36TH
INTERNATIONAL CONFERENCE

AWCBR

Australasian Winter Conference
on Brain Research

2018
Programme and Abstracts

25-29 August 2018
Crowne Plaza Hotel, Queenstown, New Zealand
www.otago.ac.nz/awcbr

NEUROLOGICAL FOUNDATION OF NEW ZEALAND
PROGRESS THROUGH RESEARCH

Australasian Neuroscience Society

Saturday 25 August

3.00-6.00 pm	Registration, Crowne Plaza Hotel
6.00 pm	Opening Reception, Cash Bar and light food
7.00 pm	Opening Remarks
9.35 PM	Rugby: NZ vs Australia Cash bar and light refreshments available

7.15 pm

1. PLENARY LECTURE:

Chair: Ruth Empson

Wendy Imlach, *Monash University, Australia*

Pain pathways - Decoding spinal circuit function in chronic pain

2. Sensory and Motor Systems

Chair: Stephanie hughes

8.00 pm	2.1	**Yiwen Zheng, *University of Otago, New Zealand*** Can metabolic changes in the blood predict changes in the brain in rats following acoustic trauma?
8.15 pm	2.2	**Philip Sanders, *University of Auckland, New Zealand*** Effects of high frequency multisensory stimulation on early visual evoked potentials in young and elderly adults
8.30 pm	2.3	**Cecilie Topp, *Aalborg University, Denmark*** Examining underlying mechanisms of neglect patients' reaction to the Wall method through flash visual evoked potentials
8.45 pm	2.4	**Rosie Melchers, *University of Otago, New Zealand*** Effects of intermittent theta-burst stimulation on interhemispheric inhibition throughout stroke recovery
9.00 pm	2.5	**Kathryn Todd, *University of Auckland, New Zealand*** The subthalamic nucleus modulates striatal dopamine release from a distinct population of dopamine neurons

Sunday 26 August
Morning Session

7.30-8.30 am Light Breakfast Available

3. PLENARY LECTURE:

Chair: Sue Schenk

8.30 am	**Juan Canales, *University of Tasmania, Australia***
	Neurobiology of drug addiction in humans and animal models

9.15 am Tea/Coffee break

Sunday 26 August
Morning Session

4. Disorders of the Nervous System (I)

Chair: Ping Liu

9.30 am	4.1	**Dorothy Oorschot, *University of Otago, New Zealand*** Synaptic triad arrangement within an aversive pathway in the normal uninjured brain
9.45 am	4.2	**Jarred Griffin, *University of Auckland, New Zealand*** ADAMTS4 AAV-gene therapy combined with rehabilitation is therapeutic after spinal cord injury
10.00 am	4.3	**Steve Seo, *University of Otago, New Zealand*** Changes in midbrain dopamine circuitry in the maternal immune activation rat model of schizophrenia
10.15 am	4.4	**Shabah Shadli, *University of Otago, New Zealand*** Ketamine effects on EEG during therapy of treatment-resistant generalized anxiety and social anxiety
10.30 am	4.5	**Gina Forster, *University of Otago, New Zealand*** Glucocorticoid modulation of accumbal dopamine release is disrupted during amphetamine withdrawal

Sunday 26 August
Afternoon Session

2.45-3.45 pm	Neurological Foundation Discussion
	Light refreshments available
3.45-4.15 pm	Afternoon Tea Available

5. Cognition and Behavior

Chair: Andrea Kwakowsky

4.15 pm	5.1	**Reece Roberts, *University of Auckland, New Zealand***
		Reassessing the functional role of fMRI BOLD variability in cognitive performance
4.30 pm	5.2	**David Moreau, *University of Auckland, New Zealand***
		Structural correlates of dyslexia and dyscalculia: Revisiting common assumptions
4.45 pm	5.3	**Kristina Wiebels, *University of Auckland, New Zealand***
		The role of location details in the construction of future events

6. MINI-ORAL INFOBLITZ

CHAIR: IAN KIRK

5.00 pm	6.1	**Marcus Wilson, *University of Waikato, New Zealand*** Using neural fields to model motor evoked potentials due to transcranial magnetic stimulation
5.04 pm	6.2	**Andy Gibson, *University of Canterbury, New Zealand*** Effect of background music and dialect variation on auditory ERPs: Research plan
5.08 pm	6.3	**Catherine Theys, *University of Canterbury, New Zealand*** The neural basis of stuttering: where and when do differences in brain activation occur?
5.12 pm	6.4	**Sonja Muller, *University of Canterbury, New Zealand*** Patterns of brain activation during overt speech production in adults with persistent developmental stuttering
5.16 pm	6.5	**Petra Mossop, *University of Canterbury, New Zealand*** Neurophysiological correlates of stuttered speech: Creating a pipeline for removal of muscle artefacts during overt speech production
5.20 pm	6.6	**Alice Freeman, *University of Otago, New Zealand*** Investigating the role of leptin in arcuate AgRP neuron development

5.24 pm	6.7	**Kristina Aluzaite,** ***University of Otago, New Zealand*** Circadian lights in a hospital setting to improve sleep, recovery and decrease psychological distress: Study concept and pilot baseline assessment results
5.28 pm	6.8	**Jena Macapagal,** ***University of Auckland, New Zealand*** Pericytes can contribute to tumour immune system evasion in glioblastoma multiforme through dampened expression of ICAM-1, VCAM-1 and MCP-1
5.32 pm	6.9	**Florian Kurth,** ***University of Auckland, New Zealand*** Age effects on subareas of the amygdala

Conference Dinner

7.30 pm

Skyline Restaurant

Tickets must be purchased in advance.
The ticket includes return gondola transport to the restaurant.

The Skyline is a licensed restaurant but wine and beer will be provided.
The function room will be open from 7.00 pm,
with dinner commencing at 7.30 pm

Musical entertainment will be provided.

Monday 27 August
Morning Session

7.30-9.00 am — Light Breakfast Available

9.00 am

7. PLENARY LECTURE:

Chair: Victor Dieriks

Ronald Melki, *Paris-Saclay Institute of Neurosciences, France*

Prion-like propagation of alpha-synuclein assemblies in distinct synucleinopathies

9.45 am — Tea/Coffee break

8. Symposia: Parkinson's Disease

Chair: Victor Dieriks

10.00 am	8.1	**Victor Dieriks, *University of Auckland, New Zealand*** Non-neuronal cells enable transmission of α-synuclein in Parkinson's disease
10.15 am	8.2	**Taylor Stevenson, *University of Auckland, New Zealand*** Quantification of non-neuronal cells containing intracellular α-synuclein in the human Parkinson's disease olfactory bulb
10.30 am	8.3	**Campbell Le Heron, *University of Oxford, United Kingdom*** Distinct effects of apathy and dopamine on effort-based decision making in Parkinson's disease
10.45 am	8.4	**Rebekah Blakemore, *University of Otago, New Zealand*** Parkinsonian tremor can be diminished by will power
11.00 am	8.5	**Kyla-Louise Horne, *University of Otago, New Zealand*** Significant-others underreport the impact of hallucinations in Parkinson's disease patients with normal cognition

9. POSTER SESSION

- COMBINED WITH MEDSCI

NB: RYDGES HOTEL

4.00 - 6.00 pm	Presenters will be in attendance during this time and posters can be set up from 3.00 pm. Presenters for odd number posters will be in attendance from 4.00-5.00 pm Presenters for even number posters will be in attendance from 5.00-6.00 pm Poster board numbers shown in brackets
9.1 (A1)	**Adelie Tan, *University of Auckland, New Zealand*** Characterisation of classical Huntington's disease neuropathology in a human tissue microarray
9.2 (A2)	**Alex Maan, *Victoria University of Wellington, New Zealand*** Resistance to extinction following methamphetamine self-administration in rats
9.3 (A3)	**Alice McDouall, *University of Auckland, New Zealand*** Electrochemical and electrophysiological characterisation of L-DOPA-derived dopamine in rat brain slices
9.4 (A4)	**Amy Alder, *Victoria University of Wellington, New Zealand*** Evaluating the side effect profile of the G-Protein biased Mu opioid receptor agonists Kurkinorin and Kurkinol
9.5 (A5)	**Andrea Gu, *University of Auckland, New Zealand*** In vitro wounding models using the Electric Cell-Substrate Impedance Sensing (ECIS)-Zɵ Technology
9.6 (A6)	**Ashwini Hariharan, *University of Otago, New Zealand*** Endothelial nitric oxide synthase deficiency leads to increased urea levels in the brain

9.7 (A7)	**Bede Byers, *University of Otago, New Zealand*** Generalisation of an anxiety process biomarker from speeded response to bimanual fixed time responding
9.8 (A8)	**Benjamin Austin, *University of Queensland, Australia*** A neurocognitive model to explain the relationship between occupational stress in physicians and adverse patient outcomes
9.9 (A9)	**Beth Elias, *University of Canterbury, New Zealand*** Autobiographical memory in Parkinson's disease
9.10 (A10)	**Blake Highet, *University of Auckland, New Zealand*** Presence of genetic disease-specific aggregates in the anterior olfactory nucleus of the human olfactory bulb
9.11 (A11)	**Brittney Black, *University of Auckland, New Zealand*** Receptor studies in the human globus pallidus
9.12 (A12)	**Catherine Theys, *University of Canterbury, New Zealand*** Comparison of usability of three AAC systems: EyeLink, eye tracking camera and P300 speller
9.13 (A13)	**Chitra Vinnakota, University of Auckland, New Zealand** Extrasynaptic Alpha 5 Type GABAA receptors as therapeutic targets For Alzheimer's disease
9.14 (A14)	**Chloe Rayner, *University of Auckland, New Zealand*** Astrocyte-specific GFAP-AAV Vector-mediated secretion of chondroitinase ABC as a potential therapy following spinal injury
9.15 (A15)	**Connor Clemett, *University of Auckland, New Zealand*** Tumour necrosis factor receptor 1 acts partially through the PI3K/Akt pathway to induce pro-inflammatory phenotypes within the cerebral endothelium
9.16 (A16)	**Doreen Hansmann, *University of Canterbury, New Zealand*** Hearing, seeing, and feeling speech: A pilot EEG study

Poster Session

9.17 (A17)	**Emma Peterson,** ***University of Canterbury, New Zealand*** Oddball event-related potentials in Parkinson's disease patients with normal cognition
9.18 (A18)	**Emmett Power,** ***University of Otago, New Zealand*** Population plasticity at the cerebellar Parallel fibre to Purkinje neuron synapse
9.19 (A19)	**Faezeh Tashakori-Sabzevar,** ***University of Otago, New Zealand*** Functional circuitry of basal forebrain underlying enhanced attention by reward anticipation
9.20 (A20)	**Farah Khokhar,** ***University of Waikato, New Zealand*** Designing, measuring and modelling a small-scale coil and stimulation circuit for Transcranial Magnetic Stimulation
9.21 (A21)	**Grace Fitzallen,** ***University of Queensland, Australia*** Preterm birth and childhood psychopathology: Linking neonatal neurological alterations with the preterm behavioural phenotype
9.22 (A22)	**Harriet Lawford,** ***University of Queensland, Australia*** Utility of acoustic cry characteristics assessment as a potential marker of neurological integrity in high-risk infants
9.23 (A23)	**Jayarjun Ethiraj,** ***University of Auckland, New Zealand*** Age- and gender-specific changes of the GABA signalling components in the human hippocampus
9.24 (A24)	**Jessy Zhang,** ***University of Otago, New Zealand*** Maternal immune activation affects hippocampal nNOS immunoreactivity and microglia in postnatal day 35 rat offspring
9.25 (A25)	**Joyeeta Roy,** ***University of Otago, New Zealand*** MicroRNA expression in the diagnosis of Parkinson's disease
9.26 (A26)	**Julia Newland,** ***University of Auckland, New Zealand*** Investigating liposomes for local drug delivery in SCI

9.27 (A27)

Laverne Robilliard, *University of Auckland, New Zealand*

The importance of multi-frequency impedance sensing of endothelial barrier formation using ECIS technology for the generation of a strong and durable paracellular barrier

9.28 (A28)

Lewis Forrester, *University of Otago, New Zealand*

The role of maternal obesity during oligodendrocyte development in the offspring amygdala

9.29 (A29)

Maize Cao, *University of Auckland, New Zealand*

The effect of AAV mediated knockdown of xylosyltransferase-1 in reactive astrocytes

9.30 (A30)

Megan Livingstone, *University of Canterbury, New Zealand*

Theory of mind in Parkinson's disease: A longitudinal follow-up

9.31 (A31)

Meyrick Kidwell, *Victoria University of Wellington, New Zealand*

Reduced HRV in SERT knockout rats: Further translational validity as an animal model of depression and anxiety

9.32 (A32)

Micah Austria, *University of Auckland, New Zealand*

Cerebellar degeneration correlates with motor symptoms in Huntington's disease

9.33 (A33)

Miran Mrkela, *University of Auckland, New Zealand*

The effect of Tonabersat in reducing chronic inflammation following spinal cord injury

9.34 (A34)

Nikita Potemkin, *University of Otago, New Zealand*

Amyloid-β increases SH-SY5Y neuroblastoma cell viability

9.35 (A35)

Oluwatobi Eboda, *University of Otago, New Zealand*

ATP13A2: Characterization of novel human iPS cell models of Parkinson's and Batten's disease

9.36 (A36) **Panzao Yang, *University of Auckland, New Zealand***

Effects of connexin hemichannel blockade on cortical interneurons after global cerebral ischaemia in term-equivalent fetal sheep

9.37 (A37) **Petra White, *University of Auckland, New Zealand***

Validation of NODDI-MRI for detection of cortical brain injury following peripheral inflammation in neonatal rats

9.38 (A38) **Quenten Highgate, *Victoria University of Wellington, New Zealand***

A comparison of the effects of abstinence on MDMA and cocaine self-administration in rats

9.39 (A39) **Reza Shoorangiz, *University of Canterbury, New Zealand***

EEG-based resting-state functional connectivity in Parkinson's disease with normal cognition

9.40 (A40) **Rhys Livingstone, *University of Otago, New Zealand***

Arc protein expression in response to secreted amyloid precursor protein-α in primary hippocampal cultures

9.41 (A41) **Ross van de Wetering, *Victoria University of Wellington, New Zealand***

Regional ΔFosB expression associated with chronic MDMA self-administration

9.42 (A42) **Sanduni Malluwawadu, *University of Waikato, New Zealand***

Modelling the spiking behaviour of neurons in human cortex

9.43 (A43) **Nitthiya Siva Subramaniam, *University of Adelaide, Australia***

Non-radioactive isotope labelled breath test for potential early diagnosis of Huntington's disease

9.44 (A44) **Sivaporn Tasananukorn, *University of Canterbury, New Zealand***

Impaired spatial memory, reduced exploration and increased hippocampal microglia density are associated with senescence but are not reduced by a connexin hemichannel blocker

Poster Session

9.45 (A45)	**Sophie Mathiesen,** ***University of Otago, New Zealand*** Assessing the efficacy of adeno-associated viral vectors in targeting the brain
9.46 (A46)	**Susanna Szakats,** ***University of Otago, New Zealand*** Brain development and the Amh locus
9.47 (A47)	**Yashna Sagar,** ***University of Queensland, Australia*** Functional neuroimaging correlates of executive function following preterm birth
9.48 (A48)	**Young-Ho Lee,** ***Hanyang University Medical Center, Korea*** Prognostic factors to G-CSF with stem cell therapy for the children with cerebral palsy

7.00 pm Posters to be removed at this time

Monday 27 August
Evening Session

10. Opening of Queenstown Research Week

Venue: Rydges Hotel

6.00 pm	Opening Address **Peter Shepherd** ***University of Auckland, New Zealand***
6.10 pm	Official Opening **Juliet Gerrard** ***Prime Minister's Chief Science Adviser***
6.25 pm	Nobel Lecture **Elizabeth Blackburn** ***University of California, San Francisco, United States of America*** 2009 Nobel Prize in Physiology or Medicine for discovery of how chromosomes are protected by telomeres and the enzyme telomerase
7.30 pm	QRW Social
8.00 pm	AWCBR Student Dinner Venue: Smiths Craft Beer House ANS Sponsored Student Quiz

Tuesday 28 August
Morning Session

7.30-8.30 am — Light Breakfast Available

11. Symposia:
The Basal Ganglia in Health and in PD:
Making and Breaking Habits of a Lifetime

Chair: John Reynolds

8.30 am	11.1	**Peter Redgrave, *University of Sheffield, United Kingdom*** Parkinson's disease: Where did all my habits go?
9.00 am	11.2	**Christine Arasaratnam, *University of Auckland, New Zealand*** Contrasting changes in DARPP-32 and calbindin immunoreactivity in medium spiny neurons in Parkinson's disease
9.15 am	11.3	**Nico Vautrelle, *University of Otago, New Zealand*** Development of a minimally-invasive technology for spatially- and temporally-controlled drug delivery into the brain
9.30 am	11.4	**Mariana Leriche, *University of Otago, New Zealand*** Failure of the habit system in Parkinson's disease
9.45 am	11.5	**Peter Freestone, *University of Auckland, New Zealand*** An optogenetic Channelrhodopsin-assisted mapping investigation of network organization within the subthalamic nucleus
10.00 am	11.6	**Louise Parr-Brownlie, *University of Otago, New Zealand*** Anatomical and physiological changes at basal ganglia-motor thalamus synapses in rat model of Parkinson's disease

10.30 am — **ANNUAL GENERAL MEETING**
All conference participants are invited to attend
Tea/Coffee will be available for AGM attendees

Tuesday 28 August
Afternoon Session

3.30-4.00 pm Afternoon Tea Available

12. Disorders of the Nervous System (II)

Chair: Emma Scotter

4.00 pm	12.1	**Chris Shaw, *King's College London, United Kingdom*** ARPP21 mutations reveal the role of RNA granule dysfunction in ALS and FTD
4.20 pm	12.2	**Ping Liu, *University of Otago, New Zealand*** Altered arginine metabolism in the frontal cortex of patients with major depression
4.35 pm	12.3	**Helen Murray, *University of Auckland, New Zealand*** Multiplex Immunohistochemistry of 10+ markers to assess unfolded protein response activation in the Alzheimer's disease olfactory bulb
4.50 pm	12.4	**Phil Heyward, *University of Otago, New Zealand*** Activity-dependent actions of Li+ in brain network connectivity

13. SYMPOSIA:

NEURODEVELOPMENT OF HIGH-RISK NEWBORNS

CHAIR: SAMUDRAGUPTA BORA

5.05 pm	13.1	**Jacki Henderson, *University of Canterbury, New Zealand*** Development of behavioural self-regulation in preschool-age children prenatally exposed to methadone
5.20 pm	13.2	**Victoria Gill, *University of Queensland, Australia*** Confirmed vs suspected neonatal infection: associations with neonatal neurological abnormalities following preterm birth
5.35 pm	13.3	**Theresa Chin, *University of Queensland, Australia*** Characterising the impacts of complex and simple congenital heart defects on executive function
5.50 pm	13.4	**Maddie Pascoe, *New Zealand Brain Research Institute, New Zealand*** Adults born with very-low-birth-weight demonstrate alterations in grey matter volume, perfusion, and White Matter integrity, and associations with birth weight

Wednesday 29 August
Morning Session

7.30-8.30 am — Light Breakfast Available

14. PLENARY LECTURE:

Chair: Juliette Cheyne

8.30 am	14	**Karen Zito, *University of California, United States of America*** Sculpting the nervous system: Cellular and molecular mechanisms of neural circuit refinement
9.15 am		Tea/Coffee break

15. Symposia: Development and Autism Spectrum Disorders

Chair: Juliette Cheyne

9.30 am	15.1	**Anthony Hannan, *University of Melbourne, Australia*** Gene-environment interactions in mouse models of neurodevelopmental and cognitive disorders
9.45 am	15.2	**Yukti Vyas, *University of Auckland, New Zealand*** Influence of maternal high zinc diet on the development of autism-associated behaviours
10.00 am	15.3	**Maya Wilde, *University of Auckland, New Zealand*** Tonotopic mapping in a mouse model of autism spectrum disorder
10.15 am	15.4	**Rodrigo Suárez, *University of Queensland, Australia*** Investigating the development and evolution of cortical circuits using in vivo assays in marsupials

16. Symposia: Computational Neuroscience

Chair: Tim David

10.30 am	16.1	**Soroush Safaei,** ***University of Auckland, New Zealand*** Using bond graphs to provide a consistent framework for coupling cerebral circulation with tissue exchange mechanisms
10.45 am	16.2	**Tim David,** ***University of Canterbury, New Zealand*** Integrated models of neurovascular coupling and BOLD signals
11.00 am	16.3	**Stewart Dowding,** ***University of Canterbury, New Zealand*** The Astrocyte-Neuron Lactate Shuttle's role in neurovascular coupling
11.15 am	16.4	**Allanah Kenny,** ***University of Canterbury, New Zealand*** Large scale tissue slice simulations of cortical spreading depression

11.30 am Closing Remarks and Student Prize Presentation

Light Lunch Atrium, Crowne Plaza

Acknowledgements
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ABSTRACTS

1.

Pain pathways - Decoding spinal circuit function in chronic pain

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Chronic pain is a major global health burden that results in hypersensitivity to sensory input so normally innocuous stimuli becomes painful. Many chronic pain states are linked to neural circuit dysfunction, which can be traced back to the spinal level in the majority of cases. Neuropathic pain, one of the most intense types of chronic pain, is caused by malfunction of the nervous system and involves persistent changes in signaling within pain pathways. The sensory signs of neuropathic pain have been linked to reduced inhibitory signalling in the spinal cord, but specific circuits that lose inhibitory input have not been identified. In this talk, I will discuss our recent identification and characterization of a nociceptive circuit that becomes more excitable in a rat model of chronic pain. Using patch-clamp electrophysiology, optogenetic and imaging approaches we have identified specific circuit components that are affected by disinhibition through pre- and post-synaptic mechanisms. The second part of this talk will focus on our approaches to pharmacologically target the activity of affected neurons. Here we have used novel inhibitors of glycine transporters to increase inhibitory signalling and allosteric modulation of adenosine receptors to decrease excitability and reverse the symptoms of neuropathic pain in vivo. Understanding the molecular, cellular, and physiological basis of changes in circuit activity in disease is central to the development of more effective therapeutics.

2.1

Can metabolic changes in the blood predict changes in the brain in rats following acoustic trauma?

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It is increasingly recognised that tinnitus is likely to be generated by complex network changes. Using metabolomics, we reported that acoustic trauma that causes tinnitus induced significant changes in multiple metabolic pathways in the brain, however it is not clear whether those metabolic changes could also be reflected in blood samples, which is crucial for translating biomarkers into clinical use. Here we analysed brain and serum metabolic changes in rats following tinnitus-inducing acoustic trauma using metabolomics. Tissues from 11 different brain regions, as well as serum samples, were collected from animals ~3 months following acoustic trauma. Using GC/MS, a total of 102 distinct peaks were found in the brain extracts and 107 in serum samples. Among these, 82 molecules from serum and 76 from brain were authentically identified. Data were analysed using both principal component and partial least squares projection to latent structure-discriminant analysis. There was a clear metabolic shift in the acoustic trauma animals in a number of brain regions. There was also a significant metabolic shift in serum samples. Further metabolic pathway analysis suggested that there is a considerable predictive relationship between the changes in the serum and those in the brain. A Pearson correlation analysis showed that urea and glutamine levels in the serum were significantly correlated with the degree of an animal's hearing loss. Our results suggest that metabolic changes in blood samples may be used as a useful marker in reflecting changes in the brain following acoustic trauma and/or tinnitus.

2.2

Effects of high frequency multisensory stimulation on early visual evoked potentials in young and elderly adults

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Sensory abilities decline with ageing but multisensory integration can compensate for some of these losses. Cognitive decline can also accompany ageing. Research into brain plasticity may be important for early detection of sensory and cognitive decline. We examined plasticity in sensory brain regions, and whether audiovisual stimulation enhances this plasticity relative to visual-only stimulation using a non-invasive technique. Visual evoked potentials (VEPs) were measured with electroencephalography in elderly and young adult groups, before and after high frequency stimulation (HFS) with visual and audiovisual stimuli. Previously reported group-level effects on the visual N1b component were not replicated and effects varied between individuals. However, age and HFS modality differences were observed on other components. The P1 peak was potentiated in the elderly group after HFS with both types of stimuli regardless of the order of modality presentation. Audiovisual HFS potentiated the P2 peak in the elderly group. The magnitude and direction of the N1 peak potentiation differed between age groups after visual HFS with the young showing a potentiation and the elderly showing depotentiation. Audiovisual HFS affected VEP waveforms differently to visual HFS and effects differed between age groups. It was unclear whether differences in plasticity induced by multisensory relative to visual HFS reflected enhancements. Ageing does appear to affect plasticity induced by HFS but characterising these effects requires further research. Group differences in plasticity effects have been important in developing the HFS technique but individual differences may prove to be more useful in predicting cognitive abilities.

2.3

Examining underlying mechanisms of neglect patients' reaction to the Wall method through flash visual evoked potentials

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With current diagnostic methods it is difficult to distinguish between spatial neglect and loss of vision. With inclusion of the Wall method (the patient sits with the ipsilesional side next to a wall) in the examination of patients, some neglect patients move their gaze towards the contralesional side indicating neglect. To study the impact of the Wall method, this study aims to determine if the method's underlying mechanisms can be identified by means of flash visual evoked potentials (VEP). One patient with left-sided spatial neglect and seven healthy subjects participated in the study. Electroencephalography was recorded from relevant cortical areas, while 3 Hz left- and right-sided flash stimuli from green LEDs were presented in the visual space with and without inclusion of the Wall method. The hemispheric differences in power spectrum between the patient and the healthy subjects were evaluated with factors of stimuli (left- and right-sided) and Wall method (inclusion and exclusion). A significant difference was found between the healthy subjects and the patient ($p<0.05$). Furthermore, a significant difference between the left- and right hemispheric VEP was found in the patient without the inclusion of the Wall method ($p<0.05$), but not when the Wall method was included. The results indicate the presence of a hemispheric difference between healthy subjects and the patient and a reduction of this difference with inclusion of the Wall method for the patient, but the underlying mechanisms of the Wall method were not clearly determined as the single electrode sites were not analysed because of the limited study population.

2.4

Effects of intermittent theta-burst stimulation on interhemispheric inhibition throughout stroke recovery

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Following motor cortex (M1) stroke, there is an increase in interhemispheric inhibition (IHI) initiated by the unlesioned cortex, which has been implicated in poor recovery. Previously, we used implanted electrodes in the contralateral M1 to deliver low-intensity intermittent theta-burst stimulation (iTBS; bursts of 3 pulses at 50Hz delivered at 5Hz) and showed using intracellular recordings from single neurons that this acutely reduced IHI in normal rats and improved motor recovery subacutely following stroke. The present study aimed to determine whether iTBS modifies IHI subacutely in the rat. To study effects of stroke and iTBS, lesions were induced by injecting Endothelin-1 into M1 and sub-cortex and electrodes implanted to measure IHI in freely-moving animals. Sham stimulation or iTBS was delivered for 15 days, followed by three weeks of no stimulation. Behaviour was recorded throughout, using grid walking and pasta handling tasks. Baseline IHI was 17.0 ± 4.9% and was increased to 31.5 ± 6.3% one week following lesion induction (paired t-test: $p<0.05$; $n=21$). In the final week of the study, animals receiving iTBS showed a reduction in foot faults from their post stroke grid walking performances of 43.9 ± 8.5% ($n=12$), compared with 8.40 ± 22.3% ($n=8$) worsening of performance in the sham group ($p<0.05$). In addition, delivery of iTBS reduced IHI to a greater degree than the spontaneous reduction observed in the sham group (linear mixed model: $p<0.05$), both in the weeks during and following stimulation. Our results show that IHI and behavioural recovery are modified by iTBS stimulation, and suggest that IHI reduction is associated with recovery following iTBS stimulation.

2.5

The subthalamic nucleus modulates striatal dopamine release from a distinct population of dopamine neurons

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Precise striatal dopamine release from terminals of substantia nigra pars compacta (SNc) neurons is crucial for normal function of the basal ganglia, which is involved in motor control and impaired in Parkinson's disease (PD).We have shown that SNc dopamine activity is modulated by endocannabinoids and that this mechanism is initiated by the subthalamic nucleus (STN). Recent anatomical evidence has revealed that STN neurons terminate on dopamine neurons which preferentially project to the posterior (tail) striatum over the centre (dorso-lateral) striatum. The tail striatum could therefore be an important target for the investigation of STN-initiated endocannabinoid modulation of dopamine release. We investigated how both basal and evoked-dopamine release differ between the centre and tail striatum. Experiments were conducted in urethane-anaesthetised Wistar rats (~290g). Fast-scan cyclic voltammetry was used to measure evoked-dopamine release following electrical stimulation (300µA, 2ms, 60Hz, 2s train) of the STN and SNc. A novel electrochemical technique – fast-scan controlled adsorption voltammetry – was used to measure basal dopamine levels. Basal dopamine level was significantly higher in the centre striatum (333±31nM) compared to the tail striatum (242±48nM). STN-evoked dopamine release was larger and faster in the tail striatum (Δ53.4±13.9nM; tau, 1.9±0.3s) compared to the centre striatum (Δ13.8±4.1nm; 16.2±3.3s). The reverse occurred with SNc-evoked dopamine release as it was larger in the centre striatum (Δ403.5±146.9nM) compared to the tail striatum (Δ9.2±4.2nM). These results confirm that STN neurons terminate on dopamine neurons which preferentially project to the tail striatum. This new information is of particular interest given the role of the STN in both symptoms and treatment of PD.

3.
Don't have it yet

4.1

Synaptic triad arrangement within an aversive pathway in the normal uninjured brain

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Bursting activity of midbrain dopamine neurons promotes reward-related behaviors. Strong and reliable inhibitory pauses in midbrain dopamine cell activity, in response to stimuli predicting no reward or aversive non-rewarding negative events, suggest that there are multiple inhibitory inputs to the somata and primary dendrites of these neurons. We investigated this hypothesis in a recently discovered pathway involving GABAergic neurons in the rostromedial tegmental nucleus (RMTg) that innervate midbrain dopaminergic neurons in the posterior ventral tegmental area (pVTA). Viral vector technology was used to selectively target GABAergic RMTg neurons in adult male Sprague-Dawley rats. The synaptic innervation by these targeted neurons onto immuno-labelled tyrosine hydroxylase-positive pVTA dopaminergic neurons was investigated using transmission electron microscopy of serial sections. RMTg GABAergic axon terminals formed symmetrical synapses with pVTA dopaminergic dendrites. Three GABA+ve presynaptic terminals were traced through 25-35 serial sections and one of these was tracked to its unmyelinated axonal origin. Importantly, there was a complex synaptic triad in all 13 examined synapses and no multiple synaptic innervation of dopaminergic somata. Specifically, RMTg GABAergic presynaptic terminals were consistently innervated by one or two asymmetric, presumably glutamatergic, synapses. This is the first description of a complex pattern of inputs onto RMTg GABAergic terminals that innervate midbrain dopaminergic dendrites. We hypothesize that excitatory synapses onto the GABAergic terminals could modulate the inhibitory GABAergic synapse on the dopaminergic dendrites, thus fine-tuning inhibitory signalling during negative-reward processing. Our findings may have important implications for understanding drug addiction, which is characterized by dysregulation of the non-reward circuit investigated. This circuit may also be affected in schizophrenia.

4.2

ADAMTS4 AAV-gene therapy combined with rehabilitation is therapeutic after spinal cord injury

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Reactive astrocytes are key contributors to the deposition of chondroitin sulphate proteoglycans (CSPGs) after spinal cord injury (SCI), which are potent inhibitors to axon regeneration and plasticity. A disintegrin and metalloproteinase with thrombospondin motifs-4 (ADAMTS4) is a human enzyme that catalyses the proteolysis of CSPG protein cores. Infusion of ADAMTS4 into the damaged spinal cord was previously shown to improve functional recovery after SCI; however, this therapy is limited in its enzyme form. Gene therapy is a method that allows for long-term expression of therapeutic molecules. Since astrocytes play an important role in SCI pathology, we created an AAV vector that elicits selective, robust and widespread ADAMTS4 gene expression in spinal cord astrocytes. Primary spinal cord astrocyte cell cultures that were transduced with AAV-ADAMTS4 showed increased ADMATS4 expression. This led to decreased TGFβ1-induced increases in CSPGs. Following this, in a spinal cord contusion rodent model sustained expression of ADAMTS4 expression was achieved, which led to widespread degradation of CSPGs. AAV-ADAMTS4 resulted in significantly decreased lesion size, increased neuroplasticity and improved motor functions after moderate contusive SCI. Whilst histologically, the effects of AAV-ADAMTS4 appeared to be large, improvements to motor functions were only modest. Hindlimb-specific exercise rehabilitation was then used as a method to drive and strengthen the formation of beneficial connections whilst pruning aberrant connections. Indeed, the combination of hindlimb rehabilitation with AAV-ADAMTS enhanced the therapeutic effect. Thus, widespread and long-term degradation of CSPGs through AAV-ADAMTS4 gene therapy, from a single administration, represents a promising candidate for clinical translation.

4.3

Changes in midbrain dopamine circuitry in the maternal immune activation rat model of schizophrenia

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Schizophrenia is a debilitating neuropsychiatric disorder that is prevalent in ~1% of the population worldwide. Despite extensive research, however, little is known about the microscopic changes in neural circuits that may contribute to the behavioural manifestation of schizophrenia. Recently, we have identified a complex pattern of inputs onto the dopaminergic neurons in the posterior ventral tegmental area (pVTA) of the midbrain, involving inhibitory inputs from the rostromedial tegmental nucleus (RMTg), which in turn are modulated by excitatory glutamatergic inputs. Here, we investigated the hypothesis that the underlying causal mechanism of schizophrenia is due to altered synaptic input onto pVTA dopaminergic neurons, which results in excessive dopamine release. We combined cutting-edge lentiviral technology and a peroxidase-immunogold double labelling method to selectively label RMTg GABAergic neurons and pVTA dopaminergic neurons. Three-dimensional serial transmission electron microscopy was then used to analyse the synaptic inputs to the pVTA in the maternal immune activation (MIA) rat model of schizophrenia versus controls. We found a marked decrease in the size and length of GABAergic synapses between RMTg GABAergic neurons and pVTA dopaminergic neurons of MIA rats compared to the control rats. Furthermore, we found that glutamatergic axons modulating RMTg GABAergic inputs are located more distally to the GABAergic synapses in the MIA rats compared to the controls. These data suggest that in schizophrenia, impaired inhibition of pVTA dopaminergic neurons results in excessive release of dopamine, leading to a hyperdopaminergic state of the brain and manifestation of schizophrenic symptoms. Further understanding of the core mechanism underlying schizophrenia will allow for a mechanism-driven approach to pharmacotherapy.

4.4

Ketamine effects on EEG during therapy of treatment-resistant generalized anxiety and social anxiety

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Ketamine is swiftly effective in a range of neurotic disorders that are resistant to conventional antidepressant and anxiolytic drugs. The neural basis for its therapeutic action is unknown. Here we report the effects of ketamine on the EEG of patients with treatment-resistant generalised anxiety disorder (GAD) and social anxiety disorder (SAD). Twelve patients with refractory DSM-IV GAD and/or SAD provided EEG during 10 minutes of relaxation before and 2-hours after receiving double-blind drug administration. Three ascending ketamine dose levels (0.25, 0.5 and 1 mg/kg) and midazolam (0.01 mg/kg), were given at 1-week intervals to each patient, with the midazolam counterbalanced in dosing position across patients. Anxiety was assessed pre- and post-dose with the Fear Questionnaire (FQ) and HAM-A. Ketamine dose-dependently improved FQ scores but not HAM-A scores, decreased EEG power most at low (delta) frequency and increased it most at high (gamma) frequency. Only the decrease in medium-low (theta) frequency at right frontal sites predicted the effect of ketamine on FQ score. Ketamine produced no improvement in Higuchi's fractal dimension at any dose, nor systematic changes in frontal alpha asymmetry. Ketamine may achieve its effects on treatment-resistant GAD and SAD through reduction in right frontal theta, a mechanism common to conventional anxiolytic drugs. However, in the current study midazolam did not have such an effect. Beyond anxiety disorders, it remains to be determined whether, unlike conventional anxiolytics, ketamine changes right frontal theta when it is effective in treatment-resistant depression.

4.5

Glucocorticoid modulation of accumbal dopamine release is disrupted during amphetamine withdrawal

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Stress plays an important role in drug seeking and relapse. The ventral hippocampus is a critical interface between stress and reward neurocircuitry, with high levels of glucocorticoid receptor (GR) expression and stimulatory projections to the nucleus accumbens (NAc). The goal of our research is to establish whether GR activation in the ventral hippocampus directly modulates dopamine release in the NAc, and to determine how this is affected by psychostimulants to produce stress sensitivity during drug withdrawal. Infusion of a stress-relevant concentration of corticosterone (0.48 ng/µl) in the ventral hippocampus of male rats increased dopamine release in the NAc, measured by *in vivo* chronoamperometry. This effect was dependent upon cytosolic GRs in the ventral hippocampus, as it was blocked by pre-treatment with mifepristone and also by conjugating corticosterone to BSA to reduce its cellular permeability. Western blot experiments demonstrated reduced GR expression in the ventral hippocampus of rats undergoing amphetamine withdrawal, and corticosterone infused in this region actually reduced dopamine release in the NAc. This is likely a result of corticosterone's predominant effects on mineralocorticoids receptors in the ventral hippocampus during amphetamine withdrawal, since the effect was blocked by spironolactone. Combined, findings show that glucocorticoids can stimulate accumbal dopamine release via actions in the ventral hippocampus in drug naïve conditions. However, amphetamine withdrawal is characterized by attenuated glucocorticoid-induced accumbal dopamine release, which we suggest underlies dysphoric states during withdrawal. Supported by NIH NIDA grant R01 DA019921.

5.1

Reassessing the functional role of fMRI BOLD variability in cognitive performance

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BOLD variability (BOLD-var) is a powerful predictor of age and cognitive performance. This is commonly interpreted as BOLD-var being uniquely positioned to measure adaptive properties of neural systems (e.g., dynamic range) that facilitate fast responding. However, evidence for this comes primarily from blocked designs with trials fixed to a length substantially longer than response times (RTs). Consequently, it is possible that during task blocks, participants – particularly fast responders – toggle between on-task states (in between stimulus and response) and off-task states (during response-to-next-stimulus interval, RSI). If true, it might not be the case that increased BOLD-var endows people with fast-responding abilities, but simply that increased BOLD-var in fast responders is an artefact of fixed-length designs. To test this hypothesis, we compared BOLD-var effects from trials that were of a fixed-length or self-paced (i.e., terminating upon a response). We predicted that fixed-length blocks would be associated with (i) greater BOLD-var and (ii) stronger relationships between RT and BOLD-var than self-paced conditions, as fixed-length trials would result in fast responders having longer RSIs within which to engage in state-switching. Results of partial least squares analyses were mixed. While fixed-length conditions did result in increased BOLD-var, the relationship of BOLD-var with RT was not stronger in fixed-length relative to self-paced conditions. However, follow-up analyses revealed the RT–BOLD-var relationship was not significant when only fixed-length conditions were analysed. While failing to replicate previous findings, this result may reflect the restricted age range of our participants. Nevertheless, these findings raise questions about the functional significance of BOLD-var as a measure of adaptive brain function.

5.2

Structural correlates of dyslexia and dyscalculia: Revisiting common assumptions

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Learning disabilities such as dyslexia, dyscalculia, and their comorbid manifestation are prevalent, affecting as much as 15% of the population. Structural neuroimaging studies have indicated that beyond their behavioral manifestations, these disorders can be related to differences in gray and white matter characteristics. Here, we present evidence to nuance those claims, and show that the between-group differences typically associated with dyslexia and dyscalculia are not systematic, in a sample of 48 adults with dyslexia, dyscalculia, both disorders, or none. Using Bayesian hypothesis testing, we provide support for the null hypothesis of no group difference across a range of structural brain measures, including gray matter volume, cortical thickness, surface complexity, and fractional anisotropy (all quantified by Bayes Factors). These results were corroborated by all equivalent frequentist analyses (all $p > .05$). We conclude that the neuroanatomical differences commonly associated with dyslexia and dyscalculia might not be as reliable as previously thought, or that they may not persist into adulthood, and discuss the implications of these findings. Importantly, we further advocate for a precise quantification of the evidence for structural correlates of these disorders, to improve on current practices relying solely on dichotomized findings based on statistical significance.

5.3

The role of location details in the construction of future events

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The scene construction hypothesis proposes that spatial information, such as location details, contributes more to the process of imagining events than other details (e.g., people), yet few studies have investigated this question. We have previously shown that repeatedly imagining the same future event results in drastic reductions in constructive demands, and leveraged this phenomenon to investigate the relative contributions of location and people details to event construction. Participants imagined future events involving two memory details (person, location) and then reimagined the event i) exactly the same (*no change*), or ii) with a different person (*person change*) or iii) in a different location (*location change*). We predicted that if generating spatial information is particularly important for event construction, a change in location will have the greatest impact on three measures of constructive demand: response time (RT), construction difficulty and level of detail. For RT, a Bayesian model comparison favoured a model in which location changes had the greatest impact on construction times, followed by the person change and no change conditions. A Bayesian *t*-test complemented by Bayesian parameter estimation confirmed the difference between person and location change conditions was present and meaningful. In contrast, for construction difficulty and detail, Bayesian model comparisons favoured a model in which location and person change conditions did not differ, but were associated with greater difficulty and less detailed events than the no change condition. These results suggest that while location details influence the speed of construction more than other details, consistent with theories highlighting the central role of spatial processing in episodic simulation, other autobiographical details also facilitate this constructive process.

6.1

Using neural fields to model motor evoked potentials due to transcranial magnetic stimulation

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Neural field models, in which populations of neurons are described through ensemble-averaged properties such as firing rate and axonal flux, have been well-used to describe electroencephalogram (EEG) effects in natural sleep, anaesthesia and epilepsy. Changes in EEG due to stimulation by electromagnetic fields have also been studied. However, experimental data concerning transcranial magnetic stimulation (TMS) is dominated by measurements of motor-evoked potentials (MEPs). To use neural fields for TMS, a model of the MEP is required. In this work, an existing model has been augmented by addition of populations of cells describing stages of the MEP pathway previously neglected by neural field models. The model includes coupled populations of excitatory and inhibitory layer 2/3 cortical neurons, stimulated by an external field. These populations feed an additional population of layer 5 neurons, which also couples weakly to the external field. The layer 5 neurons feed motoneurons, from which a measure of the motor-evoked potential is constructed. After some tuning of parameters, the extra populations have resulted in a better model of the MEP than previously present in neural field models. The model reproduces the non-linear response to an increase in stimulation amplitude. With a paired-pulse protocol it reproduces the experimental effects of intracortical facilitation and long-interval intracortical inhibition, though it shows only weak short-interval intracortical inhibition. The experimental waves of activation from the layer 5 neurons, direct and indirect, are not adequately reproduced. Small changes in synaptic weight can give much greater changes in MEP response. In conclusion, the model is promising but it raises questions about whether neural field models are really appropriate for the study of many TMS effects.

6.2

Effect of background music and dialect variation on auditory ERPs: Research plan

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Sociolinguistic studies indicate that American accents are highly normative in popular music singing, to the extent that it requires awareness and effort for a New Zealander to sing in a New Zealand accent (Gibson and Bell 2012). Following exemplar models of speech perception and production (Pierrehumbert 2006), this project argues that phonetic variants become associated with social and contextual categories, so that speech is produced in a context-appropriate manner. We learn, for example, to speak louder in a car, and do so even in a quiet environment with the engine off (Hay et al. 2018). My hypothesis is that singing is so contextually different to speech that when a listener is expecting to hear singing, they will also expect an American accent. I discuss the design of an auditory ERP experiment to test this hypothesis. Van Berkum et al. (2008) found that N400 effects are associated not just with semantic incongruity, but also with words that are incongruent with speaker voice. Attempts to extend this finding to expectations about speaker dialect (e.g. Loudermilk 2013, Martin et al. 2015) have had mixed results, with incongruence effects often occurring in later ERP components, rather than in N400. The proposed experiment involves variably priming popular music contexts, then presenting words in New Zealand or American accents. Along with the experiment design, I discuss preliminary findings from a pilot study of five participants which show that auditory ERPs N100, P200 and N400 can be identified when listeners hear words in the context of background music.

6.3

The neural basis of stuttering: where and when do differences in brain activation occur?

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One child in twenty develops stuttering. For a significant proportion, the disorder persists into adulthood. Adults with persistent developmental stuttering (APDS) are faced with well-documented vocational and social challenges (e.g., fear of speaking). Recent brain imaging studies have linked stuttering with abnormalities in neural processing. While such studies have provided convincing evidence for a neural basis of stuttering, it is not known what the observed differences in APDS represent – are they the key components of the long searched for *cause* of stuttering, or should they be regarded simply as *consequences* of stuttering? To answer this fundamental question, studies that provide accurate localisation of neural differences are necessary, but insufficient if conducted in isolation. Because speech production depends on rapidly changing neural processes, examination of the time course of neural activations is also vital. We give an overview of a New Zealand-based study with the overall aim of determining which component(s) of the neural speech production network constitute the primary deficit of stuttering, and which are associated with secondary deficits. For the first time, our study will combine a technique with excellent localisation ability (fMRI) with another with exceptional temporal resolution (EEG) to map the neural basis of stuttering. Our predictions are formulated from a network perspective, using the DIVA neurocomputational model as framework. The study will extend our fundamental understanding of the neural basis of stuttering and lead to the development of a biologically and behaviourally plausible neurocomputational model of stuttered speech.

6.4

Patterns of brain activation during overt speech production in adults with persistent developmental stuttering

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Stuttering is a debilitating speech disorder, affecting 1% of people world-wide. Advances in neuroimaging techniques provide the opportunity to study patterns of neural activity in people who stutter (PWS) during overt speech production. Several differences between the neural functioning of PWS and fluent speakers have been noted in the literature. Yet, the question remains; which differences are the primary cause of stuttering and which are consequential? To address this, functional Magnetic Resonance Imaging (fMRI) data was gathered using a sparse temporal sampling technique in adult PWS and controls across 4 randomised conditions: (1) speech production – naming pictures aloud; (2) auditory masking – naming pictures while not hearing their own production; (3) speech perception - listening to a recording of their own speech, and (4) baseline – looking at scrambled pictures. For my Honours project, I am analysing the data of 10 PWS and their controls. Based on previous studies and the DIVA neurocomputational model of speech production, we will test the hypothesis that PWS show differences in activation in the basal ganglia, frontal (premotor) areas and temporal (auditory) areas. We predict that differences in auditory areas (feedback loop of speech production) will occur as a consequence of the problems in the motor feedforward loop, and will therefore be eliminated by auditory feedback masking. We also expect that this difference will be eliminated when listening to their own speech production. The results will increase our understanding of the neural basis of stuttered speech production, and contribute towards a neurocomputational model of speech production in PWS and more effective treatment options.

6.5

Neurophysiological correlates of stuttered speech: Creating a pipeline for removal of muscle artefacts during overt speech production

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Recent studies have provided convincing evidence for a neural basis of stuttering. Most of these studies used techniques with good spatial but poor temporal resolution. Because speech production depends on rapidly changing neural processes, examination of the time course of neural activations is also vital. To date, few studies in People Who Stutter (PWS) have used temporally sensitive techniques in an attempt to capture these fast-changing processes. These studies have suggested that timing plays an important role in stuttering, as evidenced by amplitude and latency differences in the preparatory and speech perception phases of speech. However, we do not know yet what happens during overt speech production as analysis of electro-encephalogram (EEG) signals during the production of speech is complicated by the presence of artefacts from facial and articulatory movements. These electromyographic (EMG) signals may obscure the brain activity of interest. The aim of this project is to create a pipeline for the removal of EMG artefacts from overt speech EEG during an overt picture naming task. After high-pass filtering and standard artefact removal, a Blind Source Separation with Canonical Correlation Analysis technique (BSS-CCA) was used to identify and remove EMG signals from electrophysiological recordings. This method allows reconstructing a cleaned cortical signal for analysis whilst minimising the introduction of additional signal contamination in the process. Therefore, the use of BSS-CCA to remove muscle artefacts enables examination of the cognitive components of interest without interference from EMG signals. This will allow us to study the fast-changing brain processes during stuttered speech production.

6.6

Investigating the role of leptin in arcuate AgRP neuron development

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Maternal obesity during pregnancy increases the risk of the offspring themselves developing obesity later in life. In part, this is likely due to altered development of the hypothalamic arcuate nucleus (ARC) circuitry, a region of the brain central to body weight regulation. While structural changes in the ARC have been characterised, the mechanisms underpinning these changes remain poorly understood. Preliminary data suggests that leptin signalling, which is known to play a critical role in modulating the development of the ARC projection pathways, may be altered. Here, we aim to better understand leptin's contribution to the normal postnatal development of ARC Agouti-relate peptide (AgRP) neurons. Initially, we aim to characterise the development of normal leptin signalling in the ARC across the early postnatal period. To do this, qPCR will be used to measure the expression of Socs3, a known leptin-responsive gene, in leptin treated tissue compared to saline treated control, at a variety of ages. Following this, the expression of a number of developmentally-associated putative leptin-responsive genes, previously identified by ChIP-Seq analysis, will be measured in samples derived from the ARC of wild-type mouse pups following leptin (or saline, control) injection. Finally, RNAscope, a novel in situ hybridisation technology, will be used to investigate the expression of the putative leptin-responsive genes within AgRP neurons.

6.7

Circadian lights in a hospital setting to improve sleep, recovery and decrease psychological distress: Study concept and pilot baseline assessment results

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Light is a key environmental zeitgeber that entrains the circadian pacemaker. Specific effects of light depend on its timing, intensity and spectral composition; intrinsically photosensitive retinal ganglion cells are the most sensitive to short wavelength light. Insufficient daytime illumination and evening light deregulate circadian rhythms and sleep, which can negatively impact overall health and quality of life. Hence long-stay hospital inpatients can suffer considerable sleep and circadian disturbances. We hypothesize that installing lights that mimic natural sunlight variation would result in healthy circadian rhythms, improved sleep and better health outcomes in a hospital setting. We are comparing sleep, psychological and healthcare outcomes in two lighting settings – current and circadian lighting in an older adult rehabilitation unit. Objective sleep and circadian measures (actigraphy), questionnaires on anxiety and depression, daytime alertness, sleep quality, overall well-being and chronotype are being used. For pilot baseline assessment we studied 14 long-stay (≥7d) inpatients for 7-22 days. Study sample was 64% male, median 79 years-old, and spent 2-50 days in the hospital prior to the study. Patients exhibited a variety of sleep issues, with low duration and poor quality. Average scores per person indicate that 21%, 36% and 57% of patients had signs of moderate/severe anxiety, moderate/severe depression, and sub-threshold/clinical insomnia, respectively. This study is one of the first to investigate the effects of improved lighting in a hospital setting. Pilot baseline data indicate substantial sleep deregulations, high levels of anxiety and depression and daytime sleepiness. We are currently conducting a full-scale efficacy trial.

6.8

Pericytes can contribute to tumour immune system evasion in glioblastoma multiforme through dampened expression of ICAM-1, VCAM-1 and MCP-1

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Glioblastoma Multiforme (GBM) is the most aggressive, fatal, yet most common form of brain malignancy in adults. Despite advances in immune-based treatments for other modes of cancer, GBM remains a challenge due to its ability to dampen immune responses via mechanisms not yet fully understood. An emerging hallmark of GBM pathogenesis is tumour microenvironment immunosuppression. The microenvironment comprises a mixture of malignant tumour cells, stroma, blood vessels and infiltrating inflammatory cells. Despite advances in understanding the contribution of these cells in establishing an anti-inflammatory microenvironment, the contribution of pericytes, an important neurovascular mural cell that forms the blood-brain barrier, has been inadequately studied. Therefore, we investigated the changes in immune responses between the non-neoplastic brain and GBM-derived pericytes isolated directly from the same patient's tissues obtained during neurosurgery. Our results show that GBM-derived pericytes showed significantly lower induction of pro-inflammatory mediators Intracellular Adhesion Molecule 1 (ICAM-1) ($p<0.0001$), Vascular Cell Adhesion Molecule (VCAM-1) ($p<0.05$), and Monocyte Chemoattractant Protein 1 (MCP-1) ($p<0.0001$) in response to a pro-inflammatory cytokine, Interleukin 1 beta (IL-1ß) when compared to patient-matched non-neoplastic brain pericytes. Due to the involvement of these molecules in immune cell recruitment and infiltration, this decreased response may contribute to the maintenance of GBM microenvironment immunosuppression. This highlights potential targets for alleviating tumour microenvironment immunosuppression and aid in immunotherapy-based treatments for GBM.

6.9

Age effects on subareas of the amygdala

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The amygdala – an anatomical composite of three major subareas (centromedian, laterobasal, and superficial) – has been reported to decrease in size with increasing age and also to differ in size between male and female brains. However, findings are rather inconsistent across existing studies, possibly reflecting differences in the examined cohorts or the analysis approach. Thus, we investigated possible effects of age and sex on the amygdala as a whole as well as its subareas. For this purpose, we enhanced conventional imaging-based information with microscopically defined cytoarchitectonic probabilities in a sample of 100 healthy subjects (50 men / 50 women) aged 18 – 69 years. We observed significant negative correlations between age and all subareas of the amygdala indicating decreases over time, but with subarea-specific trajectories. In addition, we detected a significant quadratic association with age in the left hemisphere for the superficial subarea suggesting an accelerating volume loss over time. Such regional information may serve as a frame of reference in future studies, not only for normative samples but also potentially for clinical populations known to present with an atypical atrophy of the amygdala. There were no sex differences suggesting that the size of the amygdala is similar in male and female brains, at least when properly accounting for total intracranial volume.

7.

Prion-like propagation of alpha-synuclein assemblies in distinct synucleinopathies

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Protein intracellular inclusions within the central nervous system are hallmarks of several progressive neurodegenerative disorders in man. The protein constituents of those deposits and the affected regions within the brain differ from one neurodegenerative disorder to another. Until recently, the vicious cycle consisting of spread, seeded assembly and accumulation over time within the central nervous system of misfolded protein aggregates was thought to be restricted to the prion protein PrP. Recent reports suggest that other protein aggregates spread and amplify within the central nervous system leading to distinct diseases. I will present data illustrating the propagation and amplification propensities of alpha-synuclein assemblies. I will discuss the nature of protein assemblies that are “infectious”, how they bind to the cell membranes, what they bind to and the cellular consequences of binding. I will present a quantitative assessment of their uptake, transport and export. I will show data demonstrating that pathogenic protein assemblies disrupt the endo-lysosomal membranes to reach the cytosol where they amplify. I will describe how and why different alpha-synuclein polymorphs cause distinct diseases. Finally, I will discuss the prerequisites of strategies specifically targeting the propagation of alpha-synuclein assemblies.

8.1

Non-neuronal cells enable transmission of α-synuclein in Parkinson’s disease

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The molecular hallmark of Parkinson’s disease (PD) is the aggregation of α-synuclein (α-syn) into fibrillary assemblies in nerve cells. The aggregates, termed Lewy bodies and Lewy neurites, are first found in the vagus nerve and olfactory bulb. More and more evidence is showing that α-syn spreads in a prion-like fashion transferring aggregated α-syn from cell to cell. The involvement of non-neuronal cells in this process has been studied, but evidence of the underlying mechanisms in human tissue is lacking. Here we utilise primary neuronal cultures from human biopsies (consisting of functional neurons, microglia, astrocytes, oligodendrocytes and pericytes) and pure pericyte cultures; our *in vitro* results show α-syn precipitates are endocytosed by all cell types, but most efficiently by microglia and pericytes. Using pure pericyte cultures, we demonstrate intercellular transport of α-syn through tunnelling nanotubes and the induction of an inflammatory response. Our *in situ* work shows that the number of cells with intracellular α-syn precipitates is case dependent but affects all major cell types. Within the human olfactory bulb, neurons contain large lewy bodies whereas the non-neuronal cells contain smaller aggregates. This is the first time that a human study quantified the relative importance of all cell types involved in α-syn pathology. We show evidence that α-syn spread is attributed, in part, to intercellular transmission between non-neuronal cells trough tunnelling nanotubes. The active involvement of non-neuronal cells such as pericytes in α-syn transfer has previously been overlooked, but may offer additional therapeutic targets to conventional PD therapy.

8.2

Quantification of non-neuronal cells containing intracellular α-synuclein in the human Parkinson's disease olfactory bulb

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The neuropathological hallmark of Parkinson's disease (PD) is the presence of aggregated α-synuclein (α-syn) in the form of Lewy bodies and Lewy neurites. It has been well described that α-syn aggregates are found intracellularly within neurons with the capability of being passed on from one neuron to the next. However, we know little about the involvement of non-neuronal cells in the pathophysiology of PD. One of the first areas of the brain to be affected by α-syn pathology is the olfactory bulb, presumed to be the cause of the loss of smell (anosmia) years to decades before the onset of motor symptoms. Within the olfactory bulb, the majority of α-syn accumulates within a region called the anterior olfactory nucleus (AON), a relay point for neurons of the olfactory system. Here, we set out to quantify the presence of intracellular α-syn aggregates in non-neuronal cells in the human PD olfactory bulb. Three sections, 500 µm apart, from 11 human PD olfactory bulbs and eight control human olfactory bulbs were immunolabeled for phosphorylated α-syn, PDGFRβ for pericytes, GFAP for astrocytes and IBA-1 for microglia. Sections were imaged using a slidescanning microscope; cells with presumed intracellular α-syn were counted and reimaged using a confocal microscope to confirm intracellular α-syn aggregates in all three cell types. Within the AON, on average 3.5 pericytes/mm^2, 2.8 astrocytes/mm^2 and 6.7 microglia/mm^2 were confirmed to have intracellular α-syn. This study demonstrates the importance of non-neuronal cells in PD pathophysiology, in which non-neuronal cells may actively contribute to the disease process.

8.3

Distinct effects of apathy and dopamine on effort-based decision making in Parkinson's disease

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Apathy is a common and disabling complication of Parkinson's disease (PD), but its aetiology remains unclear. Intriguingly, the neural substrates associated with apathy also sub-serve effort-based decision making (EBDM) in animal models and humans. Furthermore, the dopaminergic system plays a core role in motivating effortful behaviour for reward, and its dysfunction has been proposed to play a crucial role in the aetiology of apathy in PD. We hypothesised that disrupted EBDM underlies the syndrome of apathy in PD, and that this may be modulated by the dopaminergic system. An EBDM task was administered to 39 patients with PD, with and without clinical apathy, ON and OFF their normal dopaminergic medications across two separate sessions, and matched controls. On a trial-by-trial basis participants decided whether to accept or reject varying offers of monetary reward in return for exerting different levels of physical effort via handheld dynamometers. The primary outcome variables were choice and the vigour of squeeze. Both apathy and dopamine depletion reduced offer acceptance, but effects were dissociable. While apathy reduced acceptance of predominantly low reward offers, dopamine increased responding to high effort, high reward offers, independent of apathy status. Dopamine also exerted a main effect on motor vigour while apathy did not. The findings demonstrate that EBDM is disrupted in PD apathy, but in a manner distinct to that caused by dopamine depletion. They provide evidence of a cognitive mechanism underlying apathy, and suggest its occurrence is not simply secondary to dopaminergic depletion of mesocorticolimbic pathways.

8.4

Parkinsonian tremor can be diminished by willpower

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We have observed that a number of patients with Parkinson's can suppress their tremor at will for brief periods. To our knowledge, the ability to consciously diminish one's resting tremor has not yet been assessed empirically. We examined changes in tremor characteristics during voluntary tremor suppression in 16 patients presenting with rest tremor in their upper limb. A tri-axis accelerometer on the index finger of the most affected hand measured tremor oscillations. Surface electromyography (EMG) measured changes in neuromuscular activity of the forearm flexor digitorum superficialis (FDS) and extensor digitorum (ED) muscles. Participants completed a four minute trial consisting of alternating 30 s periods of resting and attempted tremor suppression. Bayesian multilevel modelling found a reduction in tremor amplitude of 0.42 log(mm) (95% credible interval [0.21, 0.64]) during suppression compared to rest. Spectral analyses of tremor displacement revealed a peak power decrease of 0.9 log(W/Hz) [0.44, 1.38], and an increase in the frequency of peak power of 0.19 Hz [0.07, 0.32] during suppression compared to rest. No change in mean EMG amplitude was found; however, suppression of tremor was associated with a peak power decrease of 0.36 log(W/Hz) [0.01, 0.72], and an increase in the frequency of peak power of 0.83 Hz [0.28, 1.39] in FDS, but not ED. Both the amplitude and frequency components of tremor and associated flexor muscle activity were modulated by voluntary suppression. These data show it is possible to exert significant conscious control over parkinsonian rest tremor.

8.5

Significant-others underreport the impact of hallucinations in Parkinson's disease patients with normal cognition

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Individuals with Parkinson's disease (PD) often experience hallucinations throughout the progression of the disease. Cognitive impairment, sleep disturbances and a lack of reporting tools has resulted in hallucinations being inaccurately reported by PD patients and their significant-others (SO). To determine whether there is a difference between hallucinations that are self-reported by participants and by their SO, 120 PD participants and their SO completed the recently validated Psychosis and Hallucinations Questionnaire. Fifty-eight PD participants were classified with normal cognition (PD-N), 53 with mild cognitive impairment (PD-MCI) and 9 with dementia (PDD). The mean hallucination scores from each group of PD participants (PD-N = 1.3, PDMCI = 5.2, PDD = 8.2) and their SO (PD-N = 1.0, PDMCI = 1.8, PDD = 5.9) were collected. Poisson regression was used to determine whether there were discrepancies between participants and SO reporting of hallucinations across the cognitive groups. The mean hallucination scores reported by SO were lower than PD participants, but only underreporting in the PD-N group was significant ($p < 0.001$). No differences were found between PD participant and SO reports in the PD-MCI or PDD groups. This indicates that SO are less able to detect hallucinations in PD patients with preserved cognition, which may increase caregiver stress.

Poster 9.1

Characterisation of classical Huntington's disease neuropathology in a human tissue microarray

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Huntington's disease (HD) is a genetic neurodegenerative disease that still remains without a specific therapeutic treatment. One of the hurdles in therapeutic discoveries is the ability to screen for potential targets in a high-throughput manner. A potential tool to aid in this is the tissue microarray (TMA); a platform that consists of various tissue samples arrayed onto a single glass slide. This study aims to investigate whether the TMA is a suitable platform to study HD. Neuropathological features of HD were characterised in a human TMA that consisted of up to 28 control tissue samples and up to 28 HD tissue samples. 3'3-diaminobezidine (DAB) immunohistochemistry was performed on the TMA sections to detect pyramidal cells (SMI-32) and mHTT aggregates (1C2 and 1F8). The immunolabeled TMAs were imaged using the automated V-slide scanner and analysed using Metamorph software. A significant 27% reduction in SMI-32$^+$ pyramidal neuronal density was observed in HD samples. Additionally, there was a significant 187% and 84% increase in IC2$^+$ and IF8$^+$mHTT aggregate number respectively in HD. The TMA is a high-throughput screening method capable of generating powerful data. The reduction in pyramidal neurons and increase in aggregation counts seen in this TMA recapitulates changes seen in previous quantitative studies in whole tissue sections. This provides strong evidence that HD neuropathology is still seen within 2 mm cortical sections and as such, suggests that the TMA can not only be used to further investigate HD neuropathology but also as a screening tool for potential therapeutic targets.

Poster 9.2

Resistance to extinction following methamphetamine self-administration in rats

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Problematic methamphetamine use is characterized by a progressive increase in drug use, and high relapse rates even following extensive abstinence. Animal studies have been developed to measure drug-seeking as a correlate of relapse. One approach is to determine whether exposure to an environment that had previously been associated with drug-taking elicits drug-seeking that is resistant to extinction. Accordingly, the current study measured extinction of drug-seeking behaviours following extensive methamphetamine self-administration in rats. Rats self-administered methamphetamine (0.1 mg/kg/infusion, iv) during 10 daily 8-hour sessions. Infusions were paired with the co-incident illumination of a stimulus light. For comparison another group of rats were trained to orally self-administer sweetened condensed milk under the same conditions. Only self-administration of methamphetamine increased as a function of days during testing. Active lever responding on day 1 was approximately 14 responses, and on Day 10 approximately 77 responses. Responding reinforced by sweetened condensed milk was high on Day 1 at approximately 550 responses, and remained high for each of the subsequent test days. A forced abstinence period of 7-days followed the self-administration phase. Drug-seeking was then tested during 20 daily 1-hour sessions. During these tests, responses on the levers had no programmed consequence; neither the reinforcer nor the light stimulus were activated. For both groups, active lever responding on day 1 of the drug-seeking test was high and decreased during subsequent tests. The rate of decay of the function relating lever responses to day of testing was comparable for methamphetamine and sweetened condensed milk self-administration, suggesting similar resistance to extinction. These findings suggest that withdrawal both drug-and non-drug reinforcers can result in reward-seeking that is consistent with addiction.

Poster 9.3

Electrochemical and electrophysiological characterisation of L-DOPA-derived dopamine in rat brain slices

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Parkinson's disease is mainly caused by degeneration of nigral dopaminergic neurons and is most frequently treated with L-DOPA (Levodopa) which ameliorates motor symptoms by increasing dopamine production. However, in spite of over 50 years of clinical use of this drug, it is still uncertain whether L-DOPA-derived dopamine is released only from the remaining dopaminergic neurons, or also from other cells which express aromatic amino acid decarboxylase (AADC), and thus are able to convert L-DOPA to dopamine. Our aim was to compare dopamine production after application of exogenous L-DOPA in two regions of horizontal midbrain slices obtained from Wistar rats: (a) Substantia Nigra pars compacta (SNc; the area of somatodendritic dopamine release); and (b) the posterior lateral hypothalamus (PLH) which has no dopaminergic innervation. Extracellular dopamine was detected using fast-scan controlled-adsorption voltammetry. Dopamine production in the SNc was confirmed electrophysiologically by recording raclopride-dependent inhibition of neuronal firing. Slice perfusion with L-DOPA (50 µM, 15 min) resulted in prolonged increase in dopamine release in the SNc, enhanced by pre-treatment with the MAO blocker, pargyline (10 µM). Unexpectedly, L-DOPA also evoked dopamine release in the PLH, which in the presence of pargyline was substantially higher than in the SNc. We propose that in this non-dopaminergic brain region dopamine is produced and immediately released from glia and endothelial cells which are unable to store (and quickly metabolise, in the presence of MAO block) this neurotransmitter. In contrast, L-DOPA-derived dopamine can be partly stored in nigral neurons and its extracellular release is largely opposed by the dopamine transporter which is highly expressed in dopaminergic neurons.

Poster 9.4

Evaluating the side effect profile of the G-Protein biased Mu opioid receptor agonists Kurkinorin and Kurkinol

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Chronic pain (CP) is a global health problem that affects 1 in 5 New Zealand adults and is the most common reason to visit the doctor. Current mu opioid receptor (MOPr) agonists, such as morphine, used to treat CP have high abuse potential. The induction of on-target side effects such as tolerance and respiratory depression limit their effectiveness. Here we investigate the side effect profile of the structurally novel Salvinorin A analogues Kurkinorin and Kurkinol, using preclinical behavioural models. The dose-response tail withdrawal assay was used to determine the analgesic and tolerant effects. Kurkinorin (ED_{80} = 5 mg/kg) has equivalent potency to morphine (ED_{80} = 6.3 mg/kg), and Kurkinol (ED_{80} = 2.3 mg/kg) was three times more potent, with significantly reduced analgesic tolerance. Further investigation into the ability to induce constipation, one of the most common side effects experienced with chronic administration of MOPr agonists, showed Kurkinorin induced no significant inhibition of small intestinal transit in the charcoal meal assay compared to vehicle ($F(8, 30) = 6.1$, $p = 0.4789$). The accelerating rotarod assay, a measure of motor coordination, showed both Kurkinorin and Kurkinol cause less motor coordination impairment compared to morphine. Furthermore, we have shown that both Kurkinorin ($p = 0.014$) and Kurkinol ($p = 0.012$) show reduced preference for drug-paired chambers in the conditioned place preference assay compared to morphine. Overall, this study highlights the potential of these structurally novel compounds as potent analgesics with reduced abuse liability.

Poster 9.5

In vitro wounding models using the Electric Cell-Substrate Impedance Sensing (ECIS)-Zθ Technology

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Understanding cellular responses to neurotrauma will be important in developing treatments for these conditions. Electric Cell-substrate Impedance Sensing (ECIS) technology is a real-time, impedance-based system to produce highly reproducible wounding models by mechanically disrupting a cell monolayer. This study characterized two *in vitro* wounding models using cultured human cerebral microvascular endothelial cells (hCMVEC) with single electrode (8W1E) and multiple electrode (8W10E+) arrays, in terms of cell migration and barrier functions. Real-time measurement of the hCMVEC migration and barrier function was conducted using the ECIS technology. Wounding was applied at 48 h, a time when the hMCVEC had formed a functional barrier. Levels and localisation of junctional proteins in the cells following wounding were analysed by immunocytochemistry. Following wounding, cell migration was generally faster on the 8W10E+ array in comparison to the 8W1E array. However, barrier function of the cells was not fully restored in either model. Analysis of the endothelial junctional proteins revealed that wounding caused incomplete detachment of cellular materials on the 8W1E array, whereas on the 8W10E+ array, complete detachment of cellular materials was observed. These differences may correspond to different types of injuries. Therefore, we highlight the ability of ECIS to study cellular behaviours in response to different injuries, and its potential to help therapeutic treatments for impaired barrier function following CNS injuries. The established *in vitro* wounding models could be applied to other cell cultures which will advance our understanding of the injury response.

Poster 9.6

Endothelial nitric oxide synthase deficiency leads to increased urea levels in the brain

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Endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO) from L-arginine, and eNOS derived NO is a key regulator of cerebral blood flow dynamics. It has been proposed that cerebrovascular endothelial dysfunction during advanced aging, together with other risk factors, may trigger the neurodegenerative processes in Alzheimer's disease (AD). Mice with eNOS deficiency display age-related memory deficits, amyloid accumulation and tau phosphorylation in the brain, indicating a critical role of eNOS deficiency in the development of AD. In AD brains, eNOS protein expression is dramatically reduced and there is a build-up of urea, the product of amino acid metabolism. This project, therefore, investigated how the urea level in the brain changed in eNOS deficient mice. We found significantly increased urea levels in the cortex of male complete eNOS deficient mice at 14 months of age when compared to their age-matched wild-type controls. Interestingly, male and female partial eNOS deficient ($eNOS^{+/-}$) mice at 4 months of age displayed high levels of urea in the cortex relative to their age- and sex-matched controls. These preliminary data demonstrate the accumulation of urea in the brain of eNOS deficient mice, shedding light on the potential link between eNOS deficiency and the build-up of urea in the brain. Future research is required to further explore the role of cerebrovascular endothelial dysfunction in pathogenesis and/or development of AD. Supported by the Health Research Council of New Zealand.

Poster 9.7

Generalisation of an anxiety process biomarker from speeded response to bimanual fixed time responding

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Goal Conflict Specific 5-12Hz Rhythmicity (GCSR) measured at the right frontal site F8 in the Stop Signal Task (SST) is an anxiety process biomarker. However the SST requires stopping a uni-manual speeded response, and Stinear et al (2009) argued that stopping is better assessed in the bimanual Anticipatory Response Inhibition Task (ARIT). The ARIT also allows for three types of stop trial: stop both (SS), stop left only (SG), and stop right only (GS). Healthy participants (Experiment 1 = 30; Experiment 2 = 31) provided EEG during an ARIT. We assessed GCSR as stop-specific power at intermediate stop signal delays versus the average of short and long delays. We found significant F8-GCSR in the SG and GS conditions within the 5-12Hz frequency band. Trait anxiety (STAI-T) and Neuroticism (EPQR-N) correlated with F8-GCSR in the SS condition and GS condition. Buspirone (5HT1A agonist), Triazolam ($GABA_A$ agonist), and Pregabalin (calcium channel blocker) – which share an anxiolytic effect – were then tested on F8-GCSR. Buspirone (10mg) and Pregabalin (75mg), but not Triazolam (0.25mg) reduced F8-GCSR in the SG condition and perhaps GS condition. Contrary to prediction, the ARIT did not produce stronger GCSR than the SST and may have produced weaker drug effects. Our data demonstrate the generalisation of F8-GCSR as an anxiety process biomarker from speeded to timed responding. Source localisation suggested that goal conflict, as reported for stopping, can involve more than one right frontal circuit depending on whether slow (GS), medium (SG) or fast (SS) stopping is occurring.

Poster 9.8

A neurocognitive model to explain physician burnout and associated adverse patient outcomes

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Occupational stress occurs in many demanding jobs, including in the medical profession. Burnout, arising from excessive stress levels and associated factors, has been linked to reductions in safe and appropriate healthcare delivery. Alarmingly, physicians demonstrate higher rates of burnout than the general population, at 49% in the US and 42% in Australia. Although the association between physician burnout and patient safety is well documented, the underlying pathway remains unclear. Hence, we propose a novel, two-tier neurocognitive model that provides a conceptual framework for this association: first, occupational stress leading to burnout may result in neural alterations; second, these alterations may directly impair higher-order cognitive abilities, which may account for poorer quality healthcare delivery. For example, due to dysregulation of the hypothalamic-pituitary-adrenal axis, neural alterations may occur in areas such as the hippocampus, amygdala, and prefrontal cortex. Given the functional specialisation of these areas, reduced decision-making and knowledge acquisition capabilities are inevitable. Therefore, the adverse patient outcomes associated with physician burnout can be attributed to incorrect/incomplete knowledge acquisition and decision-making, as a result of underlying neural consequences. To test the validity of this proposed model, measures of the following are required: 1) perceived and physiological occurrence of physician burnout; 2) potential alterations in brain behaviour relationships, particularly in higher-order cognition, and; 3) frequency and nature of clinical errors and patient outcomes. The proposed conceptual model provides a framework to inform the development of novel experimental paradigms to appropriately investigate the relationship between physician burnout and resulting patient safety outcomes.

Poster 9.9

Autobiographical memory in Parkinson's disease

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Autobiographical Memory (ABM) represents the mind's knowledge of information and experiences collected over the lifespan. It can be conceptually distinguished into episodic memory for personally-experienced events; and semantic memory for personally-acquired knowledge-based facts stored about one's life. ABM may be impaired in Parkinson's disease (PD) prior to the emergence of other cognitive deficits. Here, we report ABM performance in PD patients who had not reached criteria for PD with mild cognitive impairment. These patients were part of an 8-month randomized controlled trial investigating the effects of a combined physical and cognitive enrichment intervention on neuropsychological outcomes in idiopathic PD. Irrespective of intervention or control subgroup, both semantic and episodic memory using the autobiographical memory interview was impaired in the PD patients relative to age-matched healthy controls (HC). The same episodic memory deficit in the PD patients remained despite the use of an alternative protocol (the *episodic* autobiographical memory interview) that discriminates contextual details of personal episodic memories, and which generated a clearer epoch-related recall gradient. Recall of personal events is impaired even in non-MCI PD patients but this impairment does not appear to benefit from the addition of a multi-domain cognitive and physical intervention.

Poster 9.10

Presence of genetic disease-specific aggregates in the anterior olfactory nucleus of the human olfactory bulb

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Olfactory impairments are frequently observed pre-clinically in many neurodegenerative diseases. It has been hypothesised in Alzheimer's and Parkinson's disease that olfactory dysfunction results from deposition of disease-specific protein aggregates in the olfactory bulb (OFB). However, disease-specific aggregates in the OFB have not been described in genetic diseases such as Huntington's disease (HD) and familial forms of Motor Neuron Disease (MND) which also present with olfactory deficits. To determine whether pathological protein aggregates are present in HD and MND OFBs, fluorescent immunohistochemistry was performed on post-mortem human OFB sections from eleven HD, five MND and five normal cases. Sections were stained with antibodies against disease specific aggregates and cell specific markers with previously reported expression within the OFB. We found mutant huntingtin aggregates in all HD OFBs almost exclusively within the anterior olfactory nucleus (AON). Furthermore, in two familial cases of MND (C9ORF72 mutants) we found dipeptide repeat aggregates within the AON. Both aggregate types were found to be co-localised within calbindin, calretinin, somatostatin or tyrosine hydroxylase immunoreactive cells. No staining for alternative pathological proteins including β-amyloid, tau and α-synuclein was seen in HD OFBs, however positive tau staining was seen in 3 out of 5 MND OFBs. Therefore, olfactory deficits seen across the spectrum of neurodegenerative disorders, whether sporadic or genetic, share similar aggregate pathologies in the OFB concentrated to the AON. This suggests that aggregate pathology within the AON could play a role in the common symptom of olfactory dysfunction seen across neurodegenerative diseases.

Poster 9.11

Receptor studies in the human globus pallidus

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The basal ganglia (BG) are a group of interconnected nuclei in the centre of the brain, associated with controlling mood, movement, and cognition. The globus pallidus (GP) is a core component of this assembly, ultimately becoming the main output nuclei of the many circuits which traverse the BG. Dysfunction of these nuclei and their pathways cause a variety of disorders, such as Huntington's Disease (HD). The objective of this study was to characterise the neuronal populations in the human GP, with a central focus on the subpopulations expressing glutamatergic receptors. Anatomical analysis of receptor and transporter markers will allow further understanding into the pathways of the BG, which are known to undergo pathological changes in HD. Post-mortem human brain tissue blocks containing the GP were selected for sectioning and stained using fluorescent immunohistochemistry targeted towards GABA and glutamate receptor subunits, transporters (VGLUT2/VGAT), and various neurochemicals. Characterisations of GluN1 receptors, and how they associate with GABA receptors in the normal human brain, will be used as a baseline for comparison with HD cases. By studying the excitatory and inhibitory receptor systems, we have discovered a new configuration of receptors on cells in the globus pallidus. We show two unique cell types in the GP, one containing mainly inhibitory receptors and the other containing mainly excitatory receptors. This may have implications for understanding pathways of mood and movement in the human brain and help to inform treatment design for neurological diseases such as HD.

Poster 9.12

Comparison of usability of three AAC systems: EyeLink, eye tracking camera and P300 speller

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Augmentative and alternative communication (AAC) systems are important to allow communication for individuals who are unable to speak. For people with motor impairments, systems which do not require physical movement must be used. This study aimed to compare the accuracy, speed of communication and usability of three of these systems. The first two, an EyeLink board and an eye tracking camera, are systems which are being used with patients currently. The third system, a Brain Computer Interface (BCI) using a P300 speller, is an emerging system used mostly in research settings. Ten participants used each AAC system to spell three letter words. Speed and accuracy of letter selection was measured. After using each device, the participants completed three questionnaires, evaluating usability, cognitive workload and preferences. Preliminary analyses show that the accuracy of spelling with the EyeLink board and eye tracking camera was superior to that of the BCI (t_{571} = 22.43, $p < 0.001$). In addition, the BCI also resulted in significant slower letter selection compared to the other two devices (t_{463} = -30.64, $p < 0.001$). The workload and usability were also rated more positively for the EyeLink board and eye tracking camera. These preliminary results show that, while promising, the BCI system needs to undergo further development to become more user-friendly before it can be considered as a routine clinical AAC device for clients with motor impairments who lose the ability to speak. Interestingly, the low-tech EyeLink Board and more high-tech eye tracking device resulted in similar accuracy and speed outcomes, making the decision regarding selection of the device dependent on individual client factors.

Poster 9.13

Extrasynaptic α5 type $GABA_A$ receptors as therapeutic targets for Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which no cures or cognition-restoring therapies have yet been discovered. g-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and plays a key role in regulating the balance between neuronal excitation and inhibition. There is increasing evidence in support of the remodelling of the GABAergic system in AD and thus it might represent an important therapeutic target. The compound, 3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine acts as an inverse agonist of a5 subunit containing $GABA_A$ ($\alpha5GABA_A$) receptors and has displayed cognition enhancing properties in previous studies. This study aimed to characterise the effects of the compound on amyloid beta ($A\beta_{1-42}$)-induced molecular and cellular changes in an *in vitro* AD model. Mouse primary hippocampal cultures were exposed to either $A\beta_{1-42}$, the compound and $A\beta_{1-42}$ or vehicle and changes in cell viability were assessed. Treatment with 1nM $A\beta_{1-42}$ caused 51.5% cell death after 6h. Treatment with 100nM of the compound, however, reduced $A\beta_{1-42}$-induced cell loss by 23.8% ($p<0.0001$) after 6h. Cell viability after 5 days of treatment with the compound was also measured and revealed a decrease in $A\beta_{1-42}$-induced cell death by 15.0% ($p<0.01$). Treatment with the compound altered $A\beta_{1-42}$-induced induced changes in both intracellular and extracellular GABA levels as well as changes in the expression of various GABAergic signalling components, including $\alpha5GABA_A$ receptors, at the RNA level which may underlie the neuroprotective effects. In summary, this compound might hold neuroprotective potential and represent a new therapeutic avenue for treating cognitive dysfunction in AD.

Poster 9.9

Astrocyte-specific GFAP-AAV Vector-mediated secretion of chondroitinase ABC as a potential therapy following spinal injury

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Traumatic spinal cord injury (SCI) is a unique disability that significantly affects a person's quality of life due to loss of function and heavy economic burdens. In response to contusion impact, reactive astrocytes within the glial scar upregulate and release chondroitin sulfate proteoglycans (CSPGs) into the extracellular matrix (ECM), generating an extrinsic inhibitory environment which impedes axonal regeneration and is reflected by poor functional recovery following SCI. The bacterial enzyme chondroitinase ABC (ChABC) has been demonstrated *in vitro* and *in vivo* to degrade CSPG glycosylated sugar (GAG) chains, which neutralizes much of the inhibitory properties of the proteoglycan. As stable delivery of ChABC can only be achieved by viral gene therapy, we proposed the use of adeno-associated viral vectors (AAV5 serotype) with an astrocyte-specific promotor (GFAP) as a safe and effective delivery method of ChABC into mammalian astrocytes, in order to modulate the inhibitory environment and allow neuroplasticity and improved long-term functional recovery. To validate this, we transduced our developed vector into rat primary astrocytes treated with TGF-β1 as an *in vivo* model of reactive astrogliosis. We found that we were able to get a high level of transduction in astrocyte cultures. Transduction with the vector led to decreased extracellular CSPG levels and increased digested GAG chains. These findings demonstrate this gene therapy approach as a viable and safe means of delivery to target astrocytes following SCI. The use of our unique gene therapy *in vivo* and its functional significance is currently under investigation.

Poster 9.15

Tumour necrosis factor receptor 1 acts partially through the PI3K/Akt pathway to induce pro-inflammatory phenotypes within the cerebral endothelium

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The selectively permeable blood-brain barrier (BBB) of the central nervous system (CNS) partly consists of a specialised endothelium that is subject to mechanical, metabolic and inflammatory disruption following CNS trauma. Tumour necrosis factor (TNF), a cytokine central to the vascular inflammatory response, acts through two receptors, TNFR1 and TNFR2, to elicit diverse changes in endothelial physiology. We previously reported that TNF induces a biphasic weakening and subsequent strengthening of interendothelial adhesion. This study investigated how differential modulation of TNF receptors affects this behaviour. We used receptor-selective ligands in combination with ECIS-Zθ technology to monitor the receptor-specific barrier properties of the human cerebral microvascular endothelial cell (hCMVEC) inflammatory response. Additionally, multiplex cytokine bead arrays were used to determine the receptor dependency of soluble factor release in inflammatory activation. TNF acts through TNFR1 alone to modulate endothelial barrier strength via alteration to both cell-basal and cell-cell adhesion. Inhibition of the PI3K/Akt/NF-κB pathway ablates its activation by TNFR1, as observed immunocytochemically, and prevents TNFR1-mediated endothelial barrier alteration. Profiling of factors released by the cerebral endothelium in response to receptor-selective agonists reveal that whilst TNFR2 does not promote inflammatory activation, there is varied release of cytokines induced through TNFR1 and its activation of PI3K/Akt signalling. Currently, inflammatory BBB disruption following neurological trauma poses an obstacle to effective rehabilitation. By investigating the signalling role of the major inflammatory cytokine, TNF, within the cerebral endothelium and the cellular responses it evokes, more well-defined and potentially therapeutic targets could be identified.

Poster 9.16

Hearing, seeing, and feeling speech: A pilot EEG study

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Speech perception plays an essential role in our everyday communication. While auditory signals alone can be sufficient to understand speech, many studies have shown that speech perception is a multimodal process, relying also on visual and tactile (cutaneous air puffs) speech information, especially when the auditory signal is degraded. Our recently completed behavioural study on congruent audio-visuo-tactile integration during speech perception was the first to show an advantage for identifying tri-modal audio-visuo-tactile signals compared to uni- and bimodal stimuli. While there was a behavioural advantage, we do not yet understand how the brain integrates auditory and tactile speech information, let alone all three modalities together. The current pilot EEG study aimed to identify these effects. EEG was recorded from six listeners during four speech perception conditions: auditory only, audio-visual, audio-tactile and audio-visuo-tactile. The auditory signals consisted of an aspirated "pa" and an unaspirated "ga". The tactile signal involved a slight, inaudible air puff presented synchronously with the auditory signal. Preliminary results indicate a significantly lower amplitude ($p=.05$) and earlier onset ($p=.05$) of the N100 auditory event-related potentials (A-ERP) when processing audio-visual compared to audio-only signals. This finding is consistent with previous A-ERP studies on audio-visual speech perception, indicating that presence of bi-modal information facilitates processing. N100 responses were also significantly earlier for audio-tactile ($p<.01$) and audio-visuo-tactile ($p=.05$) compared to audio-only stimuli. While amplitude differences were approaching significance for the audio-visuo-tactile condition, they were not significant ($p=.18$) for the audio-tactile compared to audio-only stimuli. These neurophysiological findings corroborate our behavioural findings, and strongly motivate a large-scale study on the effects of tri-modal integration in speech perception.

Poster 9.17

Oddball event-related potentials in Parkinson's disease patients with normal cognition

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Parkinson's disease (PD) affects multiple neural pathways in the brain and is more than just a motor disorder. Event-related potentials (ERPs) diminish in Parkinson's and Alzheimer's dementias, but we here examined ERPs in PD patients with normal cognition (N=32) compared to age-matched healthy controls (HC, N=20). EEG was recorded during a single session while the participant completed a 3-stimulus visual oddball task (frequent standard, infrequent target, and infrequent distractor). We focused on the Cz electrode and found higher N100 amplitude in PD participants than HCs for both target (PD=-3.4±2.5μV, HC=-2.17±1.3μV, p=0.018) and standard (PD=-2.7±1.6μV, HC=-1.8±1.0μV, p=0.023) stimuli. We also found higher P300 amplitudes in PD participants for both target (PD=4.4±2.4μV, HC=2.6±2.0μV, p=0.016) and distractor (PD=4.5±3.3μV, HC=3.4±2.6μV, p=0.027) stimuli. Within each group, we did not find a statistical difference between ERP components for target and distractor pairs. The PD participants had higher mean reaction-time (RT=0.54s) than HCs (RT=0.49s; p=0.019). Contrary to our expectation, the P3 component of ERP was increased, rather than decreased, for PD patients. This may suggest increased attention is allocated to the oddball task by PD patients with non-impaired cognition in order to maintain accurate performance. Future work on PD patients with mild cognitive impairment and dementia is expected to show a shift toward decreased P100 and P300 amplitudes.

Poster 9.18

Population plasticity at the cerebellar Parallel fibre to Purkinje neuron synapse

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Long term depression (LTD), a form of plasticity found at the Parallel fibre (PF) – Purkinje neuron (PN) synapse, is critical for motor learning in the cerebellum. Monitoring PN activity and plasticity is essential to understanding their role in motor learning. PN outer dendrites, the site of LTD induction, are difficult to access. Therefore LTD has classically been studied via single cell patch clamp electrophysiology recordings from the soma. To circumvent these difficulties we developed a transgenic mouse expressing a genetically encoded voltage indicator (Butterfly2.1, Bfly) specifically in PNs, allowing us to examine synaptic plasticity in multiple PNs and their dendrites simultaneously. Using slices from transgenic mice we performed fast fluorescence voltage imaging (100 Hz) of Bfly responses. In the presence of 10μM Gabazine an LTD induction protocol combining high frequency PF stimulation (5x 100Hz) with a single climbing fibre stimulation (120ms delay between stimulations) was repeated at 1Hz for 5 minutes. BFly responses to paired pulse PF stimulations were monitored for 30 minutes prior to LTD (baseline), and 60 minutes post LTD. Recordings were averaged in 10 minute bins. Results show a decreased response to PF input immediately after LTD induction compared to baseline (P<0.0001, 10-20 min post), which is maintained for at least 60 minutes (P=0.0004, 50-60 min post). LTD was detected from multiple PNs across the folia and was blocked via metabotropic glutamate receptor negative allosteric modulator JNJ16259685. Our results show how voltage imaging can successfully examine dendritic synaptic responses and plasticity at multiple PF-PN synapse sites, a task previously impossible using classical electrical recording techniques.

Poster 9.19

Functional circuitry of basal forebrain underlying enhanced attention by reward anticipation

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The basal forebrain – composed of distributed nuclei including substantia innominate, nucleus basalis and nuclei of the diagonal band of Broca – plays a crucial neuromodulatory role in the brain. In particular, its projections to the prefrontal cortex have been shown to be important in a wide variety of brain processes and functions, including attention, learning and memory, arousal, and decision-making. In the present study, we asked whether the basal forebrain is involved in recruitment of cognitive effort in response to reward related cues. This interaction between motivation and cognition is critically impacted in psychiatric conditions such as schizophrenia. Using the Designer Receptor that is Exclusively Activated by a Designer Drug (DREADD) technique combined with our recently developed signalled probability sustained attention task (SPSA), which explicitly assays the interaction between motivation and attention, we sought to determine the role of the basal forebrain in this interaction. Rats were stereotaxically injected in the basal forebrain with either hM4D (a virus that expresses receptors which silence neurons in the presence of the drug clozapine-N-oxide; CNO) or a control virus, and then tested in the SPSA. Behaviour of rats during baseline and under saline control conditions indicated an effect of reward probability, with accuracy on high probability trials being greater than accuracy on low probability trials. In the presence of CNO, differential accuracy of hM4D rats on high and low signalled probability trials was abolished. These results indicate that the basal forebrain is critical for the motivational recruitment of attention in response to reward-related cues.

Poster 9.20

Designing, measuring and modelling a small-scale coil and stimulation circuit for Transcranial Magnetic Stimulation

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In Transcranial Magnetic Stimulation (TMS) rapid electromagnetic (EM) fields are applied to the brain, via an external current-carrying coil. This technique has been tried for many neurological disorders such as stroke, Parkinson's disease and major depression. The fundamental effects of TMS are poorly understood so there is a need to carry out invasive measurements on mice to gain deep understanding about the underlying principles of TMS. However, this requires smaller coils than used for a human, equivalent to the size of the mouse brain. Based on established physics principles we designed and built a cylindrical coil consisting of 50 turns of 0.2 mm diameter copper wire around a 4 mm diameter soft ferrite core. We built a simple electronic circuit to discharge a capacitor through this coil. With an applied voltage of 45 V, we measured the magnetic flux density (B-field) with a Hall probe as 338 mT and induced electric field (E-field) with a wire loop as 10 – 15 V/m. The temperature increased by 31°C after 1200 pulses at 5 Hz. We modelled the coil using MATLAB which gave similar B-field and E-field results of around 500 mT and 8 V/m respectively. Although this coil performs better than previously constructed mouse coils, the EM fields are still considerably lower than those of typical human coil of 2 T and 250 V/m. This now allows us to stimulate mouse brains with higher B-fields and E-fields than in previous experiments.

Poster 9.21

Preterm birth and childhood psychopathology: Linking neonatal neurological alterations with the preterm behavioural phenotype

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Preterm birth is associated with a 2-to 4-fold increased risk of childhood psychopathology relative to full-term birth, with an inverse relationship between gestational age at birth and later risk and severity of psychopathology. It is now well recognised that the aetiology and manifestation of symptomatology in this high-risk population may be distinct from typical presentations. Consequently, the preterm behavioural phenotype was proposed. It describes a unique, consistent, and comorbid pattern of emotional and behavioural adjustment difficulties which are characteristic of attention-deficit/hyperactivity disorder, autism spectrum disorder and anxiety disorders. The current study is a systematic review, in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, to describe the neonatal neurological correlates of the preterm behavioural phenotype. Data were extracted from 18 peer-reviewed studies, published in English between 1990 and 2018. Results show that both brain injury (predominantly white matter injuries) and altered patterns of structural brain maturation during the neonatal period are associated with the preterm behavioural phenotype symptomatology. Along with evidence of global maturational deficits, the dorsal prefrontal region, limbic system and cerebellum appeared particularly vulnerable. These findings were generally robust to statistical adjustment for family social disadvantage associated with preterm birth, highlighting the potential role for early adverse neurological experiences on the development of psychopathology in this high-risk population.

Poster 9.22

Utility of acoustic cry characteristics assessment as a potential marker of neurological integrity in high-risk infants

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Neonatal neurological examinations are routinely performed in high-risk clinical settings to assess the maturation and integrity of the central and peripheral nervous system. However, these examinations can be time-consuming, may require formal training and specific equipment, and must be performed by healthcare professionals. Thus, accessibility in low-resource settings is a major issue and alternative assessments are warranted. If diagnostic utility can be established, the quality and/or quantity of an infant cry, briefly assessed as part of a structured neurological examination, represents a potential option to assess neurological integrity that is both accessible and independent. Moreover, studies have reported higher fundamental frequency (f0) and shorter cry duration in infants at risk of autism and those exposed to methadone or cocaine prenatally, relative to healthy comparison infants, which may be indicative of underlying neurological abnormalities. A systematic search of major clinical databases was conducted using relevant terms that yielded 13,805 references, of which 11 studies reported associations between acoustic cry characteristics and concomitant neurological outcomes. Overall, a higher f0 was found in infants at risk of neurological impairments, including those presenting with perinatal asphyxia, intraventricular haemorrhage, and congenital hydrocephalus. Additionally, a higher f0 correlated with poorer scores on a subset of neonatal neurobehavioral assessments. Despite the consideration of cry duration in neonatal neurological examinations, the length of cry showed inconsistent associations with neurological outcomes. In conclusion, existing studies suggest that there is enough preliminary evidence to justify the systematic investigation of the predictive utility and differential diagnosis of acoustic cry characteristics for neurological outcomes of high-risk neonatal populations.

Poster 9.23

Age- and gender-specific changes of the GABA signalling components in the human hippocampus

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Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the nervous system. The GABA signalling system in the brain is comprised of GABA synthesizing enzymes and GABA transporters, $GABA_A$ and $GABA_B$ receptors ($GABA_AR$ and $GABA_BR$). Differences in the expression of signalling components have been observed throughout normal aging and between genders in rodents and non-human primates. A brain area that is impaired during aging and age-related disorders is the hippocampus, the memory centre of the brain. It is composed of two main regions the Cornu Ammonis (CA1-4) and the Dentate Gyrus. These structures are interconnected with the adjacent Entorhinal Cortex (ECx). The age- and gender-specific changes of GABA signalling components in these regions of the human brain have not been studied. This study is the first to determine the effect of age and gender on the expression of GABA signalling components in the DG, CA1 and ECx, in four main case groups (younger males, older males, younger females, older females) using Western Blotting. Our results show increase in $GABA_AR$ γ2 subunit expression with age in males but not females, with older males having significantly higher γ2 expression in comparison to older females in each region of the hippocampus and the ECx. There are no significant changes in the expression of α1, α3, α5, β3 $GABA_AR$ subunits and GABA synthesising enzymes across all four groups. In conclusion, gender-specific changes in $GABA_AR$ subunit composition may influence receptor function throughout normal aging and affect GABAergic inhibition within the hippocampus.

Poster 9.24

Maternal immune activation affects hippocampal nNOS immunoreactivity and microglia in postnatal day 35 rat offspring

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Maternal immune activation (MIA) during mid-gestation leads to increased risk of schizophrenia in offspring during adulthood. Experimentally, MIA can be induced by a single systemic administration of the synthetic cytokine inducer polyinosinic–polycytidilic acid (PolyI:C) at gestational day 15 in rats. We have recently reported that MIA leads to increased intensity of neuronal nitric oxide synthase (nNOS)-immunoreactive cells, but impaired microglial migration and maturation, in the hippocampus of offspring at postnatal day (PND) 2. It is unclear, however, whether the effects of MIA on nNOS and microglia in offspring are transient or long-lasting. Using immunohistochemistry, the present study compared the immunoreactive profiles of nNOS and IBA-1 in the hippocampus of male and female MIA offspring at PND35 (equivalent to human juvenile) with their age- and sex-matched controls (n = 5/group/sex). MIA offspring at both sexes displayed significantly increased number of nNOS-positive cells, but reduced density of microglia, in the CA1, CA3 and dentate gyrus sub-regions of the hippocampus relative to their sex-matched controls. In conjunction with our recent work on PND2 MIA offspring, the present results demonstrate that a single MIA insult during mid-gestation has long-lasting effects on nNOS and microglia during postnatal development. Given the critical roles of nNOS and microglia in neurodevelopment, these changes may contribute significantly to the functional deficits seen in adult MIA offspring.

Poster 9.25

MicroRNA expression in the diagnosis of Parkinson's disease

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Parkinson's disease (PD) is characterised by progressive loss of dopaminergic neurons in the substantia nigra. As PD can only be diagnosed clinically, misdiagnosis rates can often be high. With an aging population, there is an urgent need to identify novel biomarkers to aid in the accurate diagnosis of PD. MicroRNAs (miRNAs) are small non-coding RNAs which can be easily obtained from various biofluids, including blood plasma. This pilot study aimed to find miRNAs in plasma capable of differentiating between PD and controls. A cohort of 11 pairs of PD patients, and age and sex-matched controls were included. Clinical assessments conducted include the Unified Parkinson's Disease Rating Scale (UPDRS) and the Montreal Cognitive Assessment (MoCA), which assess disease progression and cognitive abilities, respectively. Other parameters tested include sleep quality, anxiety, depression, and dyskinesia severity. Here, custom-designed low-density TaqMan arrays targeting 187 neuropathology-related microRNAs were used; 10 miRNAs were found to be differentially expressed (two-tailed t-tests, $p<0.05$). Of these 10 miRNAs, 4 were upregulated (fold change 1.21 to 8.36) and 6 downregulated (fold change 0.35 to 0.77). Receiver operator characteristic curve analysis of combinations of these 10 miRNAs demonstrated sensitivity and specificity rates between 81.82-100%. Bioinformatic analysis found the 10 differentially expressed miRNAs to be associated with NFκB and ubiquitin-associated pathways, dysfunctions of which are considered potential risk factors for developing PD. These results suggest that plasma miRNA levels are altered in PD and could potentially reflect underlying molecular pathology.

Poster 9.26

Investigating liposomes for local drug delivery in spinal cord injury

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In New Zealand, spinal cord injury (SCI) affects ~170 people annually and is primarily caused by motor vehicle accidents, falls or sports injuries. Development of targeted drug delivery is needed to limit side effects of current SCI therapies. To investigate targeted delivery, we tested hyaluronic acid (HA) tagged liposomes. CD44, a receptor for HA, is upregulated on glial cells in damaged spinal cord tissue. To determine appropriate time-frames for liposome delivery, immunohistochemistry was carried out on injured rodent spinal cord tissue from day 1 to 14 after injury using antibodies against CD44 and fibrinogen (a marker of blood-spinal cord barrier leakiness). Our results showed maximum CD44 and fibrinogen staining 1 day after SCI, which was still present but decreased by 14 days. Based on these results, liposomes were injected 1 day and also 7 days after SCI, as at this timepoint CD44 and blood spinal cord barrier leakiness was still present but at reduced levels. Rhodamine labelled liposomes were injected by tail vein into spinal cord injured rats. Spinal cord tissue was labelled with antibodies against GFAP, CD44 or CD68 to investigate co-localisation of liposomes with glia. Liposomes could not be definitively demonstrated in the spinal cord. *In vitro* flow cytometry analysis of blood samples showed rapid clearance of liposomes and analysis of spleen, liver, and kidney tissue showed the presence of liposomes. This suggests that liposomes were rapidly cleared and more research is needed to develop this into an effective local treatment of SCI.

Poster 9.27

The importance of multi-frequency impedance sensing of endothelial barrier formation using ECIS technology for the generation of a strong and durable paracellular barrier

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An important area of blood-brain barrier (BBB) biology is understanding how the physical properties of a BBB endothelial barrier are formed and regulated under normal physiological homeostasis, as well as during disease states. For *in vitro* based research this requires advanced technologies to investigate the barrier function in real-time and in a non-invasive continuous manner. In this study, we highlight the power and utility of electrical cell-substrate impedance sensing (ECIS) biosensor technology to reveal massive differences in the capability of brain endothelial cells to form a barrier under varied culture conditions. Brain endothelial cells were cultured in either medium reputed for barrier strengthening compounds or in a low serum, growth factor-free medium. ECIS was used to model the parameters of the physical barrier associated with (i) the paracellular space (R_b) and (ii) the basal adhesion of the endothelial cells (α). We demonstrate the power of ECIS to reveal that differences in culture conditions have substantial effects on barrier formation, especially at the level of paracellular resistance. Finally, we show that the temporal changes observed in the paracellular R_b can be associated with changes in specific junctional proteins (CD144, ZO-1 and catenins), which have major roles in governing the overall strength of the endothelial junctional interactions. The utility of ECIS has provided a powerful means of assessing multiple aspects of brain endothelial barrier formation, maintenance, stability, and the optimal conditions required for generation of strong (and stronger for longer) barriers.

Poster 9.28

The role of maternal obesity during oligodendrocyte development in the offspring amygdala

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Maternal obesity increases an offspring's risk to neurodevelopmental disorders, with children of obese mothers showing a greater disposition to Autism Spectrum Disorder (ASD). Mechanistically, ASD is characterized by neural circuit disruptions in regions such as the amygdala, with altered development or functionality impacting its behavioural and emotional regulatory roles. Whether maternal obesity disrupts amygdaloid development remains elusive. Preliminary qPCR results have shown elevated Chd7 mRNA expression, which encodes a protein involved in oligodendrocyte (OL) development, in the offspring of maternal high fat diet (mHFD) fed dams. This suggests amygdaloid myelination may be deregulated. To investigate this, female C57BL/6 mice were assigned a control or high fat diet at 4 weeks of age, before mating at 8 weeks of age. Offspring were collected at Gestational Day 17.5 (GD17.5) and Postnatal Day 10 (P10), and their brains extracted, with 20µm sections being prepared through the amygdala. Using immunohistochemical techniques, the OL lineage marker Olig2 was labelled for at GD17.5, with Olig2-IR cells being counted. The mature OL marker Myelin Basic Protein (MBP) was labelled for at P10, with integrated density analyses determining myelin expression levels. While Olig2-IR cells counts at GD17.5 remained unchanged, MBP expression within the amygdala at P10 increased significantly in the offspring of mHFD fed dams. This suggests that while OL progenitors or overall OL number aren't affected, differentiation may occur prematurely, leading to precocious amygdaloid myelination. Given myelin's role in axonal conduction, necessary during activity dependent neural network development, this may provide a mechanistic link between maternal obesity and the neural disturbances causal to ASD in the offspring.

Poster 9.29

The effect of AAV mediated knockdown of xylosyltransferase-1 in reactive astrocytes

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Spinal cord injury urgently requires therapeutic interventions that permit functional recovery. In order for this to occur, synaptic plasticity is crucial. One of the barriers to plasticity is a structure called the glial scar that forms at the site of injury. The glial scar forms as the result of reactive astrocytes, which release several factors into the extracellular matrix that inhibit axonal outgrowth. One of the major inhibitory factors are a family of proteoglycans known as chondroitin sulphate proteoglycans (CSPGs). Their inhibitory properties are determined by their glycosaminoglycan (GAG) side chains. In an effort to render CSPGs non-inhibitory, we targeted an enzyme that is involved in GAG side chain biosynthesis, xylosyltransferase-1. Previous studies have utilised deoxyribozymes against XT-1 to decrease production of GAG side chains, and have subsequently found improved axon regeneration around the lesion *in vivo*. To test a safer way to downregulate expression of XT-1, we utilised artificial microRNA sequences for knockdown instead of deoxyribozyme and delivered this into primary rat astrocytes using the non-immunogenic adeno-associated virus (AAV) vector. We have developed an *in vitro* model of reactive astrocytes using TGF-β1 to induce CSPG production. Astrocyte-specific transduction with the AAV vector (AAV5 serotype) was achieved with low toxicity observed in cultures. Preliminary results with the AAV-miXT1 show a decrease in CSPG-GAG secretion from reactive astrocytes, demonstrating that this delivery method may be a viable means of reducing inhibition on axon growth. The downregulation of xylosyltransferase-1 expression and its functional significance remain to be further investigated.

Poster 9.30

Theory of mind in Parkinson's disease: A longitudinal follow-up

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Theory of Mind (ToM) refers to the ability to understand the thoughts and feelings of others, and predict behaviour based on inference of others' mental states. Research suggests that ToM may be compromised in early Parkinson's disease (PD), prior to the emergence of other cognitive dysfunctions. We examined neuropsychological outcomes in patients with idiopathic PD and relatively normal cognition who had been randomised to either an 8-month combined cognitive and physical exercise intervention (n=22) or an active-control group (usual care plus researcher contact; n=20). Interim analyses on performance in a ToM card-sorting task in a subsection of PD patients relative to age- and sex-matched healthy controls (HC; n=28) showed lower scores in the PD intervention group (p=.02) at baseline but not in the PD active-control group. Post-intervention follow-up revealed increased ToM scores (p=.01) in the PD intervention group relative to baseline, but no differences were found for HC or PD active-control groups. Ten months after the end of trial, no significant differences were found between the two PD groups with no effect of time on ToM performance. Hence, the addition of cognitive enrichment and physical activity in PD patients with relatively intact cognition may have little effect on improving theory of mind function in these patients.

Poster 9.31

Reduced heart rate variability in SERT knockout rats: Further translational validity as an animal model of depression and anxiety

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Abnormalities in heart rate variability (HRV) have been observed in humans presenting with a variety of psychiatric illness, including depression and anxiety, however, to date the examination of HRV in animal models of psychiatric illness remains understudied. Genetic reductions the serotonin transporter (SERT) function have been associated with anxiety and depressive disorders in humans. Therefore, this study sought to examine HRV alterations in animals expressing a genetic reduction in SERT; these animals have previously shown depression-like symptoms such as anhedonia through reduced social reward and play behaviour, and increased anxiety-like behaviour in the successive alleys paradigm. HRV was assessed in SERT knock-out rats over 24 hours in the home cage. Furthermore, the change in HRV in response to a mild stressor (novel environment) and a moderate stressor (intraperitoneal saline injection) were also examined. A basal reduction in HRV was observed in SERT-/- rats in comparison to SERT+/+ rats. These differences were seen in both the time- and frequency domain, and were most apparent in parameters probing the parasympathetic nervous system. Differences in proportional change in response to stressors were also observed, with SERT-/- primarily exhibiting a muted change, again primarily in parasympathetic nervous system related parameters. Together these physiological data are in line with the behavioural features of the animals, and suggest that the SERT knock-out rats may represent a translationally valid animal model for depression and anxiety.

Poster 9.32

Cerebellar degeneration correlates with motor symptoms in Huntington's disease

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by variable motor and behavioural symptoms attributed to major neuropathology of mainly the basal ganglia and cerebral cortex. The role of the cerebellum, a brain region involved in the coordination of movements, in HD neuropathology has been controversial. This study utilised post-mortem human brain tissue to investigate whether Purkinje cell degeneration in the neocerebellum is present in HD, and how this relates to disease symptom profiles. Unbiased stereological counting methods were used to quantify the total number of Purkinje cells in eight HD cases and five neurologically normal control cases. Based on their predominant symptoms, the HD cases were categorised into two groups: "motor" or "mood". The results demonstrated a significant dramatic 31% loss of Purkinje cells in HD cases with predominantly motor symptoms, and no cell loss in cases showing a major mood phenotype. There was no significant correlation between Purkinje cell loss and striatal neuropathological grade, post-mortem delay, CAG repeat in the IT15 gene or age at death. This study showed a clear correlation between Purkinje cell loss in the neocerebellum of HD cases showing a predominant motor symptom phenotype, which, together with our previous human brain studies on the same HD cases, provide novel perspectives interrelating and correlating the variable cerebellar, basal ganglia and neocortical neuropathology with the variability of motor/mood symptom profiles in the human HD brain.

Poster 9.33

The effect of Tonabersat in reducing chronic inflammation following spinal cord injury

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Spinal cord injury has been shown to induce an ongoing chronic inflammatory state, beginning as soon as a few weeks post injury and sometimes persisting for years. This state of ongoing inflammation creates an inhibitory milieu around the injury site resulting in the inhibition of axonal repair/regeneration and the onset of neuropathic pain in patients. Connexin 43 hemichannels have been shown to be a major component in perpetuating this inflammatory state. Tonabersat is a validated hemichannel modulating drug which we have used to block these Connexin 43 hemichannels in an effort to reduce the chronic inflammatory environment. To date there are no therapies available which successfully limit this state of chronic inflammation. In order to investigate whether Tonabersat reduces chronic inflammation, we utilised a chronic contusion spinal cord injury rat model. Following initial contusion, the animals were given a 6 week period for the chronic inflammation to manifest, after which Tonabersat was administered orally for a 4 week period. The effect of Tonabersat on astrogliosis and microgliosis was examined. The treated animals showed a reduction in the level of astrocyte staining compared to non-treated animals. Additionally we saw a reduced presence of microglia around the lesion between treated and non-treated animals. These data indicate that connexin hemichannel modulation may be able to alleviate chronic spinal cord inflammation and potentially improve long-term outcomes.

Poster 9.34

Amyloid-β increases SH-SY5Y neuroblastoma cell viability

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Investigating the cellular effects of Amyloid-b (Ab) is crucial to understanding the molecular biology of Alzheimer's disease (AD). Reports of the cytotoxic effects of the peptide vary considerably, and a robust and consistent screening platform is needed to assess cell viability in response to Ab insult. Here, we aimed to develop such a screening platform by examining the response of SH-SY5Y neuroblastoma cells to treatment with exogenous $A\beta_{1\text{-}42}$. First, we compared the MTT and resazurin cell viability assays. The latter reported greater loss of cell viability (-24.6% ± 6.3, -50% ± 2.8 respectively; Z=4.000, 3.449; p<0.01) as well as significantly less variability (variance= 38.06, 7.86 respectively; F=3.12; p<0.05), suggesting that resazurin is more valid as a cell viability assay for *in vitro* AD research. Second, our study revealed that "ageing" $A\beta_{1\text{-}42}$ for 3 days in aCSF was sufficient to produce higher-order oligomers, considered to be the more toxic forms of the peptide. Finally, using these optimised methods, we discovered that treatment of SH-SY5Y neuroblastoma cell cultures with up to 40 mM aggregated $A\beta_{1\text{-}42}$ caused a significant increase in cell viability above aCSF alone (36% ± 4; Z=-5.57; χ^2=46.7; p<0.001). While the mechanism behind this observed increase in cell viability is unclear, these results suggest that care must be taken when investigating effects of Ab on cell cultures. Ab insult of SH-SY5Y neuroblastoma cells is not an ideal model for preclinical AD research.

Poster 9.35

ATP13A2: Characterization of novel human iPS cell models of Parkinson's and Batten's disease

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Mutations in *ATP13A2* lead to the development of two distinct neurological disorders, Kufor-Rakeb Syndrome, a juvenile parkinsonism and CLN12 Batten disease, a lysosomal storage disease. The underlying pathology of Parkinson's Disease (PD) is currently unknown, though the accumulation of misfolded proteins suggests that improper disposal of aggregate-prone proteins has an important role. Accordingly, 18 genes linked to familial forms of PD involve mutations in PARK genes which encode proteins that are involved with the autophagosome-lysosomal pathway. Conversely, Batten disease is a better characterised lysosomal storage disorder. PD associated mutations, including ATP13A2, have been modelled in animal and cell models, though none fully recapitulate the pathology seen in humans. It is imperative to develop better models for disease study and high throughput drug screening. The aim of this work is to establish ATP13A2 models of Batten disease and PD to identify why mutations in the same gene cause different disease outcomes. Our approach is to knockdown ATP13A2 expression using CRISPRi, examine the effects on pathology and then assess which of these pathologies can be corrected with different forms of ATP13A2. To date we have successfully cloned CRISPRi constructs into lentiviral backbones, generated lentivirus and used these to generate ATP13A2 deficient human iPSC lines. These cells are now ready for assessment of neuronal pathology, and potential rescue of pathology with Batten disease or PD related mutant ATP13A2 forms.

Poster 9.36

Effects of connexin hemichannel blockade on cortical interneurons after global cerebral ischaemia in term-equivalent fetal sheep

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Hypoxia-ischemia around the time of birth is a major cause of brain injury in term born babies. There is increasing evidence that disruption of cortical GABAergic neurons may contribute to the persisting neurological deficits in these infants. We previously reported that blockade of connexin hemichannel signalling using a mimetic peptide can reduce hypoxic-ischemic brain injury. However, the effects on cortical GABAergic neurons are unknown. Foetal sheep at 0.85 gestation received reversible bilateral carotid artery occlusion (30 min), followed by a 25-h intracerebroventricular infusion of vehicle (artificial CSF) or a specific mimetic peptide that blocks connexin43 hemichannels initiated 90 min after reperfusion. Sham control animals received sham ischemia. Four to six animals were used for each of the three groups: sham control, hypoxia-ischemia, and hypoxia-ischemia+peptide. Sheep were killed 7 days after hypoxia-ischemia, and brain tissues processed and stained for GABAergic neuronal markers including GAD, parvalbumin, calbindin-28k, and calretinin. The densities of the cortical neurons (cells/mm^2) were compared between the three groups. Cerebral ischemia was associated with a marked reduction in the densities of cortical neurons expressing calbindin-28k and calretinin, and a trend towards a reduction of neurons expressing GAD and parvalbumin. There was only a trend towards mild protection of various interneuron populations with mimetic peptide treatment. Cerebral hypoxia-ischemia in term-equivalent foetal sheep was associated with marked loss of cortical interneurons. However, astrocytic connexin hemichannel blockade did not improve the cortical interneuron survival. Further studies with larger animal numbers are required to confirm these findings.

Poster 9.37

Validation of NODDI-MRI for detection of cortical brain injury following peripheral inflammation in neonatal rats

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Preterm infants have high rates of neurodevelopmental disabilities associated with microstructural MRI changes. However, the exact relationship between MRI parameters and histopathological outcomes remains unclear. The Neurite Orientation Dispersion and Distribution Index (NODDI) is a novel diffusion MRI technique, proposed to measure neuronal branching. Here we aimed to validate the relationship between MRI-NODDI parameters and neuronal dendritogenesis during development of the cerebral cortex, and examine cortical changes in a preterm-equivalent rat model of inflammatory brain injury. *Experiment 1:* Sprague-Dawley rat pups collected at postnatal day (PND) 1, 7, 14, and 21, and brain tissues impregnated with Golgi solution or fixed for *ex-vivo* MRI-NODDI analysis (9.4T). *Experiment 2:* Rats received daily intraperitoneal lipopolysaccharide (LPS; 0.3mg/kg) on PND1–3, with recovery until PND21. Brain tissues were collected for Golgi/MRI-NODDI. In Golgi tissues, the complexity of pyramidal neurons in the somatosensory and motor cortices were assessed (Neurolucida). For MRI, the changes in fractional anisotropy (FA), orientation dispersion index (ODI), intracellular volume fraction, and isotropic volume fraction were calculated in the somatosensory cortex. LPS was associated with a significant reduction in cortical volume at PND21, without evidence of cell death or loss of neurons. NODDI analysis showed a significant decrease in cortical ODI, and increase in FA, at PND21. Golgi analysis also showed a significant reduction in dendritic complexity in the infragranular somatosensory cortex, and a significant reduction in total dendritic length in the motor cortex at PND21. Analysis of dendritic changes and the relationship with NODDI parameters during development is ongoing. Validation of NODDI may provide a novel technique for assessing cortical pathology in preterm-born infants.

Poster 9.38

A comparison of the effects of abstinence on MDMA and cocaine self-administration in rats

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3, 4-methylenedioxymethamphetamine (MDMA) is self-administered by laboratory animals but the latency to acquire self-administration is relatively long and not all rats acquire self-administration. We have suggested the preferential release of serotonin (5-HT) during initial exposure limits the development of MDMA self-administration. However, following repeated exposure, MDMA-stimulated 5HT release is reduced and MDMA-stimulated dopamine (DA) is increased. As is the case following self-administration of other psychostimulants, including cocaine, the sensitized DA response is persistent. Unlike cocaine self-administration, there is recovery of MDMA-stimulated 5-HT following abstinence. If 5-HT inhibits self-administration, then abstinence and the recovery of 5HT neurotransmission would be expected to selectively attenuate the reinforcing effects of MDMA. To test this, we compared the effects of abstinence on MDMA and cocaine self-administration. Six-hour daily MDMA or cocaine sessions were conducted until a total of 350 mg/kg had been self-administered. Following this, rats were randomly assigned to either a 0 or 14 days abstinence group. Self-administration testing then continued for an additional seven days. The latency to self-administer 350mg/kg was shorter for rats that self-administered cocaine. The temporal distribution of responding within each test session also differed; MDMA self-administration was high during the first hour of each session, and decreased during subsequent hours whereas cocaine self-administration was evenly distributed throughout each hour of the session. Abstinence also preferentially decreased MDMA self-administration. This selective reduction of MDMA self-administration following abstinence is consistent with the idea that MDMA-stimulated 5-HT release is inhibitory to MDMA self-administration.

Poster 9.39

EEG-based resting-state functional connectivity in Parkinson's disease with normal cognition

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Functional connectivity may reflect cognitive function in Parkinson's disease (PD). Here, we used 60-channel EEG to investigate resting state functional-connectivity measures in PD patients who retained normal cognition (N=35) versus age-matched healthy controls (N=20). EEG was recorded during a 10-min wakeful eyes-closed session; participants were asked to open their eyes every 3 min to prevent sleep episodes. After visual inspection, stereotypical artefacts were minimized and surface Laplacian transformation applied. We used absolute weighted-phase-lag-index between electrode pairs to measure functional connectivity, computed across 2-s EEG segments followed by selection of delta, theta, and alpha wavebands (one connectivity-network per frequency band). Based on graph theory, six measures – mean degree, mean clustering-coefficient, transitivity, global efficiency, modularity, and mean betweenness – were computed for each network to quantify different functional aspects such as integration and segregation. Each frequency-band measure was dichotomized at one standard-deviation above its median. Only mean connectivity-degree in alpha band approached Bonferroni-adjusted significance (p=0.07), being higher in the PD group (10.8±1.8) than the healthy group (9.1±1.9). Visual inspection of network degrees in alpha band suggested higher degrees of connectivity in the posterior electrodes for PD group versus HCs. Rather than anticipated frontal connectivity deficits, these findings suggest that some aspects of stronger functional connectivity may provide a mechanism for maintained cognition during early PD.

Poster 9.40

Arc protein expression in response to secreted amyloid precursor protein-α in primary hippocampal cultures

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Secreted amyloid precursor protein-α (sAPPα) is a neuroprotective and memory-enhancing molecule, which precludes the production of Aβ, a neurotoxic peptide implicated in Alzheimer's disease. The mechanisms through which sAPPα promotes these effects is relatively unknown. Recently, we have discovered sAPPα promotes the synthesis and trafficking of GluA1 AMPA receptors to enhance long-term potentiation (LTP) in acute hippocampal slices. Furthering this work, here we describe sAPPα's ability to enhance the synthesis of the immediate early gene ARC. ARC protein is necessary for the formation of long-term memory and expression of late-phase LTP, and regulates AMPA receptor cell surface expression. Using hippocampal cell cultures (DIV 24-27) and immunocytochemistry we found that treatment with sAPPα (0.1nM, 1nM; 2h) promoted an increase in dendritic ARC protein (p = 0.0002, <0.0001; n = 40-140 cells) but was not elicited by the closely related molecule sAPPβ. This effect of sAPPα was found to be dependent on CaMKs (p <0.0001, n = 51), MAPK (p = 0.0428; n = 51), and PKG (p = 0.0001; n = 43). Furthermore, this effect is mitigated by use of the NMDAR antagonist APV (p = 0.0294). These results show, for the first time, a possible role of Arc protein in sAPPα-mediated plasticity. This work builds upon existing research, aiming to further examine the mechanisms harnessed by sAPPα in order to promote plasticity at the synapse.

Poster 9.41

Regional ΔFosB expression associated with chronic MDMA self-administration

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ΔFosB is a particularly stable transcription factor that has been suggested to regulate some of the long-term neuroadaptive changes related to the development of drug addiction. It is well established that ΔFosB accumulates within the striatum and some other brain regions following chronic exposure to drugs of abuse. The impact of chronic MDMA exposure on ΔFosB accumulation has not yet been determined, however, and was the purpose of the current study. Immunohistological analysis was used to map the expression of ΔFosB across several brain regions following the self-administration of 515 – 692 mg/kg MDMA over a 29 – 35 day period. Significant increases in ΔFosB were observed in the prefrontal cortex (anterior cingulate, infralimbic, prelimbic), striatum (nucleus accumbens core and shell, medial caudate-putamen), amygdala (central and basolateral), and dorsal raphe, while no effect was observed in the lateral caudate-putamen, ventral-tegmental area (anterior, posterior tail), and median raphe. These results provide initial insight on the role of regional specific induction of ΔFosB and compulsive drug taking.

Poster 9.42

Modelling the spiking behaviour of neurons in human cortex

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Neurons receive and transmit information via electrical and chemical signals. To date, there is a good understanding about the electrical behaviour of individual neurons. The activity of large populations of neurons can be described by mean-field models. Those models describe population activity in terms of population-average spike rates, but local fluctuations and correlations in firing activity are not yet clearly described. The Waikato Cortical Modelling Group has introduced a “true-field model” to address this issue. This new model provides a more accurate mapping from single neuron-level events to the macroscopic level. In this approach, we consider a 2D continuum of identical neurons that are coupled via both chemical and electrical synapses. The spiking behaviour of a single neuron is described by the H. R. Wilson point neuron equations. The macroscale lattice is then reblocked to form a coarser-grained network by eliminating the high-frequency spatial modes. Tuning the model parameters to ensure biologically feasible spiking behaviour is a challenging task. This requires a careful balance between the parameter values such as the area of action potential, the time constants of the excitatory and inhibitory populations, the mean number of synaptic connections and the shape and duration of the post-synaptic potentials (PSPs). We demonstrate how these parameters affect the spiking behaviour of the interacting excitatory and inhibitory populations. We show that the relative areas of the excitatory and inhibitory PSPs are of crucial importance for realistic dynamics. In particular, inhibitory PSPs need a significantly longer duration (by ~4 times) than excitatory PSPs to compensate for the larger abundance of excitatory neurons.

Poster 9.43

Non-radioactive isotope labelled breath test for potential early diagnosis of Huntington's disease

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An ideal window of application for therapies designed to slow or halt progression of Huntington's disease (HD) is during the pre-symptomatic period. Current diagnostic methods lack the ability to accurately detect subtle cellular changes in the pre-symptomatic phase before extensive brain damage occurs. Consequently, there is a vital requirement to identify alternative inexpensive biomarkers that are simple to measure and can accurately determine HD progression. The ^{13}C-methionine breath test was performed in six HD transgenic sheep and six age-matched controls to evaluate the oxidative capacity of liver mitochondria. After overnight fasting, all sheep were administered 200mg ^{13}C-methionine via intravenous injection (10mL). Breath $^{13}CO_2$ enrichment was measured at baseline and every 10 minutes thereafter for 180 minutes using isotope ratio mass spectrometry. Results were expressed as cumulative percentage dose rate over 180 minutes of exhaled $^{13}CO_2$ (%cPDR180 ± SEM), indicative of decay of mitochondrial function. Rate of $^{13}CO_2$ excretion (^{13}C dose/h) after administration of ^{13}C-methionine increased rapidly reaching a maximum mean of in minutes and in minutes in control and HD groups, respectively. In HD sheep cPDR180 was compared to controls (). This preliminary study demonstrates that non-invasive ^{13}C-methionine breath tests can be conducted reliably in sheep, with potential to form the basis of a simple test to determine the efficacy of HD therapeutics. Further studies with larger cohorts of sheep are required to determine if ^{13}C-methionine breath results differ significantly between HD sheep and controls.

Poster 9.44

Impaired spatial memory, reduced exploration and increased hippocampal microglia density are associated with senescence but are not reduced by a connexin hemichannel blocker

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Increased neuroinflammation is a neurobiological change associated with ageing. The current study is the first to investigate a potential neuroprotective agent, tonabersat, a hemichannel blocker with potential neuroprotective properties and anti-inflammatory effects. We estimated microglial cell density, using Isolectin B4-peroxidase (IB4) in the dorsal hippocampus and the thalamus of senescent rats nearing the end of their lifespan (2+ years), in middle-aged rats (1+ year) and in young adult rats (6 months; Ns = 23, 10 and 13, respectively). Two subgroups of senescent rats received daily oral administration of tonabersat in vehicle over three months (0.4mg/kg or 0.8mg/kg). All other groups were given the vehicle only. Prior to sacrifice, rats received behavioural assays of exploratory activity (open field) and spatial memory (Morris water maze). Middle-aged rats had significantly higher IB4 staining than the young adult rats in both hippocampus and thalamus. Although equivalent in the thalamus, the senescent rats had yet higher IB4 staining in the hippocampus. Behaviourally, the middle-aged and senescent rats showed similar activity in the open field, but less activity than the young group. However, similar spatial memory performance was shown by the middle-aged and young groups, whereas senescent rats showed poorer acquisition of the submerged platform. Irrespective of dose, tonabersat had no influence on any of these measures in senescent rats. Beneficial effects of tonabersat may require its introduction at an earlier age.

Poster 9.45

Assessing the efficacy of adeno-associated viral vectors in targeting the brain

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One barrier to the treatment of Alzheimer's disease is a lack of effective methods to deliver therapeutics to the brain, particularly by non-invasive routes. Adeno-associated viral (AAV) vectors used for gene therapy may provide a solution, as some vectors can cross the blood-brain barrier. A novel AAV capsid evolved *in-vivo*, AAV-PHP.eB, was recently reported to produce high transduction in mouse brain after intravenous administration. However, the increased efficiency of this vector may be limited to the C57BL/6 mouse strain it was evolved in. Here, we compared the efficacy of two AAV vectors, AAV-PHP.eB and AAV9, in targeting mouse brain after administration via various routes, and in two different mouse strains. C57BL/6 mice were administered a combination of AAV-PHP.eB encoding tdTomato, and AAV9 encoding green fluorescent protein, either by intravenous injection (n=6), intranasal injection (n=6), or intrahippocampal injection (n=5). B6C3 mice (n=4) received the same vectors via intravenous injection. Four weeks after vector administration, brain sections were qualitatively examined for reporter protein expression and cell-type transduction. AAV-PHP.eB was more effective than AAV9 at transducing the brain after intravenous injection in C57BL/6 mice. However, the two vectors showed similar, low efficacy in B6C3 mice. Both vectors showed similar efficacy after administration directly into the hippocampus, and after intranasal administration, where the vectors did not spread beyond the olfactory bulb. Both vectors transduced neuronal and glial cells. Our results show that while viral vector efficacy for crossing the blood-brain barrier can be increased, caution is required when considering translation to humans.

Poster 9.46

Brain development and the *Amh* locus

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Anti-Müllerian hormone (AMH) is a powerful regulator of sex-dimorphic development. Produced by the early testes, the hormone represses female reproductive development, and is also a strong candidate for influencing sex-specific differentiation of the developing brain. To date, research has shown that AMH contributes to male-specific phenotypes for a multitude of neuroanatomical and behavioural traits. We aim to investigate the molecular basis of sex-specific changes induced by AMH in the developing brain. An *Amh* knock-out mouse line was used to compare gene expression in developing (E15.5) brains from normal and knock-out mice of both sexes. RNA sequencing identified that $Amh^{-/-}$ males show a gene expression profile more similar to wildtype female littermates than male, consistent with the hypothesis that AMH masculinises the developing brain. Additionally, unexpected differences between normal and knock-out females indicated additional effects caused by the deletion within the *Amh* locus. *De novo* transcriptome assembly revealed a novel transcript aligning to the *Amh* locus. We have conducted further experiments to determine expression of this transcript *in vivo* and test the hypothesis that is a microRNA precursor. Our investigations highlight two functions of the *AMH* gene locus, one hormonal and the second non-protein coding, in brain development.

Poster 9.47

Functional neuroimaging correlates of executive function following preterm birth

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It is now well recognised that children born preterm (<37 weeks gestation) are at an increased risk of executive function impairments, independent of their general cognitive abilities. Moreover, significant associations have been reported between neonatal white matter injuries/abnormalities and later development of executive function in this high-risk population. Nonetheless, the functional neural correlates of executive function following preterm birth remain unclear. Thus, a coordinate-based activation likelihood estimation meta-analysis was conducted using BrainMap GingerALE 2.3.6. The analysis incorporated functional neuroimaging data from peer-reviewed published studies of working memory, inhibitory control, and cognitive flexibility, in survivors of preterm birth aged 5 to 18 years. The first-level activation likelihood estimation map for executive function, where children born full-term performed better on tasks, showed shared activation in 26 clusters with the largest activation in the inferior frontal gyrus and right precentral gyrus. Where children born preterm performed better, there was shared activation in 27 clusters, with the most activation in the left and right fusiform gyri, the middle, temporal and frontal gyri, and the posterior cingulate gyrus. Preliminary results from this meta-analysis are the first to identify neuronal locations consistently activated in relation to executive function outcomes in children born preterm. These findings may help to develop a better understanding of the pathways from preterm birth to adverse neurocognitive development.

Poster 9.48

Prognostic factors to G-CSF with stem cell therapy for children with cerebral palsy

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We observed the safety and efficacy of infusion of granulocyte-colony stimulating factor (G-CSF) followed by autologous peripheral blood stem cells to ameliorate the neurologic impairment in children with cerebral palsy. During this clinical trial, we assessed the serial cytokine changes and their clinical impact. Cytokine levels were measured before treatment, and at 1, 7, and 13 months after G-CSF infusion by enzyme-linked immunosorbent assay. G-CSF levels were significantly elevated at 1 month after G-CSF infusion and decreased to baseline at 7 and 13 months. VEGF, IL-6, and IL-10 behaved in the same way whereas BDNF and IGF-1 followed the reverse pattern, falling initially and then returning to baseline. When clinical responders and non-responders were compared, IL-6 ($p=0.05$) as well as G-CSF ($p=0.001$) were higher in the responders than the non-responders at 1 month, while BDNF ($p=0.03$) and IGF-1 ($p=0.001$) were lower. In addition, BDNF was higher at baseline in the responders than the non-responders ($p=0.03$). The changes of G-CSF itself, as well as G-CSF-induced cytokines such as IL-6, may be associated with the clinical improvement of neurologic functions. The G-CSF-induced changes of IL-6, BDNF and IGF-1, and BDNF levels before treatment, could be used as prognostic factors in G-CSF trials in children with cerebral palsy.

11.1

Parkinson's disease: Where did all my habits go?

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Progressive loss of the ascending dopaminergic projection in the basal ganglia is a fundamental pathological feature of Parkinson's disease. Studies in animals and humans have identified spatially segregated functional territories in the basal ganglia for the control of goal-directed and habitual actions. As the dopamine loss in patients with Parkinson's disease often occurs differentially in the posterior putamen, a region of the basal ganglia associated with the control of habitual behaviour, these patients may be forced into a progressive reliance on the goal-directed mode of action control mediated by comparatively preserved processing in rostro-medial striatum. Thus, many of their behavioural difficulties may reflect a loss of normal automatic control, 11.3exacerbated by distorting output signals from habitual control circuits which impede the expression of goal-directed action.

11.2

Contrasting changes in DARPP-32 and calbindin immunoreactivity in medium spiny neurons in Parkinson's disease

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While the substantia nigra is widely implicated in Parkinson's disease (PD), the involvement of the striatum and medium spiny neurons (MSNs) in PD is still unclear. Our previous work has indicated that DARPP-32 (dopamine and cAMP-regulated neuronal phosphoprotein) can be used to identify a subset of MSNs, and that DARPP-32 MSNs only partially co-label with calbindin, the traditional MSN marker. The mammalian striatum is heterogeneously organized into neurochemically distinct compartments called striosomes and matrix. Furthermore, preliminary qualitative investigations showed that the great majority of DARPP-32 positive cells in the dorsal striatum were localised in the striosomes whereas some scattered DARPP-32 positive cells were localised to the matrix. This study utilised post-mortem control and PD human striatal sections in order to investigate whether DARPP-32 and calbindin are altered in PD. Morphometric analysis using Metamorph® image analysis software revealed that although overall calbindin-positive integrated density within each striatal compartment showed no major difference from control to PD, DARPP-32 integrated density in PD striatal regions was decreased overall in comparison to control. In particular, significant decreases were noted in the putamen striosomes ($p = 0.0197$, 50% decrease), putamen matrix ($p = 0.0079$, 59% decrease), ventral striatal patches ($p = 0.0087$, 65% decrease) and ventral striatal matrix ($p = 0.0036$, 62% decrease). Histological examination also revealed weaker immunoreactivity of DARPP-32 positive MSNs with morphological and dendritic changes, particularly in the putamen. This study shows that the striatum, particularly the putamen and ventral striatum, shows loss of DARPP-32 immunoreactivity in PD, indicating that dopamine dependent proteins in the striatum are altered in PD.

11.3

Development of a minimally-invasive technology for spatially- and temporally-controlled drug delivery into the brain

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Parkinson's disease (PD) is characterised by a debilitating impairment in executing habitual movements, resulting from a loss in dopamine neurotransmission. Dopamine-replacement therapy is commonly used to restore brain dopamine levels and alleviate motor symptoms. Unfortunately oral medication of the dopamine precursor levodopa becomes less effective over time, resulting in fluctuations between normal mobility and complete cessation of movement. The progressive increase in levodopa dosage necessary to overcome these fluctuations, results in the progressive emergence of debilitating involuntary movements (dyskinesias) that contaminate normal mobility. It is thought that dyskinesias reflect abnormal reinforcement of motor outcomes induced by the slow non-physiological fluctuations in dopamine levels resulting from oral medication. To tackle the issue of improved PD treatment with fewer side effects, we developed a drug delivery system offering the potential of emulating the physiological fluctuations in dopamine levels (seconds to minutes) occurring in healthy brains. In a proof of concept experiment, we exposed the striatum of anaesthetised rats to focused ultrasound delivered outside the dura, and demonstrated local release of dopamine agonists from sonosensitive liposomes circulating in the cerebral bloodstream. Using 3D modelling and brain imaging techniques in a large mammal, the sheep, we have established a translational methodology for the transcranial delivery of focused ultrasounds to specific brain areas. This technology offers the potential to improve dopamine-replacement therapy by mimicking the physiological patterns of dopamine release observed into the brain, which could reduce the development of dyskinesias.

11.4

Failure of the habit system in Parkinson's disease

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Parkinson's disease (PD) is currently diagnosed by clinical examination, based on the presence of bradykinesia and muscular rigidity or resting tremor. These motor signs appear when the disease is well advanced, after ~70% of neurons in the lateral region of the substantia nigra pars compacta (lSNc) have died. However, the misdiagnosis rate is 47%, underlying the urgency for the development of a reliable test to detect PD. Recently, we tested a new class of behavioural biomarker based on the fact that lSNc degeneration in PD first impairs the expression of habits (the automatic actions we have learned to do without thinking). Behaviour under habitual control is inflexible and can cause errors under unexpected circumstances. Participants with early PD and age-matched controls performed two different tasks where habits cause errors: typing sentences on the keyboard and playing a computer game when the control of the mouse was reversed. We found that while PD participants committed more errors overall, they nevertheless committed fewer errors induced by persisting habits. These results indicate that the two tasks are sensitive to the loss of habitual control and could be used to detect and monitor the early stages of PD.

11.5

An optogenetic Channelrhodopsin-assisted mapping investigation of network organization within the subthalamic nucleus

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The basal ganglia is a sub-cortical structure receiving a wide range of inputs almost from the entire brain. As such, it is involved in motor control, learning, memory and reward-driven behaviour. The subthalamic nucleus (STN), a major glutamatergic nucleus of the basal ganglia projecting to the substantia nigra pars reticulata and pars compacta nuclei, plays a crucial role in the *indirect* and *hyperdirect* pathways. Previous electrophysiological studies suggest that STN neurons also make internal synapses through axon collaterals with other glutamatergic neurons in the nucleus. Our aim was to apply the optogenetic technique of channelrhodopsin (ChR2)-assisted circuit mapping to rapidly investigate synaptic connectivity between neurons within the STN. CD-1 mice expressed ChR2 in STN neurons under the CaMKIIα promotor after injection of the viral (AAV5) construct into the nucleus. Mapping was conducted in horizontal brain slices (250µm) using a digital mirror device to sequentially illuminate individual squares (20µm^2; 6 mW/mm^2, 5ms) of a grid (740 µm^2), while recording post-synaptic currents from a single whole-cell patch-clamped STN neuron. Using this approach, we detected light-evoked inward currents at multiple discrete locations within the STN. Light-evoked currents were delayed (4-8 ms light onset) and blocked by CNQX, confirming a synaptic origin. STN light-evoked post-synaptic currents were recorded from GABAergic neurons in the substantia nigra pars reticulata and varied significantly in magnitude and latency, consistent with a multisynaptic excitatory network. The role of this internal excitatory network in normal basal ganglia function, as well as in the Parkinson's disease state, remains to be determined.

11.6

Anatomical and physiological changes at basal ganglia-motor thalamus synapses in rat model of Parkinson's disease

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Profound alterations in basal ganglia neuronal activity underlie movement deficits in Parkinson's disease (PD). We have previously shown that motor thalamus neuronal activity is also impaired in parkinsonian rats. To understand anatomical and physiological changes at basal ganglia-motor thalamus synapses that contribute to motor thalamus dysfunction, we injected lentiviral vectors (GAD67-GFP or GAD67-ChR2-mCherry) to transduce GABAergic neurons in the substantia nigra pars reticulata (SNr) of sham (control) and 6-hydroxydopamine lesioned parkinsonian rats. To visualise SNr boutons in ventroanterior (VA) thalamus by electron tomography and electron microscopy, we converted GFP to an electron dense label. SNr terminals in control rats contained multiple mitochondria, pleomorphic vesicles and formed large calyx-like boutons that contained multiple symmetric synapses. In contrast, SNr boutons in parkinsonian rats were 50% smaller and had significantly fewer synapses per SNr bouton ($p = 0.049$). In control rats, optogenetic stimulation of GABAergic SNr axons produced short latency increases in VA thalamic neuron firing rates via hyperpolarization-induced activation of T-type calcium channels, evidenced by reduced firing rates following intracerebral drug infusion. Dopamine lesion induced anatomical changes at SNr-VA synapses may underlie VA thalamic neuron pathophysiology because optogenetic stimulation-induced VA thalamic firing rate changes were significantly smaller in parkinsonian rats ($p = 0.045$). Midbrain dopamine neuron degeneration appears to have widespread anatomical and physiological changes in basal ganglia-thalamocortical networks, which need to be considered when designing new treatment strategies for PD. Research was supported by the Neurological Foundation of New Zealand.

12.1

ARPP21 mutations reveal the role of RNA granule dysfunction in ALS and FTD

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Amyotrophic Lateral Sclerosis (ALS) and fronto-temporal lobar dementia (FTD) are associated with the pathological aggregation of proteins involved in RNA processing, most commonly TAR-DNA binding protein (TDP)-43 and rarely fused in sarcoma (FUS) protein. Many other mutant genes can contribute to TDP-43 aggregation and some of these are also directly involved in RNA processing (ATXN2, hnRNPA1, hnRNPA2B1 and MATR3). We will present unpublished evidence that novel variants in ARPP21 are associated with ALS and FTD. ARPP21 encodes a neuronally expressed, cytoplasmic RNA-binding protein involved in mRNA transport. Mutations increase the propensity of ARPP21 and TDP-43 to aggregate and become insoluble in an RNA-binding dependent manner. Mutations disrupt RNA granule transport in primary neurons and enhance neurotoxicity in the Drosophila eye. This discovery reveals new insights into the role of RNA granule dysfunction in ALS and FTD and challenges several assumptions about the pathophysiology of these neurodegenerative disorders

12.2

Altered arginine metabolism in the frontal cortex of patients with major depression

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L-arginine is a versatile semi-essential amino acid with several bioactive molecules. Altered arginine metabolism has been implicated in the pathogenesis of a number of psychiatric disorders including major depression, and agmatine (decarboxylated arginine) has anxiolytic and antidepressant-like effects. The present study, for the first time, systematically compared the metabolic profile of L-arginine in the frontal cortex (Brodmann's area 8) obtained post-mortem from individuals with major depression and age- and gender-matched non-psychiatric controls (n = 20/group). The enzyme assays revealed lower nitric oxide synthesis activity, but higher arginase activity, in the depression group. High performance liquid chromatography and liquid chromatography/mass spectrometric assays confirmed significantly reduced levels of agmatine, spermidine and glutamine/glutamate ratio, but increased glutamate/GABA ratio, in patients with major depression. Regression analysis indicated a negative correlation between L-arginine and the duration of illness. The present study demonstrates marked alterations of arginine metabolism in the frontal cortex of patients with major depression. The findings further support the link between arginine metabolism and major depression, and suggest a biological basis for agmatine as a promising candidate for treatment of the disease.

12.3

Multiplex immunohistochemistry of 10+ markers to assess unfolded protein response activation in the Alzheimer's disease olfactory bulb

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The unfolded protein response (UPR) is a cellular process that occurs due to accumulation of misfolded proteins. This pathway, involving endoplasmic reticulum protein kinases called PERK and eIF2α, is strongly implicated as a potential mechanism of degeneration in cellular and animal models of Alzheimer's disease (AD). Fluorescent immunohistochemistry (IHC) can be used to identify the phosphorylated (activated) forms of these kinases in post-mortem human brain tissue. In collaboration with the National Institutes of Health (Bethesda, USA), we performed multiplex fluorescent IHC using antibody stripping that allowed visualisation of 10+ proteins simultaneously in post-mortem human tissue. We applied this technique to paraffin embedded human olfactory bulb tissue, as this is one of the first regions affected by amyloid and tau in AD. Using manual cell counting we determined the density of cells showing UPR activation and co-localisation with cellular markers and intracellular tau aggregates. Our results show a 10-fold increase in the density of cells expressing phosphorylated PERK and eIF2α within the anterior olfactory nucleus of the AD olfactory bulb. We also found neurons expressing these markers contain diffuse tau aggregates rather than neurofibrillary tangles. These results indicate the UPR is activated in this region of the AD brain and may precede the formation of advanced tau tangles. The application of multiplex IHC to human brain tissue studies in New Zealand offers a novel opportunity to study protein interactomes across a range of neurological conditions.

12.4

Activity-dependent actions of Li^+ in brain network connectivity

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Bipolar disorder (BD) is characterised by swings between hyperactive and hypoactive states. Neuroimaging in BD shows aberrant coupling (functional and structural connectivity) in networks associated with the regulation of emotion. Functional coupling depends physiologically on coherence (stable phase relationships) and synchrony in synaptic networks driving electrical oscillations in brain networks. BD can be described as resulting from aberrant coherence or synchrony in brain networks. BD is treated primarily with Li^+, or with selected antiepileptic drugs (AEDs). The therapeutic mechanism of Li^+ is unknown. The AEDs are activity-dependent agents; they selectively supress the output of highly active neurons, limiting network oscillation and synchrony. We have investigated activity-dependency of Li^+ action in mouse olfactory bulb brain slices. Networks in the slice generate spontaneous oscillations, involving excitatory synaptic coupling between synchronously active output neurons which can be entrained by stimulating the olfactory nerve (ON). We simulated the ON at low (0.03 Hz) frequency to monitor network excitability, before and after a period of high frequency network activation (5 Hz ON stimulation for 5 s), with and without 1-2 mM Li^+. Our results show, for the first time, that Li^+ can have activity-dependent, bidirectional effects on network activity. Li^+ increased spontaneous activity, post-synaptic excitability and output neuron synchrony when network activity had been relatively low, but had the opposite effects when synaptic network activity had been high. Li^+ enters neurons through Na^+ channels, to block K^+ channels located in the axon and increase excitability and synchrony. We suggest that high frequency synaptic activity increases Li^+ entry into dendrites through glutamate receptors, resulting in blockade of NMDA receptors, and decreased network excitability and synchrony.

13.1

Development of behavioural self-regulation in preschool-age children prenatally exposed to methadone

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Opioid abuse during pregnancy remains an increasing public health concern worldwide. Methadone Maintenance Therapy, a synthetic opiate-based treatment, is the most common and often regarded as one of the best treatment options for pregnant women with an opiate addiction. Despite early evidence of neonatal neurobehavioural and emerging neurocognitive difficulties, the impact of prenatal methadone exposure on long-term child neurodevelopmental outcomes remains largely unknown. Using data from a prospective longitudinal cohort, the aim of this study was to examine the development of behavioural self-regulation abilities using the classic Delay of Gratification Task paradigm at age 4.5 years. The sample consisted of a regional cohort of 58 children born to opioid-dependent mothers maintained on methadone during pregnancy and 81 comparison children born to non-opioid using mothers. Results showed preschool-aged children prenatally exposed to methadone had poorer self-regulation abilities relative to the comparison group as exhibited by shorter wait times for the reward (mean wait time = 357 vs 562 seconds, p=.003). Furthermore, significant positive correlations (r = .27, p = .02) were evident in the comparison group between children's regulatory skills, maternal age and maternal education. In contrast, similar associations were not found in the methadone-exposed group. This is noteworthy, despite the high prevalence of psychosocial adversities in these families, lower quality of their home environment didn't completely explain their poorer behavioural maturation. These findings imply that the mediating role of clinical and neurological factors also needs to be explored for a better understanding.

13.2

Confirmed vs suspected neonatal infection: Associations with neonatal neurological abnormalities following preterm birth

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Infants born preterm (<37 weeks gestation) are at an elevated risk of contracting infections as well as developing neurological abnormalities during the neonatal period. However, it remains unclear the extent to which these neonatal infections may account for neurological abnormalities. Furthermore, little is known about the impact of infection that is suspected, based on clinical presentations, but not confirmed with pathology findings. To examine the associations between confirmed and suspected infection and the risk of neurological abnormalities during the neonatal period following preterm birth, a meta-analysis was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Nine cohorts fulfilled the selection criteria, with all reporting on confirmed (n=656) and no infection (n=3,582), and four reporting on suspected infection (n=1,172). Results showed infants born preterm with confirmed or suspected neonatal infection were at a significantly increased risk of neurological abnormalities, compared to those with no infection. Specifically, using fixed-effects models, the pooled odds ratios [95% Confidence Intervals] for comparisons of infants with confirmed and no infection ranged from 1.87 [1.39, 2.51] to 2.86 [1.51, 5.42]. Similarly, the odds ratios for comparisons of infants with suspected and no infection ranged from 1.55 [1.28, 1.87] to 2.23 [0.96, 5.16]. No significant differences were evident for comparisons between infants with confirmed and suspected infection. Current findings suggest little difference between confirmed and suspected infection for neurological outcomes, at least during the early developmental period. Future research should address if these relationships persist in the longer-term. These findings have implications for neonatal neuroprotection and long-term neurodevelopmental follow-up of all infants with possible infection.

13.3

Characterising the impacts of complex and simple congenital heart defects on executive function

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Congenital heart defects (CHD) are structural malformations of the heart at birth, presenting a critical risk factor for developmental delays and/or deficits in executive function. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was used to conduct a meta-analysis for describing the nature of executive function in 3- to 18-year-old children with complex and simple CHD. Data were drawn from 12 independent cohorts born after 1980, reporting performances of children with and without CHD on standardised assessments of the three core executive function domains. Results showed children with CHD as significantly more likely to exhibit developmental impairments in executive function than their non-CHD peers (p<.001). The pooled effect sizes, assessed using fixed-effect models and reported as standardised mean differences [95% Confidence Intervals], were as follows: visual working memory = -0.44 [-0.58, -0.30]; verbal working memory = -0.49 [-0.62, -0.36]; inhibitory control = -0.90 [-1.14, -0.66]; and cognitive flexibility = -0.84 [-0.98, -0.69]. Moreover, children with complex CHD exhibited significantly poorer performance relative to non-CHD children across all three core executive function domains, with standardised mean differences ranging from -0.82 to -0.39, p<.001. In contrast, children with simple CHD were at an elevated risk of poor inhibitory control compared to non-CHD children (p<.001), but not working memory impairments. No data on cognitive flexibility in the simple CHD group was available. Current findings provide the first high-level evidence profiling the nature of executive function in children with complex and simple CHD. These have implications for clinical management and for informing the development of targeted interventions to improve neurocognitive outcomes and quality of life in this high-risk population.

13.4

Adults born with very-low-birth-weight demonstrate alterations in grey matter volume, perfusion, and white matter integrity

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Very-low-birth-weight (VLBW) is associated with alterations in brain structure and function throughout childhood, adolescence and adulthood. The New Zealand VLBW study cohort comprised 413 infants born VLBW in 1986. Of 338 who survived to discharge home, 250 (77% survivors) were assessed at 27-29 years, when 150 VLBW and 50 healthy controls completed MRI on a 3T scanner. We aimed to investigate whether VLBW participants would exhibit reduced grey matter (GM) volume (via structural MRI), perfusion (via arterial spin-labelling) and white matter (WM) health (via diffusion tensor imaging) compared to controls, and to assess associations with birth weight. Grey matter volume was reduced in VLBW within frontal, temporal, parietal and occipital cortices, bilateral caudate and right cingulate gyrus, while increases were noted within limited frontal, temporal and occipital areas. Reduced GM perfusion was observed in VLBW within bilateral inferior temporal gyri and hippocampi, left thalamus, right superior temporal gyrus and frontal orbital cortex. Diffusion tensor imaging revealed reduced fractional anisotropy (FA) and axial diffusivity (AD) (measures of WM microstructural integrity) within principal WM tracts including forceps major and various fasciculi. Among VLBW participants, GM volume and GM perfusion positively correlated with birth weight within widespread cortical and subcortical regions; FA and AD were associated with birth weight in numerous principal WM tracts. Our findings suggest that robust structural and functional brain differences exist in VLBW adults compared to their term-born peers. Furthermore, birth weight shows an association with the state of the brain in early adulthood.

14

Sculpting the nervous system: Cellular and molecular mechanisms of neural circuit refinement

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One of the most remarkable properties of the brain is its ability to undergo adaptive modifications in response to changing environments. This property, known as experience-dependent plasticity, is essential not only for the fine-tuning of developing circuits, but also for behavioural changes, such as learning and memory, in adults. Over the past two decades, advances in fluorescent labelling and imaging techniques have enabled direct visualization of the structural reorganization of neuronal circuits during experience-dependent circuit plasticity. Dendritic spines have been a major focus of these studies; the gain or loss of spines is associated with the establishment or elimination of neural circuit connections, and the enlargement or shrinkage of spines accompanies an increase or decrease in the strength of synaptic connections. I will present the results of our efforts to define the neural activity patterns and downstream signalling mechanisms that drive the structural and functional modifications of dendritic spines during experience-dependent plasticity. Results from our experiments will lead to a better understanding of the signalling mechanisms driving spine structural plasticity during neuronal circuit development and should provide new insights into how dysregulation of these plasticity mechanisms contributes to neurological disorders.

15.1

Gene-environment interactions in mouse models of neurodevelopmental and cognitive disorders

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We have explored mechanisms of pathogenesis in mouse models of neurodevelopmental disorders, including schizophrenia and autism spectrum disorder. We have been investigating how various environmental manipulations selectively alter gene expression, cellular plasticity and associated cognitive processes and behaviours. We have demonstrated that environmental enrichment (enhancement of cognitive stimulation and physical activity) has beneficial effects in mouse models of various brain disorders, including schizophrenia. Environmental enrichment and physical exercise induce changes in gene expression, which exhibit temporal specificity and regional selectivity, and also act as cognitive enhancers. These findings have been extended to include other environmental manipulations as well as pharmacological interventions. Our experimental approaches may facilitate the development of 'enviromimetics' for a variety of brain disorders known to be modulated by environmental stimuli. We have also explored the transgenerational effects of paternal environmental exposures. Our findings reveal significant experience-dependent effects on cognitive and affective function of offspring via transgenerational epigenetic inheritance, which occurs via epigenetic modifications in the sperm of the fathers. We are exploring the impact of specific environmental and pharmacological factors, including exercise and stress hormone elevation, and the relevance of these discoveries in mice to human transgenerational epigenetics. Our findings, and their relevance to the proposed transgenerational inheritance of increased predisposition to various cognitive and affective disorders, have major public health implications.

15.2

Influence of maternal high zinc diet on the development of autism-associated behaviours

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Autism Spectrum Disorders (ASDs) are characterised by repetitive behaviours and impaired social communication. Many ASD-associated mutations occur in the Shank family of synaptic proteins resulting in weakened synapse function. Zinc deficiency is a risk factor in ASD, and low zinc levels have been found in autistic children. Interestingly, zinc enhances Shank3 stability and recruitment to synapses, enhancing synapse function. Here we aimed to determine the effect of raising dietary zinc during pregnancy and lactation on the development of ASD-associated behaviours in Shank3 knockout (KO) and wildtype (WT) mice. Excessive grooming (cylinder test), anxiety (light-dark test) and social interaction (three-chamber test) were assessed in 3 and 9 week old WT and Shank3 KO offspring born from mothers on high zinc (150ppm) or control zinc (30ppm) diet. High maternal zinc supplementation prevented the development of social deficits, such that lack of social preference and inability to recognise social novelty were not evident in Shank3 KO mice exposed to high zinc from their mother during pregnancy and lactation. These effects were maintained into adulthood. However, phenotypes that presented later in development, such as repetitive grooming, were not rescued by exposure to high zinc from the mother. Some anxiety behaviours, such as latency to enter bright arena, were rescued by maternal high zinc diet; whereas other anxiety phenotypes, such as time spent in bright arena, were not rescued. Together these data suggest that zinc supplementation throughout brain development has differential effects on the prevention of ASD-related behaviours, with the most significant effect being to prevent ASD-related deficits that present early in development.

15.3

Tonotopic mapping in a mouse model of autism spectrum disorder

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Autism spectrum disorder (ASD) affects around 1 in 100 New Zealanders. Symptoms of ASD include auditory hypersensitivity and language impairment. It is therefore possible that the auditory cortex develops differently in ASD, leading to these symptoms. Differences in the tonotopic layout of sound representation in the auditory cortex have been shown in a chemically-induced rat model of ASD, using electrophysiological techniques. These differences notably included an overrepresentation of response to high-frequency sound. *In vivo* calcium imaging is a relatively new method of measuring neuronal activation, which can act as an alternative method to electrophysiological recording. Therefore, we have developed a technique to image neuronal activity in the auditory cortex in response to sound. To do this we inject fluorescent calcium dye (Cal520) into the auditory cortex of anaesthetised mice and use wide-field imaging to detect responses following presentation of tones ranging from 5 kHz to 50 kHz. This allows generation of tonotopic maps through comparison of areas activated by each frequency. This method will be used to compare these tonotopic maps between wild type and *Shank3b* knockout ASD mice to elucidate the differences caused by this ASD-related mutation. Increasing our knowledge of the cortical manifestations of ASD phenotypes will enhance our understanding of the basis of ASD symptoms such as auditory hypersensitivity and language impairment. If our results support those found with electrophysiology in a different model of ASD, they will form a robust case for translation to human patients, and may inform future directions for treating these symptoms.

15.4

Investigating the development and evolution of cortical circuits using *in vivo* assays in marsupials

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The six-layered cerebral cortex integrates sensory perception with motor action, and mediates higher-order cognitive processes such as attention, learning and language. Healthy brain function relies on the precise formation of cortical circuits, and subtle developmental defects can lead to several conditions such as autism, attention deficit and schizophrenia. Most of our knowledge on healthy and pathological cortical development comes from studies in rodents and primates, as mammals are the only vertebrates that evolved a cerebral cortex. However, important questions remain open due to the lack of experimental paradigms to study the developing cortex *in vivo*, inside the uterus. Here I will present a marsupial model of extra-uterine cortical development (inside the pouch), the Australian fat-tailed dunnart (*Sminthopsis crassicaudata*). We have established a dunnart breeding colony and the in-pouch electroporation technique, which allows unprecedented access to selectively transfect multiple neuronal populations. By combining high-throughput RNA sequencing, molecular development and microscopy in mice and dunnarts, we are currently investigating the development and evolution of the transcriptional control of axon guidance, as only placental mammals (but not marsupials or monotremes) evolved a corpus callosum. Moreover, the skull of pouch-young dunnarts is highly translucent (hence amenable for optogenetics), allowing two-photon imaging of calcium activity in the developing neocortex at stages equivalent to prenatal humans and rodents. These features highlight the potential impact of laboratory marsupials to study the genetic and environmental influences on cortical development, while also providing important clues on the evolution of brain developmental systems.

16.1

Using bond graphs to provide a consistent framework for coupling cerebral circulation with tissue exchange mechanisms

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A key challenge for the physiology modelling community is to create a comprehensive public domain resource for cardiovascular researchers. In this work, we have developed a computational infrastructure for the cardiovascular model which provides near real-time computation of Oxford blood flow and pressure in all parts of the body. The model deals with vascular beds in specific tissues and the computational infrastructure provides links into CellML models of cell function and tissue function. Bond graphs provide a formalism for building models of biophysical processes in a way that guarantees conservation of mass (or charge) and conservation of energy across multiple types of physical system. The bond graph model runs at close to real time on a desktop computer. We have implemented the bond graph approach with the declarative CellML language in the open source program OpenCOR. These software tools are developed as part of the Physiome Project and made available in the public domain. Our overall goal for this work is to create an anatomically detailed model of the cardiovascular circulation that can be run in real time and can be coupled with tissue exchange models at the capillary level. The model presented here will be made available in the public domain with freely available open source tools that will allow users to examine pressures and flows at any point in the circulation under a variety of physiological conditions. The bond graph formulation makes it straight forward to include various tissue exchange mechanisms and to incorporate tissue and cellular parameters that characterise various chronic diseases.

16.2

Integrated models of neurovascular coupling and BOLD signals

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Neurovascular coupling is the ability of the cortical tissue to regulate the blood supply *locally*. Blood oxygen level dependent (BOLD) signals represent neuronal activity, via measurement of de-oxyhemoglobin. We have developed a complex numerical model of neurovascular coupling which now combines the ability to simulate the fMRI BOLD responses due to continuous neuronal spiking, bursting phenomena and task orientated stimulation. Simulated BOLD responses are compared to experimental BOLD signals observed in the rat barrel cortex. We hypothesised that for long stimulations a particular pathway including the locus coeruleus would recruit a network of both cortical excitatory and inhibitory neurons resulting in substantial cortical activity and increased cerebral blood flow, essentially a neuromodulatory effect. By introducing this additional pathway in the numerical model our results showed excellent agreement. Bursting phenomena provide relatively clear BOLD signals as long as the time between bursts is not too short. Numerical BOLD responses were compared to human experimental BOLD signal data obtained during finger tapping and quad tasks. Variations of the strength of the neuronal Na^+/K^+ATPase exchange pump which restores ionic homeostasis upon neural activation and the parameter describing the morphological relationship between neurons and astrocytes provided BOLD responses with different amplitudes and shape. By mapping experimental data to the simulations, statistical distributions of three parameters (O_2 consumption by the ATPase pump, maximum pumping rate and neuron/astrocyte coupling) are obtained. These distributions indicate the variational range expected of the three BOLD signal mechanisms during tasks.

16.3

The Astrocyte-Neuron Lactate Shuttle's role in neurovascular coupling

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The astrocyte-neuron lactate shuttle (ANLS) hypothesis is that lactate may be shuttled from astrocytes to neurons and subsequently used as a nutrient during pathological conditions to help meet the energy requirements of the cell. In particular, the ANLS might provide energy to fuel neurovascular coupling (NVC). NVC can be defined as the regulation of cerebral blood flow (CBF) in response to neural activity. The Neurovascular Unit (NVU) models this coupling; it comprises neuron, astrocyte, smooth muscle cell, endothelial, and extracellular space compartments, and is able to predict local vascular responses to neural stimuli. The most recent addition to the NVU was a model of cerebral energy metabolism (CEM), including the ANLS. Simulations of healthy conditions with the extended NVU model showed good agreement with original NVU results, as well as experimental results from which the CEM model originated. During neuronal stimulation, NVC was responsible for generating a CBF response, which in turn drove up the production of astrocytic and neuronal ATP. Increased ATP production was able to maintain the increased Na+/K+ ATPase pump rates, resulting in unimpaired NVC. Simulating pathological conditions emphasised the importance of maintaining Na+/K+ ATPase pump rates for NVC. The reduction of input glucose and oxygen resulted in greatly lowered ATP production in neurons and astrocytes. Consequently, the activities of both neuronal and astrocytic Na+/K+ ATPase pumps dropped. Our results suggested lactate concentration in the astrocyte was too low to be effectively shuttled at a rate able to meet the energy demands of neurons. However, the shuttle's contribution was not insignificant and maintained some degree of activity via the conversion of lactate to pyruvate catalysed by lactate dehydrogenase.

16.4

Large scale tissue slice simulations of cortical spreading depression

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Neuronal activity evokes a localised increase in cerebral blood flow in a response known as neurovascular coupling (NVC), achieved through communication via the neurovascular unit (NVU). Dysfunctional NVC can lead to pathologies such as cortical spreading depression (CSD), a slow moving wave of neuronal depolarisation and high extracellular potassium levels. CSD is associated with several neurological disorders such as migraine, Alzheimer's disease and stroke. CSD can be affected by the presence of an astrocytic gap junction network which is able to transport potassium away from areas of high concentration, though the precise role of this network is under debate. Our research group has developed a large scale numerical model able to simulate NVC in a vascularised cortical tissue slice. "In silico" experiments are performed which are impossible in the wet-lab, providing an experimentally validated test-bed for a variety of neurological phenomena such as CSD. Under pathological conditions the model is able to simulate propagating waves of high extracellular potassium travelling at 6.7 mm/min comparing well with experimental findings. The high potassium concentration induces a corresponding wave of vasoconstriction (with decreased blood flow) then slight vasodilation, achieved through communication via the NVU. This behaviour is seen in multiple experimental results. Our results show that the CSD wave is mediated by the extracellular electric field since simple diffusion produces a "sub-excitable" condition and the wave stops. Nutrient supply is severely reduced during the wave causing possible cellular damage or stress on the lactate system. Increasing the density of astrocytic gap junctions within the tissue slice reduces the duration and amplitude of the vasoconstrictive wave, and for high enough density the vasoconstrictive behaviour outside the stimulated area is eliminated.