35TH
INTERNATIONAL CONFERENCE

AWCBR

Australasian Winter Conference
on Brain Research

2017
Programme and Abstracts

2-6 September 2017
Copthorne Hotel, Queenstown, New Zealand
www.otago.ac.nz/awcbr

Saturday 2 September

3.00-5.15 pm	Registration, Copthorne Hotel
5.30-6.00 pm	Student Meet and Greet
6.00 pm	Opening Reception, Cash Bar
7.00 pm	Opening Remarks

7.15 pm

1. PLENARY LECTURE:

Gary Housley, *University of New South Wales, Australia*

Bionic array directed gene electrotransfer (BaDGE): From neuroscience discovery to clinical applications

Chair: Karl Iremonger

2. Sensory and Motor Systems

Chair: Karl Iremonger

8.00 pm	2.1	**Peter Thorne, *University of Auckland, New Zealand*** Inflammation and fibrosis following cochlear implantation in a guinea pig model
8.15 pm	2.2	**Yiwen Zheng, *University of Otago, New Zealand*** Effect of tinnitus-inducing acoustic trauma on neurotransmitter release in response to sound stimulation in the inferior colliculus of rats: Preliminary results
8.30 pm	2.3	**Ann-Maree Vallence, *Murdoch University, Australia*** Characterising age-related changes in motor cortical function
8.45 pm	2.4	**Paul Smith, *University of Otago, New Zealand*** Effects of selective electrical stimulation of semi-circular canal and otolithic vestibular receptors on field potential activity in the rat hippocampus

Sunday 3 September
Morning Session

6.30-8.00 am Light Breakfast Available

3. Neurogenomics Symposium

Chair: Stephanie Hughes

8.00 am	3.1	**Antony Cooper, *Garvan Institute of Medical Research, Australia*** Neurogenomics of neurodegeneration *Sponsored by In Vitro Technologies*
8.30 am	3.2	**Steven Robertson, *University of Otago, New Zealand*** Defining the genetic architecture of a human disorder of neurogenesis
8.45 am	3.3	**Margaret Ryan, *University of Otago, New Zealand*** Changes in circulating microRNA during disease progression in a mouse model of Alzheimer's disease
9.00 am	3.4	**Jessie Jacobsen, *University of Auckland, New Zealand*** Using whole genome sequencing to unravel structural variants in New Zealanders with neurodevelopmental disorders
9.15 am		Tea/Coffee break

Sunday 3 September
Morning Session

4. Disorders of the Nervous System (I)

Chair: Cliff Abraham

9.30 am	4.1	**John Reynolds, *University of Otago, New Zealand*** Electrical stimulation of contralesional motor cortex to augment stroke recovery
9.45 am	4.2	**Ailsa McGregor, *University of Otago, New Zealand*** Delayed varenicline administration increases inflammation and white matter damage and is detrimental to functional recovery after stroke
10.00 am	4.3	**Phil Heyward, *University of Otago, New Zealand*** Lithium may enhance brain network coherence by acting on K+ channels
10.15 am	4.4	**Jian Guan, *University of Auckland, New Zealand*** A novel biomarker for IGF-1 function: The application in aging and neurological conditions
10.30 am	4.5	**Mohamed Ibrahim, *University of Otago, New Zealand*** Enhanced KCC2 expression in the cerebellar molecular layer in a mouse model of spinocerebellar ataxia type 1
10.45 am	4.6	**Brigid Ryan, *University of Auckland, New Zealand*** Identifying early markers of frontotemporal dementia

Sunday 3 September
Afternoon Session

4.00 pm

5. PLENARY LECTURE:

Lucy Palmer, *University of Melbourne, Australia*

The role of dendrites in shaping cortical function

Chair: Juliette Cheyne

6. In Vivo Imaging and Recording

Chair: Juliette Cheyne

4.45 pm	6.1	**Malinda Tantirigama, *Australian National University, Australia*** Circuit manifestation of odour habituation in the mouse piriform cortex in vivo
5.00 pm	6.2	**Joon Kim, *University of Otago, New Zealand*** Rapid modulation of stress neuron activity dynamics
5.15 pm	6.3	**Saba Gharaei, *Australian National University, Australia*** Impact of the superior colliculus on cortical processing of somatosensory (whisker) input
5.30 pm	6.4	**Emmet Power, *University of Otago, New Zealand*** Mesoscopic voltage imaging of neuronal activity in mice using genetically encoded voltage indicators (GEVI)
5.45 pm	6.5	**Juliette Cheyne, *University of Auckland, New Zealand*** Development of the auditory cortex in autism spectrum disorder mice

Conference Dinner

7.30 pm

Skyline Restaurant

Tickets must be purchased in advance.
The ticket includes return gondala 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 4 September
Morning Session

6.30-9.00 am — Light Breakfast Available

9.00 am

7. PLENARY LECTURE:

Jason Berwick, *University of Sheffield, United Kingdom*

Neurovascular function in health and disease

Chair: Tim David

8. Novel Methods and Technology Development (I)

Chair: Tracy Melzer

9.45 am	8.1	**Elshin Mathias, *University of Canterbury, New Zealand*** Simulated BOLD responses for neural activities such as continuous spiking, bursting and cortical spreading depression
10.00 am	8.2	**Timothy Galt, *University of Otago, New Zealand*** EEG biofeedback of the posterior cingulate cortex for memory
10.15 am	8.3	**Simon O'Carroll, *University of Auckland, New Zealand*** Electric cell-substrate impedance sensing (ECISTM) for sensitive measurement of blood brain barrier integrity
10.30 am	8.4	**Michelle Goodman, *University of Canterbury, New Zealand*** Understanding cortical spreading depression patterns through numerical cell modelling
10.45 am	8.5	**Mandana Hunter, *University of Auckland, New Zealand*** The adult human subventricular zone has a distinct lipidome

9. NEURAL EXCITABILITY, SYNAPSES AND GLIA: CELLULAR MECHANISMS

CHAIR: PING LIU

4.00 pm	9.1	**Wickliffe Abraham**, ***University of Otago, New Zealand*** Long-term potentiation expands information content of hippocampal dentate gyrus synapses
4.15 pm	9.2	**Jesse Ashton,** ***University of Auckland, New Zealand*** Increased spontaneous synaptic activity in neurons of the intracardiac plexus of hypertensive rats
4.30 pm	9.3	**Alison Clare,** ***University of Otago, New Zealand*** Transcriptome profiling of layer 5 intratelencephalic-projection neurons in the mature mouse motor cortex
4.45 pm	9.4	**Praghalathan Kanthakumar,** ***University of Otago, New Zealand*** Lithium may block the delay current (ID) in olfactory projection neurons
5.00 pm	9.5	**Regina Hegemann,** ***University of Otago, New Zealand*** Cell firing-induced down-regulation of future long-term potentiation
5.15 pm	9.6	**Bronwyn Kivell,** ***Victoria University of Wellington, New Zealand*** Do biased opioid agonists hold the key to developing better safer opioid therapeutics for addiction and pain?

Monday 4 September
Evening Session

10. Opening of Queenstown Research Week

Venue: Rydges Hotel

6.00 pm	Opening Address
6.10 pm	Nobel Lecture **Bruce Beutler** ***University of Texas Southwestern Medical Center, United States of America*** Discoveries concerning the activation of innate immunity
7.00 pm	QRW Social Venue: Trades area, Rydges Hotel
8.00 pm	AWCBR Student Dinner Venue: Winnies Gourmet Pizza and Bar, 7-9 The Mall, Queenstown

Tuesday 5 September
Morning Session

6.30-8.00 am Light Breakfast Available

11. Cognition and Behavior

Chair: Peter Thorne

8.00 am	11.1	**Brian Hyland,** ***University of Otago, New Zealand*** Dual-site autoregulation modulates the effect of dopamine transporter blockade on phasic dopamine signals
8.15 am	11.2	**Kelly Paton,** ***Victoria University of Wellington, New Zealand*** Analgesic effects of novel kappa opioid receptor agonists in mice
8.30 am	11.3	**Kyla-Louise Horne,** ***University of Canterbury, New Zealand*** Patient-reported hallucinations are associated with future progression to dementia in Parkinson's disease, but cognition is more informative
8.45 am	11.4	**Thomas Elston,** ***University of Otago, New Zealand*** Exploration and persistence signals in the anterior cingulate cortex and the ventral tegmental area
9.00 am	11.5	**Jingwen Mao,** ***University of Auckland, New Zealand*** What do we know about uncanny valley?
9.15 am	11.6	**Sandila Tanveer,** ***University of Canterbury, New Zealand*** Robustness and longevity of negative priming; evidence for selective attention and memory retrieval

Tuesday 5 September
Morning Session

12. Novel Methods and Technology Development (I I)

Chair: Rebekah Blakemore

9.30 am	12.1	**Dan Johnstone, *University of Sydney, Australia*** Developing remote photobiomodulation as a neuroprotective intervention for Parkinson's disease
9.45 am	12.2	**Nicolas Vautrelle, *University of Otago, New Zealand*** Development of a sheep model of hemi-Parkinson's Disease
10.00 am	12.3	**Tim van Ginkel, *University of Canterbury, New Zealand*** Detailed modelling of neuronal calcium spiking dynamics
10.30 am		**ANNUAL GENERAL MEETING** All conference participants are invited to attend Tea/Coffee will be available for AGM attendees

13. DISORDERS OF THE NERVOUS SYSTEM (II)

CHAIR: JOHN DALRYMPLE-ALFORD

4.00 pm	13.1	**Nigel Birch, *University of Auckland, New Zealand*** The effects of site-specific glycation of Aβ(1-42) on fibrillation and aggregation kinetics
4.15 pm	13.2	**Hannah Best, *University of Otago, New Zealand*** Therapeutic targeting of autophagy in neurodegenerative Batten disease
4.30 pm	13.3	**Shabah Shadli, *University of Otago, New Zealand*** Generalization of goal conflict specific rhythmicity to a bimanual anticipatory response inhibition task shows sensitivity to anxiolytics
4.45 pm	13.4	**Jennifer Robertson, *Australian National University, Australia*** Electrical kindling causes cell-type specific changes to inhibitory neurons in the piriform cortex
5.00 pm	13.5	**Alison Cook, *University of Western Australia, Australia*** Outer hair cell auto-regulation and measurement of slow basilar membrane movements in vivo
5.15 pm	13.6	**Rebekah Blakemore, *University of Otago, New Zealand*** Stress-evoking emotional stimuli exaggerate deficits in motor function in Parkinson's disease

14. POSTER SESSION

- COMBINED WITH QMB AND MEDSCI

NB: RYDGES HOTEL

6.00 - 8.00 pm	Presenters will be in attendance during this time Presenters for odd number posters will be in attendance from 6.00-6.45 pm Presenters for even number posters will be in attendance from 6.45-7.30 pm Poster board numbers shown in brackets
14.1 (A1)	**Angela Jacques,** ***Queensland University of Technology, Australia*** Microanatomy of fear memory within the prefrontal cortex and amygdala
14.2 (A2)	**Dawei Fan,** ***University of Auckland, New Zealand*** Blackcurrant anthocyanins supplementation reduced HDAS and increased cyclic glycine-proline in the cerebrospinal fluid of Parkinson patients
14.3 (A3)	**Yukti Vyas,** ***University of Auckland, New Zealand*** Synaptic changes in Shank3-/- Autism Spectrum Disorder associated mouse model
14.4 (A4)	**Harry Jordan,** ***University of Auckland, New Zealand*** The effects of bilateral priming on motor cortex function in healthy adults
14.5 (A5)	**Diana Atigari,** ***Victoria University of Wellington, New Zealand*** Investigating the anti-cocaine and analgesic properties of MP1104, a dual acting kappa and delta opioid agonist
14.6 (A6)	**Betina Nair,** ***University of Otago, New Zealand*** Impact of chronic stress on the neuroendocrine axis in the mouse

Poster Session

14.7 (A7)	**Javier Jimenez-Martin,** ***University of Otago, New Zealand*** Establishing reliable methods to assess motor skill learning and motor performance in mice
14.8 (A8)	**Emma Deeney,** ***University of Otago, New Zealand*** Does voluntary exercise improve motor performance and/or cerebellar architecture in SCA1 moderately ataxic mice
14.9 (A9)	**Manju Ganesh,** ***University of Otago, New Zealand*** Pericyte therapeutics to repair the stroke-lesioned brain
14.10 (A10)	**Jade Yip,** ***University of Otago, New Zealand*** Understanding the Batten disease associated protein CLN5
14.11 (A11)	**Megan Stark,** ***University of Canterbury, New Zealand*** Parkinson's disease: No association between amyloid PET imaging and cognitive status
14.12 (A12)	**Pranav Vemula,** ***University of Otago, New Zealand*** Hippocampal arginine metabolism shifted to favour the polyamine pathway in a mouse model of tauopathy
14.13 (A13)	**Brittney Black,** ***University of Auckland, New Zealand*** Glutamate receptor studies in the human globus pallidus
14.14 (A14)	**Micah Austria,** ***University of Auckland, New Zealand*** Characterising the perivascular cells in Alzheimer's disease human tissue microarrays
14.15 (A15)	**Hueytieng Tan,** ***University of Otago, New Zealand*** Neurotransmitter changes in the auditory and non-auditory brain regions of rats following tinnitus-inducing acoustic trauma
14.16 (A16)	**Molly Abraham,** ***University of Auckland, New Zealand*** Expression and function of hyaluronan, hyaluronan synthases, and hyaluronidases in developing hippocampal neurons

14.17 (A17)	**Haiyang Jin,** ***University of Auckland, New Zealand*** The effect of stimulus duration on the ERP components for face and non-face stimuli
14.18 (A18)	**Julia Gouws,** ***University of Otago, New Zealand*** Regulation of CRH neuronal network activity by noradrenergic stress signals
14.19 (A19)	**Rungrudee Srisawat,** ***Suranaree University of Technology, Thailand*** Alpha-mangostin prevents scopolamine-induced lipid peroxidation in rat brains
14.20 (A20)	**Mariana Leriche,** ***University of Otago, New Zealand*** Detection and monitoring of Parkinson's disease using a computer game
14.21 (A21)	**Andrea Kwakowsky,** ***University of Auckland, New Zealand*** Age- and gender-specific expression changes of the GABAA receptor subunits in the human cortex
14.22 (A22)	**Hollie Wicky,** ***University of Otago, New Zealand*** A role for secreted proteins in CLN6 BATTEN disease therapy
14.23 (A23)	**Amy Alder,** ***Victoria University of Wellington, New Zealand*** Investigating the analgesic effects of novel Mu opioid receptor agonists
14.24 (A24)	**Megan Elder,** ***University of Otago, New Zealand*** Secreted amyloid precursor protein alpha regulates AMPA receptor synthesis and trafficking
14.25 (A25)	**Shweta Haldankar,** ***University of Auckland, New Zealand*** The potential mechanisms underlying delayed on-set of radiation necrosis: Time of biological events
14.26 (A26)	**Fengxia Li,** ***University of Auckland, New Zealand*** High-fat diet induced obesity impairs neuroplasticity in rats
14.27 (A27)	**Nianzeng Zhong,** ***University of Auckland, New Zealand*** First fixation location moderates face holistic processing and recognition

Poster Session

14.28 (A28)	**David Moreau,** ***University of Auckland, New Zealand*** Investigating dyslexia and dyscalculia comorbidity through diffusion tensor imaging
14.29 (A29)	**Lalida Rojanathammanee,** ***Suranaree University of Technology, Thailand*** The hippocampal Insulin-like growth factor (IGF-1) level and synaptic density in Ames dwarf mouse
14.30 (A30)	**Beth Elias,** ***University of Canterbury, New Zealand*** Theory of mind in Parkinson's disease: Improvement after physical and cognitive exercise
14.31 (A31)	**Emma Peterson,** ***University of Canterbury, New Zealand*** Motor outcomes in Parkinson's disease patients: An RCT of physical exercise and cognitive enrichment
14.32 (A32)	**Megan Livingstone,** ***University of Canterbury, New Zealand*** Maintaining Independence in Parkinson's disease: Cognitive effects of a combined cognitive and physical exercise intervention
14.33 (A33)	**Shivam Kalhan,** ***University of Otago, New Zealand*** Response-conflict and set-shifting signals in the ACC and VTA
14.34 (A34)	**Matthew Fields,** ***University of Auckland, New Zealand*** Imaging and analysis of post-implantation cochlear fibrosis via micro-computed tomography
14.35 (A35)	**Ryan Sutcliffe,** ***University of Otago, New Zealand*** Aging, emotion recognition, and neuropsychological benefits of music training
14.36 (A36)	**Kristina Wiebels,** ***University of Auckland, New Zealand*** Binding of episodic details into future simulations
14.37 (A37)	**Allanah Kenny,** ***University of Canterbury, New Zealand*** Neurovascular coupling and the BOLD response: Multi-scale tissue slice simulations

Poster Session

14.38 (A38)	**Kaitlin Wolfe, *University of Otago, New Zealand*** Anti-inflammatory characteristics exhibited by heterocyclic cyclohexanone curcumin derivatives against LPS-induced inflammation
14.39 (A39)	**Rose Melchers, *University of Otago, New Zealand*** Measuring the effects of intermittent theta-burst stimulation on interhemispheric inhibition after stroke
14.40 (A40)	**Ashwini Hariharan, *University of Otago, New Zealand*** Altered neurovascular coupling and glutamine metabolism in endothelial nitric oxide synthase deficient mice
14.41 (A41)	**Ekta Dahiya, *Auckland University of Technology, New Zealand*** P-glycoprotein up-regulation in rifampin primed lamotrigine-resistant pentylenetetrazole kindled mice: A new experimental murine model of drug-resistant epilepsy
14.42 (A42)	**Matthew Cowie, *University of Auckland, New Zealand*** Distinct motor cortical inhibitory processes are engaged during reactive and proactive response inhibition
14.43 (A43)	**Wayne Meighan, *University of Otago, New Zealand*** Maternal immune activation in rats produces a subjective internal state that is similar to human psychosis
14.44 (A44)	**Matt Hall*, University of Otago, Dunedin, New Zealand*** Lithium promotes stereotyped responses to synaptic input – an in vitro olfactory bulb study
8.00 pm	Posters to be removed at this time
8.00 pm	Fashionomics (Rydges)

Wednesday 6 September
Combined Day with MedSci

6.30-8.00 am — Light Breakfast Available

10.00 am — Tea/Coffee break at Rydges

Joint Session with MedSci
Circadian Clocks in Health and Disease

Venue: Rydges

10.30 am — **Guy Warman, *University of Auckland, New Zealand***
The effect of general anaesthesia on sleep and the circadian clock

11.00 am — **Oliver Rawashdeh, *University of Queensland, Australia***
The role of PERIOD1 within the central circadian clock network: When evolution lags behind

11.30 am — **Alexander Tups, *University of Otago, New Zealand***
Circadian rhythms and the regulation of body weight

12.00 pm — **Richard Piet, *University of Otago, New Zealand***
Regulation of the GnRH neuronal network by circadian output neuropeptides

12.30 pm — Closing Remarks

Light lunch and Student Prize Presentation - rydges - reds bar

Acknowledgements
We are deeply indebted to Norma Bartlett, Department of Psychology, University of Otago for her help with the conference programme, secretarial assistance, and also Hadyn Youens, Department of Psychology, University of Otago, for help with the abstract submssion. We are very grateful to the Neurological Foundation of New Zealand for its generous financial assistance toward student travel and registration.

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Prize Winners

Goddard Prize and Poster Prize Winners

1990	**Steven Morrison,** University of Otago, New Zealand
1991	**Oliver Davidson,** University of Otago, New Zealand
1992	**Nadia Solowij,** University of New South Wales, Australia
1993	**Kjesten Wiig,** University of Otago, New Zealand
1994	**Niki Butterworth,** University of Auckland, New Zealand
1995	**Gerald Ahern,** John Curtin School of Medical Research, Australia
1996	**Judy Swanson,** University of Otago, New Zealand
1997	**Donna Briggs,** University of Otago, New Zealand
1998	**Johanna Montgomery,** University of Otago, New Zealand
	Suzanne Habjan, University of Sydney, Australia
1999	**Wendy Brooks,** University of Otago, New Zealand
2000	**John Lin,** University of Auckland, New Zealand
2001	**Tina Hinton,** University of Sydney, Australia
	Michael Christie, University of Canterbury, New Zealand (Poster)
2002	**Gemma Irvine,** University of Otago, New Zealand
2003	**Evangelene Daniela,** Victoria University of Wellington, New Zealand
2004	**Bronwen Kelly,** University of Canterbury, New Zealand
2005	**Adam Errington,** University of Otago, New Zealand
	Wendy Imlach, AgResearch, New Zealand (Poster)
2006	**David Cumin,** University of Auckland, New Zealand
	Andrew Tattersfield, University of Auckland, New Zealand (Poster)
2007	**Carthur Wan,** University of Auckland, New Zealand
	Suzanne Ackerley, University of Auckland, New Zealand (Poster)
2008	**Thomas Park,** University of Auckland, New Zealand
	Joan Liu, University of Auckland, New Zealand (Poster)
2009	**Bill Connellly,** University of Otago, New Zealand
	Bridget Simonson, Victoria University of Wellington, New Zealand (Poster)
2010	**Tracy Melzer,** Van der Veer Institute, New Zealand
	Yeri Kim, University of Otago, New Zealand (Poster)
2011	**Kajsa Igelstrom,** University of Otago, New Zealand
	Malinda Tantirigama, University of Otago, New Zealand (Poster)
2012	**Malinda Tantirigama,** University of Otago, New Zealand
	Malvindar Singh-Bains, University of Auckland, New Zealand (Poster)
2013	**Amy Smith,** University of Auckland, New Zealand
	Peter Bosch, Victoria University of Wellington, New Zealand
	Laura Boddington, University of Otago, New Zealand (Poster)
2014	**Emmet Power,** University of Otago, New Zealand
	Lakshini Mendis, University of Auckland, New Zealand (Poster)
2015	**Christine de Lance,** University of Canterbury, New Zealand
	Christine Arasaratnam, University of Auckland, New Zealand (Poster)
2016	**Jennifer Robertson,** Australian National University, Australia
	Allanah Kenny, University of Canterbury, New Zealand (Poster)

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Abstracts in Presentation Order

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ABSTRACTS

1.

Bionic array directed gene electrotransfer (BaDGE): From neuroscience discovery to clinical applications

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We have coined the term Bionic array Directed Gene Electrotransfer (*BaDGE* ©) to describe the use of arrays of electrodes developed out of bionic neural interface technology, which have utility for close-field electroporation. Using cochlear implant arrays and HEK293 cell monolayers, we showed that electric field focusing determined the shape and density of regions of cells transduced with naked DNA encoding nuclear localized green fluorescent protein (GFP) reporter. This translated to highly efficient DNA transfer into mesenchymal cells lining the perilymphatic compartment of the guinea pig cochlea when the naked DNA was injected via the round window membrane. As a preclinical proof of concept, a bicistronic gene cassette was developed encoding flag-tagged brain-derived neurotrophic factor (BDNF) and nuclear localized GFP. In chemically deafened guinea pigs, application of this plasmid with BaDGE enabled regrowth of the peripheral processes of the cochlear nerve within a week, and functional improvement of cochlear implant-based hearing as determined by electrically-evoked auditory brainstem responses. The proof of concept for transfer of this technology to CNS applications has been enabled by targeting the globus pallidus region of the guinea pig brain with plasmid DNA encoding GCaMP5G, a genetically encoded Ca^{2+} reporter, and ReaChR, a red-shifted channelrhodopsin. Here brief trains of light pulses produced Ca^{2+} transients in neurons co-transduced with both plasmids; this CNS optogenetics neuromodulation approach may complement Deep Brain Stimulation treatment of Parkinson's Disease akinesia. Supported by ARC LP140101008 & LP0992098, ARC DP151014754, and NHMRC Development Grant APP1091646. Studied approved by the UNSW Sydney Animal Care and Ethics Committee. IP around the *BaDGE* platform is held by UNSW Innovations, UNSW Sydney.

2.1

Inflammation and fibrosis following cochlear implantation in a guinea pig model

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Cochlear implants (CIs) are an important intervention for people with severe to profound sensorineural deafness. The introduction of the implant into the cochlea, however, can cause tissue injury resulting in fibrosis and loss of residual cochlear function. Preservation of residual hearing after cochlear implantation is desirable for improved performance and preservation of the cochlea for future technology improvements. Using a guinea-pig model of cochlear implantation we are investigating the mechanisms and dynamics of the inflammatory response and tissue injury and developing otoprotective strategies during implantation. Here we describe the development of the model and an analysis of the time course of the inflammatory response and development of the fibrosis using Dynamic Contrast MRI (DCE-MRI), µCT and histology respectively. Guinea-pigs were exposed to noise (16kHz, 120dBSPL, 30min) to produce a lesion in the basal cochlear turn and permanent high frequency (>8kHz) threshold shift of 60-80dB, assessed using Auditory Brainstem Responses. A dummy (non-functional) CI electrode was inserted via a cochleostomy to induce low frequency sensorineural hearing loss, which is comparable to that seen in humans with severe hearing loss provided with cochlear implants. Within three days after the implantation, the cochlea showed a significant ($p<0.001$) increase in vascular permeability, measured using DCE-MRI and taken as an index of cochlear inflammation (Ktrans increased from 0.0067±0.0001 to 0.0022±0.0028 at 3 days and recovered to 0.008±0.001 min^{-1} by 6 days). The extent of fibrosis was qualitatively examined by µCT, following staining with 1%OsO_4 and, using 3D reconstruction techniques, quantified throughout the cochlea. The fibrosis developed around the electrode, extending from the entry site and making attachments to the basilar membrane and lateral wall by 4 weeks after implantation. The nature of the fibrosis and connections was qualitatively examined by histology of the same cochlea. These data define the time course of inflammation and development of fibrosis for otoprotective studies during cochlear implantation to stem the inflammatory response and reduce the tissue injury.

2.2

Effect of tinnitus-inducing acoustic trauma on neurotransmitter release in response to sound stimulation in the inferior colliculus of rats: Preliminary results

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Animals exposed to tinnitus-inducing acoustic trauma have shown increased spontaneous neuronal firing rate, synchronized firing as well as a reorganised tonotopic map in the inferior colliculus, a major relay nucleus in the auditory pathways. The responses to sound stimulation are also affected in both excitatory and inhibitory units. Therefore, an imbalance between excitatory and inhibitory systems may play an important role in tinnitus development. However, its neurochemical basis remains to be elucidated. In the present study, we investigated changes in the release of the excitatory and inhibitory amino acids at different time points following acoustic trauma as well as in response to sound stimulations using *in vivo* microdialysis. Briefly, the animals were divided into sham and acoustic trauma groups (n = 8 per group). At various times after acoustic trauma or sham exposure, the animals were anaesthetised with urethane (1.5 g/kg) and a microdialysis probe (CMA 12 Elite 2mm, Sweden) was inserted into the inferior colliculus. The microdialysis probe was perfused with artificial cerebrospinal fluid and after 2h equilibration, the samples were collected every 15 min during the presence of sound stimulations (2 – 40 kHz, at 70 dB SPL). The preliminary results showed that at 1 week following acoustic trauma, there was a decrease in glutamine levels and an increase in GABA levels in the dialysates. Furthermore, different amino acids showed different patterns of response to the sound stimulations. Our results provide the first evidence that acoustic trauma alters neurotransmitter release in response to sound, which may underlie the development of neuronal hyperactivity and tinnitus.

2.3

Characterising age-related changes in motor cortical function

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Aging is accompanied by a decline in manual dexterity, thought to be mediated by age-related decline in brain structure and function. Age-related decline in brain function is associated with alterations in the excitability of intracortical circuits in the primary motor cortex (M1) and connections between cortical motor areas. We used transcranial magnetic stimulation (TMS) and the Purdue pegboard to investigate associations between age-related changes in motor cortical function and manual dexterity. Paired-pulse TMS was used to assess the balance between inhibition and facilitation in M1 in younger and older adults. Intracortical inhibition was not different between younger and older adults, and in both groups, the magnitude of inhibition positively correlated with manual dexterity. In contrast, the balance between intracortical inhibition and intracortical facilitation was shifted more towards facilitation in older adults compared to younger adults, but the inhibition—facilitation balance was not associated with manual dexterity. These findings suggest an age-related change in the balance of intracortical inhibition and facilitation, and that greater inhibition is associated with better dexterity. Dual-coil TMS was used to investigate interactions between the supplementary motor area (SMA) and M1. Results show a facilitatory interaction between SMA—M1 in younger adults that was reduced in older adults. Furthermore, SMA—M1 facilitation was positively associated with bimanual performance. These findings suggest that SMA—M1 facilitation is functionally relevant and is reduced with age. Together, the current findings show age-related changes in motor cortical function that are associated with voluntary movement.

2.4

Effects of selective electrical stimulation of semi-circular canal and otolithic vestibular receptors on field potential activity in the rat hippocampus

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Vestibular dysfunction leads to impairments in learning and memory as well as a disruption of head direction, place and grid cells. Therefore, it is clear that vestibular input is necessary for the normal function of the hippocampus. Less clear is how vestibular sensory information is used by the hippocampus. In these studies we attempted to selectively electrically stimulate the horizontal, anterior and posterior semi-circular canals as well as the utricle and saccule in anaesthetized Wistar rats and record field potentials in the hippocampus. Rats (n = 53) were anesthetized and a 16 electrode microarray was implanted into the bilateral hippocampi. Field potentials were recorded while electrically stimulating specific receptors within the vestibular labyrinth using bipolar electrodes and currents ranging from 50 to 400 µA. Field potentials were evoked throughout the hippocampus by stimulation of the different receptors, with significant differences in amplitude between the anterior, horizontal and posterior canals as well as the utricle and saccule, depending on the current used. Responses were obtained bilaterally from unilateral stimulation and the latencies were usually at least 20 ms; amplitudes were usually greater in dorsal regions compared to ventral regions. These results demonstrate that vestibular input to the hippocampus is complex and that all semi-circular canal and otolithic sensory receptors are represented.

3.1

Neurogenomics of neurodegeneration

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Parkinson's disease (PD) is a complex, progressive neurodegenerative disease yet effective targets for disease-modifying therapies are lacking due to our poor understanding of PD's molecular pathology. Our neurogenomic analysis of multiple patient brains regions at different stages of pathology provided unparalleled insights into the transcriptional changes demonstrating the involvement of long non-coding RNAs (lncRNAs) and alternative splicing, while providing blood biomarkers for PD diagnosis. Examination of a high-risk PD genomic loci identified lncRNA PARNA, whose expression is reduced >80% in patients' brains prior to neurodegeneration. PARNA regulates up to 65 protein-coding and lncRNA genes, many connected to pathways dysfunctional in PD. PARNA knockdown reproduces features of PD including oxidative phosphorylation deficits and increased αSynuclein levels while elevated PARNA expression ameliorates these deficits and presents a unique opportunity for therapeutic intervention to restore multiple pathways. We discovered extensive RNA splicing dysregulation in PD that is: (1) enriched in familial PD genes and pathways as well as revealing pathways not previously associated with PD, and (2) preferentially alters protein domains that likely change function and/or subcellular localization. The transcripts alternatively spliced in PD were enriched for RNA-binding motifs of splicing factors that themselves were differentially spliced. This suggests that these splicing factor isoforms might be significant contributors to the spectrum of altered AS observed in PD, and offer therapeutic targets to impact multiple pathways. Many transcripts dysregulated in the brain were also dysregulated in the blood of patients. Machine learning on these transcripts has identified a biomarker set for accurately diagnosing patients.

3.2

Defining the genetic architecture of a human disorder of neurogenesis

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Disorders of neuronal mispositioning are phenotypically heterogeneous and characterised clinically by epilepsy and intellectual disability. In periventricular neuronal heterotopia (PH) neurons fail to populate the outer cortex of the brain resulting in their heterotopic positioning along their sites of origin – the lateral ventricles. Currently, only 25% of sporadic instances of the disease have a definable molecular genetic cause. To characterise the contribution of rare genetic variants towards the causation of PH we performed exome sequencing on 65 probands and their parents and filtered for de novo and rare recessive genotypes. 50 rare, coding, de novo or rare biallelic variants were identified and although no two patients were mutated at the same locus across the entire cohort, a likelihood analyses, accounting for gene size and mutability, identified an excess of de novo variants in loci intolerant to functional change (P = 1.28x10-12). An estimated 28% of these de novo variants contribute to the causation of the PH phenotype (95% CI: 16–42%). Specifically focusing on a set of genes linked to human neural stem cell transcriptional network demonstrated an excess (P = 0.024) of de novo variants at these loci. Finally a knockout of a human-specific isoform was identified and further studies of this spliceform in mouse and human brain organoids suggest a regulatory role in human neurogenesis. PH exhibits considerable genetic heterogeneity with genes that are mutated to cause the condition being preferentially embedded in neural stem cell networks and primate-novel regions of the coding genome.

3.3

Changes in circulating microRNA during disease progression in a mouse model of Alzheimer's disease

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Identification of specific biomarkers reflective of Alzheimer's pathology throughout the early preclinical and later stages of the disease is critical to the development of effective treatment strategies. MicroRNA levels are altered in Alzheimer's disease and as stable brain-derived microRNA are found in blood fractions, international attention has focused on circulating microRNA as biomarkers of Alzheimer's processes. However, as yet, no studies have identified a reliable microRNA biomarker signature that can predict, prior to symptom onset, individuals who will develop Alzheimer's. Here, we have utilised a transgenic mouse model of Alzheimer's (APP/PSEN1), characterised by amyloidosis and deficits in memory, to investigate how circulating microRNA alter prior to and during amyloid deposition (4, 8, 15 m; n=8-10). Using custom designed low-density Taqman arrays we analysed 185 neuropathology-related microRNA in plasma from transgenic and litter-matched wild-type mice. Our study found that plasma microRNA profiles differ during development of Alzheimer's-like pathogenesis, with 9, 6 and 7 microRNA altered at 4, 8 and 15 m, respectively. Bioinformatics analysis of these microRNA revealed various common biological pathways were enriched throughout the disease process, while protein synthesis and calcium signalling were enriched specifically early in the disease. Further, NF-κB signalling and amyloid processing were enriched from 8 m in parallel with the development of amyloid-ß plaques. This study shows that distinct stage-dependent microRNA patterns are evident in blood plasma during amyloidopathy development. These microRNA may prove useful as early pre-symptomatic biomarkers of Alzheimer's disease or provide new insights into the development and progression of the disease.

3.4

Using whole genome sequencing to unravel structural variants in New Zealanders with neurodevelopmental disorders

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Structural variants are over-represented in children with neurodevelopmental disorders, yet their functional impact on health and well-being remain poorly understood. Currently, structural variants are detected using low-resolution techniques (molecular karyotype) in standard diagnostic practice, making their significance and thus clinical relevance difficult to ascertain. Our aim is to refine structural variant breakpoints to base-pair resolution in a cohort of New Zealand children with neurodevelopmental disorders (mindsforminds.org.nz) to better understand the clinical relevance of this type of genetic variation. We have employed whole genome sequencing and structural variant detection tools (including our own in-house 'Read Balance Validator' software) to identify putative structural variations, that weren't detected using standard diagnostic molecular karyotype thresholds. The results have unravelled new biology, and importantly led to refined diagnoses and treatment options for families. These results illustrate the power of whole genome sequencing for the identification of causative structural variants and subsequent diagnosis of rare neurodevelopmental disorders.

4.1

Electrical stimulation of contralesional motor cortex to augment stroke recovery

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Upper limb (UL) deficits persist in over 2/3 of stroke survivors. Previous studies investigating augmenting rehabilitation using implanted electrodes have stimulated the ipsilesional (stroke-affected) motor cortex without lasting benefit. Here we translated a paradigm targeting interhemispheric inhibition that was effective at improving stroke recovery in rats, by applying theta-burst stimulation (TBS) to contralesional motor cortex (M1). We evaluated the safety of implanting electrodes over contralesional M1 and feasibility of administering TBS in conjunction with an intensive structured UL rehabilitation programme. We describe results from a 58-year-old man 18 months following subcortical stroke, who consented to implantation of an internal pulse generator and extradural electrodes overlaying contralesional M1. Following surgery, he was randomised to a delayed-start programme, receiving daily rehabilitation therapy for 12 weeks with sham stimulation from weeks 1-6 followed by real stimulation for weeks 7-12, with participant and therapist blinded throughout to stimulation status. At week 6, UL function was unaltered by rehabilitation alone. Following real stimulation at week 12, his Upper Extremity Fugl-Meyer (UEFM) score increased from 25 to 40, Action Research Arm Test (ARAT) from 4 to 14 and grip strength from 0 to 10kg. After another 3 months with the stimulator off, his UEFM partially reversed to 32 and ARAT returned to 4 but grip strength remained elevated at 8kg. This case report demonstrates that TBS applied to the contralesional motor cortex is safe and feasible, and may improve moderate/severe UL impairment greater than can be achieved with rehabilitation alone. A larger study will further explore this approach.

4.2

Delayed varenicline administration increases inflammation and white matter damage and is detrimental to functional recovery after stroke

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Pharmacological activation of α7 nicotinic acetylcholine receptors has been shown to confer short-term improvements in outcome in experimental stroke models. We have previously demonstrated increased impaired forelimb use in varenicline-treated animals 10 days after stroke. Functional recovery was associated with decreased EGFP and increased GAP43 expression in the striatum of CSF-1R EGFP mice. To extend these findings, we investigated the effect of delayed varenicline administration on sensorimotor and skilled motor deficits, white matter structure integrity, and inflammatory cytokine expression profiles up to 6weeks following experimental stroke. CSF-1R EGFP ('MacGreen') mice were subjected to transient middle cerebral artery occlusion and administered varenicline (2.5mg/kg/day for 7 days) or saline (n=10 per group) starting 3 days after stroke. Performance in the sticky label and staircase tests was assessed at 1, 2, 4 and 6 weeks. *Ex vivo* diffusion tensor imaging and inflammatory cytokine expression profiles were used to evaluate the effect of varenicline on white matter structural integrity and inflammation respectively. Delayed varenicline administration impaired skilled motor and sensorimotor function post stroke and increased pro-inflammatory cytokine expression in the striatum. Disruption of fiber tracts in the corpus callosum, internal capsule and anterior commissure were highlighted by decreased FA and increased voxel volume in varenicline treated animals compared to controls. While delayed varenicline treatment promotes short term improvements in spontaneous motor function, it has a detrimental effect on long term functional recovery after stroke.

4.3

Lithium may enhance brain network coherence by acting on K^+ channels

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Li^+ is the primary treatment for bipolar disorder. The effectiveness of Li^+ as a mood stabilizer has been known for over 60 years, but its mechanism of action is not known. Recent gene-association studies suggest that bipolar disorder involves altered ion channel distribution and expression; functional imaging studies suggest altered network activity in cortico-limbic circuits. We have investigated how clinically relevant concentrations of Li^+ may affect neuronal excitability and network activity, recording from limbic system projection neurons (olfactory bulb mitral cells) in mouse brain slices. Mitral cells generate population bursts of action potentials in response to olfactory nerve stimulation, and spontaneous bursts coupled to oscillations in network activity. We have found that Li^+ increases the regularity of spontaneous network activity, revealing frequency modulation of burst frequency, over 10s of seconds. This effect is associated with the appearance of regular, periodic modulation of burst duration (and action potential count per burst), over seconds. When bursts of mitral cell activity are evoked by olfactory nerve stimulation, Li^+ decreases burst latency and variability, increases the regularity of burst duration and increases action potential frequency. At the single cell level, in response to depolarizing current injection with synaptic networks blocked, Li^+ decreases a variable delay to action potential generation, increases action potential frequency, and facilitates integration of repetitive depolarizations modeling excitatory synaptic inputs. These findings suggest that Li^+ affects a potassium current, the delay current (I_D), and are reproduced in mitral cells by specific blockers of I_D. Our results suggest that Li^+ promotes coherent, oscillatory activity within and between brain networks through modulation of I_D, consistent with its effectiveness in bipolar disorder.

4.4

A novel biomarker for IGF-1 function: The application in aging and neurological conditions

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Insulin-like growth factor-1 (IGF-1) is critical in cognitive function and wound healing. IGF-1 declines with age and is associated with age-related cognitive impairment and poor recovery. Reliable biomarkers for IGF-1 function can identify individuals with high risk to cognitive impairment and predict ability of recovery. However plasma IGF-1 concentration does not associate with IGF-1 function. Cyclic glycine-proline (cGP) regulates bioavailability of IGF-1. We evaluated the changes of cGP and IGF-1 in 4 clinical trials: 1) during 3 months recovery of stroke; 2) aged population with normal cognitive function; 3) Parkinson Patients with or without cognitive impairment; and PD patients with supplementation of blackcurrant anthocyanins (BCA) that reduced anxiety. Compared to controls, plasma cGP was lower in stroke patients and then increased during recovery. The base line cGP concentration correlates with recovery at 3 months, suggesting cGP level at time of stroke may predict the ability of recovery. While IGF-1 reduced with age plasma cGP was higher in the group >70 year old than the group <70 year old, suggesting a potential biomarker prior to cognitive impairment. The treatment of BCA reduced anxiety and depression of PD patients and increased cGP in the CSF, indicating a trophic role for cGP. Plasma cGP reduced in PD patients with cognitive impairment compared to the PD patient with normal cognitive function, this may be related to the loss of ability in regulating IGF-1 bioavailability leading to cognitive impairment.

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4.5

Enhanced KCC2 expression in the cerebellar molecular layer in a mouse model of spinocerebellar ataxia type 1

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Spino-cerebellar ataxia type 1 (SCA1) is a human autosomal dominant movement disorder characterized by motor incoordination and degeneration of Purkinje Neurons (PN), the main output neurons of the cerebellar cortex. The SCA1 (82Q) mouse model overexpresses 82Q repeats in the ataxin-1 gene, specifically in the PN and recapitulates many of the features of human SCA1 disease. In addition PNs from these mice exhibit a decreased firing frequency, indicating increased phasic inhibition in these neurons. PN inhibition is heavily dependent on GABA-A receptor (GABA(A)R) dependent activity. The potassium chloride co-transporter molecule, KCC2, is expressed in adult cerebellar PNs where it ensures the availability of chloride ions to drive (GABA(A)R) mediated inhibition. We hypothesized that KCC2 expression levels might be altered in the cerebellar molecular layer (ML) of 82Q mice and therefore examined its expression in the cerebellum of 12 week old symptomatic 82Q mice using fluorescence confocal immunohistochemistry. KCC2 expression was enhanced in 82Q mice compared with age-matched wild type mice (WT), specifically in the upper 2/3 of the ML ($P < 0.05$, unpaired t-test, $n = 5$), indicating increased GABA-ergic inhibition in these mice. In line with this, PN firing frequency recorded from acutely prepared cerebellar slices was partially rescued by blocking GABA(A)R activity with picrotoxin and to a greater extent than in WT ($P < 0.05$, un paired t-test, $n = 5$). Our results suggest that enhanced KCC2 expression contributes to enhanced GABA-ergic inhibition in SCA1 PNs and disrupts firing behaviour. Thus we propose targeting enhanced KCC2 activity as a promising approach to treat SCA1 disease.

4.6

Identifying early markers of frontotemporal dementia

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Frontotemporal dementia (FTD) is a common cause of early-onset dementia and is characterized by personality change and progressive loss of executive function. By the time FTD is diagnosed clinically, cell death in the frontal and temporal lobes is extensive and likely irreversible. Thus, a preventive approach is only possible if FTD is diagnosed in the pre-clinical stage. This study aims to identify pre-clinical diagnostic markers of FTD. Studies of families with autosomal-dominant mutations that cause dementia provide a unique and powerful way of investigating diagnostic markers during the pre-clinical stage. We have established a prospective longitudinal observational study of a large New Zealand family cohort with a genetic mutation that is known to cause FTD (MAPT IVS 10+16 C>T). We will perform annual assessments of putative diagnostic markers, namely blood-derived microRNAs, plasma proteins, neuronal-derived exosome components, olfactory function, and cognitive function for a total of 5 assessments (n = 25) and perform within-subject analyses of longitudinal changes in mutation carriers versus non-carriers. This presentation will report on the establishment of this longitudinal study and present demographic details of this unique family cohort. In addition, preliminary findings of early pathology in a complementary mouse model of FTD (hTau; n = 28) will be presented. Early intervention is vital to mitigate the devastating impact of FTD. Identification of putative pre-diagnostic markers of FTD in this cohort will provide a springboard to establish clinical utility in sporadic FTD.

5.

The role of dendrites in shaping cortical function

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The task of understanding how neurons translate input to output is central to explaining brain function. Since the majority of synaptic inputs arrive at the dendrites of neurons, it is important to understand how dendrites transform this information. The rules governing dendritic integration and the effect this has on network activity and overall brain function is just beginning to emerge. This lecture will discuss our current knowledge about how dendrites receive and transform sensory input, and the influence of these processes on neural network activity will be highlighted. The importance of dendritic activity during behaviour will also be addressed, bridging the gap between system and cellular neuroscience.

6.1

Circuit manifestation of odour habituation in the mouse piriform cortex *in vivo*

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Olfaction employs habituation to de-emphasize static or repetitive odour inputs in order to process novel, potentially more important odours. Piriform cortex (PC) is the first cortical destination of odour information and little is known about how habituation to an odour manifests in the PC circuitry. We applied repetitive odour stimuli and simultaneously measured the responses of up to 250 neurons in the PC of anesthetized mice using 2-photon calcium imaging. A given odour excited a unique ensemble pattern of neurons. With each reapplication of the odour, neurons participating in the ensemble were dropped or replaced, but the total number of excited cells declined, indicative of habituation. Reinstatement of the responses occurred over a recovery period of >60min. The habituated state was absent when a novel odour was presented and a different ensemble of neurons was excited; thus, habituation is odour-specific. We next tested whether habituation arises locally within the PC or is inherited from the upstream mitral/tufted (M/T) cells in the olfactory bulb. Local superfusion of NMDA channel blocker MK801 into PC blocked habituation in PC. Furthermore, the M/T cells did not diminish their odour-responses upon repeated exposure. These findings suggested that habituation arises from a local cortical mechanism involving NMDA receptors, and perhaps by recruiting local inhibitory circuits that suppress neuronal activity. Imaging activity in somatostatin-expressing (SOM) interneurons using conditional expression of GCaMP6f in Cre mice (*SOM-IRES-Cre*) revealed an upregulation of SOM cell activity to repeated delivery of the same odour. The findings indicate long-lasting odour-specific NMDA receptor-dependent changes to odour representation in the PC that are accompanied by upregulated inhibitory activity, despite maintained input from the olfactory bulb.

6.2

Rapid modulation of stress neuron activity dynamics

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Corticotropin-releasing hormone (CRH) neurons are the final output cells that drive the neuroendocrine stress response, resulting in corticosteroid (CORT) release. To prevent excessive activation of the stress circuits, CORT acts back at the brain to inhibit the activity of CRH neurons. However, the activity dynamics of CRH neurons in vivo remain unknown, which has hampered our understanding of how their excitability is controlled. Using fibre photometry, we report optical recording of the natural activity of CRH neurons in awake behaving mice. We report that CRH neuron population excitability can be rapidly modulated, resulting in distinct patterns of activity at rest, during stress, and after stress. The CRH neuron population is tonically active independently of changes in circulating CORT, with low stochastic patterns of activity. In response to an acute white noise stress, CRH neurons are rapidly sychronised with peak activity observed within 5 seconds of stress onset. This increase in activity continues post stress, in oscillating burst like dynamics, lasting >20min. Furthermore, these changes in stress neuron activity could be moderately suppressed by CORT negative feedback. These data reveal that CRH neurons are surprisingly vigilant, receive real-time information and respond rapidly in response to threat.

6.3

Impact of the superior colliculus on cortical processing of somatosensory (whisker) input

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Superior colliculus (SC) is a midbrain structure, which is highly conserved across species. It is well established that SC receives direct input from the primary sensory cortices. What is not known is whether (and if so how) the SC modulates information processing in sensory cortex. To address this question, we combined optogenetic activation of SC with whole-cell and extracellular recordings in primary vibrissal somatosensory cortex (vS1) of adult C57BL6/J mice (n=31). Using multi-electrode array recording in SC, we identified whisker responsive neurons and confirmed their reliable activation with blue light. Consistent with the idea that SC can have an impact on cortical processing, photo-activation of ChR2 in SC led to light-evoked responses in vS1 neurons. Photo-activation of SC also led to a leftward shift in the input-output relationship of cortical neurons during whisker input, resulting in an enhanced capacity to detect low intensity stimuli. Given the absence of a direct anatomical projection from SC to vS1, we investigated and confirmed two potential pathways for this functional modulation of vS1 by SC: (i) a projection from SC to facial nucleus, which is responsible for whisker movements though the facial nerve and (ii) an indirect thalamic pathway from SC to vS1 through the rostral sector of the posterior nucleus of the thalamus (Pom). Activation of vS1 was unaltered after cutting the facial nerve, indicating that SC primarily impacts on sensory processing in vS1 via Pom. Taken together, our results suggest that the SC, which plays a key role in attentional network, modulates sensory processing in primary somatosensory cortex via an indirect pathway through the thalamus.

6.4

Mesoscopic voltage imaging of neuronal activity in mice using genetically encoded voltage indicators (GEVI)

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Understanding the relationship between neuronal electrical activity and behavioural output is a huge challenge and one of the ultimate goals of neuroscience. The development of optical imaging approaches to assess neuronal activity provides a promising avenue for achieving this goal, particularly if voltage indicators (or reporters) can be genetically targeted to specific neuronal populations. Here we report functional targeting of a genetically encoded voltage indicator the FRET-based voltage sensitive fluorescent protein Butterfly 2.1 (VSFP Bfly) to examine neuronal activity *in vivo*. Using two different intersectional targeting approaches in mice we report functional expression of BFly specifically in layer 2/3 cells of the cortex and in Purkinje neurons of the cerebellum (validated *in vitro* using slice electrophysiology). Mesoscopic imaging of fluorescent activity in these regions after skull thinning allows us to record fluorescence-based membrane voltage activity under deep anaesthesia and during quiet wakefulness. Because BFly is a FRET based GEVI it provides the unique ability to correct for hemodynamic (blood flow) and movement artefacts *in vivo*. Our aim is to use this methodology to image neuronal activity over many days from the same mouse during the acquisition of behavioural tasks. In this way we aim to better understand the relationship between electrical activity in specific classes of neurons and motor behaviour.

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6.5

Development of the auditory cortex in autism spectrum disorder mice

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Autism Spectrum Disorders (ASD) are defined by impaired learning, sensory disorders, social deficits and stereotyped behaviours. Because ASD symptoms appear during infancy, it is crucial to examine how brain development is altered, as this could underlie behavioural deficits. The social and communication difficulties in ASD are thought to be due to distorted processing of sounds, which in turn impairs language abilities. We hypothesise that auditory cortex circuitry develops incorrectly, which results in abnormal neuronal connectivity and impaired ability to process sound. Here we utilize *in vivo* recording techniques to determine how the development of the mouse auditory cortex is different in ASD, using an ASD mouse model.

7.

Neurovascular function in health and disease

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Dynamic and local regulation of brain blood supply according to the metabolic demands of neural tissue is termed neurovascular coupling. Functional magnetic resonance imaging (fMRI) exploits the fine spatial and temporal regulation of neurovascular coupling to provide image the contrast behind the blood oxygenation level dependent (BOLD) response. Although fMRI has revolutionised the field of cognitive neuroscience by increasing the ability to probe the workings of the human brain, it does suffer from a limitation that it is only measuring a secondary hemodynamic marker of neural activity. A complete understanding of the BOLD signal source with regard to metabolism and neural activation is still lacking and is of critical importance especially as it is being used as a biomarker in many disease states such as dementia. There is a distinct possibility that BOLD signals in disease may not be driven entirely by neural activation but result as a consequence of a perturbed vascular system. This has implications not only for task evoked BOLD studies but spontaneous connectivity research. My research uses multi-modal imaging and electrophysiology methods in rodent models to understand neurovascular coupling in health and how it may be changing in disease. This presentation will focus on how non-neuronally driven BOLD signals could be generated when the vascular system is perturbed, the importance of a stable physiological mouse preparation and some initial results from investigating neurovascular breakdown in a mouse model of Alzheimer's Disease.

8.1

Simulated BOLD responses for neural activities such as continuous spiking, bursting and cortical spreading depression

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Understanding the quantitative relationship of the factors controlling neurovascular coupling will enable better interpretation of the fMRI BOLD signals. To this end, a mathematical model describing the experimentally well supported K^+ signalling hypothesis of neurovascular coupling, its associated metabolism and its fMRI BOLD response was developed and compared to experimental data from hippocampal and cortical regions. Our model predicts the well-known variations of the BOLD response such as initial dip, positive and negative BOLD signals, post stimulus undershoot arising due to the neurovascular and neurometabolic responses. Continuous spiking generated an expected positive BOLD response whilst bursting generated a mix of positive and negative BOLD signals. Cortical spreading depression simulation generated large negative BOLD signals. In addition seizure simulation produced large negative BOLD profiles. Comparison of simulated CBF and BOLD responses to experimental data in the cortex showed good agreement. However for short bursts of neuronal stimulation the CBF and associated BOLD signals did not agree well. These discrepancies indicate the possible existence of other vasoactive factors such as the arachidonic/EET pathway, animal dependent wall mechanics or different patterns of neuronal activity in the region. The full model, consisting of complex neurovascular and BOLD components is the first of its kind and will therefore provide further understanding between the neuronal activity and the resulting macroscale BOLD signal.

8.2

EEG biofeedback of the posterior cingulate cortex for memory

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Source localised EEG biofeedback is a therapeutic tool which could improve memory in older people. EEG data is analysed and source localised using sLORETA. This is displayed back to the subject so that they can take conscious control over it. A pilot study of this procedure showed promising results. We conducted a randomised controlled trial of biofeedback of the Posterior Cingulate Cortex (PCC). The trial had three arms, a broadband feedback group, training theta and alpha frequencies (4-14Hz); a narrowband feedback group, training only alpha frequencies (8-14Hz); and a placebo feedback, who received a randomly generated stimulus. Activity was source localised to voxels in the ventral PCC. Participants did fifteen 45 minute biofeedback sessions, over 5 weeks. Participants' memories were tested before training, after training and 6 weeks following training using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Participants were included if their immediate memory index score was below 90. 53 participants were recruited into the trial, evenly distributed between the three arms. Alpha activity in the PCC increased in the narrowband feedback group, indicating that some training effect had occurred, however this was only true for in-training EEG recordings and this was not seen in the resting state recording. This change was not correlated with the change in memory scores. No difference was found between the groups' immediate memory score at either the follow up immediately after training or at the follow up 6 weeks after training (Randomisation*Time effect $F_{2, 53.2}$=0.072, p=0.931). This study suggests that source localised feedback can result in real training that can be observed in EEG pattern of the participants.

8.3

Electric cell-substrate impedance sensing (ECIS™) for sensitive measurement of blood brain barrier integrity

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The blood-brain barrier (BBB) is vital for the maintenance of brain homeostasis. BBB dysfunction due to loss of barrier strength contributes to the pathogenesis of neuroinflammatory and neurotraumatic conditions like multiple sclerosis, Alzheimer's disease, spinal cord injury and stroke. Understanding changes that occur at the BBB is crucial in developing potential treatments for these conditions. Electric cell-substrate impedance sensing (ECIS™) is a non-invasive biophysical approach to monitor living cells in real time. Cells are grown on the surface of gold-film electrodes and the AC impedance of the cell-covered electrode is then measured as a function of time. By recording time-resolved impedance measurements, alterations in metabolism due to chemical, biological or physical stimuli can be followed in real time. We have developed a model using the ECIS technology and human brain microvascular cells to monitor changes in endothelial barrier strength. Using this model we can monitor the endothelial barrier in real time over an extended period (up to 1 week) and detect rapid and subtle changes in barrier integrity. Our results show that we are able to monitor real-time changes in barrier strength due to treatment with cytokines, drugs, and due to wound healing, immune cell infiltration and melanoma cell attachment/infiltration. We have novel findings on the response of endothelial cells that that would not be possible to detect with other methods. Our data demonstrates the power of the ECIS system for accurately monitoring changes in endothelial cells which is crucial to understanding the true response of these cells to insult or drug treatment.

8.4

Understanding cortical spreading depression patterns through numerical cell modelling

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Cortical Spreading Depression (CSD) has been linked to migraines as a cause of visual auras. CSD in migraines is characterised as waves of depolarisation causing irregular blood flow that is centred in the occipital lope of the brain. Recognising which cells are affected relative to the source, and thus which experience partial shutdown, is critical to understanding migraine symptoms. Depolarisation seen with CSD is linked to the dramatic efflux of excitatory amino acids, such as glutamate, from nerve cells. This release of glutamate, through a series of pathways, leads to the increased formation of Inositol-1,4,5-trisphosphate (IP_3). Increased IP_3 can induce oscillations in intracellular calcium concentrations. The spikes in calcium concentration, due to diffusion, are theorised to cause spikes in calcium concentration in larger areas of neuronal cells than previously modelled. Simplified mathematical cell models, such as Goldbeter *et.al.* (1990), were used to calculate rates-of-change of ionic concentration within individual cells (microscale). A homogenisation process was then applied to simulate cellular behaviour when many cells are coupled together (macroscale). By applying diffusion and a spatially varying IP_3 stimulus we were able to observe a comparatively larger area of ionic spiking than uncoupled cell models. Furthermore, by studying the underlying mechanics we are able to understand and quantify the extent to which an enlarged region of cells is affected. Being able to link the microscale cellular mechanics via homogenisation has led to predictions about physiological events occurring at the macroscale. In particular, waves are seen that penetrate farther along the cortical surface than predicted by simple analysis. Such effects may be relevant for recognising and predicting the occurrence of CSD in migraines.

8.5

The adult human subventricular zone has a distinct lipidome

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Adult neural stems cells are dependent on lipid synthesis, suggesting a role for lipids in neurogenesis. We hypothesised the existence of specialised lipid microenvironments within neurogenic niche, the subventricular zone (SVZ). This study characterised the lipidome of the human SVZ using high-resolution matrix-assisted laser desorption/ionisation (MALDI) imaging mass spectrometry. Caudate nuclei (CN) from four neurologically-normal donors (three males, one female) were obtained from the Neurological Foundation Douglas Human Brain Bank. Sections on target slides were coated with 1,5-diaminonaphthalene or 2,5-dihydroxybenzoic acid matrices by sublimation. MALDI imaging was performed using a Bruker UltrafleXtreme at 10 µm raster width. Spectra were aligned using FlexAnalysis and pre-processed and analysed in SCiLS Lab. Luxol fast blue and haematoxylin and eosin micrographs were co-registered with MALDI images to delineate the SVZ and its constituent layers. High-dimensional features of the data were explored using principal component analysis, whereas co-localisation of mass signals with the SVZ used Pearson correlation, receiver-operating characteristics and t-statistics. Species of interest were identified by liquid chromatography-tandem mass spectrometry and database searching of accurate masses derived by Fourier transform ion cyclotron resonance. The SVZ showed a distinct lipidomic signature that could be discriminated from the CN using principal components. The SVZ was rich in sphingomyelins and phosphatidylserines. Analysis of the constituent laminae of the SVZ identified the ependyma to be rich in phosphatidylinositol. The myelin layer showed high concentrations of sulphatides and triglycerides. This study is the first to characterise the lipidomic architecture of the human SVZ. Species identified are in keeping with functional contributions to neurogenesis.

9.1

Long-term potentiation expands information content of hippocampal dentate gyrus synapses

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A new approach combining signal detection theory and precise three-dimensional reconstructions from serial electron microscopy was used to investigate effects of synaptic plasticity on information storage capacity at medial perforant path synapses in adult hippocampal dentate gyrus in vivo. Control hemispheres exhibited 7.4 distinct spine sizes for 2.9 bits of storage capacity. Induction of long-term potentiation expanded the distribution of both small and large spines 30 minutes later, and this was associated with an expansion to 9.4 distinct spine sizes (3.2 bits) without affecting synaptic precision (coefficient of variation). This bidirectional expansion also occurred in such a way that there was a complete heterosynaptic counterbalancing of total synaptic area per unit length of granule cell dendrite. In contrast, control hippocampal CA1 synapses exhibited more information storage capacity (4.7 bits) and much greater synaptic precision than either control or potentiated dentate gyrus synapses. Overall, synaptic plasticity alters information storage capacity, but hippocampal subregions can nonetheless differ significantly in their synaptic storage capacity, reflecting their diverse functions, activation histories and, possibly, dendritic arborisation patterns.

9.2

Increased spontaneous synaptic activity in neurons of the intracardiac plexus of hypertensive rats

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The autonomic neurons located in ganglionated plexi (GP) on the heart are proposed to modulate and transmit neural activity to the myocardium, and also play a critical role in the development and propagation of arrhythmias. However, little is known about the properties of the synapses formed on and by GP neurons and how these properties change in states of arrhythmia. In this study, spontaneous post-synaptic currents were recorded from GP neurons in rats prone to atrial arrhythmia (spontaneously hypertensive rats, SHRs, n=4, 14-16 months old) and age-matched controls (normotensive Wistar-Kyoto rats, WKYs, n=8) using the whole-cell patch clamp technique. No significant difference was observed between the mean amplitude of post-synaptic excitatory currents between WKY and SHR neurons (31.12 ± 3.31 vs. 39.18 ± 3.28 pA, p=0.106), however the cumulative frequency distribution showed there was a higher proportion of large amplitude currents recorded from SHR neurons ($p<0.001$). Furthermore, there was a higher proportion of short intervals between synaptic events for SHR vs. WKY (p=0.0012) indicating a higher frequency of synaptic activity in the SHR GP. These changes in synaptic function show chronic hypertension may be associated with enhanced excitability of GP neurons, which could contribute to the increased arrhythmia burden seen in this condition.

9.3

Transcriptome profiling of layer 5 intratelencephalic-projection neurons in the mature mouse motor cortex

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The mature cortex hosts hugely diverse populations of pyramidal projection neurons, critical to normal forebrain circuits. Characterising this complexity is essential to our understanding of the healthy cortex. We recently identified two distinct intratelencephalic-projection neuron (IT-PNs) subtypes in layer 5 of the motor cortex (M1), defined by the presence or absence of *Fezf2* expression. Comparatively each IT-PN type has a distinct electrophysiological phenotype and the *Fezf2*-positive IT-PNs display a unique apical dendritic tuft. Here, we aimed to expand our understanding of the molecular underpinnings defining these unique IT-PN types. Using a *Fezf2*-GFP reporter mouse, retrograde labelling techniques and fluorescence activated cell sorting (FACS), combined with a novel approach to low-input RNA-sequencing, we isolated mature *Fezf2*+ and *Fezf2*- IT-PNs for transcriptome profiling. Through the comparison of *Fezf2+* and *Fezf2*- IT-PN gene expression profiles, we identified significant enrichment of 81 genes in the *Fezf2+* IT-PNs and 118 genes in the *Fezf2*- IT-PNs. Further bioinformatics analysis of these enriched genes found significant overrepresentation of the calcium-binding EF-hand domain in *Fezf2+* IT-PNs, alluding to a greater importance for calcium handling in these neurons. Of the *Fezf2*- IT-PN enriched genes an unexpected and unique enrichment of genes previously associated with immune cells of the brain were identified. Our dataset identify the molecular profiles of two unique IT-PN types in the mature M1, providing important targets to investigate for maintenance of these neurons in the healthy mature brain. This will be essential for understanding the function of IT-PNs in health and disease.

9.4

Lithium may block the delay current (I_D) in olfactory projection neurons

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Bipolar disorder is a debilitating neuropsychiatric disease characterized by periodic depressive and manic episodes, associated with altered ion channel gene expression and disturbed brain network activity. Lithium (Li^+) is a first-line treatment for bipolar disorder, but its therapeutic mechanism of action remains unknown. Hypothetical targets for the action of Li^+ range from intracellular signalling messengers to membrane transporters and ion channels. We used whole-cell patch clamp recordings to investigate the effect of Li^+ on the integration of simulated excitatory post synaptic potentials (sEPSPs) by main olfactory bulb output (mitral) cells. The olfactory bulb is a part of the limbic system that is concerned with behaviour and mood. We found that Li^+ increased mitral cell action potential frequency, decreased after-hyperpolarization (AHP) amplitude, and decreased the decay slope of action potentials. These findings indicate that Li^+ blocks an outward current that plays a role during repolarization and AHP phases of action potentials. Further, Li^+ decreased the delay to action potential generation during a train of sEPSPs, consistent with cumulative inactivation of an outward current. Finally, application of 4-aminopyridine (4-AP) at a concentration that selectively blocks I_D (5 micromolar), and 100nM α-dendrotoxin, reproduced the effects of Li^+ on mitral cell responses to sEPSPs and on action potential phases. Together, these data are consistent with an action of Li^+ on the delay-current (I_D). This current contributes to temporal integration of depolarizing signals due to its exceptionally long kinetics of inactivation and recovery from inactivation, and so can influence cortical network synchrony and spike time precision. Li^+ actions on I_D might therefore influence cortical network activity, contributing to its therapeutic effects in bipolar disorder.

9.5

Cell firing-induced down-regulation of future long-term potentiation

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Synaptic plasticity phenomena such as long-term potentiation (LTP) are at least partially driven by the patterns of action potential (AP) firing during plasticity induction. Moreover, cell firing patterns can influence the induction LTP in the future by engaging metaplasticity mechanisms. There are inconsistencies in the literature, however, as to whether activity up- or down-regulates future LTP. To address this controversy, we conducted single cell sharp-electrode recordings from CA1 pyramidal cells in acute hippocampal slices from 6-8 week old male Sprague-Dawley rats. Pyramidal cells were primed with depolarising current pulses (1.4 nA/2ms) into the soma to induce APs, using priming protocols previously reported to have opposing effects on LTP. LTP was induced 15 min later with one train of theta-burst stimulation (TBS), delivered to Schaffer collaterals. Both priming protocols (3 sets of 3xTBS trains and 2 sets of 3x100Hz trains of depolarising current pulses) significantly impaired subsequent LTP (control (n=7): 99.9 ± 14.4 %; 3x3 TBS primed (n=6): 55.7 ± 10.1 %, $p < .05$; 2x3 100 Hz primed (n=6): 22.5 ± 17.7 %, $p < .05$), measured 30 min post-induction. Interestingly, primed cells fired fewer APs during LTP induction than control cells, which was predictive of the amount of LTP induced by synaptically delivered TBS. Surprisingly no intrinsic excitability measures changed following priming in a way that explained the impairment of LTP or reduced cell firing. Taken together, our findings suggest that cell firing affects intracellular signalling pathways which downregulate synaptically driven cell firing and LTP induction without directly affecting intrinsic excitability.

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9.6

Do biased opioid agonists hold the key to developing better safer opioid therapeutics for addiction and pain?

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Drug abuse is a major global problem with no FDA approved therapeutics available to treat psychostimulant abuse. Development on safer mu-opioids are also urgently needed to reduce opioid abuse and overdose. Moreover, kappa-opioids have desirable analgesic effects and anti-reward properties. However, side effects currently limit their widespread therapeutic use. We hypothesise that development of biased agonists may provide the molecular mechanism underlying the potential separation of desirable therapeutic effects from undesirable side-effects. In collaboration with medicinal chemists we are utilising structural analogues of chemicals derived from natural products including Salvinorin A, and Kratom and evaluating signalling in both G-protein pathways and βarrestin pathways. Kurkinorin is a selective analogue of Salvinorin A activating the mu-opioid receptor with similar analgesic effects to morphine. In the warm-water tail-withdrawal assay Kurkinorin has the same duration of action as morphine (15-120 min). In the intradermal formalin model of inflammatory pain showed significant anti-inflammatory effects ($p<0.01$). More importantly we saw significantly reduced analgesic tolerance (in the warm-water tail withdrawal assay in mice) and rewarding properties in rodents in conditioned place preference assays (significantly reduced place-preference compared to morphine; $p<0.05$ in rats). This is matched to reduced signalling in βarrestin recruitment assays with a bias factor of 0.5 in βarrestin signalling compared to G-protein activation (cAMP recruitment assays). This data provides evidence that biased agonism at opioid receptors has potential for separating out the desirable therapeutic effects from undesirable side-effects.

11.1

Dual-site autoregulation modulates the effect of dopamine transporter blockade on phasic dopamine signals

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Reward signalling features phasic dopamine elevations superimposed on the tonic background. Dopamine transporter (DAT) blockers like methylphenidate prolong dopamine signals after individual action potentials, elevating tonic dopamine levels. We previously reported that methylphenidate only increases dopamine reward signals under dopamine D2-receptor (D2R) blockade, suggesting modulation by negative feedback of tonic dopamine. To investigate underlying mechanisms we first measured the effect of methylphenidate, D2R antagonist (raclopride), or the two drugs together on striatal stimulus-evoked dopamine using fast scan cyclic voltammetry in brain slices. There was a significant effect of drug treatments (area-under-curve, AUC; $F_{2,25} = 27.8$, $p < 0.001$). Both raclopride and methylphenidate increased AUC ($p < 0.05$, $p < 0.001$, respectively, post hoc Tukey's tests). Importantly, the combined effect was larger than the algebraic sum of the individual effects ($P < 0.001$, Student's t-test), indicating D2R-autoregulation restraint on the methylphenidate effect. Second, we recorded dopamine-neuron activity in midbrain slices. Firing rate was inhibited following methylphenidate treatment alone ($p < 0.001$, compared to baseline) but this was reversed to excitation by addition of raclopride ($p < 0.05$). These data suggest that homeostatic autoregulation processes need to be taken into account to understand the actions of methylphenidate in the awake behaving animal.

11.2

Analgesic effects of novel kappa opioid receptor agonists in mice

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Current pain medications are highly addictive. As an alternative, kappa opioid receptor (KOR) agonists have been shown to have analgesic effects without rewarding properties. Novel compounds 16-ethynl Salvinorin A (16-ethynyl SalA) and 16-bromo Salvinorin A (16-bromo SalA) are potent analogues of KOR agonist Salvinorin A (SalA) which have previously been shown to attenuate cocaine-prime induced drug seeking behaviour in rats without causing sedative, anxiogenic, aversive or pro-depressive side effects. Here, we investigated the ability of 16-ethynyl SalA and 16-bromo SalA to modulate pain behaviours in preclinical models of nociceptive, inflammatory and neuropathic pain. The tail withdrawal assay was used to measure the centrally-mediated analgesic properties, both novel compounds showed an analgesic effect with a longer duration of action than the parent compound SalA, and the dose response effects revealed the compounds were more potent than SalA. Intraperitoneal administration of 16-ethynyl SalA and 16-bromo SalA at 2 mg/kg in the formaldehyde (2%) footpad model decreased both nociceptive and inflammatory pain and also caused a decrease in footpad oedema compared to formalin treated mice. The KOPr antagonist nor-binaltorphimine reversed the analgesic effect. Mechanical and cold allodynia were measured in the paclitaxel-induced model to assess neuropathic pain. 16-ethynyl SalA reduced mechanical and cold allodynia in the paclitaxel-induced neuropathic pain model with more potency than SalA, traditional agonist U50,488 or morphine. Furthermore, we have shown for the first time the use of kappa opioid receptor agonists as an effective treatment of chronic neuropathic pain. This study demonstrates that novel kappa opioid receptor agonists significantly reduce nociceptive, inflammatory and neuropathic pain without the risk of abuse.

11.3

Patient-reported hallucinations are associated with future progression to dementia in Parkinson's disease, but cognition is more informative

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Neuropsychiatric symptoms may be associated with the decline to dementia in PD. 123 non-demented PD patients were followed over 3.5-4.5 years; 27 progressed to PDD during the study. All received Level II neuropsychological testing. Neuropsychiatric evaluations included the Neuropsychiatric Inventory (NPI), Geriatric Depression Scale, the Unified PD Rating Scale (UPDRS) hallucination and depression items, and the PD Questionnaire (PDQ) emotional well-being, hallucination and distressing dream items. ROC tests were used to analyse whether measures at study entry were associated with future PDD progression. Patient-reported hallucinations at study entry were the only neuropsychiatric measures that showed predictive value for future PDD (PDQ hallucinations: AUC=0.70, CI=0.60-0.80; UPDRS hallucinations: AUC=0.69, CI=0.57-0.80); significant other reported hallucinations on the NPI did not discriminate patients in terms of future PDD. Marginal utility for risk of future PDD was evident for the NPI total score (AUC=0.62, CI=0.50-0.74) and the NPI anxiety measure (AUC=0.62, CI=0.50-0.73). Neither patient-reported hallucinations (OR=1.70, CI=0.73-4.03) nor motor function (OR=1.02, CI=0.97-1.09), however, added any useful information above a global cognition score (OR=26.34, CI=6.44-184.71) and age (OR=1.28, CI=1.11-1.54). No additional benefit of patient-reported hallucinations was again evident when the analysis was restricted to the sub-group meeting PD-mild cognitive impairment criteria at study entry (n = 46). Cognitive ability is a stronger and sufficient predictor of conversion to PDD within 4 years than neuropsychiatric measures.

11.4

Exploration and persistence signals in the anterior cingulate cortex and the ventral tegmental area

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The anterior cingulate cortex (ACC) is thought to encode a 'search value' signal indicating the value of exploring alternative, non-default courses of action. However, it is unclear how ACC 'search value' signals are translated into the motivation to search. To address this question, we monitored ACC single units and local field potentials (LFPs) as well as LFPs in ventral tegmental area (VTA) of rats performing a cost-benefit foraging task with changing contingencies. Through a combination of behavioral, electrophysiological, and modeling analyses, we found that the initiation of exploratory behavior and the persistence of behavioral change were associated with ACC à VTA signaling. Additionally, we characterize the content of ACC neuronal task models, showing that ensembles of ACC neurons encode simple actions, value, and action-value combinations. We also demonstrate that value-coding elements of ACC neuronal task models are particularly influenced by the VTA à ACC signaling.

11.5

What do we know about uncanny valley?

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New technologies have facilitated in creating extremely real and human-like computer generated characters, especially in video games or human-machine interaction areas. It is believed that highly realistic characters increase user experience. The positive feeling holds until a certain point where the character is nearly human yet not human, a sense of discomfort and weirdness, namely the uncanny valley, emerges. It remains unclear what uncanny valley actually is and if we as human physiologically respond to the uncanny. As a result, we studied how our brain reacts to highly realistic computer generated faces at neurological level using psychophysiological measures such as EEG to explore the psychophysiological response of viewing these faces. 54 participants were recruited for the task. They viewed facial expressions of happiness (at 20% and 40% intensity levels), anger (at 20% and 40% intensity levels), surprise (at 100% intensity level) and neutral for both photo faces and simulated (computer generated) faces. All expressions were displayed for 300ms. Our preliminary results suggested that the brain responds to the differences between photo and simulated faces as early as at the P1 component. We also found photo faces elicit larger N1 than simulated faces and N1 at the right hemisphere is larger for both conditions. The findings suggested that at neurological level, we are tuned to detect faces that are very human-like but not yet very human.

11.6

Robustness and longevity of negative priming: Evidence for selective attention and memory retrieval

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This study investigated the long-term priming effects produced by formerly attended targets and formerly rejected distractors using conditions used by Neumann and DeSchepper (1991). With lower versus upper-case words as the selection cue, participants were required to name the prime target word followed by a making a word/non-word judgement to the probe target. Whereas, the longevity of priming effect was explored by presenting prime target or distractor 151 trials (302 attentional displays) away as probe target or distractor. Experiment 1 explored the longevity of priming effects by presenting prime target as probe target (TT) and prime distractor as probe target (DT). Although no long-term positive priming was observed in TT condition, long-term negative priming remained intact ($p<0.05$). In Experiment 2, the priming effects produced by condition in which prime distractor repeated as probe distractor (DD) was compared with that of DT condition. Results replicated the robustness of negative priming effect obtained by DT manipulation ($p<0.05$). Interestingly, the facilitation effect produced by DD condition in Neumann and DeSchepper (1991) seems to vanish away in the current long-term manipulation. Evidence of this sort is of immense theoretical significance as it could indicate that task-irrelevant information leaves a memory trace that impacts performance over time.

12.1

Developing remote photobiomodulation as a neuroprotective intervention for Parkinson's disease

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Photobiomodulation (PBM) – the irradiation of tissue with low-intensity 600–1100nm light – exhibits strong neuroprotective properties in rodent models of Parkinson's disease. However the clinical utility of transcranial PBM is hindered by limited light penetration across the human skull and cortex. Attempting to overcome this barrier to translation, we investigated whether PBM targeted at peripheral tissues ("remote PBM") also provides protection of the brain, in animals exposed to the parkinsonian neurotoxin MPTP. Applying PBM (670nm, 50mW/cm^2, 180s/day) to the body of either Balb/c or C57BL/6 mice during MPTP insult (50mg/kg over 24h) mitigated loss of functional dopaminergic neurons in the substantia nigra pars compacta (SNc) by 50% ($p<0.05$). Furthermore, pre-conditioning with remote PBM (90s/day) for 10 days prior to MPTP insult maintained SNc dopaminergic cell numbers ($p<0.05$) and striatal neuronal activity ($p<0.0001$) at healthy control levels. In a pilot study, MPTP-treated macaques receiving PBM to either the lower leg or abdomen (670nm, 50mW/cm^2, 180s/day) had fewer clinical signs than untreated monkeys (average score 2-20 vs 31) and more midbrain dopaminergic cells (20-50%). Remote PBM caused brain transcriptome changes consistent with the hypothesis of mesenchymal stem cell activation and mobilisation as a key mechanism underlying remote PBM-induced neuroprotection. Collectively, these data indicate that remote PBM offers neuroprotection against MPTP insult, substantiating the viability of remote PBM as a treatment modality for overcoming tissue penetration issues associated with transcranial delivery of light therapy. Current studies are exploring the putative molecular and cellular mediators underlying this phenomenon, and evaluating the utility of remote PBM for other neurodegenerative diseases.

12.2

Development of a sheep model of hemi-Parkinson's Disease

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Many animal models of Parkinson's Disease (PD) have been developed over the past decades. Toxin-induced models focus on reproducing degeneration of the dopaminergic neurons innervating the dorsal striatum, while genetic models replicate mutations associated with genetic forms of PD. The use of these models has contributed to widening our understanding of the molecular, cellular and systemic changes underlying PD, allowing the identification of potential pharmacological and surgical targets. However, the limited number of large mammalian models has constrained the translation of new technologies to PD treatments, with only the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model available. Yet, the significant biohazard risk of MPTP for both the animal and experimenter and the desire to limit non-human primate research has made this model less desirable. In an effort to address the gap in large animal PD models, we used in sheep stereotaxic injection of the selective dopamine toxin hydroxydopamine, the commonest model used in rats. Due to the limited and often breed-specific stereotaxic information available for sheep, we first determined the coordinates to facilitate reproducible injections of toxin into the *substantia nigra pars compacta* (SNc) of Romney-Cross sheep. Following successful surgeries, we established that as in rodents, the extent of the unilateral dopaminergic depletion could be assessed behaviourally. We determined that the magnitude and direction of rotational behaviour induced by administration of the dopaminergic agonist apomorphine was associated with the accuracy and extent of lesion location. This newly established sheep model of PD provides an opportunity for developing and testing new technologies for transfer to clinical research, without the safety concerns associated with MPTP.

12.3

Detailed modelling of neuronal calcium spiking dynamics

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Neurovascular coupling describes the vasculature's ability to regulate cerebral perfusion based on neuronal activity. The cells involved in this process are neurons, glial cells and vascular cells, which together comprise a neurovascular unit (NVU). Our research group has developed a model of the NVU to quantify the process of neuronal activation to vascular response. However, the majority of ionic concentrations and fluxes modelled, and by extension the model, are difficult to verify experimentally. While neuronal calcium concentrations can be verified with existing experimental data, the calcium dynamics in the current NVU do not accurately capture concentration spikes observed in vivo on time scales less than one second. We use biophysically realistic models of calcium dynamics in cerebral Purkinje cells to implement advanced neuronal calcium dynamics in the NVU. This enables more rigorous validation of the NVU model, through comparison of the calcium concentrations within the modelled neurons' compartments to experimental data. The model presented uses a compartmentalised lumped parameter approach. We show this is able to generate physiologically realistic calcium spikes in the cytoplasm of the post-synaptic neuron in response to neuronal activation through a pre-synaptic calcium pulse. This is achieved through synaptic glutamate release, followed by hypo-polarisation of the postsynaptic neuronal membrane and the draining of calcium stored in the ER into the cytoplasm. Upon removal of the input stimulus, return to equilibrium is observed on a physiologically realistic timescale. This is a significant improvement on the primary component of the NVU that can be readily verified experimentally. The results of the neuronal calcium model generated are more physiologically accurate than those of the currently implemented model, capturing behaviour observed in vivo.

13.1

The effects of site-specific glycation of Aβ(1-42) on fibrillation and aggregation kinetics

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Aggregation of amyloid-β (Aβ) peptides into amyloid fibrils is a pathological signature of Alzheimer's disease. Aβ is a substrate for non-enzymatic glycation and several reports have suggested that glycated Aβ (Aβ-AGE, Advanced Glycation End-Products), is a common pathological feature of patients with Alzheimer's disease and may be more pathogenic than Aβ itself. In this study we have examined the effects of site-specific glycation of Aβ on aggregation into amyloid fibrils. We have used a combination of organic and solid phase peptide synthesis to substitute the naturally occurring lysines at position 16 and 28 of $Aβ_{1-42}$ with a commonly occurring AGE, *N*-(carboxyethyl)lysine (CEL), to produce three analogues, Aβ-CEL_{16}, Aβ-CEL_{28} and Aβ-$CEL_{16\&28}$. We have incubated $Aβ_{1-42}$ and CEL-modified peptides under conditions known to produce fibrillar forms of the peptide and assessed fibrillation using transmission electron microscopy (TEM) and aggregation using a Thioflavin T (ThT) assay. All three CEL-derivatives displayed significantly reduced amounts of fibrils at 24 h compared to native $Aβ_{42}$. Extended analysis over a further 96 h suggested delays in fibril formation were more pronounced for Aβ-CEL_{16} compared to Aβ-CEL_{28} while Aβ-$CEL_{16\&28}$ displayed little fibrillation at all time points. End point ThT aggregation assays at 24 h indicated reduced aggregation of all three CEL-derivatives compared to $Aβ_{1-42}$ with further changes seen out to 96 h. The Aβ-$CEL_{16\&28}$ peptides showed the lowest levels of aggregation at all time points. Together these studies demonstrate significant impacts of site-specific glycation on the biophysical properties of Aβ.

13.2

Therapeutic targeting of autophagy in neurodegenerative Batten disease

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Batten disease refers to a genetically diverse group of neurodegenerative disorders characterised by the lysosomal accumulation of undigested cellular components and progressive neurodegeneration. Mutations in CLN6 are predominantly responsible for a human variant late-infantile form, and have also been identified in sheep ($CLN6^{-/-}$) and mouse (*Cln6*^{nclf}). These animal models have been critical to the understanding of disease pathways and potential therapeutics. Neural cultures isolated from these models show pre-clinical development of autophagy-lysosomal pathway defects and progressive accumulation of storage material, leading to the hypothesis that increasing autophagy may ameliorate disease-progression. One documented autophagy-inducing mechanism is via activation of transcription factor EB (TFEB), a master regulator of lysosomal biogenesis. Here, *Cln6*^{nclf} mice were treated with Gemfibrozil, a Food and Drug Administration approved lipid-lowering compound, shown to induce TFEB and lysosomal biogenesis. Male and female *Cln6*^{nclf} mice were dosed via oral gavage with 120 mg/kg over a period of 2 months, beginning at 4 weeks of age. Gemfibrozil treatment significantly lowered the burden of storage material and activated astrocytes in the cortex of treated animals, suggestive of increased autophagy and reduced inflammation. This study provides the first preliminary data on the beneficial effects of gemfibrozil for the treatment of CLN6 Batten disease. These findings are particularly relevant to disorders resulting from deficiencies in membrane-bound proteins, such as CLN6, which are anecdotally harder to treat with gene therapy or stem cell transplantation. These conclusions are also applicable to the broader field of neurodegenerative storage disorders, many of which share neuroinflammatory and/or aberrant storage accumulation.

13.3

Generalization of goal conflict specific rhythmicity to a bimanual anticipatory response inhibition task shows sensitivity to anxiolytics

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Right frontal goal-conflict-specific-rhythmicity (GCSR) in a simple stop signal task (SST) is a potential human EEG anxiety process biomarker. Anticipatory response inhibition tasks (ARIT) produce a similar stopping challenge to the SST but without the pressure to produce a speeded go response, allow direct comparison of left, right and both handed stopping, and are reported by participants to generate substantial subjective conflict. We modified a standard ARIT to match our SST in having three sets of stop signal delays (SSD): short, intermediate, and long. The intermediate SSD values tracked 50% correct stopping to maximize goal conflict, short and long SSD values were set towards the end and start of a trial, respectively. Right frontal (F8) GCSR (the EEG power contrast of stop-go x quadratic of SSD type) was compared across stop left, stop both, and stop right trials and tested for correlations with trait anxiety and neuroticism and tested for sensitivity to anxiolytic drugs. The stop left and, to a lesser extent, stop right conditions produced 5-12 Hz GCSR that significantly correlated with trait anxiety and neuroticism. Double blind administration of triazolam (0.25mg), pregabalin (75mg) buspirone (10mg), or placebo showed, like the SST, that stop left F8 GCSR was sensitive to all three anxiolytics. Stop right F8 GCSR was sensitive to pregabalin and buspirone but not triazolam. These results show that elicitation of right frontal GCSR generalizes from the SST to the ARIT both in relation to personality and pharmacology particularly with left hand stopping.

13.4

Electrical kindling causes cell-type specific changes to inhibitory neurons in the piriform cortex

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The primary olfactory (piriform) cortex has been shown to be important for the generalisation of epileptic seizures. A small number of studies have shown that epilepsy causes cell death in the piriform cortex. However, the effect of epilepsy on specific types of inhibitory cells has not previously been investigated. This study aimed to determine the effect of electrical kindling on each of the major inhibitory cell types in the piriform cortex. Experiments used GAD67-GFP+ mice, which allowed us to identify inhibitory neurons by their expression of GFP. Mice were kindled using an olfactory bulb electrical kindling method, and compared to control and sham-kindled mice. Animals were perfusion-fixed and 100µm thick slices prepared. Slices were immunohistochemically processed to detect a range of markers, including parvalbumin, calbindin, vasoactive intestinal peptide and somatostatin, each of which is associated with a known type of interneuron. Sections were imaged using a Nikon confocal microscope and cells counted using a custom ImageJ macro. We found a 13% overall reduction in the number of inhibitory neurons in the piriform cortex in the kindled mice compared to the sham and control ($p=0.009$, n=22,614 neurons, n=216 slices, n=12 mice). We found a specific reduction in the number of bitufted cells, regular-spiking multipolar cells and layer 2 neurogliaform cells ($p<0.05$). However, the number of horizontal cells, fast-spiking multipolar cells and layer 1 and layer 3 neurogliaform cells remained unchanged ($p>0.05$). This study provides the first rigorous characterisation of the effect of epilepsy on different inhibitory cell types and may provide insight into the mechanism of seizure generalisation through the piriform cortex.

13.5

Outer hair cell auto-regulation and measurement of slow basilar membrane movements *in vivo*

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To measure slow displacements of the organ of Corti (OC) in the living mammalian cochlea, we have developed a novel displacement-sensitive probe with an active stabilization system, with a resolution of nanometres (without signal averaging). We present the first direct measurements of slow OC movements *in vivo.* The accurate, stable detection of near-atomic sound movements in the mammalian cochlea is achieved by a specialised set of receptor cells, the outer hair cells (OHCs), that detect the sound-evoked vibration of the OC, and enhance it 1000-fold by active cell length changes, cancelling friction cycle-by-cycle. This process is prone to significant changes in sensitivity due to large, slow mechanical and electrical disturbances that can occur physiologically (just a 10% change in efficiency results in a 10-fold or 20dB loss of vibration). In view of this, the existence of OHC auto-regulatory mechanisms seems inescapable. Furthermore, many hearing losses are likely to be a result of failure of such auto-regulatory systems (e.g. Menière's syndrome). These regulatory mechanisms may involve OHC stereocilia changes, or slow OHC length changes (mediated by the motor protein *prestin*, intracellular electrical potential and intracellular calcium). Changes in OHC receptor current during experimental perturbations suggest such slow movements do occur, however electrical measurements cannot distinguish passive OC movements from active OHC length changes. Direct measurement of OC displacements will help us to understand what slow movements of the OC take place *in vivo*, what auto-regulatory processes exist in the normal cochlea, and may indicate possible modes of failure of these processes. This technique could also be applied to similar compliant sensory membranes (e.g. vestibular system) or other tissue (e.g. airway, gut, or cardiac muscle).

13.6

Stress-evoking emotional stimuli exaggerate deficits in motor function in Parkinson's disease

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Recent animal studies have shown that stress can profoundly affect motor behaviour and worsen motor deficits associated with Parkinson's disease (PD) by acting on the dopaminergic system, possibly due to stress-associated emotional changes. However, systematic investigation of the influence of acute emotional stressors on motor function in PD is scarce. Here we examined the effect of repeated exposure to negative emotional stimuli on isometric grip-force control in PD. Eighteen patients with idiopathic PD (tested off-medication) and 18 healthy control volunteers produced an isometric precision grip contraction at 15% of maximum force in four conditions: while viewing visual feedback of force output, or while viewing a series of unpleasant, pleasant, or neutral emotional images (blocked presentation; without visual feedback of force output). Force output was continuously recorded together with change in forearm muscle activity using electromyography. While viewing unpleasant images, PD participants exhibited increased force variability and 4-8 Hz oscillations of force output, and greater forearm flexor muscle activity. With feedback occluded, the decay in force amplitude was pronounced in PD, but not modulated by emotion. In contrast, in controls, the decay in force amplitude during force maintenance was attenuated while viewing unpleasant images compared with pleasant and neutral images. The findings in PD may reflect an increased number of motor units discharging and reduced ability to use sensory feedback to alter the descending drive. Modulation of synaptic input to the motoneuron pool could result from acute stress-induced enhancement of sympathetic activity and/or amplification of dopamine depletion. Corroborating previous findings in animal models of PD, exposure to stress-evoking emotional stimuli can exacerbate impairments in fine motor control in individuals with PD.

Poster 14.1

Microanatomy of fear memory within the prefrontal cortex and amygdala

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Post-traumatic stress disorder (PTSD) is a memory-based disorder characterized by intrusive memories and an inability to experience pleasure. In order to understand the microanatomical organization of fear memory processes a complete understanding of the anatomical and molecular events underlying fear memory consolidation and extinction is required. Following Pavlovian fear conditioning, (CS+US x3), rats received 3 days (d) of 'extended extinction' (20xCS), then 3d home cage prior to a fear memory test (3xCS). We investigated Arc and pMAPK immunoreactivity to measure microcircuit localization of memory in the amygdala and the medial prefrontal cortex (N=40). Initial results generated from memory test (3xCS) showed extinction animals reduced responding to the CS (freezing 10.17 +/- 0.73%, n=10) compared to controls (47.17 +/- 7.25%, n=10) ($p=0.0352$), suggesting animals were fully extinguished. The relative contribution of pMAPK and ARC were measured in LH and RH hemispheres respectively (n = 6 animals). We found numerically similar contributions of activity in neurons occur during extinction memory recall within the LA ($p=0.8133$) and IL ($p=0.8584$). Initial investigation also reveals specific sub regions and cortical layers differ in expression of pMAPK and Arc during extinction recall. These findings begin to identify the spatial and temporal properties of extinction memory microcircuits. As relapse is a leading clinical obstacle in the treatment of PTSD, identifying the precise biological mechanisms and brain subregions involved in fear memory extinction provides knowledge for improved pharmacological and behavioural therapeutic targets.

Poster 14.2

Blackcurrant anthocyanins supplementation reduced HDAS and increased cyclic glycine-proline inthe cerebrospinal fluid of Parkinson patients

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High consumption of Blackcurrant anthocyanins associates with low risk of Parkinson diseases (PD), the condition with impaired insulin-like growth factor-1 (IGF-1) function. Cyclic glycine-proline (cGP) normalizes IGF-1 function through improving IGF-1 bioavailability. This study evaluated Psycho-cognition and cGP, IGF-1 and IGF binding proteins (IGFBPs) in the CSF and plasma of PD patients after supplementation of blackcurrant anthocyanins (BCA). The motor and psycho-cognitive functions of 11 PD patients were assessed and Plasma and CSF samples were collected before and after 28 days supplementation of BCA. The concentration of IGF-1, cGP, IGF binding protein 1-3 were measured using ELISA and c-GP using High Performance Liquid Chromatography mass spectrometry assay. The supplementation reduced Hospital-associated Anxiety and Depression Scale (HADS, $p=0.004$) and increased cGP concentration in the CSF ($p<0.01$), which was correlated with plasma cGP concentration ($r=0.68$, $p=0.016$) and ratio of cGP/IGF-1 ratio ($r=0.84$, $p=0.014$). There was no change of IGF-1 and IGF binding proteins in both CSF and plasma. The reduced HADS after supplementation of BCA in PD patients may be medicated through improving bioavailability of IGF-1. The increase in cGP in the CSF may be a trophic response to IGF-1 resistant in PD patients to increase IGF-1 bioavailability in the plasma, which transferred to the brains. Thus, the change of cGP or cGP/IGF-1 ratio may be a potential biomarker for IGF-1 function in PD, which needs to be further evaluated in a larger study.

Poster 14.3

Synaptic changes in Shank3$^{-/-}$ Autism Spectrum Disorder associated mouse model

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Autism Spectrum Disorders (ASDs) are characterised by repetitive behaviours and deficits in social communication. ASDs have a strong genetic basis with many ASD-associated mutations are found in synaptic proteins. Shank proteins are master regulators of excitatory synapses and mutations in all three isoforms (Shank1, Shank2 and Shank3) have been found in ASD patients. The SAM domains of both Shank2 and Shank3 bind zinc, a commonly found mineral in the brain, and this results in Shank protein stabilisation within the postsynaptic density (PSD). The Shank3$^{-/-}$ mouse model of ASD (B6.129-*Shank3*^{tm2Gfng}/J) displays excessive repetitive grooming behaviours as well as reduced peak evoked AMPAR-mediated currents and slower NMDAR-EPSC decay kinetics in the cortico-striatal pathway. Zinc deficiency is a risk factor in ASD, and low zinc levels have been found in autistic children. We have recently established that dietary zinc supplementation rescues some ASD phenotypes in Shank3$^{-/-}$ mice including repetitive grooming. To further understand the mechanisms underlying this rescue, levels of synaptic Shank2 were measured in cortico-striatal slices from wildtype and Shank3$^{-/-}$ mice fed normal (30ppm) and high (150ppm) zinc diets. Dietary zinc supplemented Shank3$^{-/-}$ mice were observed to express significantly higher intensity levels of synaptic Shank2 in comparison to wildtype and Shank3$^{-/-}$ mice on the normal zinc diet. However, this increase in Shank2 intensity was not accompanied by a rescue of synaptic density. These data suggest that high dietary zinc enhances the recruitment and stability of Shank2 at cortico-striatal excitatory synapses which may contribute to the zinc supplementation induced rescue of ASD phenotypes in Shank3$^{-/-}$ mice.

Poster 14.4

The effects of bilateral priming on motor cortex function in healthy adults

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Bilateral priming is an adjuvant that has shown potential to assist upper limb motor recovery at the subacute stage post-stroke. It involves the use of a table-top device to couple the upper limbs together such that active flexion and extension of one wrist leads to passive movement of the opposite wrist in a mirror symmetric pattern. Bilateral priming increases corticomotor excitability (CME) in the primary motor cortex (M1) controlling the passively driven limb, however the neurophysiological mechanisms underlying this CME increase remain unclear. The aim of this study was to explore these mechanisms using transcranial magnetic stimulation to investigate two facilitatory networks within the passively driven M1: intracortical facilitation (ICF) and short-interval intracortical facilitation (SICF). ICF was recorded using posterior-anterior (PA) current stimulation while CME and SICF were recorded using both PA and anterior-posterior (AP) current stimulation. Motor evoked potentials were recorded from the left extensor carpi radialis (ECR) and first dorsal interosseous (FDI) muscles of 23 healthy adults before priming (Baseline) and again five minutes and 35 minutes after a single 15-minute session of priming ($Post_5$ and $Post_{35}$, respectively). Priming increased PA CME at $Post_{35}$ and this remained elevated until the end of the experiment, while AP SICF was facilitated at both $Post_5$ and $Post_{35}$. Priming had no effect on AP CME, ICF and PA SICF. Despite increasing AP SICF, this is most likely not the mechanism underlying the increased PA CME due to the differing timelines of their effects and the separate interneuron circuits activated by the PA and AP stimulation. These results suggest priming does not increase CME through alterations of these intracortical facilitatory circuits.

Poster 14.5

Investigating the anti-cocaine and analgesic properties of MP1104, a dual acting kappa and delta opioid agonist

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Addiction to drugs of abuse including opioids and psychostimulants is a major problem worldwide. There are currently no FDA approved treatments for psychostimulant abuse and abuse of prescription opioids is growing. Therefore, the development of non-addictive pain therapies and effective treatment for psychostimulant abuse are urgently needed. Kappa opioid receptor (KOPr) activation reduces drug-seeking behaviours in preclinical models of drug use and also attenuates pain and inflammation, without abuse potential. However, side-effects such as sedation, dysphoria, aversion and depression currently limit their clinical use. Delta opioid receptors (DOPr) also influence addiction behaviours and may alleviate withdrawal behaviours associated with activation of KOPr's. Therefore, we hypothesise that the mixed actions of both KOPr and DOPr agonists may be developed into effective treatments for drug addiction with fewer side effects. MP1104, is a dual KOPr/DOPr agonist with highest affinity for KOPr. In the warm-water tail withdrawal assay in rats, MP1104 has shown to be potent (EC50 =0.54), long-lasting analgesic ($p<0.0001$). In rats trained to self-administer cocaine, we show that MP1104 reduced cocaine-prime reinstatement of drug-seeking behaviour at doses of 0.3 mg/kg ($p<0.01$) & 1 mg/kg ($p<0.001$). Moreover, MP1104 showed reduced sedation in tests of spontaneous locomotor activity, showed no aversion in place-aversion tests, and no anxiogenic effects in the elevated maze test in rats. Findings from this ongoing study will provide more information on the behavioural properties of the mixed KOPr/DOPr agonists, which may be useful in developing non-addictive treatments for pain and drug abuse.

Poster 14.6

Impact of chronic stress on the neuroendocrine axis in the mouse

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Stress results in the activation of hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoid stress hormones. Chronic stress can induce hyperactivation of the HPA axis which subsequently disrupts numerous physiological processes. Here we set out to investigate how chronic stress impacts hypothalamic neuroendocrine pathways, which are essential for maintaining normal body homeostasis. Male and female mice were exposed to 14 days of mild chronic variable stress (CVS). At the end of the 14 days, blood, brain, pituitary and endocrine organs were collected for analysis. We found that mice exposed to CVS lost weight compared to controls ($p<0.01$, $n=6$), however, this was not due reduced food intake ($p=0.55$, $n=6$). We found a significant increase in the levels of stress induced corticosterone in both male and female mice that experienced CVS compared to controls ($p=0.01$, $n=6$). Stress evoked prolactin release was also higher in CVS exposed males ($p=0.03$, $n=6$) but not female mice. Blood luteinizing hormone levels were unchanged. We next investigated the effects of CVS on the expression of neuropeptides in the hypothalamus. In the paraventricular nucleus (PVN), CVS significantly increased the mRNA levels of vasopressin in male mice ($p=0.03$, $n=6$) and somatostatin in female mice ($p=0.03$, $n=6$). Overall, these data show that exposure to CVS induces alterations at multiple levels of the neuroendocrine axis in a sex dependent manner.

Poster 14.7

Establishing reliable methods to assess motor skill learning and motor performance in mice

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The acquisition of complex movement sequences is termed motor skill learning (MSL). MSL has been studied in rodents using reaching and acrobatic locomotor tasks (ALT). Here we trialled an approach to assess MSL using a combination of reaching and ALT in the same mice. To evaluate skilled forelimb motor learning and dexterity we used the single pellet reaching (SPR) where we modified the SPR apparatus from rat procedures. In this modification mice must learn to make a precise grasp for successful retrieval to encourage dexterous movement and are prevented from simply pulling the pellet. Mice performed the SPR showing an initial increase in the percentage of successful pellet reaches over the first three days of testing ($n=5$, $p<0.05$, repeated measurements One-Way ANOVA) followed by a plateau to their reaching performance by the sixth day of testing. In the same mice we used the accelerating (AR) and rocking rotarod (RR) to assess their ability to learn an acrobatic motor task that includes fast postural adjustments. The time to fall of the mice in the AR increased over the first two days ($n=5$, $p<0.05$, repeated measurements One-Way ANOVA) with no further improvement on the third day. Mice were then subjected to repeated changes in the rotation direction of the rod (RR) when their time to fall decreased ($n=5$, $p<0.05$, repeated measurements One-Way ANOVA) compared with the last day of AR indicating the acquisition of an additional acrobatic motor learning component. Our results indicate that a combination of reaching, dexterous learning and ALT is possible in mice and involves the acquisition and consolidation of new motor patterns.

Poster 14.8

Does voluntary exercise improve motor performance and/or cerebellar architecture in SCA1 moderately ataxic mice

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SCA1 is an autosomal dominantly inherited form of ataxia caused by a CAG repeat expansion in the SCA1 gene. SCA1 patients have progressive ataxia, dysarthria and nystagmus which starts to show during 3rd-4th decade of life. To date there is no cure for SCA1, however exercise may benefit these patients. My aim is to determine the effect exercise has on motor performance and cerebellar Purkinje neuron (PN) morphology in a mouse model of human SCA1. The SCA1 82Q (SCA1) mouse model overexpresses CAG repeats in the Ataxin-1 gene specifically in cerebellar PNs and recapitulates human balance and coordination problems. Twelve week old mid-stage SCA1 and wild-type (WT) exercising/non-exercising mice were individually housed and allowed access to a running wheel, where appropriate for 3 weeks. Mice were then tested daily on an accelerating rotarod to investigate motor performance/learning based on their latency to fall scores. Exercised WT mice performed better on this motor test when compared to non-exercised WT mice ($p=0.0008$), but the performance of SCA1 mice remained similar. To investigate whether cerebellar morphology changed with exercise we analysed climbing fiber (CF) synapses and PN morphology using vGluT2 and calbindin labels respectively, as a CF-PN ratio. WT mice exhibited a mean CF-PN ratio ≥0.80, larger than that seen in non-exercised SCA1 mice where CFs retract and PNs shrink ($p=0.0034$). Remarkably, in exercised SCA1 mice this ratio was restored towards WT levels ($p=0.0231$), suggesting 3 weeks of exercise can improve the disrupted cerebellar morphology normally associated with the disease, even though motor performance was unaffected.

Poster 14.9

Pericyte therapeutics to repair the stroke-lesioned brain

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Stroke results from blockage of the blood supply to the brain that leads to subsequent degeneration of brain tissue. The brain has little spontaneous repair capacity within the injured region so there is an urgent need to develop new therapeutic strategies. Pericytes are a subtype of mesenchymal stem cells that ensheath endothelial cells and reinforce the vasculature. Following stroke, brain pericytes migrate and may help repair the damaged region by improving vasculature and neuronal networks. The multipotent nature of pericytes make them an ideal source for brain circuit regeneration. This project aims to identify the therapeutic potential of pericytes to migrate and functionally integrate within the stroke damaged cortex. Prior to integration, we initially isolated, enriched and characterized brain pericytes from 4-6-week-old mice. The isolated pericytes were then transduced with lentivirus expressing near infra-red fluorescent protein (iRFP) in order to tag the pericytes prior to grafting. Our preliminary results indicate that the 7-day passage-3 cultures were enriched for pericytes as determined by immunohistochemistry and fluorescence assorted cell sorting. Lentivirus transduced the pericytes with approximately 40% efficiency with addition of 3.6×10^5 functional units. These promising preliminary findings take us a step closer to grafting RFP tagged pericytes into the stroke lesioned motor cortex in order to observe both the therapeutic efficiency and migration status of the grafted pericytes. Our approach could make a significant contribution to brain vascular regeneration and possibly pave the way for autologous patient specific cell therapy.

Poster 14.10

Understanding the Batten disease associated protein CLN5

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The neuronal ceroid lipofuscinoses (NCL, Batten disease) are a group of autosomal recessive neurodegenerative lysosomal storage diseases that typically result in loss of vision, epilepsy, loss of motor function and cognitive decline. Mutations throughout the CLN5 gene are predominantly responsible for a late-infantile variant of NCL. The CLN5 protein is a soluble lysosomal protein of unknown function, with no strong sequence identity to any previously characterised protein. Here we aim to better understand the normal role of the CLN5 protein by investigating its structure and potential function. Using secondary structure prediction, sequence profile matching, and homology modelling, we have found that CLN5 shares weak homology with proteases that utilise a cysteine histidine catalytic dyad. Based on this, the predicted catalytic cysteine was mutated via site directed mutagenesis to investigate whether this mutant can rescue disease-associated phenotypes present in CLN5-/- affected cells. Prior to testing for phenotypic rescue, we will compare the trafficking and secretion of mutant and wildtype CLN5. Complementary to functional studies, an optimised expression construct for CLN5 has been designed for purification and crystallisation studies. HEK293FT cells have been modified using lentiviral transduction to overexpress CLN5. CLN5 protein has been collected from the media of these cells and purified using nickel affinity chromatography. Future work is aimed at determining the structure of CLN5. Combined, this work will lead to a better understanding of the normal function of CLN5, and as to why mutations in the gene lead to NCL.

Poster 14.11

Parkinson's disease: No association between amyloid PET imaging and cognitive status

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Cognitive decline in Parkinson's disease (PD) significantly impacts a patient's quality of life, and leads to dementia (PDD) in over 80% of cases. Recent work suggests that misfolded beta-amyloid protein, a pathological hallmark of Alzheimer's disease (AD), may also contribute to the multifactorial neuropathology of PDD. We therefore examined cortical amyloid accumulation in 108 individuals with PD, using 18F-Florbetaben positron emission tomography. Patients with mild cognitive impairment (PD-MCI) were targeted, as they are known to be at high risk of developing PDD. Prior to scanning, cognitive status was determined using a comprehensive neuropsychological battery. Participants were classified as having PD with normal cognition (PD-N; n=21), PD-MCI (n=74), or PDD (n=13). We found that clinical positivity for amyloid did not vary according to cognitive status (PD-N: 24% [5/21]; PD-MCI: 23% [17/74]; PDD: 23% [3/13]), and global amyloid deposition did not correlate significantly with global cognitive ability. PD can affect several cognitive domains, so their association with planned regional analyses of amyloid deposition will also be explored. Amyloid deposition may be a factor in some patients, however the low prevalence of amyloid in the PD-MCI and PDD groups compared with that seen in amnestic MCI (~50-70%) and in AD dementia (~80-95%) indicates that alternative pathology such as alphasynucleinopathy, and perhaps tauopathy, predominates in cognitively impaired PD patients.

Poster 14.12

Hippocampal arginine metabolism shifted to favour the polyamine pathway in a mouse model of tauopathy

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Intracellular accumulation of hyperphosphorylated and aggregated microtubule protein tau is a histopathological feature of Alzheimer's disease (AD) and frontotemporal dementia. It has been shown that multiple pathogenic mutations in microtubule-associated protein tau (MAPT) are associated with diverse frontotemporal dementia syndromes. Experimentally, transgenic mouse lines bearing the MAPT P301 mutation have been used to mimic human frontotemporal lobar degeneration. Recent evidence implicates altered metabolism of L-arginine in the pathogenesis of AD, and polyamines decrease tau aggregation and promote microtubule assembly. The present study quantified the levels of L-arginine and its downstream metabolites in the hippocampus of male wildtype (WT) mice and PS19 mice bearing the human tau P301S mutation at 4, 8 and 12 months of age using high performance liquid chromatography and liquid chromatography/mass spectrometric assays. PS19 mice displayed significantly increased levels of L-ornithine (at all ages) and its downstream metabolites putrescine (at 8 and 12 months) and spermidine (at 12 months), as well as L-arginine (at 12 months), but decreased levels of agmatine (at 4 and 12 months). Moreover, there were increased, but decreased, glutamate levels in PS19 mice at 4 and 12 months of age, respectively, with no genotype effects on L-citrulline, glutamine and GABA. These findings demonstrate that arginine metabolism in the hippocampus is altered dramatically in PS19 tau mice in a neurochemical-specific and age-related manner. Shifting L-arginine metabolism to favour the polyamine pathway may be a protective mechanism to combat tau pathology.

Poster 14.13

Glutamate receptor studies in the human globus pallidus

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The basal ganglia are a group of interconnected nuclei in the center of the brain, associated with controlling mood and movement, and converge on the internal segment of the globus pallidus (GPi). The GPi is the main output nucleus of the basal ganglia, projecting to the thalamus. Dysfunction of the basal ganglia nuclei and their pathways cause a variety of movement disorders including Huntington's and Parkinson's disease. These are two devastating neurological disorders that are characterized by opposing motor symptoms. The objective of this study is to characterize the neuronal populations in the human globus pallidus, with a focus on the subpopulations expressing glutamatergic receptors and to compare between normal and disease states. Using fluorescent immunohistochemistry, the GP of normal human brains are microscopically examined and imaged. The 70µm slices are immunostained for glutamatergic receptors (GluN1, GluR2/3), GABAergic receptors ($GABA_A\alpha_1$, $GABA_A\beta_{2/3}$), vesicular transporters (VGLUT2, VGAT), calcium binding proteins (Parvalbumin, Calretinin, Calbindin), Substance P and Enkephalin. We have discovered a new configuration of excitatory and inhibitory receptor systems on cells in the GP. The results indicate that there are separate input patterns converging on two different cells types in the GP, where it has been previously accepted as converging on only one, suggesting that there are at least two unique cell types within the human GP. Some of which contain mainly inhibitory receptors and others which contain mainly excitatory receptors. If this is true, it will change the way we think about how the basal ganglia operates: two different pathways. Thus having major implications for understanding the processing of mood and movement in the human brain and how we may develop more effective treatments for neurological diseases.

Poster 14.14

Characterising the perivascular cells in Alzheimer's disease human tissue microarrays

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Alzheimer's disease (AD) is the most common neurodegenerative disorder. Increasing evidence implicates the involvement of non-neuronal cells in the pathogenesis of AD, with current studies focusing on the different components of the neurovascular unit. The aim of this project is to characterise neurovascular disruption in AD post-mortem human brain tissue by examining non-neuronal cells involved in the neurovascular unit of the middle temporal gyrus (MTG). Immunohistochemistry was carried out on human brain tissue microarrays (TMAs) from the MTG. Each TMA consisted of at least 21 control and 21 AD cases from the Human Brain Bank. Antibodies to alpha-smooth muscle actin (α-SMA) and platelet-derived growth factor receptor-beta (PDGFRβ) were used to investigate perivascular cells (smooth muscle cells and pericytes, respectively) of the neurovascular unit. The immunolabelled TMAs were imaged using the V-slide scanner automated imaging system. Densitometric analysis for staining intensity and load was carried out on the acquired images using Metamorph. Parametric methods were used to compare the mean intensity and load of each marker for the AD and control cohorts. Preliminary findings show a significant increase in α-SMA expression ($p<0.01$) in probable smooth muscle cells surrounding arterioles in AD, which is not attributable to a change in arteriole number. Furthermore, there is a significant reduction of PDGFRβ intensity ($p<0.001$) and load ($p<0.01$) in pericytes surrounding capillaries in AD. These findings suggest that separate populations of perivascular cells are differentially compromised in the temporal cortex in AD, as evidenced by differences in the expression patterns for pericytes lining capillaries, and smooth muscle cells lining arterioles.

Poster 14.15

Neurotransmitter changes in the auditory and non-auditory brain regions of rats following tinnitus-inducing acoustic trauma

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Tinnitus has been suggested to arise from neuronal hyperactivity in the auditory and non-auditory brain regions. Thus, an imbalance between excitatory and inhibitory neurotransmission in these regions may be the pathophysiological mechanism underlying tinnitus. However, the neurochemical basis of tinnitus remains elusive. This study investigated changes in amino acid levels in auditory and non-auditory brain regions of rats at one week following tinnitus-inducing acoustic trauma. Hearing thresholds were determined before and immediately after unilateral acoustic trauma (16 kHz pure tone, 115 dB for 1h, under anaesthesia) or sham exposure (n = 8 per group) using auditory brainstem-evoked responses (ABR). One week later, each hemisphere was dissected into 12 distinct anatomical regions. Neurochemical analyses were performed using high-performance liquid chromatography coupled with electrochemical detection. Data were analysed using a Linear Mixed Model. The ABR thresholds were significantly elevated in the exposed ear immediately after exposure ($p<0.05$). A significant exposure effect on glutamine levels was detected ($F_{1, 14.14} = 15.07$, $p<0.05$), which was due to a marked elevation of glutamine levels across all regions examined. The exposure × region × side interaction for glycine levels was significant ($F_{11, 57.58} = 2.03$, $p<0.05$), and this was attributed to a 25% increase in glycine levels in the cochlear nucleus contralateral to the noise-exposed ear of exposed animals. We found no statistically significant changes in glutamate, serine, threonine, taurine, alanine and GABA levels between the sham and exposed groups. The widespread increases in glutamine may contribute to neuronal hyperactivity related to tinnitus development. The increase in glycine levels could be a compensatory inhibitory response to counteract neuronal hyperactivity following acoustic trauma.

Poster 14.16

Expression and function of hyaluronan, hyaluronan synthases, and hyaluronidases in developing hippocampal neurons

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Hyaluronan is a glycosaminoglycan that forms an essential part of the brain's extracellular matrix. Hyaluronan metabolism is regulated by the family of hyaluronan synthases (HAS1-3) and hyaluronidases (Hyal1-4 and SPAM1). Although there is increasing evidence for a role of the extracellular matrix in the control of neuronal signalling, the function of hyaluronan and its specific production and degradation by neurons during early development, remains controversial. This study aimed to examine whether neurons express functional HAS and Hyal enzymes, and investigate the role of neuronally-produced hyaluronan in the development of neuronal morphology. Primary hippocampal neuronal cultures were established from embryonic day 18 rats. Neurons were collected at days *in vitro* 1 (DIV1), DIV3, DIV7, DIV14, and DIV21 to assess the time course of neuronal HAS1–3, Hyal1–4 and SPAM1 mRNA and protein (immunocytochemistry) expression. For functional studies, neuronal cultures were treated with either the broad HAS1–3 inhibitor, 4-methylumbelliferone (4-Mu; 300µM), or the hyaluronidase inhibitor L-ascorbic acid 6-hexadecanoate (VCPAL; 50µM), at DIV0, and cultures were imaged at DIV1, 2, and 3. DMSO treated cultures were used as controls. For morphological analyses, neurons were imaged using the Nanolive 3D cell explorer, a holographic tomographic microscope, and analysed with Neurolucida software. Neurons exhibited robust expression of HAS1–3, Hyal1–3 (but not Hyal4, 5, or SPAM1), and hyaluronan at all ages. Additionally, cultured neurons degraded a hyaluronan-based growth matrix, suggesting functional Hyal activity. Analysis of the morphological effects of HAS or Hyal inhibition are currently underway. These data show that neurons are capable of independent hyaluronan synthesis and degradation, which may be important in regulating neuronal development.

Poster 14.17

The effect of stimulus duration on the ERP components for face and non-face stimuli

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The present study runs two experiments to explore the role of stimulus duration in eliciting the ERP components for face and non-face stimuli. In Experiment 1, twenty participants (n = 20) were presented with face and house images for different duration (17ms, 50ms, 100ms, or 200ms) and were asked to judge whether the image was a face or house via a keypress. Experiment 2 (n = 20) controlled for lower-level confounds across stimulus types by matching luminance and introducing an additional factor: intact vs pixel-scrambled images. In both experiments, scalp EEG activity was recorded with a 128-channel EGI setup. Behaviorally, accuracy for differentiating intact faces from houses was above 90%, while discrimination of scrambled stimuli in Experiment 2 was at chance level (50%) across all stimulus durations. Repeated measures ANOVAs were separately conducted for the amplitudes and latencies of the P1 and N170 components. Significant main effects of stimulus duration were found for P1 and N170 amplitudes in both experiments, but no interactions between stimulus duration and stimulus type (faces vs. houses) were noted. No significant effects about stimulus duration on component latencies were found. This result suggests that the stimulus duration does influence the amplitude of ERP components, but this effect does not appear to be specific to faces.

Poster 14.18

Regulation of CRH neuronal network activity by noradrenergic stress signals

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The stress response is crucial for allowing adaptation to an ever-changing external environment. Stress responses are controlled by corticotropin-releasing hormone (CRH) neurons located within the paraventricular nucleus (PVN) of the hypothalamus. During stress, noradrenaline (NA) is released within the PVN to activate CRH neurons and drive stress hormone secretion. This study aimed to investigate the impact of NA on CRH neuronal network activity, using genetically encoded calcium indicators. *In vitro* calcium imaging was performed on brain slices containing the PVN from CRH-GCaMP6f mice. We found that NA (10 mM) induced a robust increase in CRH neuron excitability, with most CRH neurons switching into a bursting pattern of activity. NA induced excitation was blocked with the adrenergic α_1 receptor antagonist prazosin (10 mM). In control, NA activated, on average, 7.3 ± 1.0 CRH neurons per slice, however, in slices treated with prazosin, NA only activated 0.9 ± 0.3 CRH neurons per slice (NA, n = 8 slices; Prazosin, n = 14 slices; unpaired t-test, $p < 0.05$). The excitatory effects of NA on CRH neurons persisted if either ionotropic glutamate receptors were blocked with CNQX (10 mM) and AP5 (40 mM) (# neurons active per slice: 11.3 ± 1.0, n = 10 slices) or ionotropic GABA receptors were blocked with picrotoxin (50 mM) (# neurons active per slice: 10.3 ± 1.1, n = 7 slices). This data demonstrates that CRH neurons adopt a bursting pattern of activity when excited by NA, and that this is mediated through direct activation of the α_1 adrenergic receptors. These findings shed light on how stress relevant neural signals regulate CRH neuronal network activity.

Poster 14.19

Alpha-mangostin prevents scopolamine-induced lipid peroxidation in rat brains

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Increases of oxidatively damaged lipids or products thereof, 4-Hydroxynonenal (HNE) and malondialdehyde (MDA), play a role in the pathogenesis of neurodegenerative diseases. HNE and MDA served as markers for lipid peroxidation were markedly increased in hippocampus which is associated with cognitive deficits. The extract from the fruit rind of mangosteen (*Garcinia mangostana* L.) was recently reported to protect against oxidative stress *in vitro*. We therefore examined the ability of alpha-mangostin (α-MG), an aprenylated xanthone derivative from the extract, to attenuate scopolamine (SCOP)-induced lipid peroxidation in rat brains. Eight groups (n=8 each) of 8-weeks-old male Wistar rats were i.p. injected with donepezil (2 mg/ml/kg), α-MG (50 mg/ml/kg), α-MG (100 mg/ml/kg), or vehicle (1 ml/kg) followed by SCOP (2 mg/ml/kg, i.p.) or NSS (1 ml/kg, i.p.). Four hours later, the animals were sacrificed and three brain regions (basal forebrain, cerebral cortex, and hippocampus) were dissected and homogenized for biochemical analysis to investigate MDA levels. In all studied brain regions, no significant difference was found between groups in NSS treatment. SCOP significantly enhanced MDA levels in all brain regions, compared to their respective NSS groups ($P<0.05$). Pretreatment of donepezil and α-MG (50 mg/ml/kg), but not α-MG (100 mg/ml/kg), significantly attenuated the increase of MDA levels induced by SCOP in cerebral cortex and hippocampus ($P<0.05$). In basal forebrain, all pretreatments had no effect on the increase of MDA levels induced by SCOP. These findings suggest that α-MG has potential therapeutic value in preventing SCOP-induced lipid peroxidation in the brain which its mechanism might be related to oxidative stress hypothesis of neurodegenerative diseases. Supplementation of α-MG may be useful as a new pharmaceutical therapy for neurodegenerative diseases treatment.

Poster 14.20

Detection and monitoring of Parkinson's disease using a computer game

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Parkinson's Disease (PD) is a motor disorder characterized by rigidity, akinesia and tremor, caused by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). At present no diagnostic tools or biomarkers are available. Currently, the disease is diagnosed by clinical examination, based on the presence of motor signs which appear when 60-80% of SNc neurons have already died. The central region of the SNc controls voluntary goal-directed behaviours whereas the lateral part, which degenerates first in PD, deals with habits (automatic actions). We developed a computer game to aid the detection and monitoring of Parkinson's disease symptoms, based on the differential neurodegeneration of brain regions controlling automatic and goal directed motor actions. Our game is a computer version of a mirror-drawing task where a motor action has to be performed while only an inverted image is available. Seventy-two volunteers (35 with early PD) were recruited and performed the game on normal and inverted condition. As expected, in the normal condition the control group performed better, emitting less errors compared to the PD group. However, when the right-left reversal condition was applied, the control group showed an increase of 42% in the number of errors, whereas the patients with PD maintained their performance at pre-reversal levels. The results indicate that people with early loss of neurons from the habit controller (PD group) may be distinguished by their response to right-left reversal.

Poster 14.21

Age- and gender-specific expression changes of the GABAA receptor subunits in the human cortex

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Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the nervous system. GABA A receptors (GABAAR) are pentameric ionotropic channels. Subunit composition of the receptors is associated with the affinity of GABA binding and its downstream inhibitory actions. Fluctuations in subunit expression levels with increasing age has been demonstrated in animal and human studies. Also, a few studies found that hormonal changes have implications on the GABAAR expression suggesting gender-related changes in GABAAR subunit composition. However, our knowledge is highly based on animal models that produce inconsistent findings. This study is the first detailed analysis of the age- and gender-specific changes of the GABAAR subunit expression in the human superior- (STG), middle- (MTG), inferior temporal gyrus (ITG) and cerebellum (CER) using Western blotting and immunohistochemistry. We observed a significant gender-dependent difference in alpha1 subunit expression; males presenting significantly higher levels compared to women across all stages of life in STG. No significant age- or gender-related differences were found in alpha2, beta3 and gamma2 subunit expression in the STG. However, we found significantly lower $GABA_AR$ alpha3 subunit expression in the STG in young females compared to young males ($P<0.05$) and old males showed higher expression compared to young males ($P<0.001$). Older females showed significantly lower alpha5 subunit expression compared to old males ($P<0.05$) in the STG. Furthermore, GABAARs were well preserved during normal aging and between genders in the human MTG, ITG and CER. In summary, age- and gender-related GABAAR subunit composition changes might influence GABAAR function and affect GABAergic neurotransmission.

Poster 14.22

A role for secreted proteins in CLN6 BATTEN disease therapy

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Batten disease is a group of neurodegenerative lysosomal storage disorders characterised by cognitive impairment, motor deficits, blindness and premature death. Disease is caused by mutations in one of at least 13 different genes, including CLN5, a soluble lysosomal protein, and CLN6, an endoplasmic reticulum membrane protein. Gene therapy approaches have shown most success with secreted proteins, potentially due to 'cross-correction', a process by which soluble proteins can be secreted by transduced cells and taken up by neighbouring cells. Although CLN6 itself cannot undergo cross-correction, previous work has suggested that it may regulate the secretion of other proteins, including CLN5. The aim of this study was to investigate the therapeutic potential of secreted proteins, namely CLN5, in the $CLN6^{-/-}$ ovine culture model and the *Cln6*^{nclf} mouse model. We have previously identified autosomal-lysosomal pathway (ALP) biomarkers in ovine $CLN6^{-/-}$ cultures. Utilising these biomarkers we found that media from $CLN6^{+/-}$ (control) cells corrects lysosomal phenotype. To assess whether this effect could be due to CLN5 in the media, we overexpressed CLN5 in the ovine $CLN6^{-/-}$ cultures. LV.CLN5 in $CLN6^{-/-}$ cells restored ALP changes to control levels. In response to *in vitro* correction, we carried out an *in vivo* gene therapy trial, overexpressing CLN5 in the *Cln6*^{nclf} mouse. AAV9.CLN5 overexpression partially corrected motor function and altered ALP but did not correct other disease pathologies. This suggests that while CLN5 may possess some therapeutic benefit, there are likely other secreted factors which play a role in CLN6 disease. Identifying these factors is a focus of our current research.

Poster 14.23

Investigating the analgesic effects of novel Mu opioid receptor agonists

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Chronic pain (CP) is a global health problem that affects 1 in 5 New Zealand adults. The effectiveness of mu opioid receptor (MOPr) agonists such as Morphine, that are common in the treatment of CP, are limited by associated side effects. This study aimed to determine the ability of the novel MOPr agonist, New Kurkinorin, to induce analgesia *in vivo*. The hot water tail-flick assay (50 °C) was used to determine duration of action of a single intraperitoneal (ip) dose of New Kurkinorin (5 mg/kg) verses Morphine (10 mg/kg) in adult male C57 BL/6 mice (20-28g), with repeated measurements between 1 and 150 min. A cumulative dose-response tail-flick assay was then carried out on drug naive mice, and following daily subcutaneous (sc) administration of New Kurkinorin (5 mg/kg) or Morphine (10 mg/kg) for 9 days to evaluate the induction of chronic tolerance. Maximum possible effect (MPE) was calculated from the withdrawal latencies. New Kurkinorin was shown to produce significant antinociception, with an effect of both time ($F(9,27) = 47.51$, $p < 0.0001$) and drug ($F(2,6) = 218.1$, $p < 0.0001$). Significant differences were determined between the potency of New Kurkinorin (ED_{50} 2.095 mg/kg) and Morphine (7.84 mg/kg) on day 1. Following 9 days of sc administration both compounds showed tolerance, with New Kurkinorin showing significantly less tolerance (ED_{50} 2.94 mg/kg) compared to Morphine (ED_{50} 16.66 mg kg). The preliminary data indicates an induction of centrally mediated antinociception with significantly improved potency and tolerance compared to Morphine.

Poster 14.24

Secreted amyloid precursor protein alpha regulates AMPA receptor synthesis and trafficking

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Long-term potentiation (LTP) is reliant on trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid glutamate receptors (AMPARs) to the postsynaptic membrane, as well as rapid translation of extant mRNA and new gene expression. Interestingly, a secreted fragment of the amyloid precursor protein, sAPPα, has been shown to enhance synaptic protein synthesis, gene expression and LTP yet the underlying molecular mechanisms are not fully elucidated. We hypothesized that sAPPα may regulate LTP by enhancing the synthesis of AMPAR subunits GluA1 and GluA2. Using the FUNCAT-PLA technique to specifically label newly-synthesized proteins in primary hippocampal neurons, we confirmed that sAPPα (1 nM, 2 h) upregulated protein synthesis ($p < 0.0001$, one sample t-test), and discovered that GluA1 levels were increased three-fold ($p < 0.0001$), while GluA2 synthesis was unaffected. Curiously, although a significant increase in the surface expression of pre-existing GluA1-containing AMPARs was observed in response to sAPPα ($p = 0.0003$), no difference in the expression of *de novo* synthesized GluA1 was found. Together, these data suggest sAPPα results in enhanced synthesis of *de novo* receptors, as well as increasing the cell surface expression of existing GluA1-containing AMPARs in cultured hippocampal neurons, and suggests that this is a mechanism through which sAPPα enhances LTP.

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Poster 14.25

The potential mechanisms underlying delayed on-set of radiation necrosis: Time of biological events

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Cerebral radiation necrosis (RN) is a delayed complication of radiation therapy for brain tumours, leading to neurological anomalies and death. The RN pathophysiology has yet to be clarified. Similar to clinical RN, RN mice develops delayed necrosis 6 weeks after Gamma knife. Using the window of opportunity, this study aims to investigate the biological changes prior to necrotic brain damage. Mice brains were collected at 6, 24, 96hrs, 1, 2 and 3weeks after radiation. Immunohistochemistry (IHC) of GFAP for astrocytes, IB-4 for microglia, Connexin-43 for gap junction of capillaries, fibrinogen for BBB leakage, IL-1β and NLRP3 for inflammation were performed on coronal brain sections. Images were analysed using ImageJ. Data were analysed using Prisim. Compared to the control hemispheres the expression of Cx-43 ($p=0.0023$) and IL-1β ($p=0.0179$) were elevated in radiated hemispheres from 96h after radiation. Radiation associated increase of GFAP ($p=0.0004$) and fibrinogen ($p=0.0009$) were later from week1 followed by microglia ($p=0.0002$) from week2. Our result implies that activation of pro-inflammatory cytokines, for example IL-1β and damaged gap junctions of capillary are the earlier events that lead to activation of astrocytes and microglial cells several days later. Therefore, we can assume that changes of gap-junction may activate pro-inflammation cytokines, leading to glial cell associated inflammation in the brain regions. As the activated glial cells could be the contributor to BBB breakdown eventually causing necrosis.

Poster 14.26

High-fat diet induced obesity impairs neuroplasticity in rats

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Cognitive impairment is closely linked with obesity. Intake of a high-fat diet (HFD), characterized by high levels of saturated fats and simple carbohydrate is one of the main inducements of obesity. This study evaluated the spatial memory and neuroplasticity in rats with HFD induced obesity. Rats were fed with either commercial high-fat diet (D12451) or normal chow from day post natal week 3 to 15. Morris water maze test was conducted from week 12-15. Body composition was measured and brains were collected for neuroplasticity analysis thereafter. The immunohistochemistry of synaptophysin, glutamate receptor-1(GLUR-1), tyrosine-hydroxylase (TH) and GFAP were conducted in the hippocampus and striatum. The positive staining was evaluated using image J analysis. The data was analysis using Prism software. Rats fed with HFD for 12 weeks gained more weight and greater body fat when detected by dual X-ray absorptiometry (DXA), with comorbidities of glucose and lipid metabolic disorders. Compared to the control group, the HFD did not alter the performance of MWM. However, obese rats showed a reduced expression of synaptophysin, glutamate receptor 1, GFAP positive astrocyte in the hippocampus, but an increase expression of synaptophysin in hypothalamus. There was a trend towards reduction in TH expression in the striatum. HF diet induced obesity is associated with poor neuroplasticity in the hippocampus, particular the glutamate trafficking.

Poster 14.27

First fixation location moderates face holistic processing and recognition

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Identifying a face is one of the most common activities in daily life, most people can recognize a face quickly and accurately. Studies have found that one fixation, that is the first fixation, could have a strong influence on face recognition, and subsequent fixations have weak effects. Moreover, the first fixation is not only functional but systematic as well. The first fixation location differs in individuals, and people have a preferred fixation location, no matter when they saw an own- or other-race face, and no matter it happened in the lab or in real life. Less is known about why do preferred fixation location differ in individuals, and why could different initial fixation locations have different influences on face identification. Since holistic processing has been considered as having a crucial role in face perception, it is possibly related to holistic processing. To investigate this hypothesis, this study uses eye-tracker to manipulate and record participants' eye movements and uses the composite face task to measure holistic processing and the face identification task to measure face recognition ability. This study examines whether individuals have a preferred fixation location in when performing holistic processing of a face, and whether this location is the same as that observed for face identification first. And then, this study examines whether changing their preferred fixation location would impair holistic processing in the same way as occurs for face identification. We expect that each participant has the same preferred fixation location in both tasks, while the locations are different among participants. And changing their preferred fixation locations could impair their performance in both tasks.

Poster 14.28

Investigating dyslexia and dyscalculia comorbidity through diffusion tensor imaging

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Learning disabilities such as dyslexia, dyscalculia and their comorbid manifestation are prevalent, affecting as much as fifteen percent of the population. Structural neuroimaging studies have indicated that these disorders can be related to differences in white matter integrity, although findings remain disparate. In this study, we used a unique design composed of individuals with dyslexia, dyscalculia, both disorders and controls, to systematically explore differences in fractional anisotropy across groups using diffusion tensor imaging. Specifically, we focused on the corona radiate and the arcuate fasciculus, two tracts associated with reading and mathematics in a number of previous studies. Using Bayesian hypothesis testing, we show that the present data favor the null model of no differences between groups for these particular tracts—a finding that seems to go against the current view but might be representative of the disparities within this field of research. Together, these findings suggest that structural differences associated with dyslexia and dyscalculia might not be as reliable as previously thought, with potential ramifications in terms of remediation.

Poster 14.29

The hippocampal Insulin-like growth factor (IGF-1) level and synaptic density in Ames dwarf mouse

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Insulin-like growth factor-1 (IGF-1) is an important neurotrophic hormone. It plays a complex role in brain function including cognitive and synaptic functions. It has shown that the decline in cognitive function with age is associated with a decrease in the growth hormone (GH)/IGF-1 axis and an increase in oxidative stress. Ames dwarf mice are GH-deficient with decreased plasma IGF-1. However, the levels of plasma and brain IGF-1 in dwarf mice differ and the effect on brain function remains unclear. In this study, we examined the relationship between hippocampal IGF-1 level and synaptic density in Ames dwarf mice. We investigated the expression of synaptophysin and PSD95, proteins that indicate pre- and post-synaptic density respectively. The synaptophysin in 3- and 12-month-old dwarf mice was significantly higher than wild type mice at the same age. PSD95 was significantly greater in 12-month-old dwarf mice compared to wild type mice. However, there was no significant difference in behavioral performance as assessed by the number of alternations on the T-maze between wild type and dwarf mice at each age. These data suggest that synaptic density differ between Ames dwarf and wild type mice and that the expression of growth factors may be involved.

Poster 14.30

Theory of mind in Parkinson's disease: Improvement after physical and cognitive exercise

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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 impaired early in Parkinson's disease (PD), prior to the emergence of other cognitive deficits. Here, we report an interim analysis on performance on a ToM card-sorting task in PD patients who did not meet 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. At baseline, PD participants randomized to the intervention group (n=22) but not those within the PD active-control group (usual care plus frequent researcher contact; n=20) produced lower ToM scores (p=.02) compared with an age and sex-matched healthy control group (HC; n=28). A significant pre-post RCT interaction effect was also found (p=.01), due to the mean ToM score increasing in the PD intervention group to a similar mean score of both the HC and PD active-control groups. These preliminary findings suggest support for the efficacy of a combined physical and cognitive intervention to improve theory of mind performance in patients with PD, at least in those whose cognition is relatively intact.

Poster 14.31

Motor outcomes in Parkinson's disease patients: An RCT of physical exercise and cognitive enrichment

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An 8-month randomized controlled trial (RCT) allocated 43 patients with Parkinson's disease (PD) into either an "enrichment" arm (intervention group) or an "active control" arm (usual care plus frequent researcher contact). PD patients were volunteers recruited from a movement disorders clinic who showed relatively intact cognitive abilities at baseline (i.e. not meeting criteria for mild cognitive impairment). On a weekly basis, enrichment participants received both (1) exercise sessions supervised at a physiotherapy centre and (2) a variety of cognitive exercises that covered 5 cognitive domains associated with different large scale neural networks; both activities were tailored to the individual and progressively increased in difficulty according to the patient's abilities. Thus far, 35 of these patients have completed the RCT. Here, we provide an interim report on two movement outcome measures: a 6-minute walk test; and the Mini-BESTest. Preliminary analysis confirms equivalent performance on both outcome measures at baseline for the two groups, and no significant overall change over time or effect of enrichment interaction between pre and post testing. The general stability in performance over time suggests that a longer follow up is needed in mildly impaired PD patients and that additional physical and cognitive activities do not produce improved movement in a short-term design.

Poster 14.32

Maintaining Independence in Parkinson's disease: Cognitive effects of a combined cognitive and physical exercise intervention

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Non-motor symptoms, especially mild cognitive impairment (MCI) and dementia, are recognised as primary issues for most Parkinson's disease (PD) patients. PD Patients have increased risk of developing MCI with progression to dementia evident in 80-90% of patients. Here, we report an interim analysis of a randomized controlled trial examining the effects of a combined intervention of systematic physical exercises and cognitive activities on clinical and neuropsychological outcomes in cognitively intact PD patients. We used computer generated stratified randomisation based on age, PD duration, and MCI risk to allocate 42 people diagnosed with idiopathic PD into either an enrichment-intervention or active-control arm. Enrichment-intervention participants underwent an 8-month intervention of weekly physiotherapy sessions, and cognitive stimulation folders changed on a fortnightly basis. The active-controls received usual medical treatment with additional researcher contact. Cognitive performance on MoCA, SDMT, Stroop, and BVMT remained stable from pre- to post-testing for both groups (enrichment, n =16; control, n =19). Map Search showed a mild decline at post-test ($p<0.01$) in both groups with no effect of enrichment. The generally stable, intact performance in these patients suggests that a longer follow up may be required to fully evaluate the effects of non-pharmacological interventions.

Poster 14.33

Response-conflict and set-shifting signals in the ACC and VTA

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The ability to flexibly shift between different sets of decision strategies in different contexts is the core of executive function. The anterior cingulate cortex (ACC) is implicated in set-shifting. However, there are instances when ACC is unable to resolve which set ought to guide subsequent behaviour; these episodes are termed response conflict. Despite recent work indicating that set-shifts are behaviourally implemented by ACC modulation of the ventral tegmental area (VTA), a dopaminergic region implication in motivation, the relationship between the ACC and VTA during response conflict remains unknown. To assess the relationship between the ACC and VTA during response conflict, we simultaneously recorded local field potentials from the ACC and VTA of rats trained to perform a set-shifting task. In this task, rats had to determine whether to turn left or right in a maze such that only one choice in any block of trials yielded reinforcement. After approximately 10 trials, the rule-switched and the rats needed to shift and sustain responses to the alternative decision. We found that rats took longer to make choices on incorrect trials, suggesting that the rats experienced response conflict. During response conflict episodes, we found elevated ACC 4 Hz power and ACC-VTA 4 Hz coherence. A similar effect was detected on the trial immediately following an incorrect choice. When we modelled the magnitude and directionality of information transfer between the ACC and VTA, we found significant ACC→VTA signalling on the trial immediately after an incorrect choice but that VTAàACC signalling was significantly elevated during the response conflict episode. These results suggest that mesocortical signalling is a key component of response conflict and that subsequent adaption depends on ACC→VTA signalling.

Poster 14.34

Imaging and analysis of post-implantation cochlear fibrosis via micro-computed tomography

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Intracochlear fibrosis is a well-described sequela of cochlear implantation, and together with inflammation is thought to contribute to the loss of residual hearing frequently observed in cochlear implant (CI) recipients. Targeting the processes underlying fibrosis formation may be one method through which to improve preservation of residual hearing, and limit risk of ossification which can affect electrode performance. Conventional histological approaches are poorly suited to quantifying overall the extent and pattern of cochlear fibrosis, or measuring effectiveness of potential therapies. As such, we are investigating methods using microCT to visualise and quantify CI-induced fibrosis in a guinea-pig model of cochlear implantation. Through this approach we have observed fibrotic tissues *in situ* within the intact cochlea, and developed methods of analysing the extent and morphology of fibrosis. Guinea-pigs received non-metallic dummy CI electrodes via cochleostomy, and were euthanised at 6 days or 4 weeks post-implantation. Cochleae were stained using 2% osmium tetroxide to enhance contrast of intracochlear soft tissues in microCT projection images, and reconstructed to generate a three-dimensional model of the cochlea at 1µm resolution. A range of approaches for analysing fibrosis and implant positioning have been developed, including segmentation through 3D co-registration of scans acquired both before and after staining, and automated volumetric analysis of fibrosis structure and extent. These approaches have enabled characterisation of three distinct fibrosis morphologies (confirmed via histology), and begun to outline the dynamics of fibrosis formation following implantation. As such, microCT shows considerable potential for future use in analysing the effectiveness of anti-inflammatory compounds, and approaches directed at suppressing post-implantation fibrosis.

Poster 14.35

Aging, emotion recognition, and neuropsychological benefits of music training

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Age-related declines in facial emotion recognition have been extensively studied, although less is known about auditory emotion recognition. This study investigated age differences in facial and musical emotion recognition and explanatory hypotheses regarding older adults' typically worse emotion recognition. Healthy older adults (M_{age} = 73.86, N = 50) and young adults (M_{age} = 19.37, N = 52) labelled emotions using a standard set of facial stimuli and a novel set of music clips. Participants also made age estimations in another set of faces to examine whether potential relations between the face and music emotion tasks would be shared with the age estimation task. Older adults performed worse in each the tasks, and had specific difficulty with sad, angry, and fearful faces, as well as happy, sad, peaceful, angry, and fearful music clips. Older adults' difficulties in each of the three tasks – music emotion, face emotion, face age – were not correlated with each other. General cognitive decline did not appear to explain the results as increasing age predicted emotion performance even after fluid IQ was controlled for within the older adult group. Interestingly, music training was associated with better facial emotion recognition in the older group. The results motivated a review of research investigating a neurodegeneration explanation for emotion recognition declines. While a neuropsychological account is plausible, direct investigation is lacking. Furthermore, growing evidence indicates that music training might promote emotion recognition and general cognition via engagement of associated brain networks. Music training might therefore be instrumental in combating age-related neurocognitive decline. Lastly, I outline forthcoming research that will investigate music learning as a tool to promote healthy cognitive and emotional aging.

Poster 14.36

Binding of episodic details into future simulations

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It has been proposed that the increased neural activity associated with imagining the future relative to remembering the past reflects more intensive cognitive demands when constructing *novel* events (Schacter et al., 2012). In a previous study (van Mulukom, 2013), we had participants repeatedly imagine past and future events, and measured the decrease in construction times across repetitions (RT benefit) as an index of initial construction demand. We reported larger RT benefits for future than past events, confirming that future events are associated with more intensive constructive demands. However, the nature of this additional processing still remains unclear. Here, we investigated whether it reflects the binding of content details (e.g., people) into novel scenarios during imagination, and/or the construction of a novel spatial context. Using the logic from van Mulukom's (2013) study, we tested whether changing a person or the location of the imagined event reduced RT benefits upon repetition. Participants repeatedly imagined future events either with the same details (*No change*), with a different person (*Person change*), or a different location (*Location change*), and construction times were collected. A Bayesian repeated-measures ANOVA showed overwhelming evidence for the main effect of condition ($BF_{10} > 10^3$). Bayesian pairwise comparisons with default priors indicated that a change in either person or location reduced the RT benefit of repetition relative to the *No change* condition (both $BF_{10} > 10^3$); there was no difference between the *Person change* and *Location change* conditions ($BF_{10} = 0.58$). Together, these results suggest that increased demands associated with future imagination reflect binding details related to both content and spatial context into a coherent episode, with the type of detail not affecting construction demands.

Poster 14.37

Neurovascular coupling and the BOLD response: Multi-scale tissue slice simulations

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The cerebral vasculature is able to regulate perfusion in response to local changes via the process of neurovascular coupling (NVC), an intercellular communication system between neurons, astrocytes, smooth muscle cells, endothelial cells and the extracellular space. Together these components comprise a neurovascular unit (NVU). NVC is characterised by an increase in neuronal activity followed by a rapid dilation of blood vessels and increased localised blood supply. Our research group has developed a large scale numerical model able to simulate NVC. The model consists of a number of NVUs embedded in a "tissue like" structure coupled to a single vascular tree. The leaves of the tree correspond to penetrating arterioles, where each arteriole is coupled to a single NVU. Numerical procedures are implemented in parallel making it possible to simulate thousands of NVUs corresponding to a tissue slice of 8mm x 8mm or larger. We show that the model is able to simulate arteriolar dilation in the vascular tree in response to a variety of current inputs into a localised selection of neurons within the tissue slice. The model is also able to describe hemoglobin dynamics and the fMRI blood-oxygen-level-dependent (BOLD) response over a section of tissue, driven by localised changes in blood flow and blood oxygenation. These results can be directly compared with experimental BOLD signals, showing excellent agreement within the variations in BOLD response such as the initial negative dip followed by a positive signal. In addition, oxygenation levels over the tissue slice in our model show similar spatial variation to experimental imaging data (Bouchard et al., 2009; Hillman, 2014).

Poster 14.38

Anti-inflammatory characteristics exhibited by heterocyclic cyclohexanone curcumin derivatives against LPS-induced inflammation

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Curcumin, a natural polyphenol, has been studied thoroughly for its various medicinal properties. The instability and fast metabolism of curcumin has necessitated the development of curcumin derivatives. A series of heterocyclic cyclohexanone curcumin derivatives (RL compounds) have been created to improve the solubility and pharmacokinetic limitations of curcumin. This study aimed to evaluate toxicity and anti-inflammatory effects of 5 RL compounds (RL66, RL71, RL91, RL118, and RL121) against LPS-induced inflammation by measuring extracellular field potentials in hippocampal slices. Hippocampal slices were randomly allocated into 3 experimental groups: LPS, LPS with RL, and untreated controls. Hippocampal slices were incubated in LPS for a minimum of 3 hours before undertaking electrophysiology assessment. Input/output and paired pulse paradigms were used to assess neuronal excitability, response threshold, maximal neuronal response, and local circuit inhibition in CA1 region. Slices that were co-incubated with RL66 and RL121 showed significantly reduced LPS-induced damage ($p<0.05$). RL121 showed significant improvement of slice health greater than control slices at both 5uM and 20uM doses, indicating possible neuroprotective potential. The results of this study show that RL66 and RL121 have promising anti-inflammatory characteristics that could be beneficial against brain inflammation.

Poster 14.39

Measuring the effects of intermittent theta-burst stimulation on interhemispheric inhibition after stroke

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After stroke, increased interhemispheric inhibition (IHI) originating from the un-lesioned motor cortex (M1) has been associated with impaired recovery, however its characterisation using non-invasive stimulation techniques is problematic. We showed previously using neural recordings that low-intensity intermittent theta-burst stimulation (iTBS; bursts of 3 pulses at 50Hz delivered at 5Hz) applied to contralateral M1 using implanted electrodes can acutely reduce IHI in normal rats and can improve motor recovery subacutely following stroke. The present study aimed to determine if stroke and iTBS modify IHI subacutely in the rat. We used extra-dural field recordings to measure IHI in urethane-anaesthetised Wistar rats. The effect of IHI on an ipsilaterally-elicited M1 response was determined using low-intensity conditioning stimulation applied to a contralaterally-implanted M1 electrode, at interstimulus intervals similar to our previous intracellular recording experiments. Under such conditions, IHI was -7.8% (92.2 ± 2.8% [mean ± SEM] peak response compared to non-conditioned response; n=15). The acute effects of iTBS and continuous theta-burst stimulation (cTBS) on IHI was also measured, with cTBS increasing IHI, (by -5.2 ± 2.7%; n=3), but preliminary results trending towards only a small decrease following iTBS (+1 ± 3.0%, n=4). To study effects of stroke and iTBS, lesions were induced in M1 and sub-cortex by injecting Endothelin-1 and electrodes implanted to measure IHI in freely-moving animals. Sham stimulation or iTBS was delivered for 15 days. Preliminary results suggest baseline IHI was -26.3 ± 5.0% (n=4) and was reduced by approx. +10.8% ± 7.6% during delivery of iTBS. Thus, our results show that IHI can be determined using minimally-invasive recordings and compared before and after stroke induction.

Poster 14.40

Altered neurovascular coupling and glutamine metabolism in endothelial nitric oxide synthase deficient mice

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Nitric oxide (NO) produced from L-arginine by endothelial NO synthase (eNOS) is a key regulator of cerebral blood flow dynamics. Recent research has demonstrated that eNOS deficient ($eNOS^{-/-}$) mice display age-related increases in amyloid beta in the brain and memory deficits, suggesting a role of eNOS dysfunction (hence cerebrovascular dysfunction) in the development of Alzheimer's disease. The present study, for the first time, systematically investigated how cerebral blood perfusion, neurovascular coupling and the metabolic profile of L-arginine changed in $eNOS^{-/-}$ mice at 4 and 14 months of age using a real-time microcirculation imager and high performance liquid chromatography and liquid chromatography/mass spectrometric assays. While there was no significant genotype difference in the basal cerebral blood perfusion, surprisingly male and female $eNOS^{-/-}$ mice at both ages displayed marked increases in blood perfusion response to whisker stimulation in the barrel cortex, relative to their age- and sex-matched wild-type controls. When the tissue concentrations of L-arginine and its nine downstream metabolites in the fontal cortex, hippocampus and parahippocampal region were quantified, the only significant genotype effect observed was reduced glutamine levels in $eNOS^{-/-}$ mice at both sexes and ages. These findings demonstrate early and long-lasting alterations in neurovascular coupling and glutamine metabolism in both male and female mice with eNOS deficiency. The underlying mechanisms and functional significance of these changes remain to be investigated.

Poster 14.41

P-glycoprotein up-regulation in rifampin primed lamotrigine-resistant pentylenetetrazole kindled mice: A new experimental murine model of drug-resistant epilepsy

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P-glycoprotein (P-gp) is a multidrug efflux transmitter that has been shown to be up-regulated in experimental models besides clinically for drug-resistant epilepsy. This study investigates the role of P-gp inducer in drug resistance epilepsy with a new murine model. The rifampin (RIF) primed lamotrigine (LTG)-resistant pentylenetetrazole (PTZ) kindled model was developed in Swiss albino mice by administering RIF (200 mg/kg, i.p., once for four days) in PTZ kindled animals. The reference model (LTG-resistant PTZ kindled model) was validated previously by pretreating animals with LTG (5 mg/kg, i.p.) followed by PTZ (30 mg/kg, i.p., every other day) for six weeks to induce kindling. The test model was validated for the effectiveness of antiepileptic drugs (carbamazepine (CBZ), phenytoin (PHT), valproic acid (VPA), and levetiracetam (LEV)). On administering the PTZ challenge dose, pre-treatment with LTG (15 mg/kg, i.p.) showed resistance to antiepileptic activity in the test model which was extended to CBZ and PHT but not for VPA. The combination of LEV and VPA significantly enhanced the effect of VPA ($p<0.001$). Increased P-gp concentration estimated by ELISA and immunogold labelling with transmission electron microscopy supports the findings. The test model showed a significant overexpression of P-gp compared with the reference model ($p<0.05$), PTZ kindled ($p<0.001$) and vehicle treated ($p<0.001$) group. Conclusively, the results supported the hypothesis of P-gp flippase theory with this new model of drug-resistant epilepsy. The resistance to counteract seizures by selective antiepileptic drugs hints the unavailability of drugs to reach the brain and is probably linked to P-gp overexpression. This model could potentially be used for bio-evaluation of drugs for pharmacoresistant epilepsy targeting P-gp expression.

Poster 14.42

Distinct motor cortical inhibitory processes are engaged during reactive and proactive response inhibition

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A central component of effective motor control is the ability to cancel a pre-planned movement, termed response inhibition. When stopping is unexpected, response inhibition is reactive and associated with a non-selective reduction in motor cortical excitability. If stopping is forewarned, response inhibition can be proactive and excitability may be selectively decreased. Here we examine modulation of primary motor cortex inhibitory networks in proactive and reactive response inhibition using paired-pulse transcranial magnetic stimulation. Long- and short-interval intracortical inhibition (LICI and SICI), indicative of $GABA_B$- and $GABA_A$-receptor mediated inhibition respectively, were examined from motor evoked potentials obtained in task-relevant and task-irrelevant hand muscles while participants performed reactive and proactive response inhibition. When the participant was cued to stop only a subcomponent of the bimanual response, the remaining response was delayed, and the extent of delay was greater in reactive than proactively cued trials. For LICI, inhibition was reduced in both muscles during all types of response inhibition trials compared with the pre-task resting baseline. In reactive trials where left hand responses were suddenly cancelled, task-relevant LICI positively correlated with response times of the responding right hand. In proactive trials where left hand responses were executed, task-relevant SICI was reduced, revealing a motor set indicative of responding. Conversely, task-relevant SICI was not modulated in reactive trials, when response conditions remained uncertain. These novel findings indicate that the $GABA_B$ receptor mediated pathway may set a default inhibitory tone according to task context, whereas the $GABA_A$ receptor mediated pathways are recruited proactively with response certainty.

Poster 14.43

Maternal immune activation in rats produces a subjective internal state that is similar to human psychosis

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A key problem with animal models of psychosis lies with the animal's inability to self-report its own internal state. In the present study, we used the drug discrimination paradigm, an assay that can provide an objective measure of an animal's subjective internal state, to assess whether the subjective internal state experienced by rats that model a specific etiological schizophrenia risk factor (maternal immune activation; MIA) is similar to that experienced in human psychosis. MIA (rats born from dams exposed to Poly:IC, a viral mimetic that produces activation of the immune system) and control rats were trained to discriminate 7.5 mg/kg ketamine from saline in a two-lever operant chamber. After discriminative control was established, dose-effect determinations were made, and finally a pre-feeding challenge evaluating satiety as a non-drug internal cue. The results showed MIA rats were impaired in drug discrimination, with the difference in discrimination between MIA and control rats particularly apparent in the psychotomimetic dose range for ketamine (3-10 mg/kg). These results were not due to a general decrease in sensitivity to internal states in MIA rats, as these animals were more sensitive to the satiety cue. Overall these data provide support for the assertion that the subjective state of MIA rats is similar to that experienced in human psychosis and indicate that the drug-discrimination paradigm may be a useful tool for understanding the neurophysiological underpinnings of human psychosis in animal models.

Poster 14.44

Lithium promotes stereotyped responses to synaptic input – an in vitro olfactory bulb study

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Li+, the first line treatment for Bipolar Disorder (BD) is toxic in large doses and/or over long time scales. While a number of mechanisms have been proposed (largely involving intracellular 2nd messengers), no therapeutic mechanism has been established. BD involves the periodic cycling of mood (mania/depression) correlated with aberrant patterns of connectivity and rhythmicity in brain networks. Reflecting the electrophysiological properties of neurons, brain network function is dependent upon membrane ion channel function. BD is strongly associated with disturbances in genes responsible for ion channel expression, localisation and structure and can be treated with some antiepileptic drugs, acting directly on ion channels. Thus, ion channel dysfunction is strongly implicated in BD. Using electrophysiological techniques on a conserved microcircuit (olfactory bulb glomeruli / mitral cell) in rodent brain slices, we have found effects of Li+ at multiple timescales and differences in response to Li+ in spontaneous versus evoked spike trains. Following afferent synaptic depolarisation, in the presence of Li+, mitral cells show a decrease in interspike interval (ISI), variation of ISI, latency to first spike and variation of latency to first spike. However, in spontaneously bursting cells, Li+ increases burst duration, variance of burst duration and the number of spikes per burst. Intriguingly, the presence of Li+ in spontaneously bursting cells reveals a periodic cycling of burst duration / spikes per burst and of burst frequency. The source of mitral cell excitation in the case of evoked responses, is glutamate from olfactory nerve terminals. However, the source of spontaneous bursting is currently unknown. Further experimental work at the level of the glomerulus may reveal the source of excitation and thus, the mechanism behind the different responses to Li+.