specific representations in the basolateral amygdala to guide behavior. We next show, at single cell level, that this transformation of instrumental action value emerges from contingency-dependent alterations in activity of distinct basolateral amygdala ensembles of reward and aversion coding neurons.

Wednesday 10:55 AM-11:20 AM
Johanna Montgomery
The role of plasticity in disorders of the central and peripheral nervous systems

Professor Montgomery's research presentation will focus on the physiology of synapses in the central and peripheral nervous systems. Her laboratory combines electrophysiology, molecular biology, and imaging techniques to investigate how changes in synapse function could underlie developmental disorders including autism, and neurodegenerative disorders such as Alzheimers Disease. In her talk Prof Montgomery will describe her work identifying the synaptic basis of autism, where she has led the advancement of neuronal research showing that zinc is a major regulator of synapses function in autism, into whole animal research identifying that dietary zinc can reverse autism-associated behavioural deficits. This discovery that zinc signalling is at the heart of autism now underpins her progression into zinc therapy based research in human neurons. She will also outline how her synaptic plasticity research has formed the foundation for a major new direction of peripheral nervous system plasticity and its role in cardiac arrhythmias. This research spans from the cellular to the clinical level together with bioengineers, cardiologists, cardiovascular surgeons. She has led the pioneering of cellular electrophysiological recordings from neurons of the human heart, research that has the potential to reveal the contribution of neuro-cardiac plasticity mechanisms to cardiac arrhythmias.

11:20 AM-11:45 AM
Jai Polepalli
Synaptic architecture of remote memory recall

Brief summary: The prefrontal cortex (PFC) is involved in the formation and retrieval of memories. The PFC circuits exhibit diversity in synaptic properties, enabling them to perform precise computations in a fool-proof manner that result in normal behavioural output. Neurexins and neurexin interacting proteins, including cerebellins play crucial role in determining synapse specificity. One member of the Cerebellin family, Cerebellin-4 (Cbln4) is enriched in the PFC. We show that Cbln4 in the PFC mediates long-term storage of memories. Deletion of Cbln4 in the PFC diminishes recall of remote contextual memory but not recall of recently formed memories. At the synapses, loss of Cbln4 leads to reduced numbers of GABAergic and glutamatergic synapses. Significance: Synapses are fundamental to complex cognitive processes including the formation of memory. While precise synaptic function is crucial for normal behavioural output, abnormal synaptic function, caused by mutations in synaptic proteins results in abnormal behavioural outcomes that are associated with a multitude of neuropsychiatric disorders. Mutations in cerebellins and the complex formed by cerebellins are penetrant in a multitude of diseases. Our recent findings highlight the importance of defining the molecular architecture of circuits that are responsible for behavioral abnormalities caused by manipulations of proteins that are genetically associated with brain disorders.

11:45 AM-12:10 PM
Melissa Sharpe
A novel hypothalamic-midbrain circuit for model-based learning and its implications for stance use disorder

stance use disorder is driven in part by changes in learning processes that bias behavior towards drug-related cues. Here, we reveal a novel population of dopamine neurons in the midbrain that project to the lateral hypothalamus. This circuit critically drives model-based learning about cues and reward, which includes a detailed representation of sensory-specific features of these associations. A history of methamphetamine enhances model-based learning about cues and rewards and is associated with changes in this novel hypothalamic-midbrain circuit. This work points to a novel circuit driving the reinforcement learning changes underlying stance use disorder. As such, this work could drive the development of new pharmacological compounds aimed at reducing activity in this circuit in people with stance use disorder.

12:10 PM-12:15 PM
Barbora Fulopova
Data Blitz: Repetitive transcranial magnetic stimulation (rTMS) increases structural dynamic of axonal boutons in a cell type specific manner in the aged APP/PS1 amyloidosis mouse model.

Barbora Fulopova1, 2, Bill Bennett1, Alison Canty1
1. Wicking Dementia Research and Education Centre, University of Tasmania, Hobart, Tasmania, Australia
2. Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia
A growing body of evidence highlights therapeutic potential of rTMS for use in diseases causing dementias such as Alzheimer's disease (AD). However, the individual response rate to rTMS can be variable, and the underlying neural

mechanisms of its effects are not fully understood. Previously we showed improvements in learning behaviour following rTMS in adult mice. Given that synaptic dysfunction is one of the key mechanisms associated with cognitive deficits in dementia, we investigated the effect of rTMS on cortical synapses. Focusing on excitatory axonal boutons, we performed a series of experiments using 10-12 months old APP/PS1 amyloidosis mouse model of AD and their wild-type (WT) counterparts crossed with fluorescent reporters linked to the Thy-1 promoter. Using longitudinal in vivo cranial window imaging we characterised plasticity of 2 types of axonal boutons, terminaux (TB) and en passant (EPB) boutons, in response to rTMS. Imaging was performed at 48-hour intervals for 8 days either side of a single of rTMS. We found that both types of axonal boutons showed resilience in preserving overall number of synaptic outputs between the WT and APP/PS1 groups pre- and post-stimulation. However, both TBs and EPBs showed significantly reduced dynamic fraction in APP/PS1 compared to WT pre-stimulation. Following stimulation, TB but not EPB dynamic fraction increased in both WT and APP/PS1 groups. These findings suggest possible mechanism of rTMS action that is cell type specific, and together with findings of improved functional performance following stimulation, a potential clinical benefit of rTMS in the management of AD.

Wednesday 12:15 PM-12:20 PM
Marcin Kielar
Data Blitz: Stability, reliability and performance of organic light-emitting diodes and photodetectors in optogenetic studies

Marcin Kielar1, Roger Marek1, Helen Gooch1, Cameron M. Cole2, Matthew Kenna1, Li Xu1, Soniya D. Yambem2, Ajay K. Pandey3, Pankaj Sah1
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2. School of Chemistry and Physics, Faculty of Science and Centre for Materials Science, Queensland University of Technology, Brisbane, Queensland, Australia
3. School of Electrical Engineering and Robotics, Faculty of Engineering, Queensland University of Technology, Brisbane, Queensland, Australia
Mapping neurons in the brain is important to understand the neuronal circuits involved in cognitive functions such as learning and memory formation. More importantly, understanding their dysfunction in neurological disorders and diseases could benefit patients that rely on better therapy interventions and techniques. To this aim, optogenetic tools, where light is used to control neuronal activity, and ultimately behavior, have revolutionized the field of neuroscience over the last 20 years. Current optogenetic approaches to investigate brain function involve the use of commercially available lasers and LEDs coupled to large implants, optical fibers or camera systems. Their use is usually associated with high cost, invasiveness and low spatial resolution. To address these limitations, organic electronic devices have been emerging as an alternative candidate for biocompatible, small-footprint, and high-resolution neural probes. In our own contribution to the field, we have demonstrated the successful detection of neuronal activity using organic photodetectors (OPDs) based on rubrene/C60, as well as direct optogenetic stimulation of neuronal activity using OLEDs based on Super Yellow. Here, we extend our previous work by demonstrating the stability and reliability of OPDs and OLEDs in optogenetics, and the effect of oxygen and encapsulation on the OPD/OLED performance. We describe novel methodologies to detect ultra-dim light for sustainable optogenetic studies. We also discuss the requirements for successful long-term neural recordings and determine the detection threshold for OPDs, (i.e. the required sensitivity to detect activity in a single neuron), as well as the minimum performance requirements in OLEDs to evoke neuronal activity.

12:20 PM-12:25 PM
Nishita Bhembre
Data Blitz: Learning-induced remodelling of inhibitory synapses in the motor cortex

Nishita Bhembre1, Annalisa Paolino1, 2, Sumasri Guntupalli1, Sooraj Das1, Laura Fenlon2, Victor Anggono1
1. Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, University of Queensland, Brisbane, QLD, Australia
2. School of Biomedical Sciences, University of Queensland, SBMS, Brisbane, QLD, Australia
Robust structural and functional plasticity occurs at excitatory synapses in the motor cortex in response to learning. It is well established that local spinogenesis and the sequent maintenance of newly formed spines are crucial for motor learning (Yang et al, 2009). Despite local synaptic inhibition being essential for shaping excitatory synaptic input, less is known about the structural rearrangement of inhibitory synapses following learning. In this study, we performed in utero electroporation of plasmids that encode a structural marker (td-Tomato) and a mEmerald-tagged intrabody against Gephyrin in wild-type CD1 mice. This allowed us to visualise endogenous Gephyrin puncta that label inhibitory synapses in the layer 2/3 cortical neurons of the motor cortex. Both male and female adult mice (electroporated) exhibited robust motor learning when subjected to a one-day accelerated rotarod learning task. We observed a significant increase in dendritic spine density in the motor cortex of trained mice compared to mice not subjected to any motor task, confirming the emergence of newly formed spines upon motor learning. Although there were no changes in the number of Gephyrin puncta, we found significant increases in the surface area and volume of these puncta 24-hour post accelerated rotarod task. Therefore, our data suggests that learning induces experience-

dependent remodelling of existing inhibitory synapses to fine-tune intrinsic plasticity and input-specific modulation of excitatory connections in the motor cortex.

Wednesday 12:25 PM-12:30 PM
Courteney Westlake
Data Blitz: Modulation of NMDA Receptor Synthesis and Surface Expression by sAPPα

Courteney M Westlake1, Harriet E Spoelstra1, Rhys W Livingstone1, Joanna M Williams1
1. Univerisity of Otago, Dunedin, OTAGO, New Zealand
Alzheimer's disease (AD) is a progressive neurodegenerative disorder underpinned by the erosion of synaptic connections and manifests canonically as impaired memory and cognition. Recently developed therapeutic strategies have targeted reducing the amyloid-beta (Aβ) load within the brain with promising effectiveness. However, soluble Aβ also attacks synapses. Thus, enhancing synaptic efficacy may be an additional important co-therapy for AD treatment. Recent work from our lab and others has shown in rodent models of AD, that the endogenous neuromodulator secreted amyloid precursor protein-alpha (sAPPα), demonstrates neuroprotective and memory-enhancing properties and may be a promising therapeutic avenue for AD.
To understand the molecular mechanisms underpinning sAPPα's effects, we have investigated how sAPPα regulates of the synthesis and cell surface expression of N-methyl-D-aspartate receptors (NMDARs), pivotal to synaptic plasticity. Utilizing FUNCAT-PLA (fluorescent non-canonical amino acid tagging with proximity ligase assay) and immunocytochemistry in primary rat hippocampal cultures, we found that sAPPα rapidly and transiently withdraws NMDARs from the neuronal surface, while concurrently enhancing the synthesis of specific plasticity-related NMDAR units.
Together these results suggest that sAPPα may be exerting its neuroprotective effects through potentially preventing Ca2+-induced excitotoxicity while also enhancing the plasticity capacity of the synapse through de novo receptor synthesis.

Wednesday 10:30 AM-12:30 PM
Merja Joensuu

Symposium 6: Exploring the link between viral infections and neurodegeneration

Great room 2

Merja Joensuu1, 2, Pranesh Padmanabhan3, Giuseppe Balistreri4, Julio Aguado2, Vicki Lawson5, Trent Woodruff6
1. Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia
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The primary objective of this symposium is to delve into the latest developments in the fascinating field of the viral infections and neurodegeneration, with special emphasis on SARS-CoV-2 and Influenza. The increasingly recognized correlation between viral infections and their impact on the brain has significant implications. It not only helps us comprehend the cause of numerous diseases but also assists in defining the cellular basis of neurodegenerative disorders such as Alzheimer's and Parkinson's disease. As these viruses continue to pose a significant threat to global health, understanding their effects on the brain has become even more crucial. By bringing together experts in this field, the symposium aims to enable researchers and medical professionals to explore new opportunities for preventing and treating neurodegenerative diseases. Ultimately, the goal of the symposium is to help unlock new insights into the relationship between viral infections and neurodegeneration, paving the way for new treatments and therapies that can improve the lives of millions of people worldwide.

The symposium will feature presentations from four esteemed researchers. Dr. Merja Joensuu and Dr. Pranesh Padmanabhan, both early career scientists from the University of Queensland, will serve as the symposium Chairs. Adjunct Assistant Professor Giuseppe Balistreri is a virologist from the University of Helsinki, Finland. His laboratory studies host-virus interactions, and in his talk, Dr Balistreri will discuss the link between viral infections such as those caused by Influenza, herpesviruses and SARS-CoV-2, and the elevated risk of having a neurodegenerative condition such as Alzheimer's, Parkinson's disease, or multiple sclerosis later in life.

Dr Julio Aguado, a Senior Research Fellow at the University of Queensland, works on the role of viral infections accelerating human aging, including induced neurotoxicity and chronic inflammation. He will speak about his research on senolytic therapy that alleviates physiological human brain aging and COVID-19 neuropathology. Dr Julio Aguado obtained his PhD in 2018 from the European School of Molecular Medicine (University of Milan) as a Marie Curie fellow of the European Union, and is an early career scientist.

Associate Professor Kirsty Short completed her PhD at the University of Melbourne in 2013 and was awarded a prestigious NHMRC CJ Martin Early Career Fellowship to study severe influenza infections. Her current research focuses on investigating the role of host susceptibility factors in viral diseases, pandemic preparedness, and anti-viral immunity. Dr Short will speak about flu neurotropism.

Professor Trent Woodruff leads a research team at The University of Queensland, Australia, and has over 20 years of research training. He is an NHMRC Leadership fellow and President-elect of the International Complement Society. Professor Woodruff's research revolves around the innate immune system, and its role in neurodegenerative diseases such as ALS and Parkinson's disease. He also has emerging interests in the impact of ageing and viral infections in the development of these diseases. Professor Woodruff will be speaking about viral infections and the brain, and what implications it has for Parkinson's disease.

10:30 AM-10:55 AM
Giuseppe Balistrer

The mechanisms of SARS-CoV-2 neuron infection

Analysis of human health records indicate a link between viral infections and an elevated risk of having a neurodegenerative condition such as Alzheimer's, Parkinson's disease, or multiple sclerosis later in life. Influenza,herpes viruses, and more recently the coronavirus SARS-CoV-2, are among the candidate viruses that might trigger neuro-pathologies. To better understand how and to what extent viruses are linked to brain damage, we need to systematically address fundamental questions such as: which viruses can infect brain cells and how? What is the fate of an infected cell and how do neighbouring brain tissues respond to infection? Are our endogenous retroviruses involved? I will give an overview of how different viruses, including SARS-CoV-2, infect the human brain, particularly neurons, and what are the consequences of infection. As an introduction to a broader discussion, I will present the step by-step mechanism of coronavirus neuron cell entry, intracellular trafficking, virus assembly and spreading, and possible implications with neurological conditions associated with this virus.

10:55 AM-11:20 AM
Julio Aguado

Senolytic therapy alleviates physiological human brain aging and COVID-19 neuropathology

Aging is the primary risk factor for most neurodegenerative diseases, and recently coronavirus disease 2019 (COVID-19) has been associated with severe neurological manifestations that can eventually impact neurodegenerative conditions in the long-term. The progressive accumulation of senescent cells in vivo strongly contributes to brain aging and neurodegenerative co-morbidities but the impact of virus-induced senescence in the aetiology of neuropathologies is unknown. Here, we show that senescent cells accumulate in physiologically aged brain organoids of human origin and that senolytic treatment reduces inflammation and cellular senescence; for which we found that treatment with senolytics (drugs that selectively clear senescent cells) rejuvenates human brain aging clocks. We further interrogated brain frontal cortex regions in postmortem patients who succumbed to severe COVID-19 and observed increased accumulation of senescent cells as compared to age-matched control brains from non-COVID-affected individuals. Moreover, we show that exposure of human brain organoids to SARS-CoV-2 evoked cellular senescence, and that treatment with senolytics blocked viral retention and prevented the emergence of senescent corticothalamic and GABAergic neurons. Furthermore, in vivo treatment with senolytics improved SARS-CoV-2 clinical phenotype and survival, alleviated brain senescence and reactive astrogliosis, promoted survival of dopaminergic neurons, and reduced viral and senescence-associated secretory phenotype gene expression in the brain. Collectively, our findings demonstrateSARS-CoV-2 can trigger cellular senescence in the brain, and that senolytic therapy mitigates brain aging and multiple neuropathological sequelae caused by SARS-CoV-2.

Wednesday 11:20 AM-11:45 AM
Trent Woodruff
Viral infections and the brain: implications for Parkinson's disease

Although COVID-19 is primarily a respiratory disease, there is increasing recognition that SARS-CoV-2 infection is associated with brain complications, including severe neurological manifestations and long-term effects (Long-COVID). We recently reported that SARS-CoV-2 via its spike protein promotes NRLP3 inflammasome activation inhuman microglia, activating the same inflammatory response in the brain that is exhibited in Parkinson's Disease (PD).Strikingly, viral-mediated microglial inflammasome activation was significantly enhanced in the presence of alpha synucleinfibrils and was entirely ablated by NLRP3-inhibition. To further explore links between viral infections andPD, we are using Zika a neurotropic flavivirus to study the long-term impact on the brain, identifying 3 stages of disease progression: infection, followed by viral clearance in a presymptomatic stage, and progressing to a long-term neurodegenerative clinical-stage with stantial dopamine loss in mice that have recovered from Zika. We are also testing the impact of different SARS-CoV-2 variants on human-derived brain organoids, and in mice, and are evaluating the role of the complement and inflammasome systems in these models. Our work highlights that viruses like SARSCoV-2 can trigger innate immune activation and dopaminergic degeneration in the brain, supporting the concept that viral-mediated chronic inflammation could contribute to PD. Innate immune-targeted drugs could thus be a novel therapeutic approaches to ameliorate this.

11:45 AM-12:10 PM
Victoria Lawson
Predicting the neurological impact of SARS-CoV-2 Variants of Concern

12:10 PM-12:15 PM
Frank Mobilio
Data Blitz: Ablation of interferon regulatory factor 7 confers protection in a mouse model of mild traumatic brain injury.

Frank Mobilio1, Amar Abdullah2, Peter Crack1, Juliet Taylor1
1. Department of Biochemistry and Pharmacology, The University of Melbourne, Parkville, Victoria, Australia
2. Department of Biological Sciences, Sunway University, ang Jaya, Selangor, Malaysia
Traumatic brain injury (TBI) is a major cause of mortality and morbidity worldwide. We have previously confirmed the type-I interferon signaling cascade as a key mediator of the detrimental neuro-inflammatory response in TBI (Karve et al., 2016). To further understand the role of the type-I IFNs in TBI, this study focused on a key modulator of their response, Interferon regulatory factor 7 (IRF7). C57BL/6 wildtype (WT) and IRF7-/- male mice (8-10-week-old) were jected to a controlled-cortical impact (CCI) mouse model of mild TBI (mTBI) (n=7-9 per group). IRF7 mRNA expression was significantly upregulated in WT mice at 24hr- and 7-day-post injury compared to sham controls (24hr: 3.04±0.41-fold vs 1.04±0.11-fold, p=0.014; 7-day: 11.06±2.02-fold vs 1.07±0.09-fold, p= 0.002, respectively, student's t-test). T2 and diffusion-weighted magnetic resonance imaging analyses of mTBI brains at 7-day-post injury, revealed a statistically significant reduction in cortical lesion size in IRF7-/- mice compared to injured WT mice (2.39±0.46mm3 vs 3.68±0.26mm3, respectively, p=0.026, student's t-test). DigiGait™ analysis aligned with the temporal profiles of lesion sizes, with pre:post injury ratios in ataxia coefficient and stride frequency increased in WT mice 7-days-post injury when compared to sham counterparts (1.09±0.14 vs 1.62±0.16, p=0.011 and 1.08±0.05 vs 1.23±0.037, p=0.018,

respectively, two-way ANOVA), with no changes observed in IRF7-/- mice. This study provides strong evidence for the involvement of IRF7 in regulating the detrimental neuroinflammation following brain injury. Current studies are focused on understanding IRF7's specific role in regulating microglial function and its contribution to the neuro-inflammatory response and secondary damage in TBI.

Wednesday 12:15 PM-12:20 PM
Merja Joensuu
Data Blitz: Unveiling the Intricacies of Neurons: Advancing Neuroscience with Live Cell Single-Molecule Imaging

Merja Joensuu2, 1
1. Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia
2. Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, QLD, Australia
Super-resolution imaging in cultured primary neurons is a cutting-edge technique used in neuroscience to surpass the limitations of traditional microscopy and achieve higher resolution and finer details of neuronal structures and dynamics. In conventional microscopy, the resolution is restricted by the diffraction limit, preventing the visualization of smaller structures and processes within neurons. However, super-resolution techniques, such as universal Point Accumulation for Imaging in Nanoscale Topography (uPAINT1,2), diffractional Tracking of Internalized Molecules (sdTIM2,3) and single particle tracking PhotoActivated Localization Microscopy (sptPALM4) circumvent this limitation. The application of these super-resolution imaging techniques in cultured primary neurons provides unprecedented insights into the intricate dynamic organization of the neurons in nanoscale. In my presentation, I will discuss how we have used super-resolution imaging techniques to study dynamic organization of synapses in healthy neurons2,3, and under an external insult such as those caused by neurotoxins5 and viruses. I will also discuss adaptation of simultaneous use super-resolution imaging techniques to perform simultaneous dual-colour super-resolution imaging5,6.

12:20 PM-12:25 PM
Kay Double
Data Blitz: Openness Agreements in Animal Research: a new era of transparency

Kay Double1
1. University of Sydney, Camperdown, NEW SOUTH WALES, Australia
Objective: The use of animals in research is tacitly approved by the community on the basis that such work is completed in a humane, ethical manner in line with appropriate animal protection regulations and for the purpose of improving welfare of people, animals or the environment. In recent years the community has sought more information about how animals are used in research; an Australian survey in 2022 found 82% of respondents want institutions to be more transparent about their use of animals. One way to achieve this is an Openness Agreement on Animal Research. Method: This presentation explains the purpose and format of such an agreement and discusses how Openness Agreements have been used internationally to support organisations which conduct, fund or are otherwise associated with the use of animals in research and teaching to promote openness and support well-informed public discussion of this area. The aims and commitments of the Openess Agreement on Animal Research and Teaching in Australia which will be launched by The Australian Council for the Care of Animals in Research and Teaching in August 2023 will be discussed, as well as how such initiatives can benefit animals in research and neuroscience researchers who use animals in their research.
*Kay Double is Chair of University of Sydney's Animal Ethics Committee 1 and a member of the ANS Animals in Research Committee.

12:25 PM-12:30 PM
Sean Coakley
Data Blitz: Spectrin forms a periodic cytoskeleton within the epidermis to preserve axonal integrity

Sean Coakley1, Igor Bonacossa-Pereira2, Massimo A Hilliard2
1. School of Biomedical Sciences, The University of Queensland, St Lucia, QLD, Australia
2. Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia
Spectrins are conserved throughout evolution and required for axonal integrity. UNC-70/ß-Spectrin has recently been show to function within the epidermis to maintain the integrity of mechanosensory neurons in C. elegans, although the mechanisms of this protection and its molecular organization are unknown. Here, using a split fluorophore strategy, combined with confocal and 3D-structured illumination microscopy, we visualized the endogenous localization of α- and ß-Spectrin tissue-specifically within the epidermis. We reveal that epidermal spectrins form an evenly spaced, crescent-shaped structure with a periodicity of ~200 nm that embraces adjacent axons, forming a scaffold that reveals an imprint of the adjacent nervous system. This epidermal scaffold is induced by the presence of the axon, and is reformed upon injury during axonal regeneration. Moreover, we show that conditional deletion alleles of either unc-70/ß-Spectrin or spc-1/ α-Spectrin selectively in the epidermis are sufficient to abolish this scaffold and induce

widespread axonal damage in both sensory and motor neurons. These findings reveal the existence and importance of an epidermal spectrin scaffold that is necessary to protect adjacent axons from mechanical damage.

Wednesday 10:30 AM-12:30 PM

Selected Orals 3: Cognitive/Computation/Sensory

Great room 3

10:30 AM-10:45 AM
Tristan Chaplin

Dendritic and somatic representations of spatial navigation in mouse retrosplenial cortex revealed by head mounted 2-photon imaging

Tristan Chaplin1, 2, 3, Troy Margrie2
1. School of Human Sciences, UWA, Perth, WA, Australia
2. Sainsbury Wellcome Centre, UCL, London, UK
3. Dept of Physiology, Monash University, Melbourne, VIC, Australia

Two photon (2P) imaging is a powerful tool for recording the activity of specific types of neurons and their -cellular compartments in vivo. When performed in behaving animals this approach can shed light on how cells and circuits process information to guide decision-making and behaviour. While standard 2P microscopes require animals to be head-fixed and stationary under the objective which limits the types of behavioural tasks that may be studied, recently developed miniature 2P microscopes may be head-mounted and permit the recording of neuronal activity during open field exploration and navigation.
Here we have imaged GCaMP7f-mediated calcium activity in 121 penk-positive and 46 penk-negative excitatory cells in layer 2/3 in the retrosplenial cortex (n=12 mice), a region known to process information required for head orienting and navigation. We found that most cells (73%) encode spatial and behavioural variables, such as head direction, location and speed, with penk-positive cells more likely than penk-negative cells to encode speed (p=0.007). Both cell types show improved encoding of behavioural variables under illumination compared to darkness indicating they receive visual sensory input. Within this cell population and during freely moving behaviour, we could record signals in both the soma and dendrites (n=47) and found that 63% of calcium events occur simultaneously in the soma and dendrite, 9% in the soma only, and 28% in the dendrite only. This suggests that dendritic calcium signals are a prominent feature of the neuronal representation of spatial and other variables during freely moving behaviours.

10:45 AM-11:00 AM
Daniel Amaya

A Multimodal Comparative Study of the Development of the Olfactory Projection in Mus musculus and Octodon degus with Enhanced Ultra-high Resolution microCT

Daniel Amaya1, Kasia Blazejczyk2, Greetje Vande Velde2, Peter Mombaerts1
1. Max Planck Research Unit for Neurogenetics, Frankfurt am Main, Germany
2. Molecular Small Animal Imaging Center (MoSAIC), Katholieke Universiteit Leuven, Leuven, Belgium

In the mouse, the development of the olfactory projection begins with the invagination of the olfactory pit at embryonic day 10.5 and proceeds by establishing the olfactory epithelium, with the olfactory bulb developing simultaneously. Here, we performed a multimodal comparative study between the laboratory mouse (Mus musculus), and the degu (Octodon degus). The degu, a rodent endemic to central Chile, is affected by several physio-pathological diseases akin to human conditions making it a valuable research model. Compared to the traditional mouse model, the degu has a long gestation period (ca. three months), offering new opportunities for detailed developmental studies. First, we compared developmental stage-specific features to determine equivalent stages. Next, specific stages of mouse and degu embryos were processed for immunofluorescence and non-destructive ultra-high resolution microCT scanning (2D and 3D). Multimodal imaging revealed that the olfactory projection is more established at birth in the degu than mouse. Glomeruli in the olfactory bulb are further developed in the degu, akin to glomeruli at later stages in the mouse. In an overall comparison of the olfactory bulb and olfactory epithelium, the degu appeared more developmentally advanced than the mouse from late embryonic stages and at birth. MicroCT analysis at birth showed that the structural organization of turbinates appears more convoluted in the degu than in the mouse. We also identified structural differences at earlier developmental stages, such as glomerular formation and axon/mitral cell connectivity. These insights have implications for the application of the degu animal model in diverse biological research.

11:00 AM-11:15 AM
Macarena Pavez

Uncovering new trafficking routes in axons

Macarena Pavez1, Emma Gowing1, Laura Gumy1
1. University of Otago, Dunedin, OTAGO, New Zealand

Intracellular trafficking involves the movement of cellular cargoes such as proteins and organelles, by motor proteins that move along cytoskeletal microtubules. In neurons, such trafficking is especially critical, because the extreme length of axons (up to 1 metre in humans) requires that cargoes originating in the cell body travel long distances to reach their destinations. Despite the critical importance of trafficking to proper neuronal functioning, the basic mechanisms regulating the distribution of cargoes in axons are poorly understood. We previously showed that axonal

trafficking relies on two microtubule associated proteins (MAPs) that localise to the initial part of the axon: MAP2 and TRIM46. Given the ubiquitous presence of MAPs in axons, these proteins are likely candidates for providing signals for a MAP code to coordinate specific trafficking routes. Using high-resolution live-microscopy, genetic and biochemical approaches we have uncovered a new trafficking pathway regulated by MAP1A. We found that MAP1A precisely locates between MAP2 and TRIM46 where it is required for the transport of newly synthesised TRIM46 from the cell body to the axon. Furthermore, neurons depleted of MAP1A display impaired morphology and axon growth. We propose a novel mechanism for axonal trafficking and reveal a critical role for MAP1A.

Wednesday 11:15 AM-11:30 AM
Zengmin Li
Locating causal hubs of memory consolidation in spontaneous brain network in rodents

Zengmin Li2, 1, Dilsher Athwal2, Hsu-Lei Lee2, Pankaj Sah2, 3, Patricio Opazo2, 4, Kai-Hsiang Chuang2, 5
1. School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia
2. Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia
3. Joint Center for Neuroscience and Neural Engineering, and Department of Biology, Southern University of Science and Technology, Shenzhen, Guangdong, China
4. UK Dementia Research Institute, Centre for Discovery Brain Sciences, The University of Edinburgh, Edinburgh, UK
5. Centre of Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia
Objective:
Memory consolidation after learning involves spontaneous, brain-wide network reorganization during rest and sleep, but how this is achieved is still poorly understood. Current theory suggests that the hippocampus is pivotal for this reshaping of connectivity1,2. Apart from hippocampus, where, when and how other regions are involved in facilitating this system-wide reconfiguration are still unclear. Here we examined whether we can track the dynamic of post-learning spontaneous networks caused by memory consolidation and verified whether they're causally involved in this process.
Methods:
Resting-state functional magnetic resonance imaging (fMRI) was conducted on a cohort of mice after spatial memory tasks to track the dynamics of spontaneous networks during memory consolidation, and chemogenetic inhibition was used on another cohort of mice to verify the role of identified network hubs in memory consolidation.
Key findings:
Using fMRI in male mice, we identify that a different set of spontaneous networks and their hubs are instrumental in consolidating memory during post-learning rest. We found that two types of spatial memory training invoke distinct functional connections, but that a network of the sensory cortex and cortical areas is common for both tasks. Furthermore, learning increased brain-wide network integration, with the prefrontal, striatal and thalamic areas being influential for this network-level reconfiguration. Chemogenetic suppression of each hub identified after learning resulted in retrograde amnesia, confirming the behavioural significance.
Conclusion:
These results demonstrate the causal and functional roles of post-learning spontaneous network hubs in memory consolidation and suggest that a distributed network beyond the hippocampus serves this process.

11:30 AM-11:45 AM
Dinis Gokaydin
Mapping predictions in the fly brain

Dinis Gokaydin1, Scott Bowman1, Matthew Van De Poll1, Bruno van Swinderen1
1. University of Queensland, St Lucia, QLD, Australia
In order to survive intelligent organisms build mental models of the world which allow them to predict the future, a theory often referred to as predictive coding. A manifestation of this principle at work is termed sequential effects, defined as the way behaviour and neural signals are modulated by the recent history of events in sequential tasks. Often observed in humans, sequential effects, and more broadly predictive coding, are not as well studied in other species. Here we study visual sequential effects in the fruit fly Drosophila melanogaster using a three-pronged approach: electrophysiology, calcium imaging, and behaviour. We measured event-related potentials using electrodes inserted in the fly's brain, allowing for a characterisation of sequential effects in the time-frequency domain. By measuring calcium transients in a whole-brain imaging setup we were able to locate these sequential effects spatially in the fly's central brain. We collected data from 35 flies with GCamp6s or GCamp7s expressed pan-neuronally, and in cholinergic neurons specifically, focussing on structures in the central complex associated with navigation, the ellipsoid body and fan-shaped body, and discovered different areas sensitive to the history of stimuli. To determine the behavioural relevance of these effects, we designed a closed-loop visual fixation paradigm for flying Drosophila. Results from electrophysiology and calcium imaging suggest that neural signals in the Drosophila central brain are strongly modulated by the recent history of stimuli. Moreover, sequential effects in Drosophila are similar to those observed in humans, suggesting a conserved mechanisms underlying predictive processing across different species.

Wednesday 11:45 AM-12:00 PM

Christina Mo
Transthalamic pathways to higher order cortex contribute to choice activity during perception

Christina Mo1, Claire McKinnon2, S. Murray Sherman2
1. The Florey Institute, University of Melbourne, Melbourne, VIC, Australia
2. Dept of Neurobiology, University of Chicago, Chicago, Illinois, United States
Perception is supported by direct signalling between cortical regions. However, our recent work has shown that the transthalamic pathway from primary somatosensory cortex (S1) to higher order thalamus in mice is crucial in delivering sensory information to secondary somatosensory cortex (S2) during a texture discrimination task1. We now report the cellular effects of silencing the pathway in the delay epoch of the task, during which sustained activity encodes working memory, choice and pre-motor activity.
We inhibited the projection from S1 layer 5 to terminals in higher order thalamus by selective expression of the Jaws opsin and delivery of a 633nm laser in thalamus. At the same time, 2-photon calcium activity was monitored in layer 2/3 of S1 or S2. Mice were trained on a delayed go/no-go task to discriminate between a grating texture and a smooth texture. Discrimination difficulty could be varied by presenting gratings of various coarseness.
Optogenetic inhibition of the transthalamic pathway during the delay period (1sec) on easy discrimination trials only mildly reduced behavioural performance, in accordance with minor effects on calcium responses in S1 and S2. However, during more difficult discrimination trials, silencing the pathway impaired behavioural performance and reduced the sustained activity during hit trials. This abolished the discrimination selectivity of S1 and S2 cells. Laser application in the absence of Jaws expression showed no effects.
These results suggest that the somatosensory transthalamic pathway contributes to prepatory activity that supports correct behavioural choice and is an underappreciated route for performance-relevant information during perceptual decision-making.

12:15 PM-12:30 PM
Leonie Kirszenblat
Sleep disrupts odor value processing in Drosophila.

Leonie Kirszenblat1, Hokto Kazama1
1. Riken Center for Brain Science, Saitama, Select a state..., Japan
Publish consent withheld

12:30 PM-01:30 PM
Break
Lunch, Exhibition and Poster Display
Foyer/Studio 1/2/3/4

Wednesday 01:30 PM-03:30 PM
Jason Mattingley

Symposium 7: Risk, uncertainty and reward: Understanding the computational and neural mechanisms of decision making in health and disease

Great room 1

Agnieszka Tymula1, Carsten Murawski2, Laura Bradfield3, Dragan Rangelov4, Jason Mattingley4
1. University of Sydney, Sydney, NSW, Australia
2. University of Melbourne, Melbourne, VIC, Australia
3. University of Technology Sydney, Sydney, NSW, Australia
4. The University of Queensland, St Lucia, QLD, Australia

The ability to make well-judged and timely decisions is fundamental for adaptive, goal-directed behaviour. Some decisions are life or death: Is it safe to cross the road? Others are more mundane: What should I wear today? Still others can affect our quality of life for years to come: Should I buy a house? The apparent ease with which we make decisions belies the enormous computational complexity involved in weighing relevant information, learning from experience, and selecting appropriate actions. Impairments of decision-making are a hallmark of many neurological and psychiatric conditions, and poor decision-making ability has been linked to such diverse conditions as problem gambling and obesity. Moreover, decision-making is not a uniquely human capacity. All animals, from worms and flies to rats and mice, must make adaptive decisions to survive.

In the last 20 years there has been an explosion of new research on the neural and computational processes that regulate decision-making in health and disease. This symposium will showcase the latest developments in the neuroscience of decision making. It brings together some of Australia's best decision scientists, both established and emerging, from a diverse range of disciplines, including cellular and systems neuroscience, experimental psychology, neuroeconomics and cognitive neuroscience.

Professor Agnieszka Tymula is Director of the Experimental Economics Laboratory at the University of Sydney. She will discuss her work on the neural mechanisms of risk in decision making in humans and non-human primates, with a focus on gambling and the role of socioeconomic status on decision-making behaviour. Professor Carsten Murawski is Director of the Centre for Brain, Mind and Markets at the University of Melbourne. He will present his work on hardness' in decision-making and highlight recent brain-imaging findings on the neural systems involved in making complex decisions. Dr Laura Bradfield is a Senior Research Fellow and Head of the Brain and Behaviour Laboratory in the School of Life Sciences at the University of Technology Sydney. She will present recent work from a rodent model of decision-making which suggests that striatal neuroinflammation causes dysregulated goal-directed action control in a regionally specific and astrocytically controlled manner. Finally, Dr Dragan Rangelov is a Research Fellow at The University of Queensland, where he holds joint appointments between the Queensland Brain Institute and the School of Economics. His recent brain imaging and computational modelling investigations have revealed that integrative perceptual decisions arise from dynamic modulation of information processing across functional networks involving primary and associative visual cortices.

We believe this symposium will be well suited to the diverse interests and expertise of those who attend the ANS Annual Scientific Meeting. The work presented will be based on studies in both animal models and humans, and will showcase a variety of experimental approaches including electrophysiology, immunohistochemistry, functional brain imaging, behavioural measures and computational modelling. The topic is also particularly timely. Research on the neuroscience of decision-making has important implications for a wide range of fields, including economics, public policy, and healthcare. Many mental health conditions, including addiction, anxiety, and depression, involve disturbances in decision-making processes.

01:30 PM-01:55 PM
Agnieszka Tymula

Risk attitude with a backward-looking reference point

Past experience affects future decisions even after passive exposure and in the absence of learning. To determine to what degree these effects are evolutionarily preserved, two rhesus monkeys (Macaca mulatta) performed a risky decision-making task as neural activity in the striatum and orbitofrontal cortex was recorded. On some trials, the animals had to view a lottery without responding. Using predictions derived from prospect theory – developed to explain human choice behaviours – we successfully modelled the activity of individual neurons. The findings show that the effect of past wins and losses on risk attitudes is remarkably consistent across species. We speculated that socioeconomic status (SES) may influence how historical outcomes affect the willingness to take risk, leading to wealth-reducing choices. Analyses of a rich data set comprising bet-level data from 10,000 gamblers over one year confirmed that past wager outcomes have a differential effect on behaviour for different SES groups, with those residing in low SES neighbourhoods being more influenced by previous day outcomes, ultimately leading to greater losses. By acknowledging differences in risk sensitivity as a potential source of economic inequality, we can begin a new discussion on how to address this important issue.

01:55 PM-02:20 PM

Carsten Murawski
Neural correlates of computational complexity

Many everyday decisions require people to solve computationally complex problems. However, little is known about the effects of computational difficulty (hardness')on the neural processes associated with solving such problems. Here, we draw on computational complexity theory to address this issue. We performed a number of experiments in which participants solved several instances of the 0-1 knapsack problem, a combinatorial optimization problem. These instances varied in task-independent measures of intrinsic computational hardness. In one experiment, we tracked participants' pupil diameter and gaze position. In another experiment, participants underwent ultra-high field(7T) functional magnetic resonance imaging (fMRI) while completing the task. Based on these data, we characterised the pupil response and adaptation of cognitive strategies to varying degrees of computational hardness. We also characterised a network of brain regions whose activation was correlated with computational hardness, including the anterior insula, dorsal anterior cingulate cortex and the intra-parietal sulcus/angular gyrus. Activation and connectivity changed dynamically as a function of computational hardness, inline with theoretical computational requirements. Overall, our results suggest that computational complexity theory provides a suitable framework to study the effects of computational hardness on the neural processes associated with making complex decisions.

Wednesday 02:20 PM-02:45 PM
Laura Bradfield
Striatal neuroinflammation impairs goal-directed decision-making via dysregulation of astrocytic function in a regionally specific manner

Striatal neuroinflammation has been identified in the brains of individuals with neuropsychiatric disorders and neurodegenerative diseases for whom goal-directed action control is impaired. However, because these studies are conducted in humans and are thus correlative, whether striatal neuroinflammation causes these impairments is unknown. We therefore investigated this question by injecting the endotoxin lipopolysaccharide (LPS) t oinduce neuroinflammation in the posterior dorsomedial striatum (pDMS) or nucleus accumbens core (NAC core) of male and female Long-Evans rats, and tested their behaviours on multiple assays of goal-directed action. Animals with LPS in their pDMS demonstrated enhanced action selection on multiple assays including Pavlovian-instrumental transfer (PIT),outcome devaluation, and progressive ratio, whereas animals with LPS injected into the NACcore demonstrated intact PIT but impaired devaluation. These effects were regulated by astrocytes in each region, as chemogenetically silencing astrocytes in the pDMS impaired PIT and devaluation whereas silencing them in the NAC core impaired devaluation only. Immunohistochemical and electrophysiological studies suggested that neuroinflammation causes the excitation of neurons as a result of astrocytic activation. Together, these results suggest that striatal neuroinflammation causes dysregulated goal-directed action control in a regionally specific and astrocytically controlled manner.

02:45 PM-03:10 PM
Dragan Rangelov
Neural mechanisms of integrated decision making

Decision making is a key cognitive function mediating sensory processing and choice behaviour. Previous studies have characterised neural and cognitive mechanisms that support decisions about a single, task-relevant stimulus. It is unknown what mechanisms regulate decisions which require integration of several, spatially discrete sensory inputs. When crossing a busy road, for example, it is necessary to consider traffic coming from both sides. Using brain imaging in combination with computational modelling, we characterised the neural mechanisms of integrated decision making. Stimulus displays comprised two patches of moving dots presented in the left and right visual hemifields. Coherent motion signals were presented concurrently in both patches and participants reported the average motion direction of the two signals. Across two separate studies, their brain activity was recorded using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Computational modelling of EEG data revealed that sensory input is sampled and accumulated in parallel across the visual hemifields. fMRI analyses revealed that the average motion direction is encoded in the primary visual cortex with a delay consistent with the need for interhemispheric integration of lateralized visual input. Overall, we show that integrated decisions rely on dynamic modulation of functional networks involving primary and associative visual cortex.

03:10 PM-03:15 PM
Laura Kimble
Data Blitz: Reversal Learning in Mice: Model-based versus Model-free Approaches

Laura M Kimble1, Suzy Alexander2, 1, James P Kesby2, 1
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Adapting to rapidly changing environments is a crucial component of cognitive flexibility, which is impaired in several neuropsychiatric disorders, including schizophrenia1,2. Reversal learning tasks (RLT), which require individuals to learn stimulus-outcome associations and then dynamically reverse these associations, are established as tests of

cognitive flexibility. While rodents are commonly tested in RLT, extensive training regimes may promote strategies that hinder its translational capacity. To better understand neural and behavioural mechanisms underlying cognitive flexibility, we explored novel RLT training approaches in mice, emphasising mixed model-based and model-free learning (akin to humans). We implemented a probabilistic RLT training regimen to generate three groups; performance-based (n=10), time-based (n=10), and mixed (n=20). Performance-based mice were trained using a protocol whereby reversals occur after 6-8 consecutive correct responses (CCR). For time-based mice, reversals occurred after 26-36 trials regardless of performance. Mixed mice were trained using both protocols. The differing training protocols significantly altered reversal learning approaches. Performance- and time-based groups could navigate reversals in their own task (i.e., performance-based on CCR), but show optimal RLT strategies (win-stay, lose-shift) on the alternative protocols. Mice trained using mixed-methods better managed either protocol, as expected for humans. We further explored how differing reward contingencies and amphetamine impact these groups. Alongside replicating our earlier work3, we show that increasing dopamine levels differentially affects performance based on mouse training protocols. This project provides the foundation for future experiments targeting specific circuits during RLT, and the sequent development of novel therapeutic interventions to improve cognitive flexibility in neuropsychiatric disorders.

Wednesday 03:15 PM-03:20 PM
Joanita D'Souza
Data Blitz: Visual attention increases spike-LFP coherence across cortical layers

Joanita F D'Souza1, Shaun L Cloherty2, Nicholas S. C. Price1, Maureen A Hagan1
1. Monash University, Clayton, VIC, Australia
2. School of Engineering, RMIT, Melbourne, VIC, Australia
Brain areas communicate with temporal precision to control complex, cognitive behaviours such as visual attention. Inputs from different areas arrive into different cortical layers. Despite being a fundamental organising principle of the brain, we have little understanding of how cells keep track of different streams of information. One hypothesis is that the frequency bands of the local field potential (LFP) may serve different functions. To test whether coherence between spiking and the phase of the LFP changes across cortical layers, we recorded from the posterior parietal cortex of an adult marmoset monkey using a semi-chronic 32-channel linear array (100um spacing) that allowed us to record spiking and LFP activity simultaneously across cortical layers (65 recording days, two array implants). The monkey was trained to perform a visually-guided saccade task. The phase of spike-LFP coherence varied dependent on frequency band (theta 4Hz, alpha 12Hz, beta 20Hz, and gamma 40Hz) and there was a significant phase shift in the spike-LFP coherence between superficial and deep cortical layers (p 0.05, random permutation test). To test whether the spike-LFP phase coherence related to cognitive behaviour, we trained the monkey to do a cued-saccade task. On a set of trials, a visual cue indicated the upcoming direction of the saccade target with 85% accuracy. The magnitude of spike-LFP coherence was greater on cued trials vs non-cued trials, across all frequency bands and cortical layers (p 0.05, random permutation test). Therefore, spike-LFP coherence may be a mechanism for cells to support cognitive behaviour.

03:20 PM-03:25 PM
Hoi Ming Ken Yip
Data Blitz: Predicting Single-trial Eye Speed and Direction from Neural Population Responses in Marmoset Area MT

Hoi Ming Ken Yip1, Tim Allison-Walker1, 2, Elizabeth Zavitz3, Shaun Cloherty2, Maureen Hagan1, Nicholas Price1
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2. School of Engineering, RMIT University, Melbourne
3. Electrical and Computer Systems Engineering, Monash University, Clayton, VIC, Australia
Ocular following is a rapid, reflexive eye movement triggered by motion of a large visual stimulus. It helps to stabilise the gaze after saccades. Previous single-unit recording and lesion studies in macaques suggest that the middle temporal area (MT) plays a critical role in sensory-motor transformations driving ocular following. However, how informative the MT neural population is in terms of representing the stimulus and predicting oculomotor responses is largely unknown. We used Neuropixels probes to record large populations of neurons in area MT of marmosets viewing broadband motion stimuli that evoked robust ocular following. We focused the analysis on an example with good recording quality (47 single units and 169 multi-unit activities recorded) and sufficient behavioural trials (n = 126). We performed Gaussian Process Factor Analysis (GFPA), a dimensionality reduction method, on the population responses. Then we correlated the component scores with eye speed or direction in consecutive non-overlapping 20 ms time windows on a trial-by-trial basis. We found significant correlations between the second component and eye speed at 20-40 ms (r = -0.24, p 0.01) and 80-140ms (r = 0.303-0.373, all p 0.01). Eye direction was also significantly correlated with the second component at 20-40 ms (r = 0.288, p .01) and 100-120 ms (r = 0.319, p 0.01). In conclusion, populational activity in MT was correlated with ocular following responses on a single trial level.

Wednesday 03:25 PM-03:30 PM
Brett Kagan

Data Blitz: Examining Neural Dynamics within Embodied Environments

Brett Kagan1, Alon Loeffler1, Forough Habibolahi1, Moein Khajehnejad2, Brad Watmuff2, Adeel Razi2
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2. Monash Univeristy, Melbourne

Understanding the cellular origin of intelligence in neural systems is a significant challenge that requires stantial technical and theoretical advancements. Previously, we developed a system which exhibits natural intelligence by harnessing the inherent adaptive computation of neurons in a real-time closed-loop structured environment. In vitro neural networks from human or rodent origins were integrated with in silico computing via high-density multielectrode array. Through electrophysiological stimulation and recording, cultures were embedded in a simulated game-world, comparable to the arcade game Pong'. We previously reported reproducible learning effects displayed by these embodied cultures along with key electrophysiological activity correlates. Here, we have now identified key nuances in network activity reorganization that is consistent with interpretation of connectivity changes at the level of functional units, along with network wide reorganization. The implications of this work provide insights into how in vitro neural cultures organize their activity in response to a structured information landscape – such as an active gameplay environment. The utility of this approach was then further extended by finding nuanced differences comparing control vs aged neural cells and demonstrating highly reproducible restorative effects in an in vitro epilepsy model when anti-seizure drugs were applied. Finally, we present key pathways proposed from the Organoid Intelligence (OI) framework before concluding outlining a useful ethical framework for the further development of this technology established through an international collaboration that is inspired by the principles of anticipatory governance.

Wednesday 01:30 PM-03:30 PM
Victor Anggono; Hilary Yong

Symposium 8: Advances in glutamate AMPA receptor regulation in health and disease: Exploring novel mechanisms

Great room 2

Victor Anggono1
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Understanding the molecular mechanisms underlying our ability to learn, store information and retrieve memory is one of the most fascinating questions in modern neuroscience. Dynamic changes in neuronal synaptic efficacy, termed synaptic plasticity, has long been postulated to underlie information coding and storage in learning and memory. One of the best-studied forms of such plasticity is long-term potentiation (LTP) which produces a persistent increase in the synaptic strength in neurons, characterised by an increase in the number of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)-type glutamate receptors. Perturbations in synaptic AMPA receptor expression and synaptic plasticity have been implicated in neurological disorders, including epilepsy, schizophrenia, intellectual disability, and Alzheimer's disease. Given the fundamental roles of AMPA receptor trafficking in maintaining synaptic transmission, plasticity, learning and memory, understanding the molecular mechanisms underpinning receptor dynamics has been an area of intense research in many laboratories worldwide. Importantly, small molecule modulators of AMPA receptors are clinically significant, including perampanel, an FDA-approved AMPA receptor inhibitor for treating epilepsy.
This symposium will highlight the latest advances in the mechanisms by which AMPA receptors can be regulated, focussing on four novel molecules, including the neural cell adhesion molecule 2 (NCAM2; by A/Prof. Vladimir Sytnyk), the microtubule-associated protein Tau (by Dr. Arne Ittner), the secreted amyloid precursor protein-alpha (sAPPα; by A/Prof. Joanna Williams) and the neuron-specific Ca2+- and phospholipid-binding protein Copine-6 (by Dr. Anson Tan). This new research has the potential to reveal novel insights into the regulation of AMPA receptors, opening up new avenues for drug development and ultimately leading to better treatments for neurological disorders. This symposium will feature research wholly conducted in Australia and New Zealand, indicating the increased interest in research on AMPA receptor function in these regions. Therefore, we believe this topic is timely and will interest the broad neuroscience community. These talks will cover many cutting-edge neurobiology techniques, including proximal-interactome analysis, live-cell imaging microscopy for visualising AMPA receptor exocytosis and super-resolution single-particle tracking of surface AMPA receptor lateral movement, all of which serve as valuable educational resources for student members and early-career researchers.
This topic was not covered in the past three ANS annual meetings. The proposed symposium is carefully designed to include speakers that represent geographic diversity (Queensland, New South Wales, South Australia and New Zealand) and encompass early-career (Dr. Anson Tan), mid-career (Dr. Arne Ittner) and senior scientists (A/Profs. Joanna Williams and Vladimir Sytnyk), while maintaining the quality of scientific content at a high standard, therefore providing a forum for the exchange of ideas across all career stages. This is an opportunity to share ideas, exchange knowledge, and establish collaborations, which can lead to breakthroughs in neuroscience. In addition, we have also included a PhD student (Miss Hilary Yong) to co-chair the proposed symposium. In conclusion, this will be an exciting and educational symposium that will lead to dynamic discussions among participants at the upcoming 41st annual meeting of the Australasian Neuroscience Society.

01:30 PM-01:55 PM
Vladimir Sytnyk
The neural cell adhesion molecule 2 (NCAM2) regulates the assembly and synaptic targeting of calcium-permeable AMPA receptors

Calcium-permeable AMPA receptors, consisting exclusively of GluA1 units, play significant roles in synaptic plasticity, behaviour, pain and addiction. However, the mechanisms of their assembly and synaptic targeting remain poorly understood. We demonstrate that in transfected CHO cells, the extracellular domain of neural cell adhesion molecule 2 (NCAM2)binds to GluA1 and inhibits the binding of GluA1 to the GluA2 unit of calcium-impermeable AMPA receptors. NCAM2 promotes the targeting of GluA1-AMPA receptors to the cell surface.NCAM2-GluA1 complexes accumulate at sites of the homophilic NCAM2-mediated adhesion. InNCAM2-deficient cultured hippocampal neurons, the cell surface levels of GluA1 are reduced while its intracellular pool is increased. The overall levels of GluA1, synaptic targeting, and enrichment relative to GluA2 are reduced in the brains of NCAM2-deficient mice. Our results indicate that NCAM2 promotes the assembly and synaptic targeting of calcium-permeable AMPA receptors. Disruptions in synaptic signaling via calcium-permeable AMPA receptors may therefore contribute to the development of neurodevelopmental disorders found in people with deletions of the NCAM2 gene.

01:55 PM-02:20 PM
Joanna Williams
Glutamate receptor remodelling by the memory-enhancing molecule sAPPα, scrutinised with super-resolution microscopy

Secreted amyloid precursor protein-alpha (sAPPα) enhances long-term potentiation(LTP) and rescues impaired memory processes in mouse models of Alzheimer's disease and thus may have important therapeutic potential. Our goal is to understand precisely how sAPPαregulates synaptic activity. Regulation of AMPA receptor expression by neuronal activity and neuromodulators is critical to the expression of both LTP and memory. In particular, GluA1-containing AMPA receptors play a unique role in these processes due to their transient, activity regulatedexpression at synapses. We have discovered that sAPPα specifically enhances the ability of synapses to respond to activity by specifically modulating synthesis of GluA1-AMPAreceptor units and that these units are rapidly transported to the cell surface. Here we have examined the characteristics of AMPAR clusters at the neuronal cell surface using super resolution(dSTORM) microscopy showing that sAPPα increases extrasynaptic GluA1 cluste rnumber, and in combination with depolarisation, increases synaptic number and area. Thus, we proposed that by promoting an increase in GluA1-AMPARs, sAPPα acts as a neuromodulator, priming synapses and underpinning enhanced responses to co-existent activity.

Wednesday 02:20 PM-02:45 PM
Arne Ittner
Protein kinases, tau phosphorylation and Alzheimer's disease: New insights on AMPA receptor regulation

The microtubule-associated protein tau is prominently involved in the pathogenesis of Alzheimer's disease. Tau is a target of protein kinases and is progressively hyperphosphorylated at multiple sites, contributing to the formation of neurofibrillary tangles and cognitive decline in Alzheimer's disease. Hyperphosphorylation is commonly considered to harm neurons and impair cognitive function. However, site-specific phosphorylation can confer unique functions of tau that are relevant to both healthy brain function and disease. Our recent work defined a mechanism that links site-specific and tau multi-site phosphorylation, raising potential ways to interfere with tau hyperphosphorylation. Phosphorylation can regulate interactions of tau with other proteins. Using proximity labelling proteomics, we determined the protein interactome of tau in the mouse brain. We find that tau interacts with and dose-dependently reduces the activity of Nethylmaleimide sensitive fusion protein (NSF), a vesicular ATPase essential for AMPA-type glutamate receptor (AMPAR) trafficking. Tau knockout neurons showed mislocalised expression of NSF and enhanced synaptic AMPAR surface levels, reversible through the expression of human tau or inhibition of NSF. Consequently, enhanced AMPAR-mediated associative and object recognition memory in tau knockout mice is suppressed by both hippocampal tau and infusion with an NSF-inhibiting peptide. Our work therefore provides new insights into tau's physiological roles in synaptic learning and memory processes. We believe this research will advance concepts involving tau interactions and tau phosphorylation that enhance our understanding of memory function and its impairment in dementia.

02:40 PM-03:10 PM
Jing Zhi Anson Tan
Copine-6 is a calcium sensor that mediates AMPA receptor exocytosis during synaptic potentiation

The recruitment of synaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionicacid) receptors underlies the strengthening of neuronal connectivity during learning and memory. This process is triggered by NMDA (N-methyl-D-aspartate) receptor-dependent postsynapticCa2+ influx. Synaptotagmin (Syt)-1 and -7 have been proposed as Ca2+-sensors for AMPA receptor exocytosis, but are functionally redundant. Here we identify a cytosolic C2 domaincontainingCa2+-binding protein Copine-6 that forms a complex with AMPA receptors. Loss ofCopine-6 expression impairs activity-induced exocytosis of AMPA receptors in primary hippocampal neurons, which is rescued by wild-type Copine-6, but not Ca2+-binding mutants. In contrast, Copine-6 loss-of-function has no effects on steady-state expression or tetrodotoxin induced synaptic upscaling of surface AMPA receptors. Loss of Syt-1/-7 significantly reducesCopine-6 protein expression. Interestingly, overexpression of wild-type Copine-6, but not theCa2+-binding mutant, restores activity-dependent exocytosis of AMPA receptors in Syt-1/-7double-knockdown neurons. We conclude that Copine-6 is a postsynaptic Ca2+-sensor that mediates AMPA receptor exocytosis during synaptic potentiation.

03:10 PM-03:15 PM
Eleanor Drummond
Data Blitz: Proteomic similarities in Alzheimer's disease and epilepsy

Eleanor Drummond1, Dominique Leitner2, Geoffrey Pires2, Tomas Kavanagh1, Thomas Wisniewski2
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Alzheimer's Disease (AD) patients are more likely to experience epileptic seizures, and cognitive impairment is a frequent comorbidity in people with epilepsy. Emerging findings suggest there may be common molecular changes in the brain in epilepsy and AD, however these have not been comprehensively examined. Therefore, our aim was to identify the common protein changes in epilepsy and AD human brain tissue using proteomics datasets. We observed a highly significant overlap in the protein changes present in epilepsy and AD: 89% (689/777) of proteins altered in the hippocampus in epilepsy were also significantly altered in advanced AD. Synapse and mitochondrial proteins were particularly decreased in both epilepsy and AD, suggesting common disease mechanisms. In contrast, ribosome

proteins were altered in the opposite direction in epilepsy and AD: ribosome proteins were significantly increased in epilepsy but significantly decreased in AD. Interestingly, proteins altered in epilepsy were significantly enriched in proteins regulated by tau (p=1.33x10-57) and protein interactors of both phosphorylated tau (p=1.99x10-15) and total tau in AD (p=4.1x10-135), suggesting that tau was a likely central mediator of common protein changes in epilepsy and AD. Immunohistochemistry confirmed the lack of phosphorylated tau aggregates and amyloid plaques in epilepsy hippocampal sections, suggesting that the common protein differences in epilepsy and AD were not a result of AD neuropathology in the broad spectrum of epilepsy syndromes evaluated. In conclusion, our results provide new insight into the common mechanisms present in epilepsy and AD and highlights pathways of particular importance for future studies.

Wednesday 03:15 PM-03:20 PM
Miaomiao Mao
Data Blitz: Disrupted activity in inhibitory spheroids derived from a Dravet patient iPSC line
Miaomiao Mao1, Cristiana Mattei1, Kay Richards1, Ingrid Scheffer2, Steven Petrou1, Snezana Maljevic1
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2. Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia
Dravet syndrome (DS) is a severe neurodevelopmental disorder with children in their infancy presenting with drug-resistant seizures and multiple comorbidities including developmental regression, motor disorders, sleep disruptions and behavioural problems. Most DS is caused by loss-of-function (LoF) mutations in the SCN1A gene, encoding the voltage-gated sodium channel NaV1.1, which is highly enriched in CNS inhibitory neurons. In this study, we created a patient induced pluripotent stem cell (iPSC) derived 3D neuronal model, using an optimised protocol that generates ventral forebrain-like spheroids enriched with GABAergic neurons. The model was validated by immunohistochemistry and qPCR, and functionally characterised by whole-cell patch clamping and two-photon (2P) calcium imaging. The inhibitory spheroids expressed SCN1A and several key GABAergic neuronal markers but lacked the excitatory neuronal marker vGLUT. Patch clamp electrophysiology confirmed their ability to fire action potentials and receive synaptic inputs after 4-5 months in vitro. 2P calcium imaging also showed abundant calcium signals in structures resembling neuronal soma and processes. Importantly, we have uncovered a distinct phenotype in which the patient inhibitory spheroids displayed less neuronal excitability and synaptic activity compared to the isogenic control. A drug commonly used to treat DS (fenfluramine) appeared to increase neuronal activity in 2P calcium imaging, potentially rescuing the loss of inhibitory neuronal function. Here, we have developed and characterised an in vitro 3D human derived platform for modelling SCN1A DS at the molecular, morphological and functional levels. Our experiments allowed the establishment of a workflow for drug screening by using patient-derived in vitro tissue.

03:20 PM-03:25 PM
Lauren Bleakley
Data Blitz: Clinical features of SYT1-associated neurodevelopmental disorder correlate with functional defects in evoked neurotransmitter release
Lauren E Bleakley1, Paul Park1, Nadia Saraya1, Eema Jawahiri2, Josefine Eck2, Mark Aloi1, Holly Melland1, Kate Baker2, 3, Sarah L Gordon1
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2. MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK
3. Department of Medical Genetics, University of Cambridge, Cambridge, UK
Synaptotagmin-1 (SYT1) is a presynaptic vesicular protein which plays a crucial role in triggering synchronous neurotransmitter release. It is comprised of two key domains: the C2B domain, which requisitely binds intracellular calcium to facilitate vesicular fusion; and the C2A domain, which plays an auxiliary role in evoked exocytosis. Pathogenic C2B domain variants cause SYT1-associated neurodevelopmental disorder, a rare condition characterised by movement disorder, developmental delay and intellectual disability1.
Recently, a number of new pathogenic SYT1 variants have been identified. These have included the first disease-associated C2A domain variants, which result in milder disease phenotypes, as well as additional C2B domain variants. These discoveries have broadened the phenotypic spectrum of SYT1-associated neurodevelopmental disorder.
Several C2B domain variants were previously shown to slow synaptic vesicle exocytosis1. However, it was unclear whether the newly-identified variants – particularly the C2A domain variants – would share this pathogenic mechanism.
Here, we investigate the effects of four novel C2A domain and four novel C2B domain variants on SYT1 function in primary hippocampal neuronal cultures. We demonstrate that both C2A and C2B domain variants slow synaptic vesicle exocytosis, but they do so in a graded manner, with C2A domain variants having a milder effect than C2B domain variants. Furthermore, the severity of exocytic defects induced by SYT1 variants strongly correlates with the severity of impairment in motor and communication abilities seen clinically in patients harbouring each variant. Together, these data suggest that exocytic defects may underpin key phenotypic features observed in patients with SYT1-associated neurodevelopmental disorder.

Wednesday 01:30 PM-03:30 PM
Selected Orals 4: Neurodegeneration

Great room 3

01:30 PM-01:45 PM
Gregor Bieri
Liver-derived exercise blood factor Gpld1 rescues cognition by targeting the brain vasculature in aging and Alzheimer's disease

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Aging changes the brain at the molecular and cellular levels, driving cognitive impairments and increasing susceptibility to neurodegenerative diseases. We recently described a liver-to-brain rejuvenation axis, in which the beneficial effects of exercise on cognition are transferred, in part, through Gpld1 – an exercise-induced, liver-derived plasma enzyme that cleaves GPI-anchored proteins (GPI-AP) from the cell surface. While increasing systemic Gpld1 is sufficient to rejuvenate cognitive functions in aged mice through a peripheral mode of action, its cellular and molecular targets remain elusive. We surveyed expression of GPI-APs and identified enrichment on endothelial cells, raising the possibility that Gpld1 may be acting on the brain vasculature. In humans, we observe that systemic Gpld1 levels in active elderly jects correlate with structural metrics of brain vascular integrity. In aged mice, systemic Gpld1 treatment restore expression and activity of the GPI-anchored phosphatase ALPL/TNAP, a regulator of brain vascular function, to more youthful levels on hippocampal blood vessels. At a cellular level, we characterize the rejuvenating effects of exercise and Gpld1 treatment on the aging brain vasculature and parenchyma using complementary vessel isolation and nuclei extraction for sequencing (VINE-seq, single-nuclei RNASeq) approaches. Lastly, we investigate the rejuvenating potential of systemically inhibiting the Gpld1 strate ALPL/TNAP and observe cognitive enhancements in both aged mice and a mouse model of Alzheimer's disease pathology. Collectively, our studies establish the brain vasculature as a critical mediator of the benefits of systemic Gpld1 and identify molecular downstream mediators as novel therapeutic targets to restore cognition in aging and disease.

01:45 PM-02:00 PM
Rebecca San Gil
A transient, post-transcriptional, chaperone response may protect neurons in the early stage of TDP-43-mediated disease

Rebecca San Gil1, Dana Pascovici2, 3, Juliana Venturato1, Heledd Brown-Wright1, Prachi Mehta4, Lidia Madrid San Martin1, Jemma Wu3, Yi Kit Chui1, Adekunle T Bademosi1, Shilpa Swaminathan1, Wei Luan1, Britt A Berning1, Amanda L Wright1, Sean S Keating1, Albert Lee4, Marco Morsch4, Roger S Chung4, Leszek Lizowski5, Mehdi Mirzaei3, Adam K Walker1
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TAR-DNA binding protein 43 (TDP-43) undergoes toxic aggregation to form neuronal inclusions in numerous neurodegenerative diseases such as amyotrophic lateral sclerosis. Little is known about the molecular mechanisms that drive disease onset and progression. To address this gap, we conducted longitudinal quantitative proteomics in a doxycycline regulatable human cytoplasmic TDP-43 mouse model of ALS (NEFH-tTA/tetO-hTDP-43δNLS, rNLS' mice). We collected cortex tissue from control and rNLS mice at different timepoints of disease; pre-onset, disease onset, early-disease, and late-disease and conducted quantitative proteomics. We identified that protein-folding proteins, or chaperones, demonstrated divergent patterns of regulation in the cortex throughout the time course of disease. For example, hierarchical clustering of 119 chaperones detected in the cortex revealed a set of chaperones that are increased prior to disease onset. This set of chaperones returned to control levels in early disease. Further investigation of this set of proteins revealed no change in transcript abundance, suggesting the increase in protein abundance is mediated by a post-transcriptional mechanism in the rNLS mouse cortex. One of these proteins, Dnajb5, a HSP40 family member, significantly decreased insoluble mutant TDP-43 levels and decreased the number of mutant TDP-43 inclusions formed in HEK293 and primary cortical neurons. Taken together, this study has identified a time course of molecular alterations in the cortex that respond to and drive TDP-43 pathology development in disease (webtool to explore data: https://shiny.rcc.uq.edu.au/TDP-map/). This work also highlights the potential for HSP40, and other proteins within this newly identified set of chaperones, to target and clear pathological TDP-43.

Wednesday 02:00 PM-02:15 PM
Rebekah Parkinson
Alpha Synuclein and Immune Interactions in Parkinson's Disease Ontogenesis

Rebekah G Parkinson1, 2, Jessica Pettitt1, Tony Xu1, Zizheng Xian2, Ilvana Ziko2, Rebecca Buckland1, Sarah Gordon3, Christopher Parish1, Anne Bruestle1, Nathalie Dehorter1, 2
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Parkinson's disease (PD) is a motor-related neurodegenerative disorder typically characterised by the loss of dopaminergic cells in the stantia nigra and accumulation of immunoreactive alpha-synuclein aggregates. Whilst α-synuclein-derived epitopes has been found to drive both innate and adaptive immunity in prodromal PD, the mechanistic role of the immune system in directly contributing to disease ontogenesis remains unknown.
Recent evidence has identified alpha-synuclein as a biomarker, with seed amplification assays yielding high sensitivity (98.6%) for sporadic cases of the disease. To determine if immune activation and alpha-synuclein together are reliable predictors of disease onset, we performed a systematic review that correlates patients' individual alpha-synuclein positive assays with immune activity and appearance of symptoms across time.
To examine whether this interaction indeed triggers Parkinson's like symptoms, we designed a novel auto-immune alpha-synuclein induced model of PD. Wildtype mice are immunised to alpha-synuclein by peripheral injection in adjuvant, inducing significant rise in whole white blood cell counts. Reactive autoimmunity was characterised by activated lymphocytes and antigen presenting cell populations in the periphery, and immune T cell infiltration to the brain. These mice display significant motor deficits in gait and locomotion, dopaminergic neurodegeneration, and increased neuroinflammation compared to control conditions (i.e., sham; non-injected mice; and mice lacking adaptive immunity, Rag1tm1Mom).
Our findings uncover a causal link between immune cells and alpha-synuclein in driving PD pathogenesis. This study provides the basis for exploring preventative and therapeutic interventions in the first immunological murine model of PD.

02:15 PM-02:30 PM
Jürgen Götz
Exploring ultrasound as a novel treatment modality in mice and humans

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2. University of Queensland, Queensland Brain Institute, Brisbane
Ultrasound is routinely used for a wide range of diagnostic imaging applications. However, given that ultrasound can operate over a wide range of parameters that can all be modulated, its applicability extends far beyond the bioimaging field and is therefore being extensively explored at low intensity and lower frequencies as a therapeutic tool (e.g. Leinenga & Götz, Nature Reviews Neurol 2016; Blackmore et al., Neuron 2023). We initiated a research program back in 2012 that took us from determining the technology's potential in mouse models of senescence and Alzheimer's disease (AD), using three fundamental ultrasound paradigms, to building a clinical trial-ready device under ISO13485 guidelines, and conducting a clinical trial in a cohort of patients with AD.
We used ultrasound in a scanning mode (SUS) and determined that ultrasound on its own (SUSonly), ultrasound applied with intravenously injected microbubbles to achieve transient blood-brain barrier opening for the uptake of blood-borne therapeutic factors (SUS+MB) and SUS+MB delivered with a range of anti-tau and anti-amyloid antibodies (SUS+MB+drug) collectively ameliorate disease and improve cognitive functions.
We will present the pros and cons of the three modalities, their safety profile, the mode of action (MoA) and which preclinical data informed the built of an ultrasound machine' and our clinical trial design. We will further present what we believe may be the way forward to implement non-invasive low-intensity ultrasound as a novel treatment modality for AD and brain disorders more generally.

02:30 PM-02:45 PM
Pawat Laohamonthonkul
Type I interferon response propagates TDP-43 pathogenesis in ALS/MND

Alan Yu1, Cynthia Louis2, Pawat Laohamonthonkul1, Cassandra Harapas2, Brooke McDonald1, Pippa S Pringuer1, Bradley Turner1, Peter J Crouch3, Seth L Masters2
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Background: Cytoplasmic TDP-43 build-up is a pathological hallmark of amyotrophic lateral sclerosis (ALS) (1). This neurodegenerative disease is associated with NF-κB and type I interferon (IFN-I) signalling, which can accelerate the disease progression (2-4). Here, we aim to identify the role of IFN-I in TDP-43 pathogenesis for new ALS treatments.
Methods: To establish the role of IFN-I in ALS, TDP-43 overexpressing SH-SY5Y and patient iPSC-derived motor neurons were jected to inhibition of the JAK-STAT pathway. For in vivo studies a transgenic mouse model expressing human TDP-43 A315T was used and crossed to mice that were genetically deficient for Ifnar1.

Results: Here we show that loss of Ifnar1 mitigates motor deterioration and neuronal loss in the cortical layer V and the spinal cord of TDP-43 mutant mice. Histochemical analyses demonstrate that TDP-43-mediated gliosis and CD45+/Ly6C+ peripheral monocyte infiltration can be prevented when Ifnar1 is depleted. Critically, RNAscope and FACS uncover that neuronal cells also produce IFNβ in response to TDP-43 abnormality in addition to microglia. This is supported by observations using the SH-SY5Y cell lines and patient iPSC-motor neurons, in which phosphorylation of STAT1 correlates with exacerbated LDH release and programmed axonal degeneration. Of note, these neuronal cell-autonomous degenerative cascades as well as TDP-43 pathology can be protected using IFNAR1 neutralisation antibody or FDA-approved JAK inhibitors.
Conclusion: We demonstrate a rationale to target IFN-I singalling to intervene in TDP-43 pathogenesis, which will be foundational for development of novel brain penetrant options to new clinical trials for ALS/FTD.

Wednesday 02:45 PM-03:00 PM
Alastair Fortune
Multiple sclerosis-associated gene variants produce motor dysfunction when introduced into C57BL/6 mice

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Multiple sclerosis (MS) is a complex polygenic disease with no accurate preclinical model. We aimed to determine whether the introduction of one or more MS-associated rare gene variants into the mouse genome, was sufficient to produce an MS-like phenotype. Blood samples were collected from 13 people across 2 families with high incidence of MS, and the DNA isolated for whole genome sequencing. Genome alignment, GATK variant calling and frequency filtering identified 2 potentially highly deleterious (CADD > 15), rare, missense variants in the affected members of Family-1, and 6 in Family-2. These individual variants were introduced into the mouse genome using CRISPR-Cas9 gene editing technology to produce 8 novel mouse lines carrying MS-associated variants. Mice underwent behavioural phenotyping (rotarod, digigait and beam-walk) and welfare monitoring for 1 year before tissue was collected for immunohistochemical or electron microscopic analyses. All mouse lines were fertile and followed a normal weight trajectory. Motor testing revealed that mice carrying the 2 gene variants from Family-1 have impaired motor function on the rotarod (p 0.0001), beamwalk and digigait tests. Mice carrying individual Family-2 gene variants have normal motor function, however, mice carrying all 6 variants from Family-2 are yet to undergo behavioural phenotyping. We have identified 8 novel MS-associated familial gene variants and successfully introduced them into C57BL/6 mice. These mice are viable, and the mice carrying the variants of Family-1 develop a spontaneous motor phenotype. Further histological characterisation will determine whether these mice recapitulate other aspects of MS pathophysiology.

03:00 PM-03:15 PM
Andrew Tosolini
BDNF-dependent modulation of axonal transport is selectively impaired in Motor Neuron Disease

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4. Comparative Neuromuscular Disease Laboratory, Department of Clinical Sciences and Services, Royal Veterinary College , University of London, London, United Kingdom
Axonal transport ensures long-range delivery of essential cargoes between proximal and distal compartments, and is needed for neuronal development, function, and survival. Deficits in axonal transport have been detected at pre-symptomatic stages in the SOD1G93A and TDP-43M337V mouse models of motor neuron disease (MND), suggesting that impairments in this critical process are fundamental for disease pathogenesis. Strikingly, in MND, fast motor neurons (FMNs) degenerate first whereas slow motor neurons (SMNs) are more resistant, and this is a currently unexplained phenomenon.
The main aim of this investigation was to determine the effects of brain-derived neurotrophic factor (BDNF) on in vivo axonal transport in different α-motor neuron (MN) types in wild-type (WT) and SOD1G93A mice.
We report that despite displaying similar basal transport speeds, stimulation of wild-type MNs with BDNF enhances in vivo trafficking of signalling endosomes specifically in FMNs. This BDNF-mediated enhancement of transport was also observed in primary ventral horn neuronal cultures. However, FMNs display selective impairment of axonal transport in vivo in symptomatic SOD1G93A mice, and are refractory to BDNF stimulation, a phenotype that was also observed in primary embryonic SOD1G93A neurons. Furthermore, symptomatic SOD1G93A mice display upregulation of the classical non-pro-survival truncated TrkB and p75NTR receptors in muscles, sciatic nerves, and Schwann cells. Altogether, these data indicate that cell- and non-cell autonomous BDNF signalling is impaired in SOD1 G93A MNs, thus identifying a new key deficit in MND.

Wednesday 03:15 PM-03:30 PM
Kay Double
Openness Agreements in Animal Research: a new era of transparency

Kay Double1
1. University of Sydney, Camperdown, NEW SOUTH WALES, Australia
Objective: The use of animals in research is tacitly approved by the community on the basis that such work is completed in a humane, ethical manner in line with appropriate animal protection regulations and for the purpose of improving welfare of people, animals or the environment. In recent years the community has sought more information about how animals are used in research; an Australian survey in 2022 found 82% of respondents want institutions to be more transparent about their use of animals. One way to achieve this is an Openness Agreement on Animal Research. Method: This presentation explains the purpose and format of such an agreement and discusses how Openness Agreements have been used internationally to support organisations which conduct, fund or are otherwise associated with the use of animals in research and teaching to promote openness and support well-informed public discussion of this area. The aims and commitments of the Openess Agreement on Animal Research and Teaching in Australia which will be launched by The Australian Council for the Care of Animals in Research and Teaching in August 2023 will be discussed, as well as how such initiatives can benefit animals in research and neuroscience researchers who use animals in their research.
*Kay Double is Chair of University of Sydney's Animal Ethics Committee 1 and a member of the ANS Animals in Research Committee.

03:30 PM-04:00 PM
Break
Afternoon Tea, Exhibition and Poster Display

04:00 PM-05:00 PM
Michael Breakspear
ANS Plenary Lecture - Sponsored by Queensland Brain Institute, University of Queensland
Great Room 1/2/3

05:00 PM-06:00 PM
Plenary
ANS Annual General Meeting & Tribute to Alan Mackay-Sim

06:00 PM-07:00 PM
Plenary
ANS Student-EMCR Networking Event
Foyer
Registration required

07:00 PM-10:30 PM-Social
ANS Party
WET Deck
ANS PartySUN & WET Decks, W BrisbaneRegistration requiredDinner Entertainment sponsored by Queensland Brain Institute, University of Queensland

Thursday 7/12/2023

09:00 AM-10:00 AM-Panel
Marcello Rosa
Equity and Diversity Panel
Great Room 1/2/3

10:00 AM-10:30 AM
Break
Morning Tea, Exhibition and Poster Display

10:30 AM-12:15 PM
Marcello Costa; Elspeth McLachlan
Symposium 9: On their shoulders: Australian neuroscience pioneers
Great room 1

Laurie B Geffen1
1. University of Queensland / Flinders University, East Brisbane, QLD, Australia
Australasian neuroscience began around the turn of the 20th century. For the first 50 years it was conducted by individual pioneers who mostly contended with the tyranny of distance from major international centres by working overseas for significant periods.
By the 1960s several neuroscience groups had emerged in university departments that were focussed on particular disciplinary areas of strength. More recently, interdisciplinary neuroscience centres and institutes have been established that now provide the wide base of basic and applied research that is manifest in the flourishing Australasian Neuroscience Society of today.
The symposium will address the role of some individual pioneers who contributed to these developments.

10:30 AM-10:55 AM
Glenda Halliday
Australasian women neuroscientists

As in other scientific disciplines, Australian women have primarily been involved in neuroscience as assistants at the bench and their contribution was only rarely recognized. A google search identifies 14 Australian women neuroscientists on FamousFix, 4 active in Australia, 5 retired, and 3 deceased. One active and all retired women were ANS members. Since ANS was formally established in 1980, Council included women from the beginning (4 current). Some acted as National Secretary (McLachlan, Potter, Young, Turnley, Double) or Treasurer (Dunlop, Phillips, Vukovic) with 5/23 presidents being women (McLachlan (9th), Halliday (14th), Dunlop (16th), Richards (20th) and now Keast (23rd)). The scientific contribution of women has been recognized by their selection as ANS Plenary Lecturers. The first was Beazley in 1989 (9th Plenary), and then Judy Morris (1999), McLachlan (2001), Dunlop (2006), Young (2012) and Margaret Morris (2013). Whereas some other invited lecturers have been women, the most prestigious has remained male dominated (34/40). Only 3 women have achieved Honorary Membership (/29) and only one woman the Distinguished Achievement Award (/12). However, the role of female neuroscientists has clearly been increasing and we can expect this to continue as about 50% of the contributors to ANS meetings now are women.

10:30 AM-11:20 AM
John Furness
Pioneering Australasian assaults on the neuroscience mountains of knowledge

The talk will begin with some very brief vignettes of early Australian Neuroscientists. It will then concentrate on two, Campbell and Eccles. Snowy Campbell (1868 to 1937) was born in the rich wheat growing district close to Canberra. In 1868, Murrumburrah had the same number of shops as it had public houses, 3 of each. Snowy was a remarkable individual whose achievements were singularly impressive, but were more-or-less lost due due to antagonism and remoteness from centres of intellectual activity in the northern hemisphere. Mervyn Eadie contends that Campbell was the greatest neuroscientist Australia ever produced. High praise indeed, considering that Jack Eccles won the Nobel Prize. John Carew (Jack) Eccles (1903 to 1997) came from country Victoria to study at Melbourne University. He won a Rhodes scholarship to Oxford where he studied under Sherrington. After a brief period as Director of the Sydney Kanematsu Institute, which also housed Kuffler and Katz, all three fleeing impending war in Europe, he took up the chair of Physiology at Dunedin, NZ. Eccles was a protagonist and then a convert in the Spark versus Soup controversy of synaptic transmission. I will discuss both the scientific and philosophical sides of Jack Eccles

Thursday 11:20 AM-11:45 AM
William Blessing
Lithium treatment for mania: John Cade's discovery re-interpreted

11:45 AM-12:15 PM
Laurence Geffen
Raymond Dart's paradigm shift on the evolution of the human brain

Raymond Dart (1892-1998) was born in Brisbane and educated at the University of Queensland and Sydney University. His seminal paper in Nature in 1925 Australopithecus africanus: The Man-Ape of South Africa challenged the prevailing paradigm that homo sapiens evolved in Europe and Asia from large brained hominids resembling the Piltdown fossil. Dart described much more ancient and smaller brained African fossils, which he named Australopithecines. He concluded their upright bipedal posture and apposable thumbs, allowing power and precision grips, enabled migration from forests to savannah with its attendant challenges. These challenges were met in part by the use of tools, the development of which became a driver for the sequent expansion of the human brain. Recent associated fossil and tool findings elsewhere in Africa, dating 2.5 to 3 million years ago, have lent credence to his foresight.

Thursday 10:30 AM-12:15 PM

Selected Orals 5: Neurodegeneration

Great room 2

10:30 AM-10:45 AM
Max Dierich

Protecting Motor Function Through the Stimulation of IL-6 Signalling Following Traumatic Brain Injury.

Max F.J Dierich1, Emily F Willis1, Jana Vukovic1, 2
1. School of Biomedical Sciences, University of Queensland, St Lucia, QUEENSLAND, Australia
2. Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia

Traumatic brain injury (TBI) frequently leads to neurological dysfunction, due to brain damage arising from both the primary impact of the injury, and the secondary spread of tissue damage. Our lab has previously shown that the secondary injury can be significantly reduced by local stimulation of interleukin-6 (IL-6) trans signalling using the designer fusion protein, HyperIL-6. In a closed cortical impact (CCI) model of TBI, local injection of HyperIL-6 spared neurons in the secondary injury site from cell death and markedly improved functional outcomes (Willis et al., 2020). However, it was unclear whether (1) HyperIL-6 treatment was neuroprotective at the primary injury site; and (2) whether diffuse stimulation of IL-6 trans signalling would be neuroprotective following TBI. Here, we used CCI to injure the motor cortex of adult C57Bl6 mice, and stimulated IL-6 trans signalling one day after injury by injecting HyperIL-6 either locally (into the cerebral ventricles), or intravenously (IV). Motor function was tested behaviourally for up to 30 days post injury. With either local or IV delivery of HyperIL-6, we saw long-lasting protective effects, with mice performing significantly better than saline-treated controls in fine motor tasks, up to 30 days post injury. These findings indicate that both central and peripheral stimulation of IL-6 trans signalling is neuroprotective following TBI.

10:45 AM-11:00 AM
Sarah Hellewell

Plasma lipid profiles on admission and one month after mild traumatic brain injury: results from a community cohort

Sarah C Hellewell1, 2, Harrison Szemray3, Aleksandra Gozt1, Chidozie Anyaegbu1, 2, Melissa Licari4, Nathan Lawler3, Michael Bynevelt5, Carmela Pestell6, Daniel Fatovich7, 8, Luke Whiley3, Melinda Fitzgerald1, 2
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4. Telethon Kids Institute, West Perth, Western Australia, Australia
5. Neurological Intervention and Imaging Service of Western Australia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
6. School of Psychological Science, The University of Western Australia, Crawley, Western Australia, Australia
7. Emergency Medicine, The University of Western Australia, Crawley, Western Australia, Australia
8. Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research, Nedlands, Western Australia, Australia

Mild traumatic brain injury (mTBI) causes damage to the axonal cytoskeleton, shedding lipids into the blood. This study aimed to examine lipidomic profiles following mTBI, or determine whether lipid alterations relate to cognitive outcomes, persistent symptoms and/or white matter structure. 30 participants with mTBI were examined at 48h (inception) and 28d (follow-up). Plasma was sampled alongside assessment of cognition (RBANS, Trail Making Tests A&B), and mood (DASS). 37 control participants underwent assessment at one timepoint. Plasma lipid concentrations were determined by liquid chromatography-mass spectrometry and correlated with cognition and mood. A sample of participants with mTBI underwent MRI scans at 30d, to examine relationships between lipids and FA in white matter tracts. The top 10 of 800 detected lipids were analysed. Lipid concentrations were similar to control at inception. At 28d there were decreased concentrations of monoacylglycerols(14:0, 18:3, 22:4) and diacylglycerol(20:0/20:20) (p0.001 vs. inception&control). We found increased concentrations of ceramide(26:0), hydroxyceramides(14:0, 16:0 & d18:0/26:0), sphingomyelin(14:0) and phosphatidylcholine(18:0/18:2) (p0.001 vs. inception&control). At inception, sphingomyelin(14:0) correlated with depression and anxiety scores and hydroxyceramides(d18:0/26:0 and 16:0) correlated with visuospatial perception. At follow-up, hydroxyceramide (d18:0/26:0) correlated with immediate memory and ceramide(26:0) correlated with processing speed. Significant correlations were found between lipids and FA of the corticospinal tract and posterior limb of the internal capsule. Linear regression revealed that concentrations of hydroxyceramide(14:0), sphingomyelin(14:0), phosphatidylcholine(18:0/18:2) and ceramide(26:0) could significantly predict FA alteration. These data suggest that plasma lipid concentrations may be dynamic biomarkers for mood alteration, cognitive deficits and white matter alteration following mTBI.

Thursday 11:00 AM-11:15 AM

Katie Lewis
Are Oligodendrocytes An Under-Appreciated Therapeutic Target in ALS?

Katie Lewis1, Georgina Craig2, 3, David Gonsalvez4, Bradley Turner1, Samantha Barton1
1. The Florey Institute, Melbourne, VIC, Australia
2. Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada
3. UK Dementia Research Institute, University of Edinburgh, Edinburgh, Southeastern Scotland, UK
4. Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia
Introduction: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterised by the degeneration of motor neurons. However, the surrounding glia, including oligodendrocytes also exhibit ALS pathology, suggesting an undiscovered and underappreciated role in disease. If oligodendrocytes and myelin are intrinsically dysfunctional, could they provide a therapeutic target? To address this, we have extensively characterised oligodendrocyte dysfunction and altered myelin behaviours in the clinically relevant TDP-43Q331K ALS mouse.
Methods: TDP-43Q331K mice (ALS; n=3-6) and wildtype littermates (WT; n=3-6) were collected pre-symptomatically, symptomatically, and at end-stage. Using a combination of EdU and BrdU, oligodendroglial cell density, proliferation, and differentiation were tracked over time in the dorsal column, ventral white matter, and ventral grey matter of the lumbar spinal cord. Myelin was examined using a combination of Spectral Confocal Reflectance Microscopy and electron microscopy (EM).
Results: In end-stage mice there were significant increases in oligodendrocyte precursor cell (OPC) density, and oligodendrocyte proliferation and differentiation in the ventral grey matter in the ALS mice compared to WT (p0.05). Both SCoRe and EM revealed that myelin density was significantly increased in the dorsal column of ALS mice (p0.05). No significant changes were found pre-symptomatically or during early symptom onset.
Conclusion: We are the first to characterise the oligodendrocyte lineage and myelin in a TDP-43 related ALS mice. Our data suggest that OPCs and oligodendrocytes display altered pathology in their proliferation and myelin generation, suggesting that they are indeed impacted in ALS and garner further exploration into their potential use as a therapeutic target.

11:15 AM-11:30 AM
Tessa Onraet
Axons eject damaged mitochondria in response to mitochondrial DNA damageegenerative changes in mice

Tessa Onraet1, Anne Hahn1, Annabel Grosser1, Chuan Yang Dai 1, Steven Zuryn1
1. Queensland Brain Institute , The University of Queensland, Brisbane , QLD, Australia
The nervous system is an energetically expensive system to run. To operate correctly, neurons require a highly functional and efficient network of mitochondria that produce ATP, the cell's energy currency. Neurons with chronic mitochondrial dysfunction, which can be caused by defects in the mitochondrial genome (mtDNA), exhibit metabolic deficits, impaired synaptic transmission, and impaired autophagic clearance, among other cellular phenotypes. Such chronic mitochondrial dysfunction is known to contribute to neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. How neurons, with their uniquely dramatic morphology, maintain a healthy population of mitochondria throughout their extended dendritic and axonal compartments is not fully appreciated. Through investigating the mechanosensory neurons of Caenorhabditis elegans, we report a novel axon-specific mechanism of selective mitochondrial quality control. In the presence of mtDNA damage, dysfunctional organelles are packaged into large vesicle-like structures, called mitophers, that bud off from the axon. Mitophers appear to effectively enable the ejection of genetically damaged mitochondria from the axons of neurons. Genetic screens have revealed multiple molecular factors that are required for the process, providing insight into how mitophers are formed and their eventual fate after ejection. The ability to selectively remove damaged mitochondria from the axon may represent an innate and manipulatable mechanism through which the neuron can maintain a healthy mitochondrial population in distal processes, ultimately maintaining optimal neuronal function.

11:30 AM-11:45 AM
Matilde Balbi
Induced gamma oscillations facilitate functional synaptic plasticity acutely after stroke

Matilde Balbi1, Cong Wang1, Montana Samantzis1
1. Queensland Brain Institute, The University of Queensland, Brisbane, QUEENSLAND, Australia
Background: Oscillatory brain patterns undergo significant changes in various neurological disorders, including stroke. Recently, gamma-range evoked neural oscillations have shown promise in restoring and maintaining intrinsic homeostatic processes in the brain. However, the precise causal relationship between stimulation and the restoration of brain function remains poorly understood.
Objective: This study aimed to elucidate the mechanisms underlying the observed neuroprotective effects following optogenetic stimulation at 40 Hz. We investigated the electrophysiology and genomic profiling of inhibitory neurons to gain insights into the therapeutic potential of gamma-wave modulation in the acute phase after stroke.

Method: We used optogenetic stimulation together with laser speckle imaging, electrophysiology, and RNA sequencing in a photothrombotic stroke model in awake mice, to investigate the effects of gamma-waves modulation in the acute phase after stroke.
Result/Conclusion: our findings demonstrate that optogenetic stimulation at 40 Hz specifically drives activation of inhibitory neurons. Furthermore, we observed that following stroke induction in the motor area (M1), 40 Hz stimulation enhances interregional communication between M1 and the parietal association area (PTA). Remarkably, this effect persists even 24 hours after stimulation. Cross-correlogram analysis revealed that optogenetic stimulation of inhibitory neurons in the gamma range leads to an increase in functional synaptic plasticity observed 24 hours after stroke induction. These results indicate that modulating cortical oscillatory dynamics may serve as a promising neuroprotective strategy after stroke by influencing synaptic connections.

Thursday 11:45 AM-12:00 PM
Igor Bonacossa-Pereira
A molecular switch in the skin protects the axons from degenerating

Igor Bonacossa-Pereira1, Sean Coakley2, Massimo Hilliard1
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2. School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia
In living organisms, the delicate neurites of touch-sensing neurons attach to and are embedded within the skin. Throughout life, they are continuously challenged with movement-induced strain, yet their integrity is maintained throughout life. This suggests the existence of an unknown, specialized neuroprotective mechanism shielding these structures from damage. Using C. elegans, we have revealed that the membrane-associated cytoskeletal spectrin network functions within the skin, in synergy with the small GTPase RAB-35, to stabilize neuron-epidermal attachment structures. This protects the axons of touch-receptor neurons against movement-induced damage caused by mechanical strain. In this context, RAB-35 activity induces axonal damage, however its full suite of activators is unknown. Here, through an unbiased forward genetic screen we have identified a guanine nucleotide exchange factor (GEF), AGEF-1, previously associated with the endocytic-recycling machinery, which impacts axonal maintenance. We show that AGEF-1 functions within the skin to promote RAB-35-induced axonal damage. Moreover, we demonstrate that the function of this GEF is highly conserved, with expression of its human ortholog ARFGEF2 able to promote axonal damage. We propose that AGEF-1 is a novel activator of RAB-35 and promotes axonal damage by modulating RAB-35 activity. Taken together, our data supports a model where the skin fine-tunes the maintenance of touch-receptor neurons by controlling cell-cell adhesion in response to movement.

12:00 PM-12:15 PM
Tim Sargeant
Autophagy decreases in the ageing mouse brain in a sex dependent manner

Lexi Martin1, Julien Bensalem1, Kathryn Hattersley1, Leanne Hein1, Sofia Hassiotis1, Tim Sargeant1
1. South Australian Health and Medical Research Institute, Adelaide, SA, Australia
Ageing is the most important risk factor for neurodegenerative diseases that cause dementia such as Alzheimer's disease. Alzheimer's disease is also genetically linked to an intracellular process called autophagy, which is responsible for suppressing hallmarks of biological ageing such as the build-up of protein aggregates. Previous research has shown decreases in brain autophagy proteins with ageing, indicative of an age-related decrease in autophagy. Despite this, no study has directly measured flux of waste material through the autophagy-lysosomal pathway and related this to ageing in the mammalian brain. To address this gap, we used the tandem-fluorescent-LC3 reporter mouse (tf-LC3) that expresses a ratiometric fluorescent probe to measure autophagic flux in the brain. As ageing, sex, and obesity all impact the risk of developing dementia in humans, we analysed autophagic flux in mouse brains at 6-, 12-, and 18-months of age, in both male and female mice, and with or without diet-induced obesity. We found an age-related decrease in autophagy in the brain in male mice only. Female mice did not display the same relationship between autophagic flux and age in the brain. Despite detecting obesity-related changes in autophagy in the heart, we did not find significant obesity-related changes in autophagy in the brain. These results show that maintaining autophagy in the brain with ageing could be of benefit. However, our results show that autophagy's relationship with brain ageing appears to be sex-dependent and this will likely impact its use as a therapeutic target relevant to neurodegeneration.

Thursday 10:30 AM-12:15 PM

Selected Orals 6: Autonomic/Glial/Limbic

Great room 3

10:30 AM-10:45 AM
Balazs Hangya
The role of basal forebrain cell types in classical conditioning

Panna Hegedus1, 2, Balint Kiraly1, 3, Katalin Sviatko1, 2, Anna Velencei1, Sergio Martinez-Bellver1, 4, Daniel Schlingloff1, Victoria Lyakhova1, Balazs Hangya1
1. Institute of Experimental Medicine, Budapest, BUDAPEST, Hungary
2. Semmelweis University, Budapest, Hungary
3. Eotvos Lorand University, Budapest, Hungary
4. University of Valencia, Valencia, Spain
Basal forebrain cholinergic neurons (BFCNs) play an important role in associative learning, suggesting that BFCNs may participate in processing stimuli that predict future outcomes. At the same time, parvalbumin (PV)-expressing GABAergic neurons of the basal forebrain (BFPVNs) were proposed to serve as a rapid and transient arousal system. To better understand the cell type specific contributions of basal forebrain neurons to these cognitive processes, we performed bulk calcium imaging and recorded spiking of optogenetically identified neurons of mice performing a probabilistic Pavlovian cued outcome task. BFCNs responded to sensory cues that were often paired with reward. Reward delivery also activated BFCNs, with surprising rewards eliciting a stronger response, while punishments evoked uniform positive-going responses. The extent of cue-driven cholinergic activation predicted sequent decision speed, suggesting that the expectation-gated cholinergic firing is instructive to reward-seeking behaviors. In contrast to BFCNs, BFPVNs responded with a gradual increase of firing rate to reinforcement-predicting stimuli and a distinctive, phasic activation to punishment, while reward only elicited slow and delayed responses. Bulk calcium imaging performed in major termination regions indicated that BFPVNs broadcast aversive information to multiple downstream targets including the medial septum, the hippocampus and the retrosplenial cortex. Optogenetic blocking of the cue-induced activation of BFCNs or the punishment-induced activation of BFPVNs prevented the formation of cue-outcome associations, suggesting a causal role of these neurons in associative learning.

10:45 AM-11:00 AM
Samantha Dando
Defining the regional heterogeneity of resident immune cells within the healthy central nervous system and its bordering tissues

Fazeleh Etebar1, Damien Harkin2, Paul Whatmore3, Samantha J Dando1
1. Centre for Immunology and Infection Control, School of Biomedical Sciences , Queensland University of Technology, Brisbane, QLD, Australia
2. Centre for Vision and Eye Research, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia
3. eResearch Office, Research Infrastructure, Queensland University of Technology, Brisbane, QLD, Australia
The central nervous system (CNS) comprises highly specialized and functionally distinct tissue compartments; however, further research is required to understand how resident immune cells are adapted to different regions of the neural parenchyma and its bordering tissues. This study investigated the transcriptomic heterogeneity of microglia within different regions of the healthy adult mouse CNS, including the olfactory bulbs, cerebral cortex, hippocampus, cerebellum and retina. Furthermore, we generated a single cell transcriptomic atlas of leukocytes within the mouse pia mater and choroid, which anatomically juxtapose the brain parenchyma and retina respectively. Bulk RNA-sequencing of freshly isolated microglia demonstrated region-specific transcriptomic profiles. Genes related to antigen presentation, phagocytosis and chemokine signalling were among the top differentially expressed genes between microglia populations. Single cell RNA-sequencing sequently revealed that the examined CNS regions contained a mixture of homeostatic microglia and unique microglia clusters, including small clusters of functionally specialised interferon-responsive microglia, chemokine-enriched microglia, and apolipoprotein-enriched microglia. These unique clusters were found in the highest frequency within the olfactory bulbs, and were spatially validated in brain tissue using immunofluorescent staining and confocal microscopy. External to the neural parenchyma, the pia mater and choroid of the eye also demonstrated tissue-specific resident immune cell populations and gene expression signatures, which potentially represent functionally specialised immunological borders to protect the underlying brain and retina. Taken together, these findings reveal the regional heterogeneity of microglia within the healthy mouse brain and retina, and enhance our understanding of the diversity of resident immune cells within the CNS bordering tissues.

11:00 AM-11:15 AM
Dominic Kaul
Single-cell and spatial analysis of astrocytes in the human brain: understanding stress and psychiatric disorders

Dominic Kaul1, Amber R Curry1, Nathalie Gerstner2, 3, 4, Anna S Fröhlich2, 3, Michael J Ziller2, 5, Elisabeth B Binder2, Janine Arloth2, 4, Sibylle G Schwab6, Naguib Mechawar7, Lezanne Ooi1, Natalie Matosin1
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5. Department of Psychiatry, University of Münster, Münster, Germany
6. School of Medical Indigenous and Health Sciences and Molecular Horizons, University of Wollongong, Wollongong, New South Wales, Australia
7. Douglas Institute, Department of Psychiatry, McGill University, Montreal, QC, Canada
Severe stress is the strongest environmental risk factor for the development of psychiatric disorders. In rodent models of stress and psychopathology, astrocytes are strongly affected, yet we have limited knowledge of if and how this translates to humans. To explore human-specific effects of stress on astrocytes in psychopathology, we first combined single nucleus RNAseq (n=87) and spatial transcriptomics (Visium; n=13) in the human postmortem orbitofrontal cortex (BA11) from individuals with psychopathology (schizophrenia, bipolar disorder and depression) exposed to stress in childhood or adulthood and matched controls. Analysis of >100,000 astrocytes revealed grey matter astrocytes, which are involved in clearing glutamate, were increased in psychopathology. Morphological analysis with fluorescent immunostaining of >10,000 cells positive for EAAT2 (an astrocyte glutamate transporter), revealed significantly increased cell size in psychopathology (Padj0.01), and increased density of grey matter EAAT2+ cells specifically in cases with a history of childhood stress (P0.05). We next explored the functional response of human astrocytes to dexamethasone to mimic the cortisol response. Astrocytes were differentiated from pluripotent stem cells and exposed to 100nM dexamethasone for 1-7 days. Neurotransmission was assessed with clearance assays (ELISA), glutamate receptor expression (qPCR), and signalling response (whole-well ratiometric Ca2+ imaging). Stimulation of iAsts transiently reduced glutamate transport (P0.001) and altered expression of neurotransmitter receptors (P0.05), most notably reducing unit 3/4 of the AMPA receptor. These results together suggest that the homeostatic roles of astrocytes at the synapse are altered in psychiatric disorders, and this may be particularly exacerbated by stress experienced early in life.

Thursday 11:15 AM-11:30 AM
Liviu-Gabriel Bodea
Alteration of protein synthesis in dementia-related pathologies

Liviu-Gabriel Bodea1, Alison K Carlisle1, Jürgen Götz1
1. Clem Jones Centre for Ageing Dementia Research (CJCADR), Queensland Brain Institute (QBI), The University of Queensland, St Lucia, QLD, Australia
Frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) are highly prevalent neurodegenerative disorders characterized by the accumulation of intraneuronal microtubule-associated Tau protein and extracellular amyloid-β (Abeta) deposits. To gain novel insights into the underlying cellular and molecular dysregulations associated with FTLD and AD, we employed cutting-edge approaches combining bioorthogonal labelling with click chemistry and proteomic analysis.
Our methodology allowed us to precisely tag and identify pathological changes in the synthesis of new proteins, shedding light on the disease mechanisms. Our in vivo investigations revealed that Aβ triggers de novo protein synthesis of Tau through a Tau-dependent pathway (Li & Götz, EMBO J 2017). Furthermore, we recently reported that Tau itself impairs the translation process (Evans et al., EMBO J 2019) and ribosomal biogenesis (Evans et al., Acta Neuropathol Commun 2021), adding to the complexity of the disease pathogenesis.
In our ongoing work, we have extended these techniques to microglial cells (Carlisle et al., STAR Protocols 2023), and our preliminary findings have shown an Abeta-induced alteration in the microglial de novo proteome. Our results suggest a potential involvement of the integrated stress response cellular pathway in AD-related microglial dysfunction.
Together, our findings provide novel insights into the cellular dysregulations contributing to FTLD and AD pathogenesis. By targeting the mechanisms underlying protein synthesis and its associated cellular responses, our research could lay the foundation for future therapeutic strategies aimed at halting or mitigating the progression of these devastating neurodegenerative diseases.

11:30 AM-11:45 AM
Andrew Butler
Vagal Nerve Stimulation, Interoception, and Anxiety: Insights from Nucleus of the Solitary Tract (NTS) Activation in Rodents.
Andrew G Butler1, 2, Mariana Del Rosso de Melo1, Angela Connelly1, Andrew Allen1, Stuart McDougall2
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Vagal nerve stimulation (VNS) affects memory and measures of anxiety in rodents. The nucleus of the solitary tract (NTS) receives vagal afferent input and projects to the locus coeruleus (LC), this pathway is thought to underlie the involvement of the NTS in modulating anxiety-like behaviour, though evidence for this is lacking. To investigate the NTS's role in modulating interoceptive associated behaviours, we short circuited VNS by employing optogenetic techniques to stimulate the NTS directly and its projections to the LC. Sprague Dawley rats were transfected with either AAV2-CAG-CHR2-mCherry (n=13) or AAV2-CAG-mCherry(n=11) to enable optical activation within the NTS. Behavioural assessments were conducted using elevated plus maze (EPM) and a novelty suppressed feeding test (NSFT), with optical stimulation of the NTS or its projections to the LC preceding each test for 5 minutes. The results demonstrated that optogenetic stimulation of NTS cells induced a small, immediate tachycardia (12±18 BPM), while the animals displayed a significant anxiogenic phenotype in the NSFT compared to the control group (time to eat in maze centre: 344±177 s vs. 164.64±89.6 s, respectively). Interestingly, rats receiving NTS stimulation ate less food after the novelty suppressed feeding test (food consumed: 2.75±0.96 g vs. 4.04±1.23 g, respectively) suggesting an effect on appetite/satiety. However, this post-test feeding effect was not observed when activating projections from the NTS to LC. These data demonstrate a direct role for the NTS to LC circuit in anxiety-like behaviour and provides a foundation for identifying the central network responsible for VNS effects.

Thursday 11:45 AM-12:00 PM
Darren Clarke
Exclusive regulation of specific hippocampal inhibitory synapses by distinct types of astrocytes

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2. Groupe de recherche sur la signalisation neurale et la circuitrie, , Université de Montréal, Montréal, QC, Canada
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4. Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Montréal, Canada
Astrocyte functional heterogeneity within a given neuronal circuit, especially concerning synaptic interactions at tripartite synapses, remains largely undetermined. Here, we examine multiple physiological characteristics of astrocytes distinguished by their specific spatial relation to synapses made on distinct hippocampal CA1 pyramidal cell domains: astrocytes covering the peri-somatic area in stratum pyramidale (SP), or the apical dendritic area in stratum radiatum (SR). Whole-cell dye-filling and confocal imaging showed a typical bushy organisation of SR astrocyte processes while those of SP astrocytes were more polarised. SR astrocytes formed a larger syncytium and displayed lower input resistance relative to SP astrocytes. Ca2+ imaging of SP and SR astrocytes in slices revealed that SR astrocytes displayed Ca2+ events with greater frequency, duration, and synchronicity, but reduced amplitude, in comparison to SP astrocytes. Using patch-clamp electrophysiology and the territorial segregation of somatostatin (dendritic) and parvalbumin (peri-somatic) inhibitory synapses, we observed that the selective activation (hM3Dq DREADD) or blockade (intracellular BAPTA) of two populations of astrocytes regulate inhibitory synapses in their own syncytial territory. Furthermore, each group of astrocytes also selectively regulate long-term depression generated discretely at each inhibitory synaptic region. These results indicate a domain-specific regulation of inhibitory synapses by distinct SP and SR astrocyte syncytia. Overall, our findings reveal a functional specialisation of distinct astrocyte types in the hippocampus, highlighting functional heterogeneity of astrocytes and their regulation of hippocampal synaptic networks underlying learning and memory.

12:00 PM-12:15 PM
Bridget Callaghan
Unveiling the Complexity of Gut-Brain Interactions: Microbiome-Brain Communication and Internalizing Symptoms in Youth

Bridget Callaghan1, Francesca Querdasi1, Jessica Uy1, Jennifer Labus1, Ai Peng Tan2, Birit Broekman2, Peter Gluckman2, Fabian Yap3, Yap Seng Chong2, Helen Chen2, Marielle Fortier2, Lourdes Mary Daniel4, Johan Eriksson2, Shirong Cai2, Jia Ying Toh2, Keith Godfrey5, Michael Meaney2
1. University of California Los Angeles, Los Angeles, CA, United States
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4. Duke-National University of Singapore Medical School, Singapore
5. Department of Epidemiology, University of Southampton, Southhampton
Mounting evidence shows that bidirectional communication between the gut microbiome and brain impacts human mental health. However, the mechanisms underlying those interactions remain elusive, especially during development when the gut microbiome and brain undergo significant maturational change. This longitudinal community-based study (N = 66) aimed to unravel the interplay between these complex systems, with a specific focus on how the gut microbiome interfaces with neural networks underlying internalizing symptomatology.
We assessed stool community microbiome composition at 2 years of age, derived intra- and inter- network resting state functional connectivity metrics for 15 brain networks at 5.5 years of age, and collected proxy reports of child internalizing symptoms from parents at 7 years of age. Using multivariate sparse partial least squares (sPLS)

regression, we discovered a novel microbiome-brain communication signature'. This signature suggests a potential pathway of microbiome influence on later emerging neural processes, providing valuable insights into the early origins of gut-brain interactions.
Interestingly, the brain networks maximally associated with the microbiome did not overlap with those showing maximal associations with internalizing symptoms in 7-year-old children. It is plausible that the link between the gut microbiome and neural networks underlying mental health may evolve as children grow older, or that microbiome features with weaker connections to brain networks supporting mental health are present but were not detected using the data-driven approach we employed here. These findings underscore the complexity of gut-brain interactions and their relation to mental health in youth.

Thursday 12:15 PM-01:00 PM

Break

Lunch, Exhibition and Poster Display

Thursday 01:00 PM-03:00 PM
Nathalie Dehorter; Silvia Velasco

Symposium 10: ADNF Symposium: Development of cortical neurons and networks

Great room 1

Mary Tolcos1, Annalisa Paolino2, Denis Jabaudon3, Belal Shohayeb2
1. RMIT University, Melbourne
2. The University of Queensland, Saint Lucia, QLD, Australia
3. Geneva University, Geneva

The ANS Developmental Neuroscience Forum (ADNF) organisers propose a symposium on the development of the cerebral cortex. This symposium will bring together 4 speakers in understanding complementary aspects of cortical developmental processes. A/Prof Mary Tolcos is an expert in the role of molecular mechanisms regulating how the cortex is formed and will speak about her latest discoveries regarding the general processes of brain anatomy such as cortical folding. Dr Annalisa Paolino (QLD), will talk about the divergences that might have contributed to the evolution of specific brain properties and structures between mammalian lineages. Prof Denis Jabaudon (Switzerland), a renowned expert who has pioneered our understanding of neuronal diversity in the developing brain, will discuss the mechanisms underlying cortical cell specification. Dr Belal Shohayeb (QLD) will report on his latest findings on the importance of specific molecular mechanisms in spines to regulate developmental synaptic activity in the cortex.
The symposium will provide a very exciting update on our current understanding of brain development, and the talks will span several levels of analysis and model systems (i.e. mouse, ferret, marsupial). Given the overall importance of the cortex for cognitive function and neurodevelopmental disorders, and the extremely high quality of the speakers, this symposium will be of very broad interest to the ANS membership.

01:00 PM-01:25 PM
Mary Tolcos
What shapes our brain? Understanding the processes that drive cortical folding

Growth and expansion of the cerebral cortex is considered an evolutionary modification of Mammalia, underlying the emergence of intelligence. One fundamental feature accompanying growth of the cerebral cortex is the onset of surface folding, or gyrification. The brain of humans and other higher-order mammals is structurally district, with the gyrification pattern being unique to the individual, somewhat like a fingerprint. We now have a clear understanding of when and where cortical folds occurs, but we do not yet fully understand the basic mechanisms that drive gyrification. With funding provided by an ARC Future Fellowship, our interdisciplinary team of national and international researchers have been studying the cellular, molecular, and functional mechanisms that drive the complex process of cortical folding using a comparative biological approach (gyrencephalic versus lissencephalic species) and gold standard techniques. We have discovered that a set of genes, important for neuronal growth and development, are abnormally expressed in the cortical plate as the developing sheep brain folds and that neuroimaging markers may predict when and where a fold occurs. Ongoing research includes transcriptomic, advanced neuroimaging, and electrophysiological analysis beneath sulci and gyri, as well as the world-first development of ferret iPSC-derived cerebral organoids for gene manipulation studies.

01:25 PM-01:50 PM
Annalisa Paolino
Shared and divergent timings of neurodevelopmental dynamics shape the brains of placental and marsupial mammals

The precise pattern of generation and maturation of neocortical neurons is crucial for the correct development of the mammalian neocortex and its connections. Although placental and marsupial mammals share a transcriptional network controlling cortical neuronal projection fate, we have previously shown that the differential timing of expression of a transcription factor, Satb2, likely underlies the different strategies of interhemispheric connections adopted by these two lineages, via the corpus callosum or the anterior commissure, respectively (Paolino et al., 2020 PNAS). Our new study extends this work by exploring how the timing of distinct processes of development scale between mammalian species, namely cell birth, cell migration, axonal extension and axonal innervation. We performed EdU birthdating, retrograde tracing, in utero and in pouch electroporations to label and track the developmental processes in these two species. Our results show that the temporal scaling rules for each of the developmental processes are not uniform between lineages nor between different processes. We further identify which stages of maturation are plastic to timing differences across species versus those that have limitations and provide insight into how divergences in developmental timing between mammalian lineages might have contributed to the evolution of specific brain properties and structures.

Thursday 01:50 PM-02:15 PM

Denis Jabaudon
Temporal controls over neuronal diversity in the developing brain

The developing brain exhibits a remarkable diversity of neuronal cell types, each with specialized functions that contribute to the proper function of the mature brain. The mechanisms underlying the generation and specification of neuronal diversity during development are complex and incompletely understood. Here, we investigate temporal controls over this process by analyzing the developmental diversity of neuronal progenitors across multiple brain regions and developmental time points. Our results demonstrate that distinct spatial and temporal transcriptional programs control the timing and pattern of neuronal differentiation and specification during brain development. Our findings provide new insights into the mechanisms underlying neuronal diversity in the developing brain and suggest novel strategies for manipulating these processes to direct neuronal identity and connectivity.

02:15 PM-02:40 PM
Belal Shohayeb
BDNF regulates Wave Regulatory Complex nanodynamics and actin remodelling in spines

Post-synaptic dendritic spines are highly dynamic and undergo rapid enlargement in response to synaptic activity (structural plasticity). Long-term potentiation, the cellular basis of learning and memory, triggers branched actin polymerization adjacent to the post-synaptic density which is a major force driving spine enlargement and sustains structural plasticity. The WAVE Regulatory Complex (WRC), a pivotal branched actin regulator via the activation of Arp2/3, controls spine morphology and therefore structural plasticity. The underlying molecular mechanisms that mediate WRC-Arp2/3 activation during spine enlargement are largely unknown. WIRS motif containing proteins (WCPs) are required to localize the WRC at restricted membrane domains where it promotes WRC-Arp2/3 mediated branched actin polymerization. Here, we investigate the role of WCPs-WRC interactions in spine morphogenesis and synaptic activity in response to BDNF, a neurotrophic factor involved in synaptic plasticity. The disruption of WCPs-WRC interactions compromised spine maturation, synaptic activity and actin polymerization. Using single molecule tracking super-resolution microscopy, we found that BDNF constrains WCPs nanoscale dynamics and induces nanoclustering which in turn influences WRC distribution at the synaptic membrane. This study reveals a novel mechanism through which BDNF regulates synaptic activity by altering WCPs-WRC interaction/nano-distribution and triggering actin polymerization in spines.

02:40 PM-02:45 PM
Huan Liao
Data Blitz: Intergenerational and Transgenerational Effects of Paternal Immune Activation Induced by Lipopolysaccharides on Offspring Behaviors

Huan Liao1, Da Lu1, Anthony Hannan1, 2
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Publish consent withheld

02:45 PM-02:50 PM
Jamila Iqbal
Data Blitz: Dysfunctional Cell Migration Patterns in Schizophrenia Patient-Derived Olfactory Stem Cells: The Role of Impaired LMO7 Signalling Pathway

Jamila Iqbal1, Jing Yang Tee1, Alexandre Cristino1
1. Griffith University, Brisbane, QLD, Australia
Schizophrenia, a multifaceted neurodevelopmental disorder, has been associated with genetic factors influencing neuronal migration. Despite extensive research, the underlying molecular pathogenesis remains elusive. Olfactory neurosphere-derived ONS cells from patients exhibit distinctive migratory behaviour characterized by enhanced directional persistence and reduced turn angles compared to controls.
In this study, we employed a comprehensive protein-cell function interaction network approach to unveil the molecular pathways governing these phenomena. Differential expression profiling of proteins in patient ONS cells identified LMO7 as the most highly interconnected node in the network. Notably, LMO7 exhibited a negative correlation with dynamic functions (Persistence time and Directionality ratio-half-life) and a positive association with cytoskeletal measures. Validation of these findings encompassed spatiotemporal analysis of endogenous LMO7 expression, along with relevant focal adhesion and cytoskeletal proteins, in ONS cells. Furthermore, we employed Dicer strate siRNA knockdown of LMO7 in ONS cells to confirm its role in cell adhesion and migration. Disruption experiments involving LMO7 knockdown in both control and patient-derived ONS cells recapitulated schizophrenia phenotype.
Collectively, our results provide compelling evidence implicating LMO7 in in mediating essential cellular processes and corroborate its involvement in the Schizophrenia phenotype, as supported by the network analysis. These discoveries not only shed light on the neurodevelopmental mechanisms but also highlight LMO7 as a promising potential therapeutic target for Schizophrenia.

Thursday 02:50 PM-02:55 PM
Nafiseh Atapour
Data Blitz: Parvalbumin as a neurochemical marker of the primate optic radiation

Nafiseh Atapour1, Gaoyuan Ma1, Katrina worthy1, Cirong Liu2, Marcello Rosa1
1. Neuroscience Program, Biomedicine Discovery Institute and Department of Physiology, Monash University, Clayton, VIC, Australia
2. Center for Excellence in Brain Science and Intelligence Technology, Institute of Neuroscience, CAS Key Laboratory of Primate Neurobiology, Chinese Academy of Sciences, Shanghai, China
Parvalbumin (PV) is a calcium-binding protein that labels neuronal cell bodies in the magno- and parvocellular layers of the primate lateral geniculate nucleus (LGN). Here we demonstrate that PV immunohistochemistry can also be used to trace the optic radiation (OR) of the marmoset monkey (Callithrix jacchus) from its LGN origin to its destinations in the primary visual cortex (V1), thus providing a high-resolution method for identification of the OR with single axon resolution. The emergence of fibres from LGN, their entire course and even the entry points to V1 were clearly defined in coronal, parasagittal and horizontal sections of marmoset brain. In all cases, the trajectory revealed by PV staining paralleled that defined by high-resolution diffusion tensor imaging (DTI). We found that V1 was the exclusive target for the PV-containing fibers, with abrupt transitions in staining observed in the white matter at the border with area V2, and no evidence of PV-labeled axons feeding into other visual areas. Changes in the pattern of PV staining in the OR were detected following V1 lesions, demonstrating that this method can be used to assess the progress of retrograde degeneration of geniculocortical projections. These results suggest a technically simple approach to advance our understanding of a major white matter structure, which provides cellular resolution suitable for the detection of microstructural variations during development, health and disease. Understanding the relationship between PV staining and DTI in non-human primates may also offer clues for improving the specificity and sensitivity of OR tractography for clinical purposes.

02:55 PM-03:00 PM
Darryl Eyles
Data Blitz: Modelling increased dorsal striatal dopamine in the schizophrenia prodrome

Darryl eyles1, 2, Sunil Srivastav1, Zilong Du1, Xiaoying Cui1, 2, James Kesby1, 2
1. University of Queensland, St Lucia, QLD, Australia
2. Queensland Centre for mental health research, Brisbane, Qld, Australia
The most robust neurochemical finding reported in schizophrenia is an increase in dopamine uptake/synthesis/release restricted to the dorsal striatum. This abnormality predicts young adults who will progress from prodromal symptoms to clinical diagnosis. Dorsal striatal hyperdopaminergia increases further as the ject transitions to diagnosis.
We have developed two models replicating a progressive hyperdopaminergia across adolescence to young adulthood using virally-packaged constructs delivered to stantia nigra (which projects to the dorsal striatum) in adolescent wild-type rats. The 1st (EDiPs), uses human tyrosine hydroxylase and human GTP cyclohydrolase 1 to increase DA synthesis capacity. The second (ErsDiPs) increases nigral neuron resting state by administering a F-Flex dependent bacterial leaky sodium channel (NaChBac) to the nigra and a retrograde construct containing F-Flex to the dorsal striatum.
These models reproduce the progressive onset of behavioural phenotypes (amphetamine-mediated locomotion/impaired pre-pulse inhibition) mimicking the prodromal onset of symptoms in patients. ErsDiPs also reproduces spatial cognitive deficits. EDiPs reveals that that increasing dopamine synthesis capacity and release leads to pre-synaptic terminal alterations consistent with increased dopamine release along with alterations in cortical connectivity and acetylcholine production in the dorsal striatum.
The progressive onset of behaviours of relevance to the positive symptoms of schizophrenia make these models unique in their ability to model the schizophrenia prodrome and may a) prove useful in trialling new prophylactic agents and b) help us to understand the impact that adolescent hyperdopaminergia has on dorsal striatum function with regards to the onset of schizophrenia.

Thursday 01:00 PM-03:00 PM
Sarah Cohen-Woods; Heidi Walkden

Symposium 11: From flies to Fitbits: the new neuroscience of sleep

Great room 2

Deborah Apthorp1, Hannah Scott2, Bruno van Swinderen3, Laura Jacobson5, 4
1. University of New England , Armidale
2. Flinders University, Adelaide
3. The University of Queensland, St Lucia, QUEENSLAND, Australia
4. The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
5. University of Melbourne, Melbourne

The Australian Brain Alliance (ABA) aims to represent scientists across Australia, bringing researchers across scientific domains together with the intention to consolidate and enhance brain science and neurotechnology, and support our thriving early- to mid- career researchers. This symposium on the latest developments in sleep research represents an exciting area, and effectively covers these goals. While the importance of sleep in the maintenance of optimal brain function and good health is accepted, there remains insufficient understanding of how this works, how much sleep is enough', and why sleep varies so much among individuals or age groups. To fully grasp and understand sleep and its impacts requires consolidation of a wide range of neuroscience research, from monitoring behaviour and brain activity, to studying molecules and synapses. In this symposium we present a series of talks linking advances in sleep monitoring in humans, to understanding the fundamental biology of why we sleep, and why it is necessarily such a complex phenomenon. We begin with a talk relevant to most: how mild sleep restriction affects our attention. Focusing on EEG readouts, A/Prof. Deborah Apthorp will talk to region-specific changes in event-related potentials and brain oscillations related to jective sleepiness and sleep restriction-associated changes in vigilance performance. Moving beyond EEG, Dr Hannah Scott will then discuss emerging technologies and algorithms to better monitor and manage sleep health and associated disorders, also providing an overview of this rapidly growing field centred on simple wearable devices. We then follow with two talks focused on animal models. Prof. Lucy Palmer will discuss how feedback input onto cortical neurons provides critical information about the temporal characteristics of sensory information in awake mice, how this is lost during disconnected states such as sleep and anaesthesia, and the implications for specific sleep functions. These ideas will then transition to Prof. Bruno van Swinderen's talk on the evolution of sleep from worms and flies to mice and humans, with a view to understanding the different conserved functions of deep sleep and REM sleep. This will bookend our symposium with further discussion on how distinct kinds of sleep in humans could be contributing to different aspects of brain function, health, and development. Neuroscience is a broad field, and this symposium is significant in breadth and coverage in the area of sleep. Relatively few attempts have been made to link new developments in sleep monitoring in humans with basic neuroscience research aimed at testing experimental hypotheses on why we need sleep. For brain sciences to advance, these often detached ends of the research spectrum need to come together and improve communication to enable innovation and collaboration. By addressing important and contemporary questions pertinent to sleep research across neuroscience, this symposium will present broad interest and value to ANS membership, covering a highly familiar topic which all participate in, yet remains quite mysterious and largely misunderstood. Finally, these talks will allow the ABA to showcase its broader agenda of promoting cutting-edge neuroscience research in Australia, and bringing scientists from diverse disciplines together.

01:00 PM-01:25 PM
Deborah Apthorp

The effects of mild sleep restriction on behavioural and neural correlates of vigilant attention

Vigilance is the ability to quickly identify and respond to unpredictable stimuli over an extended period. It is an important part of activities such as driving, flying and radar monitoring, and it is affected by sleep loss. We investigated the influence of mild sleep restriction on the behavioural and neural components of vigilance. We analysed behavioural and EEG data from the psychomotor vigilance test (PVT) for 25 participants before and after a night of restricted sleep. Participants went to bed 3 hours later than normal and rose at their regular time, monitored via FitBit and sleep diary. Results showed an increase in PVT response times and a decrease in P3 event-related potential (ERP) peak amplitude with sleep restriction. The ERP P3 amplitude decrease was localised to the somatosensory association cortex, Brodmann area 5 (BA5). We also showed a significant reduction in resting state alpha oscillations after sleep restriction, which was most prominent centrally in the right hemisphere. Changes in individual alpha and delta power were associated with changes in jective sleepiness and PVT performance. Overall, this adds to evidence that even mild sleep restriction is associated with changes in brain activity that may affect performance on tasks requiring vigilant attention.

01:25 PM-01:50 PM
Hannah Scott

New and Emerging Approaches for Monitoring the Sleeping Brain

Current approaches to quantifying sleep for the diagnosis and management of sleep disorders are imprecise, laborious, and often do not relate well to key clinical and health outcomes. Newer approaches are emerging that overcome these critical limitations and have considerable potential for improving clinical sleep medicine. This presentation will outline the major limitations of current sleep monitoring techniques and provide the latest evidence on developing and using emerging technologies to better monitor and manage sleep health and its disorders. Specific examples will include using the THIM wearable device to deliver a behavioural treatment from chronic insomnia and a new forehead electroencephalography acquisition system for more precisely detecting underlying sleep pathology to enable endotyping. The endpoint of these new approaches will be improved management of sleep disorders through more precise characterisation of underlying sleep disorder pathophysiology and through enabling individualised, precision medicine approaches.

Thursday 01:50 PM-02:15 PM
Laura Jacobson
Modulating sleep/wakefulness architecture to tackle neurodegenerative disorders: studies in tau transgenic mice

The recent invention of hypnotic orexin receptor antagonists (ORAs) has provided an unprecedented capability to modulate sleep-wakefulness architecture. Rodent polysomnography has been a valuable tool in the discovery and development of these drugs, providing findings that have proved remarkably translatable to a clinical setting. Unlike classic hypnotics ORAs increase rapid-eye movement (REM) sleep and can also provide enhancement of slow wave sleep (SWS). In this presentation we describe our work using ORAs to examine the therapeutic potential of modulating sleep-wakefulness architecture in murine tauopathy models of Alzheimer's disease and Fronto-temporal dementia-tau. Our findings show that reducing hyperarousal, a classic phenotype of tau transgenic mice, can restore cognitive function, likely via pathways that are independent of hyperphosphorylated tau burden per se, whilst highlighting important tau- and sex-dependent differences in orexin receptor pharmacology. Overall, these findings suggest that modulating sleep/wakefulness architecture may prove beneficial in resolving aspects of functional decline in neurodegenerative tauopathies.

02:15 PM-02:40 PM
Bruno van Swinderen
Conservation of sleep functions through evolution

All animals need to sleep, although this is most often observed behaviourally. There is increasing evidence however that sleep is not a simple state of quiescence in most animals but is instead complex, comprised of distinct stages that are characterized by dramatically different physiological processes and brain activity signatures. This suggests that different sleep stages, such as rapid eye movement (REM) and slow-wave sleep (SWS) in humans and other mammals, are accomplishing distinct functions that are nevertheless collectively important for adaptive behaviour and survival. While REM and SWS appear to be restricted to a set of vertebrates (e.g., mammals, birds, and possibly some reptiles), a broader range of animals, including invertebrates, demonstrate evidence of active' sleep as well as deep' sleep, which could represent the evolutionary antecedents of REM and SWS, respectively. While deep sleep functions are increasingly understood to involve cellular homeostasis and repair processes, the function of REM or active sleep remains unclear. I will discuss evidence from invertebrates and mammals supporting the view that active sleep evolved to optimise predictive processing and will discuss some implications that this view has on the evolution of consciousness in animals and the impact of sleep on human societies more generally.

02:40 PM-02:45 PM
James Kesby
Data Blitz: Inhibition of the dorsal striatum alters reversal learning performance and reward sensitivity dependent on the probabilistic uncertainty

Kyna Conn1, Joyosmita Das1, Suzy Alexander1, 2, Thomas HJ Burne1, 2, James P Kesby1, 2
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2. Queensland Centre for Mental Health Research, Wacol, QLD, Australia
Objective: The dorsal striatum is a key area involved in navigating probabilistic reversal learning. We have shown that increasing the activity of dopaminergic inputs to the dorsal striatum can impair reversal learning and loss sensitivity at specific probabilistic contingencies1, similar to that observed in early psychosis2. Here we show that inhibiting the dorsal striatum in mice produces a phenotype akin to that observed in people with persistent psychosis3. Specifically, deficits in reversal learning and reward sensitivity that are dependent on the level of probabilistic uncertainty.
Methods: To determine the role of the dorsal striatum we used chemogenetics in male mice to acutely inhibit dorsal striatal activity during reversal learning at a range of probabilistic contingencies (i.e., 80:20; 80% reward on target, 20% reward on non-target).
Key findings: Specific inhibition of the dorsal striatum impaired reversal performance (decreasing the number of reversals per 100 trials) at the 80:40 contingency, but not 80:20 or 70:30. Moreover, inhibition also decreased reward sensitivity (decreased win-stay use) at 80:40 and 70:30 contingencies.

Conclusion: Our work shows that decreasing dorsal striatal activity impairs multiple reversal- and reward-learning processes, but this is dependent on the level of uncertainty. This suggests that the dorsal striatum plays a multifaceted role in reversal learning and highlights the need for testing at multiple probabilistic contingencies. The phenotype seen in mice is similar to that seen in people with persistent psychosis3, suggesting that decreases in dorsal striatal activity may occur with illness progression and underlie these cognitive outcomes.

Thursday 02:45 PM-02:50 PM
Wei Qin
Data Blitz: Brain-wide networks underlying seizures in zebrafish larvae

Wei Qin1, Jessica Beevis2, Andre Peterson1, Ellen Hoffman3, Ethan Scott1
1. the University of Melbourne, Parkville, Victoria , Australia
2. The University of Queensland, Brisbane
3. Yale University, New Haven
Epilepsy is a neurological disorder characterized by recurrent seizures. The mechanisms underlying transitions in brain dynamics (from normal to seizure state) are not fully understood. Zebrafish (Danio rerio) are a valuable model organism for studying epilepsy, as they share genetic and physiological similarities with humans and can exhibit seizure-like behaviours in response to various stimuli and treatments. One such stimulus treatment is pentylenetetrazole (PTZ), a pharmacological agent that blocks the inhibitory signalling of the neurotransmitter GABA causing hyperexcitability in the brain and seizure-like activity. Additionally, mutations in scn1lab, encoding sodium channels, can also cause spontaneous seizures in zebrafish.
In this study, we used in vivo light-sheet calcium imaging, brain-wide and at cellular resolution, on scn1lab mutant and zebrafish larvae under baseline and PTZ conditions. We applied network analysis, information theory, neural modelling, and graph theory to quantify the differences in network topology, functional connectivity, and dynamics between the two genotypes and the two conditions. Specifically, we compared the network properties of the whole brain as well as brain regions involved in seizure generation and propagation, such as the optic tectum, the telencephalon, and the cerebellum. We found consistent and significant differences in network connectivity, information delivery, and high-order network properties between the two genotypes, suggesting that scn1lab mutations alter the brain's network structure and dynamics. Our results demonstrate the utility of zebrafish as a model for epilepsy research and provide insights into the potential network mechanisms underlying seizure susceptibility and initiation.

02:50 PM-02:55 PM
Ishara Paranawithana
Data Blitz: Topological Differences of Language Networks Emerge After the First 6-Months of Life as Revealed by fNIRS Functional Connectivity

Ishara Paranawithana1, Darren Mao2, Colette M. McKay2, Yan T. Wong1
1. Department of Electrical and Computer Systems Engineering, Monash University, Clayton, VIC, Australia
2. Bionics Institute, East Melbourne, VIC, Australia
Many studies have previously reported that auditory and language networks continue to develop rapidly in early childhood due to the exposure of novel auditory input1,2. Despite growing interest, age-related changes of language networks are not fully understood. We hypothesized that developmental effects of language networks in infants could be identified by investigating topological differences in two experimental conditions 1) resting and 2) in response to continuous speech sounds (steady state). Four-minutes of resting and steady-state data were recorded from language related bilateral temporal and prefrontal regions using functional near-infrared spectroscopy (fNIRS), a non-invasive, silent neuroimaging technique. Thirty normal hearing babies participated in this study were separated into two groups based on age 1) 6-months or below (4.07±1.39 months) and 2) above 6-months (11.60±3.94 months) with fifteen jects in each group. Binary graphs were constructed for each participant and condition after thresholding connectivity matrices at 0.01 increments. Normalized mean global efficiency and clustering coefficient were used as threshold-agnostic metrics of functional integration and segregation, respectively3,4. Language networks of infants above 6-months exhibited significantly higher functional integration in resting compared to steady state (one-sided paired Wilcoxon signed-rank test, p=0.0128) but not in the age group of 6-months or below (p=0.3599). Functional segregation was significantly lower in resting than steady state in infants above 6-months (p=0.0206), but not for infants aged 6-months or below (p=0.2807). The results indicate that topological differences which support information processing across distributed language regions and speech sound processing within local clusters emerge after the first 6-months of life.

Thursday 02:55 PM-03:00 PM
Madhusoothanan Bhagavathi Perumal
Data Blitz: Summation and temporal dynamics of parvalbumin and somatostatin expressing interneurons during binocular processing

Madhusoothanan Bhagavathi Perumal1, Saba Gharaei1, Ehsan Arabzadeh1, Greg Stuart2, 1
1. Eccles Division of Neuroscience, John Curtin School of Medical Research, , Australian National University, Canberra, ACT, Australia
2. Department of Physiology, Monash University, Melbourne, Victoria, Australia
Neuronal circuits in the primary visual cortex integrate inputs from our two eyes to generate a single binocular percept. Previous work indicates that integration of binocular inputs in layer 2/3 pyramidal neurons in the binocular visual cortex (V1B) occurs via linear summation of monocular responses. linear binocular integration in pyramidal neurons helps to preserve orientation selectivity and requires recruitment of inhibition. Here we investigate the role of specific inhibitory interneuron types in this process. We recorded the activity of two major types of inhibitory interneurons - parvalbumin (PV) and somatostatin (SST) expressing interneurons - in layer 2/3 of adult mouse V1B in vivo using Neuronexus silicon arrays. PV and SST neurons were identified by optical tagging following targeted expression of ChR2 and excitation with a blue light (470 nm). Excitatory pyramidal neurons were identified using spike width and trough-to-peak width. We then measured monocular and binocular responses to sinusoidal drifting gratings at different orientations presented to each eye separately, or together, using a haploscope. We found that both PV(n=63) and SST(n=37) neurons responded to contralateral (C) and ipsilateral (I) eye stimulation, indicating that both types of inhibitory interneurons are binocular. During binocular stimulation, pyramidal and PV neurons had responses smaller than the linear sum of the responses to activation of each eye alone, indicating linear summation binocular integration. On the other hand, SST neurons showed biphasic binocular response with an early (~100 ms) linear/supra-linear summation followed by late linear summation. Using ex vivo preparations, we identified excitatory callosal connections carrying ipsilateral eye inputs to PV and SST interneurons show depressing and facilitating synaptic dynamics, respectively. Together, our findings reveal distinct temporal course of binocular summation in PV and SST neurons that is potentially mediated by interhemispheric excitatory synaptic connections.

Thursday 01:00 PM-03:00 PM

Selected Orals 7: Neurology/Psychiatry

Great room 3

01:00 PM-01:15 PM
Bethany Masson
Paternal gut microbiota depletion impacts offspring physiology and affective behaviours

Bethany A Masson1, Carolina Gubert1, Anthony J Hannan1, 2
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Parental environmental exposures, including models of stress and administration of a high-fat diet, can alter offspring phenotypes via germline epigenetic modifications. The gastrointestinal tract incorporates a large enteric surface area exposed to external factors, including nutrients from the diet, medications, and the symbiotic relationship with the microorganisms which form the gut microbiota. Disruptions to the gut microbiota have been associated with a range of diseases, and maternal gut microbiota disruption has been demonstrated to impact offspring physiology and behaviour. This project aims to investigate the impact of paternal gut microbiota disruption on offspring physiology and cognitive and affective behaviour. The gut microbiota of male C57BL/6 mice was depleted using a cocktail of non-absorbable antibiotics administered via drinking water. After one spermatogenic cycle, these mice were bred with naïve female mice to produce offspring which were investigated for behavioural changes. Paternal gut microbiota disruption resulted in differential body weight in both male and female offspring over their lifetimes. Additionally, male and female offspring showed morphological changes in their gastrointestinal tract, with an increase in colon length. Female offspring showed altered affective behaviour, spending increased time in the centre of the open field test, a measure of anxiety-like behaviour. Furthermore, female offspring also showed increased stress responsiveness in a test of depressive-like behaviour. Depletion of the paternal gut microbiota resulted in intergenerational changes to offspring physiology and female affective behaviour. These results have prompted further investigation into changes in the epigenetic sperm profile, and the transgenerational impacts of this paternal exposure.

01:15 PM-01:30 PM
James St John
Olfactory glial bridge transplantation for repairing traumatic spinal cord injury in humans – progress towards a Phase I clinical trial

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The Spinal Injury Project is planning a Phase I blinded and randomised control trial that has been co-designed with the community to test a powerful nerve bridge technology for repairing spinal cord injury using olfactory ensheathing cells (OECs). The nerve bridge technology exploits natural cell adhesion and repulsion to facilitate organic self-organisation and self-adhesion without artificial matrices, scaffolds or gels. Critically, the cells form stable intercellular connections prior to transplantation which dramatically increase cell survival post-transplantation. In animal research, transplantation of the nerve bridges restores motor, sensory and autonomic function. Histological analyses show that OECs from the nerve bridges rapidly integrate with the host spinal cord and maintain close contact with each other to create a continuous bridge of glial cells across the injury site. Regenerating axons then project along the OECs and are ensheathed by the OECs. RNA expression analyses show upregulation of pathways related to neural regeneration including axon guidance and neurotransmitter release, and downregulation of apoptosis, macrophage activation, and TNFα expression related to neuropathic pain. Rehabilitation is critical to neural regeneration and thus in preparation for the human Phase I clinical trial, we have conducted two trials of acceptance, safety and feasibility of the long-term intensive rehabilitation programs (prehab and posthab). The trial participants had high satisfaction with the programs, extremely high levels of compliance, and experienced no significant adverse events. Thus, these trials demonstrate that the intensive long-term programs are suitable and we are now progressing this therapy to a Phase I human clinical trial.

01:30 PM-01:45 PM
Hui Xin Tan
Exercise reduces incubation of craving for alcohol-associated cues.

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Incubation of craving is the time dependent increase in craving elicited by drug-associated cues. This is well documented in clinical populations, and can be modelled in rodents by measuring changes to cue-elicited drug-seeking. Surprisingly, although incubation of craving is evident in people seeking treatment for alcohol use disorder, there are few preclinical studies that report on the mechanism underlying this effect in the specific context of alcohol. We trained rats to self-administer alcohol, and then kept them in abstinence for 28 days. Cue-induced alcohol seeking was tested on day 1 or day 29 of abstinence. In addition, half the rats had access to a running wheel across abstinence. Following test, all rats were perfused transcardially. Brains were collected, and brain-wide neural activity was estimated by quantifying expression of c-Fos protein using QUINT workflow.
Cue-induced relapse was greater on day 29 compared to day 1, and this effect was attenuated in rats that had access to running wheels (Interaction: F[2,15] = 12.18, p .001, follow up pairwise comparisons p .05). In key reward-associated neural loci, including prefrontal cortex, nucleus accumbens, basolateral and central amygdala, c-Fos immunoreactivity was similarly higher in rats tested on day 29 compared to day 1, and again this was attenuated in the exercise group.
These finding confirm that the potential for alcohol-associated cues to precipitate relapse increases across abstinence. Furthermore, they imply that neuroadaptations leading to this increase may be reversed by voluntary exercise, suggesting that exercise is a viable intervention for mitigating relapse risk.

Thursday 02:00 PM-02:15 PM
Lachlan Harris
Controlling stem cell quiescence for therapeutic gain in brain cancer.

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Glioblastoma (GBM) is the most common malignant primary brain tumour in adults. In GBM, patients die from disease recurrence, driven by significant populations of quiescent (slow-dividing) glioma stem cells (GSCs) that resist chemoradiation. Therefore, by targeting quiescent GSCs we might prolong survival in GBM. Unfortunately, much of our understanding of how quiescence is regulated comes from the study of healthy' quiescent neural stem cells, either from the adult hippocampus or ventricular zone niche of mice, rather than the direct study of gliomas. It is thereby unclear the extent to which these molecular programs governing quiescence will be conserved in GBM. In this study, we aim to address these issues by 1) comparing the quiescent state of healthy' neural stem cells to quiescent GSCs, 2) determining whether we can model GSC quiescence in a dish and 3) establishing whether it is possible to manipulate the quiescent state of GSCs. Through analysis of single-cell RNA-sequencing datasets, and specifically the reconstruction of activation trajectories, we find a remarkable conservation of molecular programs between quiescent neural stem cells and GSCs. Moreover, we find that GSCs can be induced into a state in vitro that recapitulates key features of quiescence, including induction, reversibility and resistance. Finally, we demonstrate that we can reactivate quiescent GSCs, by blockading pathways that promote quiescence in adult neural stem cells. Overall, our study points to the conserved nature of programs governing quiescence in neural tissue, and to the rationalisation of novel therapeutic strategies targeting treatment resistance in GBM.

02:00 PM-02:15 PM
Collin Anderson
Progress towards a gene therapy for Christianson syndrome

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Christianson syndrome (CS) is neurodevelopmental and neurodegenerative disorder caused by loss of function of the SLC9A6 gene and characterised by intellectual deficit, seizures, cerebellar degeneration, and progressive cerebellar motor symptoms. CS affects ~1 in every 100,000 males, and there are no treatment strategies.
We have previously published on the Wistar Furth shaker rat, a spontaneous model of cerebellar degeneration and tremor/ataxia, and we recently demonstrated that this phenotype was caused by a loss-of-function mutation in Slc9a6, which shares high homology with human SLC9A6.
In our work tying the shaker rat to Slc9a6 mutation, we performed functional complementation studies using adeno-associated viruses to deliver wildtype rat Slc9a6 to Purkinje cells, demonstrating causality of the identified mutation. In this current work, we expanded therapeutic evaluation, analysing the effects of cerebellum-specific gene replacement via the L7-6 promoter on motor function at weekly time points spanning from presymptomatic to severely affected (6 to 25 weeks), quantifying both tremor and ataxia. Further, we analysed the effects of broadly targeted expression of human SLC9A6 via the CAG promoter across a variety of doses. In both cases, we evaluated relevant molecular endpoints through western blotting.
With both constructs, we found stantial motor and molecular benefit. Interestingly, we found that cerebellar gene replacement dissimilarly modulated tremor and ataxia and stantially altered the dynamics between tremor and ataxia, finding agreement with recent findings that cerebellar tremor and ataxia arise from dissociable cerebellar mechanisms.

This work supports further investigation of gene replacement as a potential treatment strategy for Christianson syndrome.

Thursday 02:30 PM-02:45 PM
Courtney Cross
Burkholderiaceae abundance in the gut microbiota is associated with cognitive impairment and gastrointestinal symptoms in women treated with chemotherapy for breast cancer: pilot results of the PREDiCT Study

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3. Outpatients Breast Clinic, Modbury Hospital, Adelaide
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5. The Bowel Clinic, Adelaide
Chemotherapy causes profound and often chronic cognitive impairment (CICI), consistently identified as a priority concern by cancer survivors. CICI is unpredictable even in homogeneous populations, suggesting unique factors, related to the individual, dictate aetiology. Dysfunction of gut-brain communication, mediated by the gut microbiota, is increasingly recognised to contribute to other neurocognitive conditions, but has not been explored in detail in the oncology setting. Therefore, we aimed to longitudinally characterise the individual, dynamic shifts in gut microbiota and identify microbial signatures associated with the neurocognitive symptom burden caused by chemotherapy.
N=82 stool samples were collected and processed from twenty-two women, newly diagnosed with breast cancer, during the first two cycles of chemotherapy. 16S rRNA sequencing identified no significant differences in alpha diversity in women with (N=8) or without (N=14) cognitive impairment (defined by the Functional Assessment of Cancer Therapy – Cognitive Function version 3 (FACT-Cog)). However, PERMANOVA analysis revealed a compositional differences between these groups using beta diversity (P=0.0007) which was underpinned by a gut microbiota enriched for Burkholderiaceae (P0.0001) and deficient in Akkermansiaceae (P0.03) in women with cognitive impairment. Of interest, the relative abundance of Burkholderiaceae strongly associated with both cognitive impairment (FACT-Cog total score, p0.0001) and diarrhea determined using the Functional Assessment of Chronic Illness Therapy – Diarrhoea scale (p=0.0017).
These findings underscore the triadic relationship that exists in the microbiota-gut-brain axis in women with breast cancer undergoing chemotherapy, highlighting the centrality of the gut microbiota in symptom burden.

02:45 PM-03:00 PM
Volkan Uzungil
Whole-brain functional network connectivity during spatial working memory performance

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Spatial working memory is an executive function which allows an organism to navigate its environment and make decisions based upon recent information. Research has focused primarily on the role of individual brain regions and circuits during working memory, overlooking the organisation of population neural activity across brain regions. Graph theoretic analysis allows characterisation of the whole-brain functional network during spatial working memory performance, to link key features of the network to cognitive performance.
A custom designed figure 8 maze is utilised to determine spatial working memory performance in experimental mice. Whole-brain neural activity during the task is quantified ex vivo via c-Fos expression through systematic delivery of blood-brain-barrier crossing rAAV-PHP.Ax:c-Fos-EYFP. TissueCyte serial two-photon tomography is utilised to detect whole-brain c-Fos expression followed by the DeepCATS image analysis pipeline for automated cell detection. Following regional neural activity quantification, graph theoretic analysis will be conducted to determine the functional network.
Mice exhibit alternating behaviour in the figure 8 maze indicating functional working memory performance compared to control mice. TissueCyte two-photon tomography has identified whole-brain c-Fos expression dependent neural activity during spatial working memory performance. Implementation of DeepCATS algorithm has resulted in registration of serial brain sections to Allen brain atlas.
Following completion of the DeepCATS workflow, whole-brain functional network will be created via graph theoretic analysis to determine network features which underpin spatial working memory performance. Identification of the functional network will allow us to determine how this mechanism is dysfunctional in neurodegenerative disease.

Thursday 03:00 PM-03:30 PM
Break
Afternoon Tea, Exhibition and Poster Display

03:30 PM-04:30 PM
George Paxinos
Eccles Plenary Lecture
Great room 1/2/3

04:30 PM-05:00 PM
Presentation of Awards and Conference Close
Great room 1/2/3