Saturday 29 August

12.00-5.30 pm		BRNZ Core Session
3.00-5.15 pm		Registration, Copthorne Resort 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	1.1	**PLENARY LECTURE:** **George Koob, *National Institute Alcohol Abuse and Alcoholism, United States of America*** Neurobiology of addiction: Cerberus revisited

1. Neural Excitability, Synapses, and Glia

Chair: Karl Iremonger

8.00 pm	1.2	**John Reynolds, *University of Otago, New Zealand*** Dissociation between changes in cellular excitability and synaptic plasticity measured in single cells in the motor cortex following transcranial magnetic stimulation
8.15 pm	1.3	**Owen Jones, *University of Otago, New Zealand*** Astrocytes mediate heterodendritic metaplasticity in hippocampus
8.30 pm	1.4	**Antonio Berretta, *University of Otago, New Zealand*** Astrocytes selectively regulate the expression of neuronal GABA-A receptor subunits
8.45 pm	1.5	**Xinhuai Liu, *University of Otago, New Zealand*** Optogenetic activation of rat GnRH neurons
9.00 pm	1.6	**Megan Elder, *University of Otago, New Zealand*** Secreted amyloid precursor protein alpha regulates protein synthesis in primary hippocampal neuronal cultures
9.15 pm	1.7	**Erin Cawston, *University of Auckland, New Zealand*** Distinct temporal fingerprint for cAMP signalling of indole-2-carboxamides as allosteric modulators of the cannabinoid 1 receptor

Sunday 30 August
Morning Session

6.00-8.00 am — Light Breakfast Available

8.00 am 2.1 **PLENARY LECTURE:**
Michael Bruchas, *Washington University, United States of America*
Modern approaches for dissecting neuromodulation and signaling in affective behavior

2. Basal Ganglia Health and Disease (I)

Chair: Richard Faull

8.45 am 2.2 **Sonja Seeger-Armbruster, *University of Otago, New Zealand***
Optogenetic stimulation of motor thalamic terminals modulates motor cortex activity in freely moving Parkinsonian rats

9.00 am 2.3 **Rachel Sizemore, *University of Otago, New Zealand***
Complex GABAergic innervation onto ventral tegmental dopamine neurons

9.15 am 2.4 **Dorothy Oorschot, *University of Otago, New Zealand***
Delayed post-treatment with bone marrow-derived mesenchymal stem cells is neurorestorative of striatal medium-spiny projection neurons and improves motor function after neonatal rat hypoxia-ischemia

9.30 am 2.5 **Simon Fisher, *University of Otago, New Zealand***
Reinforcement signals critically modulate spike timing-dependent plasticity in the striatum

9.45 am Tea/Coffee break

Sunday 30 August
Morning Session

3. Basal Ganglia Health and Disease (II)

Chair: Dorothy Oorschot

10.00 am	3.1	**Mark Burrell, *University of Auckland, New Zealand*** A novel electrochemical approach for interrogating tonic and phasic dopamine signals in the nigrostriatal pathway
10.15 am	3.2	**Peter Freestone, *University of Auckland, New Zealand*** An optogenetic study of endocannabinoid mediated modulation of dopamine neuron activity
10.30 am	3.3	**Samantha Murray, *University of Auckland, New Zealand*** Neurochemical changes in the striatum in a transgenic ovine model of Huntington's disease
10.45 am	3.4	**Malvindar Singh-Bains, *University of Auckland, New Zealand*** Globus pallidus neurodegeneration links to symptom heterogeneity in Huntington's disease

Sunday 30 August
Afternoon Session

3.30 pm — Afternoon Tea Available

4.00 pm — 4.1 — **PLENARY LECTURE:**
David Glanzman, *University of California, Los Angeles, United States of America*

Reinstatement of long-term memory in Aplysia following reconsolidation blockade

4. Cognition and Behaviour (I)

Chair: Maurice Curtis

4.45 pm — 4.2 — **David Young, *Victoria University of Wellington, New Zealand***

Preclinical anti-addiction and side effect profile of the novel kappa-opioid receptor agonist 16-ethynyl Salvinorin A

5.00 pm — 4.3 — **Dane Aronsen, *Victoria University of Wellington, New Zealand***

The role of 5-HT1A and 5-HT1B receptors in MDMA self-administration

5.15 pm — 4.4 — **Vaidenska Juozaityte, *Monash University, Australia***

Novel role of the ETS-5 transcription factor in exploratory behaviour

5.30 pm — 4.5 — **Stuart McGill, *University of Auckland, New Zealand***

Investigating the effect of conditional probability on reinforcement evoked potentials

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 31 August
Morning Session

6.00-8.00 am — Light Breakfast Available

8.00 am — 5.1 — **PLENARY LECTURE:**

Peter Mombaerts, ***Max Planck Research Unit for Neurogenetics, Germany***

An inconvenient truth: Trpc2-expressing sensory neurons in the mouse main olfactory epithelium

5. Cognition and Behaviour (II)

Chair: Bronwyn Kivell

8.45 am — 5.2 — **Robert Munn,** ***Stanford University, United States of America***

Mechanisms of function and control of the grid cell/head direction cell spatial navigation system in entorhinal cortex

9.00 am — 5.3 — **Kyla-Louise Wood,** ***University of Canterbury, New Zealand***

Neuropsychiatric status and different MCI criteria in Parkinson's disease

9.15 am — 5.4 — **Joan Leung,** ***University of Auckland, New Zealand***

Using Mismatch Negativity (MMN) to investigate perception of changes in affective prosody in Autism Spectrum Disorder (ASD)

9.30 am — 5.5 — **Ryan Ward,** ***University of Otago, New Zealand***

Enhanced motivation in an animal model of maternal immune activation in schizophrenia

9.45 am — Tea/Coffee break

Monday 31 August
Morning Session

6. Development and Novel Methods

Chair: John Dalrymple-Alford

10.00 am	6.1	**Sharon Olsen, *AUT University, New Zealand*** The Aalborg PAS-based brain computer interface: An investigation of the duration of cortical excitability in healthy adults
10.15 am	6.2	**Elshin Joel, *University of Canterbury, New Zealand*** Physiological models of neurovascular coupling and the relationship to BOLD signals in the ageing brain
10.30 am	6.3	**Katharina Dormanns, *University of Canterbury, New Zealand*** Multi-scale modelling of neurovascular coupling in “tissue-like” structures
10.45 am	6.4	**Christine de Lancea, *University of Canterbury, New Zealand*** Cerebral arterial circle with autoregulatory resistance
11.00 am	6.5	**Imran Niazi, *New Zealand College of Chiropractic, New Zealand*** Investigating the effects of electrical stimulation modalities paired with cortical potentials generated by motor imagination
11.30 am		Student Travel Grants Distributed

7. POSTER SESSION

- COMBINED WITH MEDSCI

NB: BEN LOMOND ROOM, RYDGES HOTEL

1.30 - 4.00 pm	Presenters will be in attendance during this time Presenters for Posters A will be in attendance from 1.30 to 2.45 pm Presenters for Posters B will be in attendance from 2.45 to 4.00 pm The poster session will be followed by a postgraduate dinner to the held at Winnies at 8.00 pm
7.1 - A	**Keat Foo, *International Medical University, Malaysia*** Neuroprotective role of Centella asiatica extract on hydrogen peroxide-induced SH-SY5Y cells
7.2 - B	**Sophie Barnett, *University of Canterbury, New Zealand*** Anterior thalamic nuclei lesions, environmental enrichment and histone H3 acetylation in the extended hippocampal system
7.3 - A	**Ross van de Wetering, *Victoria University of Wellington, New Zealand*** The selective D2 dopamine receptor antagonist eticlopride prevents the development of MDMA-induced behavioural sensitisation in rats
7.4 - B	**Brook Perry, *University of Canterbury, New Zealand*** Unequal effects of anterior thalamic nuclei and mammillothalamic tract lesions
7.5 - A	**Yukti Vyas, *University of Auckland, New Zealand*** The effects of Autism Spectrum Disorder associated Shank2 mutations on excitatory glutamatergic synapses
7.6 - B	**Jennifer Hamilton, *University of Canterbury, New Zealand*** Thalamic brain lesions, theta and memory
7.7 - A	**Christine Arasaratnam, *University of Auckland, New Zealand*** The distribution of DARPP-32 neurons in the normal and Huntington's disease human striatum

Poster Session

7.8 -B	**Helen Murray, *University of Auckland, New Zealand***
	Distribution of PSA-NCAM in the brain in neurodegenerative disease
7.9 - A	**Roseanna Smither, *University of Otago, New Zealand***
	Characterising ventroanterior motor thalamus inputs to motor cortex
7.10 - B	**Hanisah Azhari, *University of Otago, New Zealand***
	Enhanced uptake of drug into the brain when delivered in BBB-targeted cubosomes
7.11 - A	**David Moreau, *University of Auckland, New Zealand***
	Cognitive remediation interventions in learning disorders: Assessing the evidence with multiple Monte Carlo experiments
7.12 - B	**Hannah Best, *University of Otago, New Zealand***
	Correction of pathology in ovine cln5 Batten disease neural cultures
7.13 - A	**Meg Spriggs, *University of Auckland, New Zealand***
	Facial recognition memory and the BDNF Val66Met polymorphism: Disentangling the neural bases of recollection and familiarity
7.14 - B	**Robert Chow, *University of Southern California, United States of America***
	Use of single-cell RNA-Seq to molecularly define human Cajal-Retzius neurons
7.15 - A	**Stephanie D'Souza, *University of Auckland, New Zealand***
	Interactive effects of DAT1 genetic variants and the antenatal environment on childhood depressive symptoms
7.16 - B	**Nicole Taylor, *University of Auckland, New Zealand***
	Immersive exer-gaming and cognitive function in sedentary young adults
7.17 - A	**Wojciech Ambroziak, *University of Auckland, New Zealand***
	Mutant huntingtin alters NMDA receptor distribution by changing the balance between SAP97 isoforms
7.18 - B	**Brigid Ryan, *University of Otago, New Zealand***
	Regulation of MicroRNAs at dentate gyrus synapses after long-term potentiation induction in vivo
7.19 - A	**Amy Ewald, *Victoria University of Wellington, New Zealand***
	16-Bromosalvinorin a modulates dopamine transporter function in a kappa opioid receptor and erk1/2-dependent manner
7.20 - B	**Bronwen Gardner, *University of Auckland, New Zealand***
	Copper, zinc, iron, and manganese in the healthy and Parkinson's disease human brain

Poster Session

7.21 - A **Leon Smyth, *University of Auckland, New Zealand***

Characterisation of human brain pericytes in situ and in vitro

7.22 - B **Jerome Plumat, *University of Auckland, New Zealand***

Measuring the inner ear permeability using DCE-MRI

7.23 - A **Richard Prentice, *University of Otago, New Zealand***

Oleoylethanolamide incorporation into lipid nanoparticles for brain delivery: Physical characterisation and in vitro cytotoxicity

7.24 - B **Jaya Prasad, *University of Auckland, New Zealand***

Targeting insulin-like Growth Factor-1 signalling for treatment of preterm brain injury

7.25 - A **Katherine Gunn, *University of Auckland, New Zealand***

White matter and cortical brain injury in the very immature rat following lipopolysaccharide-induced mild systemic inflammation

7.26 - B **Blake Porter, *University of Otago, New Zealand***

The neural mechanisms of encoding effortful space

7.27 - A **Nasim Mehrabi, *University of Auckland, New Zealand***

Interneuron loss in the cerebral cortex correlates with symptom heterogeneity in Huntington's disease

7.28 - B **Deanne Barwick, *University of Otago, New Zealand***

Prefrontal cortex stroke disrupts cholinergic pathways and impairs learning

7.29 - A **Panzao Yang, *University of Auckland, New Zealand***

Vascular degeneration in Parkinson disease

7.30 - B **James Miller, *University of Otago, New Zealand***

Characterising the target innervations of glutamatergic neurons in the reticular thalamic nucleus

7.31 - A **Anurag Singh, *University of Otago, New Zealand***

TNFα mediated heterodendritic metaplasticity in the rat hippocampus

7.32 - B **Lisa Zhou, *University of Otago, New Zealand***

Prefrontal cortex stroke induces delayed impairment in spatial memory

7.33 - A **Shadah Shadli, *University of Otago, New Zealand***

Anxiolytic [WITHDRAWN] stop signal task: α-asymmetry is not like goal conf[illegible] rhythmicity

Poster Session

7.34 - B **Azam Shirrafiardekani, *University of Otago, New Zealand***

Interplay of spontaneous activity and metaplasticity in the computational model of the dentate granule cell

7.35 - A **Anna Forsyth, *University of Auckland, New Zealand***

Investigating the neural mechanisms of analgesic properties of anaesthetic drugs with MEG

7.36 - B **Dion Henare, *University of Auckland, New Zealand***

Electrophysiological components of attentional control predict individual performance on a concurrent working memory task

7.37 - A **Gagandeep Mallah, *University of Auckland, New Zealand***

Maternal cyclic-glycine-proline treatment during lactation enhances the growth and cognition of offspring in rats

7.38 - B **Mohammed Dinnunhan, *University of Otago, New Zealand***

Reawakening adult-generated hippocampal granule cells: The effects of enriched environment on an established trend

7.39 - A **Patrick Freymuth, *Massey University, New Zealand***

The actin-binding protein moesin and memory formation in Drosophila

7.40 - B **Nicole Mckay, *University of Auckland, New Zealand***

Brain derived neurotrophic factor genotype modulates recognition memory related event related potentials

7.41 - A **Alison Clare, *University of Otago, New Zealand***

Optimisation of fluorescent activated cell sorting and RNA extraction from dissociated mature mouse cortex tissue for transcriptome profiling

7.42 - B **Madeleine Kyrke-Smith, *University of Otago, New Zealand***

Regulation of HDAC1 and HDAC2 following long-term potentiation

7.43 - A **Eric Rosentreter, *University of Auckland, New Zealand***

In search of behavioural effects correlates of visual long-term potentiation

7.44 - B **Meagan Barclay, *University of Auckland, New Zealand***

Establishing the 3D distribution of synaptic proteins around sensory receptors in the mammalian cochlea during early postnatal development

7.45 - A **Matt Oxner, *University of Auckland, New Zealand***

Steady-state evoked potentials of visual illusory flicker are modulated by concurrent auditory flutter frequency

Poster Session

7.46 - B	**Jody Cicolini, *University of Otago, New Zealand***
	The urea cycle is induced in Alzheimer's brains
7.47 - A	**Masatoshi Yamashita, *Tezukayama University, Japan***
	Role of glial-neuron interactions in central fatigue induced by alteration of tryptophan sensitivity
7.48 - B	**Nirajmohan Shivaperumal, *Victoria University of Wellington, New Zealand***
	Investigating the analgesic properties of a novel mu-opioid receptor analogue of Salvinorin A
7.49 - A	**Jodi Morrissey, *University of Otago, New Zealand***
	Fragments of amyloid precursor protein enhance rat hippocampal LTP
7.50 - B	**Natasha Bukholt, Victoria University of Wellington, New Zealand**
	Self-administration of MDMA produces a sensitised response to the locomotor activating effect of MDMA
4.00 pm	Posters to be removed at this time
8.00 pm	AWCBR Student Dinner Venue: Winnies Gourmet Pizza and Bar, 7-9 The Mall, Queenstown

Monday 31 August
Evening Session

Opening of Queenstown Research Week

Venue: Rydges Hotel, Ben Lomond

6.00 pm	Opening Remarks **Peter Shephard**
6.30 pm	Opening Lecture **Larry Young** ***Emory University, United States of America*** The neural mechanisms of social bonding: Implications for novel therapies for autism Sponsored by the University of Otago
8.00 pm	MedSci and AWCBR Social Mixer Venue: Rydges Hotel
9.00 pm	Queenstown Research Week Chico's Party Venue: Chico's The Mall - Don't forget QRW name badge for entry

Tuesday 1 September
Morning Session

6.00-8.45 am Light Breakfast Available

8. Sensory and Motor Systems (I)

Chair: Tim David

8.45 am	8.1	**Peter Thorne, *University of Auckland, New Zealand*** Measuring inner ear permeability using DCE-MRI in patients with Meniere's disease
9.00 am	8.2	**Simon Schultz, *Imperial College London, United Kingdom*** Encoding of virtual reality locomotion kinematics in the spinocerebellar vermis and lateral cerebellum
9.15 am	8.3	**Marie-Claire Smith, *University of Auckland, New Zealand*** Effects of TMS coil orientation, posture and limb dominance on lower limb motor cortex excitability
9.30 am		Tea/Coffee break

Tuesday 1 September
Morning Session

9. Sensory and Motor Systems (II)

Chair: Ping Liu

9.45 am	9.1	**Susan Tyree,** ***German Institute of Human Nutrition, Germany*** Arc expression in the mouse parabrachial nucleus following taste stimulation
10.00 am	9.2	**Phillip Aitken,** ***University of Otago, New Zealand*** Bilateral vestibular lesions increase sensitivity to non-vestibular induced theta rhythm in rats
10.15 am	9.3	**Rebekah Blakemore,** ***University of Otago, New Zealand*** Emotion-modulated force control: A multidisciplinary approach to investigate freezing reactions in humans
10.30 am	9.4	**Nathan Barlow,** ***University of Auckland, New Zealand*** Auditory attention with cochlear implants: The brief test of attention (Schretlen, 1997) in 2015
10.45 am		**ANNUAL GENERAL MEETING** All conference participants are invited to attend Tea/Coffee will be available for AGM attendees

Tuesday 1 September
Afternoon Session

3.30 pm		Afternoon Tea Available

10. Disorders of the Nervous System (I)

Chair: Debbie Young

4.00 pm	10.1	**Yu Jing, *University of Otago, New Zealand*** Blood arginine metabolic profile is altered in male Sprague-Dawley rats
4.15 pm	10.2	**Andrea Kwakowsky, *University of Auckland, New Zealand*** Impaired GABAA receptor function in Alzheimer's disease
4.30 pm	10.3	**Duyen Pham, *The University of Adelaide, Australia*** Protocadherin 19 (PCDH19) regulates estrogen receptor alpha (ERα)
4.45 pm	10.4	**Kristyn Bates, *The University of Western Australia, Australia*** Astrocytic response to low-intensity repetitive transcranial magnetic stimulation (rTMS)
5.00 pm	10.5	**Aimee Culverhouse, *Victoria University of Wellington, New Zealand*** Exploring the aversive and anxiogenic effects of novel kappa opioid receptor agonists
5.15 pm	10.6	**Nigel Jones, *University of Melbourne, Australia*** SSRI antidepressants accelerate epilepsy development – role for 5-HT2 receptors?
5.30 pm		Tea/Coffee break

Tuesday 1 September
Evening Session

11. Disorders of the Nervous System (II)

Chair: Stephanie Hughes

5.45 pm	11.1	**Barbara Mason,** ***The Scripps Research Institute, United States of America*** A proof-of-concept human laboratory study of glucocorticoid receptor antagonism as a novel treatment for alcohol dependence
6.00 pm	11.2	**Stella Cameron,** ***University of Otago, New Zealand*** Pathophysiology of the cerebellothalamic pathway in a chronic rat model of Parkinson's disease
6.15 pm	11.3	**Katharina Russell,** ***Lincoln University, New Zealand*** Improving longitudinal biomarkers of ovine batten disease: Neuroimaging and ventricular enlargement in sheep
6.30 pm	11.4	**Jennifer Robertson,** ***Australian National University, Australia*** Sniffing out the mechanism of seizure generalisation through the piriform cortex
6.45 pm	11.5	**Brian Thomas,** ***RTI International, United States of America*** Synthetic cannabinoids: Unique formulations, chemical exposures and pharmacological consequences
7.00 pm	11.6	**Kelly Paton,** ***Victoria University of Wellington, New Zealand*** Analgesic and anti-inflammatory effects of the bioactive lipid Docosahexaenoyl Ethanolamide (DHEA) in pre-clinical behavioural models of pain

Wednesday 2 September
Combined Day with MedSci

6.00-9.00 am Light Breakfast Available

Joint Session with MedSci

Plenary Lecture

Venue: Rydges

9.00 am	**PLENARY LECTURE:** **Ed Callaway, *Salk Institute, United States of America*** Deciphering brain connectivity and function with rabies virus and light
10.00 am	Tea/Coffee break

Wednesday 2 September
Combined Day with QMB

12. Joint Session with QMB
Molecular Approaches to Modern Neuroscience

Venue: Rydges

Chair: Brian Hyland

10.30 am	12.1	**Bronwen Connor, *University of Auckland, New Zealand*** Direct reprogramming to model neurological disease
10.55 am	12.2	**Helen Fitzsimons, *Massey University, Palmerston North, New Zealand*** HDAC4 and memory formation: Interaction with the actin cytoskeleton
11.20 am	12.3	**Christine Jasoni, *University of Otago, New Zealand*** Understanding how maternal obesity and fetal neuro-immune interactions modulate epigenetic regulation of neural development in the mouse
11.45 pm	12.4	**Andrew Hill, *La Trobe University, Australia*** The role of extracellular vesicles in the spread of misfolded proteins associated with neurodegenerative diseases

12.30 pm Closing Remarks

Light lunch and Student Prize Presentation - rydges

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ABSTRACTS

1.1

Neurobiology of addiction: Cerberus revisited

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Drug addiction has been conceptualized as a chronically relapsing disorder of compulsive drug seeking and taking that progresses through three stages: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation,* and can be conceptually linked to the past, the present and future like the 3 headed dog of Greek mythology Cerberus. Via these stages, drug addiction impacts multiple motivational mechanisms and can be conceptualized as a disorder that includes elements of positive reinforcement and negative reinforcement. Three key neurobiological circuits are engaged in the motivational changes driving addiction that involve dysregulation in incentive salience- reward systems, sensitization of brain stress systems, and deficits in executive function systems. Specific neurocircuitry/neurochemical elements for these functional stages and motivational changes include the basal ganglia (incentive salience- reward deficits such as those involving dopamine), the extended amygdala (recruitment of the brain stress systems such as corticotropin releasing factor and dynorphin) and the prefrontal cortex (executive function deficits such as those involving glutamate). The combination of dysregulated incentive salience-reward function, sensitized stress systems and disrupted prefrontal executive function provides a powerful motivation for compulsive drug use and the loss of control over drug taking. Understanding the neurocircuitry neuroadaptations in the reward, stress and executive function systems will provide new insights into identifying vulnerability to the past, present and future of addiction.

1.2

Dissociation between changes in cellular excitability and synaptic plasticity measured in single cells in the motor cortex following transcranial magnetic stimulation

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Transcranial magnetic stimulation (TMS) has been used clinically to alleviate intractable depression and experimentally to augment rehabilitation following stroke. Although results in some recipients are promising, wider application has been hampered by variable individual responsiveness and small effect sizes. Our overall aim is to improve human application through deeper understanding of the cellular effects of TMS, using a translational rat model to optimise stimulation protocols. Using intracellular recording under urethane anaesthesia, we examined changes in excitability within single neurons and synaptic plasticity between neurons in the motor cortex *in vivo*, after applying theta-burst stimulation (TBS) protocols. TBS was applied using a 25 mm figure-of-eight TMS coil placed above an intracellular recording electrode in the primary motor cortex. Electrical test stimuli were applied via an electrode placed in the ipsilateral cortical hemisphere. Lasting changes in rheobase current indicative of changes in cellular excitability were measured 20 minutes after TBS, with intermittent TBS (iTBS) increasing excitability on average and continuous TBS suppressing excitability. Despite the changes in excitability, there were no lasting changes in synaptic efficacy induced by either protocol, with iTBS alone inducing only short term potentiation that returned to baseline 20 minutes later. Application of a second TBS protocol induced subsequent changes in synaptic efficacy in some neurons that could be predicted by the change in excitability induced by the first protocol. Thus, optimising TMS protocols to induce changes in cellular excitability may prime a neuron for subsequent modification of the efficacy of its synapses through learning.

1.3

Astrocytes mediate heterodendritic metaplasticity in hippocampus

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Memories are maintained by changes in synaptic strength. These changes, such as long-term potentiation (LTP) or long-term depression (LTD) of synaptic transmission, are vital for cognition but must be constrained to avoid pathologically high or low levels of neuronal activity. Such regulation comes partly through *metaplasticity*, whereby neural activity at one point in time influences later LTP/LTD. We have described a unique mode of metaplasticity in hippocampal CA1 where electrical priming stimulation, delivered to inputs to the basal dendrites of pyramidal cells, restricts later LTP at synapses onto their apical dendrites, hundreds of microns away. This effect is independent of postsynaptic depolarization, NMDAR or mGluR activation, and GABAergic signalling. Thus, we hypothesised that the metaplasticity is accomplished via astrocytic networks. Ca^{2+} imaging data show that astrocytes throughout CA1 strata are activated by priming. To test their involvement directly, we manipulated astrocytic activity during priming. In acute rodent hippocampal slices, Ca^{2+} in single astrocytes was chelated with EGTA (via patch pipette) whilst simultaneously recording local synaptic potentials in stratum radiatum. Priming (6x100 Hz trains) in stratum oriens was delivered in the presence/absence of this Ca^{2+} "clamp", 30 min prior to radiatum LTP induction (2x100 Hz trains). Whereas priming reduced LTP from control levels, chelating astrocytic Ca^{2+} abolished this effect ($F_{(2,20)}$, $P < 0.05$). Further, pharmacological priming with a selective adenosine 2B receptor agonist (100 nM BAY60-6583, 10 min) mimicked the effects of electrical priming, and this too was blocked by chelating astrocytic Ca^{2+} ($F_{(2,20)}$, $P < 0.05$). These data strongly support a novel astrocytic mechanism of metaplasticity.

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1.4

Astrocytes selectively regulate the expression of neuronal GABA-A receptor subunits

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Astrocytes play a crucial role in both the formation and function of synapses and the effects of astrocyte-secreted factors is well documented for glutamate receptors. However, the astrocytic influence on GABA-A receptors has been only partially investigated. The present work aimed to elucidate whether factors released from astrocytes can influence the neuronal expression of GABA-A receptor subunits during neurodevelopment and after brain injury. Primary cultures of cortical astrocytes were prepared and their conditioned media were collected to treat primary culture of cortical neurons. Changes in neuronal expression of various GABA-A receptor subunits were assessed using real-time PCR. Treatment with control astrocyte media resulted in a significant decrease of the GABA-A α4 subunit expression in neurons at both 5 and 9 days *in vitro*. No significant difference was found in the expression of α1, β2 and γ2 subunits. Interestingly, the reduction in α4-subunit expression was more pronounced when neurons were treated with media collected from mechanically-injured astrocytes. Surprisingly, delta (δ) subunit, an extrasynaptic subunit that preferentially coassembles with α4, was increased in neurons exposed to injured astrocyte media. All together, these effects show that astrocytes selectively regulate neuronal GABA-A subunits. In particular, results from injured astrocytes suggest that brain trauma or stroke might be associated with an astrocyte-mediated change of GABA-A receptor composition. Future studies are planned to assess the location of these subunits around the surface of the neurons and the impact that this has on drug efficacy and function.

The work is supported by a grant from the Neurological Foundation of New Zealand (A.B. and A.N.C.).

1.5

Optogenetic activation of rat GnRH neurons

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The gonadotrophin-releasing hormone (GnRH) neurons represent the key output cells controlling fertility in all mammals. Until recently, the inability to manipulate the electrical activity of GnRH neurons in a selective manner *in vivo* had prevented all attempts to elucidate the pattern of activation GnRH neurons required to generate pulses of LH. In this study, we have developed transgenic Cre-GnRH rats in order to induce gain or loss of function specifically in GnRH neurons. We found that 100% of Cre-expressing cells were GnRH neurons. Channelrhodopsins (ChR2) are genetically-encodable cation channels that can be activated by blue light to excite neurons. We have injected a Cre-dependant adeno-associated virus (AAV) in the rostral preoptic area of transgenic GnRH-Cre rats to target ChR2 to the GnRH neuronal phenotype. Dual immunofluorescence studies show that ~99% of all ChR2-expressing cells also express GnRH. To characterize the ability of ChR2 to modulate GnRH neuron excitability, we prepared acute brain slices from AAV-injected GnRH-Cre rats and undertook cell-attached recordings of ChR2-expressing GnRH neurons. The analysis of spontaneous firing patterns as well as the responses to various neurotransmitters indicated that the ChR2-transfected GnRH neurons were not compromised by the presence of ChR2 channels in the membrane. Importantly, ChR2-expressing GnRH neurons can be driven to fire with high spike fidelity with blue light stimulation frequencies up to 20 Hz for second intervals and up to 10 Hz for minute periods. In summary, we have developed a model for remote optogenetic activation of GnRH neurons in conscious rats; this model will be used to define the neuronal activity GnRH neurons required to generate pulses of LH.

1.6

Secreted amyloid precursor protein alpha regulates protein synthesis in primary hippocampal neuronal cultures

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The secreted fragment of the amyloid precursor protein, sAPPα, has recently been shown to both enhance spatial memory as well as long-term potentiation, an experimental model of memory. Surprisingly little is known about how sAPPα induces changes in nerve cell activity. Since the persistence of memory and LTP is dependent on the synthesis of proteins by activated hippocampal neurons we hypothesized that sAPPα may affect protein synthesis and in early work showed that sAPPα stimulated protein synthesis in isolated nerve cell synapses. As LTP is underpinned by regulation of the AMPA-subtype of glutamate receptors, in the current study we explored whether application of sAPPα to primary hippocampal neuronal cultures regulates the synthesis of the AMPA receptor subunits GluA1 or GluA2. Following incubation with 1 nmol sAPPα, newly synthesized proteins were labelled using fluorescent non-canonical amino acid tagging plus proximity ligation assays (PLA-FUNCAT). This method incorporates a methionine analogue bound to an azide group into newly synthesized proteins. Click chemistry attaches a biotin-bound alkyne group to the newly synthesized protein, which can then be recognized with antibodies and PLA probes to determine the identity and location of newly synthesized proteins. Using PLA-FUNCAT, we found that sAPPα upregulated protein synthesis ($p < 0.05$, Kruskal Wallis test), and specifically, levels of newly synthesized GluR1 were increased threefold ($p < 0.0005$) while GluR2 levels were unaffected compared to baseline. By focusing specifically on newly synthesized proteins in cell soma we found a 2-fold increase in GluR1 synthesis compared to baseline ($p < 0.05$). These results indicate that a sAPPα-mediated increase in protein synthesis, including the GluR1 subunit of AMPA receptor, may be one mechanism through which it enhances LTP and memory.

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1.7

Distinct temporal fingerprint for cAMP signalling of indole-2-carboxamides as allosteric modulators of the cannabinoid 1 receptor

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The endocannabinoid system principally comprises of the G protein-coupled receptor (GPCR) cannabinoid receptors 1 and 2 (CB_1 and CB_2 respectively) along with the endogenous cannabinoid receptor ligands. CB_1 is present at high levels throughout the CNS and acts as a modulator of neurotransmitter release. Interest is now turning to improved drug therapies for these receptors through development of biased ligands and allosteric modulators. CB_1 has an allosteric binding site with ORG27569 being one of the most studied of the CB_1 allosteric modulators. We have recently shown ORG27569 produces a distinct temporal cAMP fingerprint, with complex, concentration and time-dependent modulation of agonist-mediated regulation of cAMP levels. The aim of this work was to characterise the cAMP signalling response of indole-2-carboxamides structurally correlated to ORG27569 and previously characterised for ability to modulate binding of [3H]CP55,940 to hCB_1. Using the real-time kinetic BRET CAMYEL assay we assessed the forskolin stimulated cAMP response of 10 µM indole-2-carboximide compounds in both the presence and absence of CP55,940 in CB_1 expressing cells. Compounds that displayed altered cAMP responses were then characterised further with regards to potency and cAMP signalling characteristics. We show that ORG27569 and three other compounds display similar temporal cAMP fingerprints in the presence of CP55,940 whereas another five compounds act as immediate allosteric inverse agonists of cAMP signalling. Data from this study will be used to further define the appropriate chemical structures for targeting therapeutically useful pathways in relation to CB_1.

2.1

Modern approaches for dissecting neuromodulation and signaling in affective behavior

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Stress and affective behaviors are largely controlled by specific neurotransmitters and their receptors in the central nervous system. Many of these signals are conveyed through activation of both neuropeptide (i.e. CRF and Opioid) and monoamine (norepinephrine, dopamine, serotonin) receptor systems. These receptors are seven transmembrane spanning G-protein coupled receptors (GPCR) and they can stimulate a variety of signaling cascades following neurotransmitter/neuropeptide release. Neuropeptide and monoamine circuits are engaged by stress, and elicit a complex array of behavioral responses relevant to anxiety, addiction, and depression. These systems and circuits have classically been studied using pharmacological approaches, *in vivo* and *in vitro* electrophysiology and biochemical methods. Here we will describe recent advances in optogenetic technology including development and implementation of cellular scale wireless optogenetic and optofluidic devices for *in vivo* behavioral measures. In addition, we report divergence of behavioral responses using optical control of discrete brain region subnucleai containing dynorphin expressing neurons in the nucleus accumbens. We find that optical control of this neuropeptide system in select regions results in differences in reward and aversion behavior. Finally, we will also discuss recent advances in controlling monoamine and peptide GPCR signaling pathways with optogenetic strategies and how these technologies reveal novel insights into neuromodulator function in affective behaviors. In sum, we will highlight some recent advances from our laboratory that dissect the role of neuromodulation in motivated behaviors.

2.2

Optogenetic stimulation of motor thalamic terminals modulates motor cortex activity in freely moving Parkinsonian rats

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Altered neuronal activity in the basal ganglia-thalamocortical loop underlies the movement symptoms of Parkinson's disease (PD). However, the specific changes in motor thalamus (Mthal) regulation of motor cortex (MCx) in parkinsonian conditions remain unknown. We are investigating this in a chronic PD model using optogenetic methods to stimulate the terminals of ventroanterior (VA) Mthal neurons, to characterise how they modify MCx activity and behaviour. Parkinsonian (unilateral 6hydroxydopamine lesion) and control (sham) rats received lentiviral vector (pLenti.CamKIIα.hChR2(H134R).mCherry) injections in VA Mthal to selectively transduce glutamatergic neurons, and a chronically implanted optrode (recording electrodes-fibreoptic probe assembly) in MCx. Extracellular neuronal activity was recorded from MCx in rats performing a reach-to-grasp task. Preliminary analyses revealed that the mean non-stimulation firing rate of MCx neurons was decreased by 45% in parkinsonian compared to sham rats ($p=0.04$). Optogenetic stimulation (blue light) of VA terminals in MCx produced complex alterations in activity in a proportion (39 %) of recorded MCx neurons. These responses were dependent on the stimulation frequency and pattern, e.g. some cells responded to one of two different patterns applied during a single recording session. Stimulation did not alter reaching performance, probably because only small numbers of VA terminals were activated by the localised light stimulation. These data confirm that MCx activity is impaired in chronically parkinsonian rats. Further, based on differences in stimulation effects, we hypothesise that Mthal-MCx synapses are not reliable, but may be improved with specific stimulation patterns.

Funded by Health Research Council of New Zealand. CBB is currently at INRA, University of Bordeaux, France.

2.3

Complex GABAergic innervation onto ventral tegmental dopamine neurons

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Midbrain dopamine neurons are involved in reward processing. Firing of dopamine neurons sometimes pause in response to no reward, aversive or non-rewarding events, which we hypothesised would be due to multiple inhibitory inputs to the somata and primary dendrites of these neurons. We investigated this hypothesis in a newly discovered pathway involving GABAergic neurons in the rostromedial tegmental nucleus (RMTg) that innervate midbrain dopaminergic neurons in the posterior ventral tegmental area (pVTA). Previous interpretation of the microcircuitry has been limited because we could not definitively identify a specific neuronal phenotype from only one pathway in the brain. To address this, we combined a lentiviral vector that targets GABAergic neurons (LV-GAD67copGFP) and immunohistochemistry for tyrosine hydroxylase, an enzyme that labels dopamine neurons in the midbrain. Electron dense GFP-tagged RMTg GABAergic axon terminals formed symmetrical synapses with pVTA dopaminergic dendrites, therefore, we selectively visualised synapses at the EM level formed by one neuronal phenotype in one brain pathway. Furthermore, there were complex synaptic triads at all examined dendritic synapses. Specifically, RMTg GABAergic presynaptic terminals were consistently innervated by one or two asymmetric synapses with features indicative of glutamatergic synapses. We hypothesise that these excitatory synapses onto GABAergic presynaptic terminals would intensify GABA release at synapses onto dopaminergic dendrites, resulting in a pause in dopamine neuron firing and reinforcing signalling in this aversive pathway controlling behavior. Our findings have important implications for understanding drug addiction because drugs of abuse exert strong rewarding effects in the pVTA, possibly via dysregulation of this circuit.

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2.4

Delayed post-treatment with bone marrow-derived mesenchymal stem cells is neurorestorative of striatal medium-spiny projection neurons and improves motor function after neonatal rat hypoxia-ischemia

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Perinatal hypoxia-ischemia is a major cause of striatal injury and may lead to cerebral palsy. We investigated whether delayed administration of bone marrow-derived mesenchymal stem cells (MSCs) on postnatal day (PN) 14, after hypoxia-ischemia on PN7, was neurorestorative of striatal medium-spiny projection neurons and improved motor function. The effect of a subcutaneous injection of a high-dose, or a low-dose, of MSCs was investigated. A subset of high-dose pups, and their diluent control pups, were injected intraperitoneally with bromodeoxyuridine, every 24h, on PN15, PN16 and PN17, to track the migration and survival of neuroblasts originating from the subventricular zone into the adjacent injured striatum. On PN21 the absolute number of striatal medium-spiny projection neurons was measured using stereological methods after immunostaining for DARPP-32 (dopamine- and cAMP-regulated phosphoprotein-32), double immunostaining for bromodeoxyuridine and DARPP-32, and after cresyl violet staining alone. There was a statistically significant increase in the absolute number of DARPP-positive, bromodeoxyuridine/DARPP-32-positive, and cresyl violet-stained striatal medium-spiny projection neurons in the high-dose and low-dose MSCs group compared to their diluent counterparts. Investigation of behavior in another cohort showed that delayed administration of a high-dose of bone marrow-derived MSCs, at one week after neonatal hypoxia-ischemia, improved long-term motor function on the cylinder test. Delayed therapy with a high- or low-dose of adult MSCs, at one week after injury, is effective in restoring the loss of striatal medium-spiny projection neurons after neonatal rat hypoxia-ischemia and a high-dose of MSCs improved motor function.

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2.5

Reinforcement signals critically modulate spike timing-dependent plasticity in the striatum

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Plasticity of synapses between cortical representations and striatal neurons is thought to play a critical role in action discovery and selection by the basal ganglia. The precise timing between pre and postsynaptic activity, termed spike timing-dependent plasticity (STDP), has been proposed, based largely on *in vitro* studies, as a generic mechanism to modify synaptic weights. However, learning a new action involves reinforcement, which can occur at much greater timescales than the millisecond timing relevant to STDP. We hypothesised that corticostriatal plasticity *in vivo* is critically modulated by reward-related signals. During intracellular recording experiments in urethane-anesthetised rats, presynaptic cortical activity either preceded ('pre-post') or followed ('post-pre') postsynaptic spiny neuron activity by 10 ms, during 60 pairings at 0.1 Hz. STDP pairings of either type alone were not sufficient to induce corticostriatal potentiation. When STDP pairings were associated with a behaviourally-relevant reinforcement set, comprised of a light flash following the pairings by one second and electrical brain stimulation reward a second later, potentiation was induced with the pre-post protocol (+13% PSP slope at 20 min, $p < 0.05$), and depression with the post-pre protocol (-28% PSP slope, $p < 0.05$). Furthermore, removal of the light abolished potentiation – instead depression was induced with brain stimulation reward alone (-18% EPSP slope, $p < 0.05$). Pharmacological manipulations indicated that dopamine and adenosine signalling are critical for the reward modulation. These findings indicate that corticostriatal STDP *in vivo* is only Hebbian when associated with reinforcement, and also highlights the potentially critical role that short-latency sensory signals can play in plasticity.

3.1

A novel electrochemical approach for interrogating tonic and phasic dopamine signals in the nigrostriatal pathway

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The complex interplay of fast (phasic) and slow (tonic) actions engenders dopamine with a vast array of functions, from movement to motivation. Electrochemical sensors, namely carbon fibre microelectrodes, have been used extensively to study the fast release of dopamine with fast-scan cyclic voltammetry (FSCV). Likewise, glass microelectrodes have been used to study the electrical activity of dopaminergic neurons. Capturing the slow actions of dopamine can be done *in vivo* with microdialysis, however this has many drawbacks. We describe a novel electrochemical technique, fast-scan controlled-adsorption voltammetry (FSCAV), that allows highly-sensitive, prolonged (>1.5 hr) measurement of tonic dopamine concentration both *in vivo* and in brain slices. Combining FSCAV with conventional FSCV allows concurrent study of stimulated release and absolute extracellular concentration. Here we demonstrate brief L-DOPA application induces increases of tonic dopamine in the dorsal striatum of rat forebrain slices (300 µm), influenced by the activity of both monoamine oxidase (MAO) and the dopamine transporter (DAT). Following inhibition of both MAO and DAT, the L-DOPA-induced increase of dopamine is sufficient to activate D_2 autoreceptors, as indicated by a sulpiride-sensitive decrease in stimulated dopamine release. We thus discuss the utility of FSCAV-FSCV for assaying autoreceptor function. FSCAV can be also performed alongside electrophysiological recordings in the Substantia Nigra pars compacta, as demonstrated by sampling tonic dopamine concentration whilst inhibiting cell firing by brief application of exogenous dopamine. FSCAV, used both *in vivo* and *in vitro*, augments the current repertoire of techniques and helps unravel the role of dopamine within the basal ganglia, both in health and disease.

3.2

An optogenetic study of endocannabinoid mediated modulation of dopamine neuron activity

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The basal ganglia are interconnected networks of nuclei that receive a wide range of inputs from throughout the brain, and accordingly, is involved in many key brain functions. Broadly divided into the *direct* and *indirect* pathways, a third less well studied *hyperdirect* pathway is also present: Cortex > Subthalamic nucleus (STN) > Substantia Nigra pars compacta (SNc)/reticulate (SNr). Activation of the hyperdirect pathway, in particular the SNc dopamine neurons, could be a key mechanism underlying the switch between activation of the direct or indirect pathways. We have recently shown that dopamine neuron activity is modulated by endocannabinoids, and that this modulation is initiated by glutamatergic STN projections to the SNc. To gain further information on this novel endocannabinoid modulation, optogenetic techniques have been applied to study the complex connectivity. CD-1 mice expressed either channelrhodopsin (ChR2) or halorhodopsin (HR) under the CaMKIIα promotor after injection of viral (AAV) constructs into the STN. Neuronal activity was monitored using whole-cell and single-unit electrophysiological recordings from horizontal midbrain slices (300 µm thick) containing the SNc, STN and SNr after 4 – 8 weeks expression. The STN was selectively illuminated using a digital mirror device and a variety of stimulation patterns (constant ON, 5 – 100 Hz, or Theta-burst; 30 sec duration, 4 ms pulse). Light activation of the STN in slices obtained from ChR2-expressing mice evoked a biphasic increase in dopaminergic neuron firing. The initial increase was reduced by bath application of CNQX (10 µM), while the delayed response was unaffected. In HR-expressing STN, a biphasic inhibition of firing was observed. The response supports an underlying glutamate driven disinhibition mediated eCBs, requiring further characterization using specific pharmacological tools. Challenges to studying dopamine neuron function using optogenetics will also be presented.

3.3

Neurochemical changes in the striatum in a transgenic ovine model of Huntington's disease

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Previous studies have shown that one of the earliest pathological changes in the inherited neurodegenerative disorder Huntington's disease (HD) is a loss of neurochemical markers and volume in the striosomal compartment of the caudate nucleus. We have developed a new large-animal HD transgenic ovine model, which shows the characteristic pathological inclusions of HD and a reduction in neurochemical markers in the striatum. This study investigates whether this model shows a loss in striosome volume which characterizes early HD. A detailed analysis of the striosomal volume in the caudate nucleus, using immunohistochemistry and stereological techniques, was undertaken in the transgenic sheep brain. At 6 months of age there is no change in the striosomal volume but at 5 years of age the transgenic sheep showed a 33% reduction in striosome volume. These findings suggest that the early changes occurring in the human brain in HD are replicated in the transgenic sheep model. This provides further evidence that this transgenic sheep is a valid model for studying the early pathogenesis of HD and for trialing novel therapeutics for HD. Gene therapy trials are currently underway in these transgenic sheep in an effort to slow down the onset of HD and we will be assessing the effectiveness of this therapy by monitoring neurochemical and striosomal volume changes.

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3.4

Globus pallidus neurodegeneration links to symptom heterogeneity in Huntington's disease

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Numerous studies have documented striatal neurodegeneration in Huntington's disease (HD). However, the globus pallidus (GP), a main output nucleus of the striatum, has received little attention. This study characterizes the pattern of neurodegeneration in the three main subdivisions of the human GP. Stereology was used to characterize regional atrophy, neuronal loss, and soma neuronal atrophy in the three components of the GP - the external segment (GPe), internal segment (GPi) and ventral pallidum (VP) - in 8 HD cases compared to 8 matched control cases. These findings were compared with HD striatal neuropathological grade, and symptom scores of motor impairment, chorea, mood and cognition. The GPe was most vulnerable with a 54% overall volume decline, 59% neuron loss and 35% reduced soma volume. GPi was less vulnerable with a 40% reduction in overall volume, 19% neuron loss and 21% reduced soma volume whereas VP showed a 31% overall volume decline, 24% neuron loss and 59% reduced soma volume. The extent of GP neurodegeneration correlated with increasing striatal neuropathological grade. GPe and VP volume decline correlated with the severity of motor impairment but not chorea. Overall GP neurodegeneration correlated positively with irritability and anxiety, and VP volume loss correlated with cognitive decline, motor impairment and irritability. Our results suggest that the heterogeneity of GP neurodegeneration between cases provides a novel perspective for understanding basal ganglia circuit dysfunction and the neural basis of clinical heterogeneity in HD.

4.1

Reinstatement of long-term memory in *Aplysia* following reconsolidation blockade

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Traditionally, long-term memories are believed to undergo a single process of consolidation and, once consolidated, to be relatively stable. However, recent evidence suggests that, upon reactivation, consolidated memories become relabilized and must undergo a new round of consolidation (reconsolidation) if they are to persist. Moreover, if reconsolidation is blocked by, for example, inhibition of protein synthesis, then the memories may be eliminated. To test whether long-term memory (LTM) can be eliminated by reconsolidation blockade, we took advantage of a simple model of LTM, long-term sensitization (LTS) of the *Aplysia* withdrawal reflex. LTS is mediated by long-term facilitation (LTF) of the monosynaptic connection between the siphon and motor neurons that mediate the reflex. We found that both LTS and LTF can be reversed by reconsolidation blockade. LTF results from the growth of new presynaptic varicosities, sites of sensorimotor synaptic contact; furthermore, reconsolidation blockade is accompanied by an overall retraction of presynaptic varicosities. However, varicosity retraction during reconsolidation blockade did not involve the simple retraction of the varicosities that grew during LTF; rather, varicosity retraction appeared random. This suggests that LTM is not stored at synapses. If so, then the reversal of LTF and LTS by reconsolidation blockade may not represent the elimination of LTM. In accordance with this idea, we showed that LTS could be reinstated following its reversal by reconsolidation blockade by modest additional sensitization training, training that did not induce LTS in naïve animals. Thus, LTM is not eliminated by reconsolidation blockade. Our results challenge the idea that synaptic change mediates LTM storage.

4.2

Preclinical anti-addiction and side effect profile of the novel kappa-opioid receptor agonist 16-ethynyl Salvinorin A

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The social and economic cost of drug abuse is estimated at $6 billion NZD annually. With no FDA-approved treatments for psychostimulant addiction, there is a need for effective pharmacotherapies. Activation of the kappa opioid receptor (KOPr) has been shown to reduce drug-seeking in preclinical models, and also decreases the self-administration of prescription opioids, suggesting KOPr agonists as candidates for reducing the abuse potential of addictive pain medications. However, traditional compounds that activate the KOPr have side effects which limit their clinical use. The structurally unique KOPr agonist Salvinorin A (SalA) has been shown experimentally to reduce drug-seeking behaviours. We show that 16-ethynyl-SalA, a novel SalA analogue, reduces cocaine-primed reinstatement of drug-seeking at doses of 0.1 and 0.3 mg/kg, and at 2.0 mg/kg in a progressive ratio self-administration model in Sprague-Dawley rats. In addition to potent anti-cocaine effects, we show that 16-ethynyl-SalA has an improved side-effects profile, with no sedative effects observed in open-field locomotor tests at 0.3 mg/kg ($p<0.05$). Preliminary data also suggests that 16-ethynyl-SalA does not have pro-depressive effects in the Forced Swim test, or cause anxiety or aversion in elevated plus maze and conditioned place aversion tests. The cellular mechanism underlying these effects is at least in part due to modulation of dopamine levels via direct activation of the dopamine transporter (DAT). Preliminary studies quantifying DAT function in cells co-expressing KOPr and DAT indicate that 16-ethynyl-SalA increases DAT function. These studies highlight the promise of novel KOPr agonists for the development of anti-addictive pharmacotherapies.

4.3

The role of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors in MDMA self-administration

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MDMA initially has less efficacy as a reinforcer in the self-administration paradigm than other drugs of abuse. However, following repeated self-administration testing, responding increases for some animals and efficacy becomes comparable to other drugs of abuse. We have previously shown that disruption of central serotonin systems facilitated the acquisition of MDMA self-administration, suggesting that MDMA-produced adaptations in the serotonin system may underlie the development of MDMA self-administration. One mechanism by which MDMA-produced serotonin release might produce this effect is through adaptations in specific serotonin receptor subtypes. The 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors are both well localised to regulate dopamine release, and have been implicated in modulating the reinforcing effects of many drugs of abuse. In these studies we tested the effects of pharmacological manipulation of the 5-HT$_{1B}$ and 5-HT$_{1A}$ receptors on the acquisition of MDMA self-administration, and assessed the effect of prolonged MDMA self-administration on behavioural responses to activation of these receptors. We show that repeated administration of the 5-HT$_{1B/1A}$ agonist, RU 24969, downregulated 5-HT$_{1A}$ receptors and greatly facilitated the acquisition of MDMA self-administration. However, substantial self-administration of MDMA failed to alter the behavioural response to activation of 5-HT$_{1A}$ or 5-HT$_{1B}$ receptors, suggesting these receptors are not critically altered by MDMA self-administration.

4.4

Novel role of the ETS-5 transcription factor in exploratory behaviour

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We have previously shown that the ETS transcription factor ETS-5 is required for carbon dioxide sensing by the BAG neurons in the nematode *C. elegans*. However, ETS-5 is expressed in 14 additional head neurons, indicating that it could be required for other, undescribed, neuronal functions. We recently found that ETS-5 is required for *C. elegans* to explore the environment. Animals carrying a null mutation in the *ets-5* gene showed defective exploratory behaviour in exploration assays in the presence of food. It is known that factors such as neuromodulatory signaling and food availability control exploratory behaviour in *C. elegans*. We also found that mutants known to have increased lipid storage, also exhibit reduced exploration behaviour. We hypothesized that reduced exploration behaviour of *ets-5* mutant animals was due to increased fat storage and have shown this to be the case. We are currently trying to decipher the cellular basis of fat storage regulation in *ets-5* mutants and how this is linked with exploratory behaviours.

4.5

Investigating the effect of conditional probability on reinforcement evoked potentials

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Learning from experience is integral for any agent occupying a variable environment. A major process underlying such learning is operant conditioning via positive reinforcement. The traditional definition of reinforcement: that delivery of a reinforcer increases the likelihood of the preceding response, has recently come into question. An alternative proposal suggests that reinforcers alter behaviour by what they signal about future availability of further reinforcement. To investigate this hypothesis, we implemented a discrete-trials-two-alternative choice procedure. Reinforcers were arranged such that the first reinforcer to an alternative signalled to continue responding while the second signalled to change to the other option. The standard mechanistic conception of reinforcement predicts that reinforcers should increase the responding on the just productive alternative while signalling suggests that responding should follow the signalled probability. High density scalp-EEG was used to compare participants' ERP evoked by continue versus change reinforcers. Previous research found the reward-positivity (RP) and the P300 as components correlated with reward processing. Additionally, the relationship between the ERP components and preference was assessed using hierarchical regressions. Preliminary results are consistent with the mechanistic account of reinforcement, with no evidence of either component being modulated by what reinforcers signalled (RP mean difference = - 0.036μV, 95% HDI [-0.388, 0.354], zero value credible; P300 mean difference = - 0.079μV, 95% HDI [-0.390, 0.247], zero value credible).

5.1

An inconvenient truth: Trpc2-expressing sensory neurons in the mouse main olfactory epithelium

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Chemoreception in the mouse olfactory system occurs primarily at two chemosensory epithelia: the main olfactory epithelium and the vomeronasal epithelium. Their sensory neurons are olfactory sensory neurons (OSNs) and vomeronasal sensory neurons (VSNs), respectively. Genes required for chemosensory transduction are, respectively, the cyclic nucleotide-gated channel subunit Cnga2 and the transient receptor potential cation channel Trpc2. Mice with a Trpc2 knockout mutation display striking behavioral phenotypes: their sexual, aggressive, and parenting behaviors are profoundly perturbed. Based on the assumption of VSN-specific expression of Trpc2 in mouse, these behavioral phenotypes have been widely interpreted in VSN-specific terms. Surprisingly, there has been no report characterizing Trpc2 expression in the mouse, the species that was the subject of the gene knockout experiments. We have discovered that the mouse main olfactory epithelium actually abounds with Trpc2+ cells, from early stages in development throughout adulthood. We have identified two types of Trpc2+ neurons: type A and type B cells. These cell types can be distinguished at the single-cell level by expression of Adcy3 (adenylate cyclase): type A cells express Adcy3, and type B cells do not. Some type A cells express odorant receptor genes. Type B cells express the soluble guanylate cyclase Gucy1b2. Our results serve as caution against the traditional interpretation of the behavioral phenotypes of Trpc2 knockout mice, as if only VSNs would be impaired in these mice, and no other neurons or no other cells in the mouse's body. Specifically, there is no reason to expect that type A or type B cells respond to pheromones.

5.2

Mechanisms of function and control of the grid cell/head direction cell spatial navigation system in entorhinal cortex

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The medial entorhinal cortex (MEC) contains a variety of distinct cell populations with specific fixed response properties. Perhaps the most striking of these are the grid cells that are thought to provide a fixed metric of space. Exactly how the cell types interact on a network level to produce this regular firing pattern is not currently known, but there are number of current models that make strong predictions about their connectivity; grid cells are thought to require information about the direction of an animal and its speed (Burak & Fiete, 2009). It is established that grid cells are transiently malleable in response to changes in environmental geometry (Barry et al., 2008; Stensola et al., 2012). In these experiments we recorded *in vivo* neurons from MEC of mice and deformed the environment by altering its size by 50% along one axis. We find that head direction cells in MEC respond transiently in response to environmental deformation, and do so in a way that is consistent with these cells providing directional input to grid cells as predicted in modelling. Using a novel knockout line, the TRIP8b deletion mutant, we find that the abolition of postsynaptic HCN channels by TRIP8b deletion blocks both the transient deformation in the grid firing pattern of grid cells, and the associated changes in the head direction signal. This constellation of findings provides evidence that the activity of head direction and grid cells are linked, and are linked in the manner supposed by models of their function. The findings also suggest that the malleability of this network depends, at least in part, on postsynaptic HCN-conducted I(h).

5.3

Neuropsychiatric status and different MCI criteria in Parkinson's disease

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Neuropsychiatric symptoms in Parkinson's disease have been associated with conversion to dementia (PDD). Cognitive status, particularly mild cognitive impairment (PD-MCI), is also associated with conversion to PDD. The most common PD-MCI cut-off criterion is 1.5SD below normative data for two cognitive scores, either within a single cognitive domain or across two domains. We followed 82 non-dementing PD patients over 4 years, 21 of whom converted to PDD over this period. We examined the neuropsychiatric status of these patients who met each of the two MCI criteria at baseline. Neither PD-MCI criterion was associated with increased total score on the neuropsychiatric inventory (NPI) compared to patients with normal cognition (i.e. those not meeting a PD-MCI criterion). In addition, the NPI total score did not differentiate patients who converted to PDD from those that did not. By contrast, the criterion of two impairments at 1.5SD within a single cognitive domain produced a high relative risk (RR) of PDD (5.6, 95% CI 2.3-13.6, $p < 0.001$); the criterion of only one impairment in each of two domains did not predict conversion to PDD (RR=1.8, CI 0.3-9.7, $p > 0.40$). Thus, it appears that symptoms reported in the NPI are not associated with conversion to dementia.

5.4

Using Mismatch Negativity (MMN) to investigate perception of changes in affective prosody in Autism Spectrum Disorder (ASD)

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Research on social communication has shown that individuals with ASD display difficulties in perceiving prosody – subtle distinctions in spoken language that convey emotion and intent. Different studies with people with ASD have reported impairments in detecting variations in intonation and pitch, and disadvantages at a neural level in processing complex stimuli such as speech. It is hypothesised that impairments in prosody processing may stem from inherent deficits at an auditory-perceptual level. So far, this study has involved five children with high-functioning ASD, four typically developing children, aged 7-13 years and six typically developing adults aged 20-40 years. Monosyllabic stimuli spoken with neutral, angry, happy, and sad emotions, were used for evoked potential recordings. The neutral stimulus was the standard stimulus, and the three other emotions were deviant stimuli used to evoke a mismatch negativity (MMN) response to changed emotion. Preliminary results show that children with ASD have later and larger fronto-parietal cortical responses in the N2 latency region to changes in emotion, compared to typically developing children and adults. There were differences in response amplitude and latency between angry, happy, and sad emotions for the typically developing children. Typically developing children had more distinct MMN components for the different emotions than the children with ASD. Larger and later MMN responses to differences in underlying emotion in the children with ASD indicate altered auditory processing of emotional stimuli. The results suggest hypersensitivity and delayed processing of these auditory variations. The lack of MMN differentiation between the three emotions is consistent with the observed behavioural impairments in emotion perception and social communication in individuals with ASD.

5.5

Enhanced motivation in an animal model of maternal immune activation in schizophrenia

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Maternal exposure to infection, and subsequent dysregulation of immune response, is increasingly implicated in schizophrenia. Motivational deficits, including deficits in goal-directed behaviour, are symptomatic of schizophrenia and significantly predict functional impairment. To date, characterization of motivational impairments has not been undertaken in animal models of maternal immune activation (MIA). We tested MIA rats in a number of operant experimental assays to determine the extent and nature of any motivational impairments. Surprisingly, in the progressive-ratio paradigm, which assesses willingness to expend effort in response to an increasing work requirement, MIA rats continued pressing longer, and had higher breakpoints than controls, indicating increased motivation. Subsequent tests showed that this was not due to a general increase in activity level, but was due to greater goal directed action in MIA rats. Enhanced motivation in MIA rats may result from increased attribution of incentive salience to reward-associated cues, and may be analogous to aberrant attribution of incentive salience in schizophrenia.

6.1

The Aalborg PAS-based brain computer interface: An investigation of the duration of cortical excitability in healthy adults

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The Brain Computer Interface (BCI)-PAS protocol uses an endogenous signal, the movement related cortical potential (MRCP), to pair an electrical stimulus at a peripheral nerve with the person's intention to move during motor imagination or execution. This novel protocol has been shown to increase corticomotor excitability in healthy people and people with stroke, for up to 30 minutes. As most rehabilitation sessions last for one hour the purpose of this research was to determine whether increases in corticomotor excitability last for one hour. Healthy volunteers (n=10) completed a visually-cued motor imagination dorsiflexion task. The peak negativity of the MRCP was calculated from electroencephalography recordings. Volunteers then completed the BCI-PAS protocol which involved electrical stimulation of the common peroneal nerve paired by timing afferent and endogenous efferent signals to coincide at the point of peak negativity. Corticomotor excitability was measured by recording motor evoked potentials (MEP's) in the tibialis anterior muscle using transcranial magnetic stimulation, before the intervention and at 0, 30, 45 and 60 minutes post-intervention. Corticomotor excitability as measured by MEP amplitude was significantly higher after the intervention compared to before the intervention, at 0, 30, and 45 minutes, but not at 60 minutes. We conclude that cortical excitability is increased after a single session of the BCI-PAS protocol in healthy participants, and this increase is maintained for 45 minutes. These findings have helped inform the timing of outcome measurements in the subsequent 4-week RCT.

6.2

Physiological models of neurovascular coupling and the relationship to BOLD signals in the ageing brain

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The mechanisms with which the neurons communicate with the vasculature to increase blood flow, termed neurovascular coupling is still unclear primarily due to the complex interactions between many parameters and the difficulty in accessing, monitoring and measuring them in the highly heterogeneous brain. Mathematical models based on existing experimental knowledge are necessary to study the relation between neural activity, the associated *vasoactive* factors released and their effects on the vasculature. Importantly the model should be validated against repetitive experiments and generate a verifiable hypothesis. We have developed a physiological model which describes the K^+ signaling mechanism coupling a CA1 pyramidal neuron, astrocytic cells and the perfusing arteriole thus enabling a simulation of a BOLD response. Our model predicts the experimental evidence of variations in the BOLD response such as initial dip, positive BOLD, negative BOLD, post stimulus undershoot culminating from the neurovascular and neurometabolic responses. We compared the simulated BOLD response to experimental BOLD signals observed in the hippocampus during hypoxia showing excellent agreement. With this model we have been able to investigate areas of variation and possible pathologies of neurovascular coupling and the corresponding BOLD signal. This approach of combined quantitative modeling of the neurovascular coupling response and its BOLD response will enhance the understanding of this complex mechanism and could provide further evidence of BOLD as one of a number of biomarkers in the ageing brain.

6.3

Multi-scale modelling of neurovascular coupling in "tissue-like" structures

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Neurovascular coupling (NVC) describes the ability of the vasculature to regulate cerebral perfusion dependent on neuronal activity. Neurons, glia and vascular cells, known collectively as a neurovascular unit (NVU) provide this important mechanism. To model NVC with a high spatial and temporal resolution our research group has developed a numerical model able to describe the process of neuronal activation to vascular response. This model is embedded into a "tissue-like" structure which includes a vascular tree capable of providing nutrients to each of the multiple NVUs. This allows complex bloodflow regulation on a large spatial scale and provides the ability to investigate how the vasculature and the NVUs interact using bidirectional NVC like stretch-activated channels and wall shear stress-mediated nitric oxide production. Abstractions of different cell types have been developed into a virtual NVU. Communication between cells is simulated by coupled sets of differential equations and validated with experimental results. Numerical procedures are implemented in parallel where the space-filling model of a vascular tree (H-tree) bifurcates into the pre-capillary bed making it possible to globally couple thousands of NVU models *via* the vasculature. We show that the model is able to regulate widening or narrowing of the H-tree arteries in response to an activation input signal. Results indicate that neuronal activity leading to potassium release into the synaptic cleft induces a membrane potential drop in the smooth muscle cells. Thence, voltage-operated ion channels close and the calcium concentration in the cytosol decreases resulting in a dilating regulation of the blood vessel diameter. The H-tree model allows us to investigate the influence of spatial and temporal inputs.

6.4

Cerebral arterial circle with autoregulatory resistance

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The cerebral arterial circle (CAC) is responsible for distributing blood to brain tissue. Blood flow through this structure is influenced by compliance and resistance of the distal vessels that perfuse the cortical tissue. Resistance is inversely proportional to the 4^{th} power of the radius of the vessel. Increased local metabolic activity releases vasodilating chemicals into the blood stream. It is not fully understood how the cerebral blood flow responds to these changes. In our previous study, the resistance was calculated as a lumped parameter; a summation of the vessels beyond the termination point of the efferent artery. The resistance was manually changed to simulate the metabolic changes. Presently, there is a bifurcating H-tree that is attached to the end of an efferent artery that propagates down to the level of the neuronal tissue where it is capped with a neurovascular unit (NVU). The NVU represents 0.2 mm^3 of neuronal tissue and calculates the ionic interactions from the vessel to the neuron. The tree bifurcates for a specified number of levels until the desired volume of neuronal tissue is obtained. Pressure is calculated for the efferent artery of the CAC. This is then communicated to the H-tree that directs the pressure down to the level of the NVUs. In return, a resistance is generated and calculated back through the levels to the CAC allowing for a new pressure to be calculated and the autoregulatory cycle continues. This is the first time the collateral flow pattern through the CAC has been studied with autoregulation. The results of the autoregulatory model are more physiological accurate than those of the lumped model as the resistance is not a static change for the entirety of the simulation.

6.5

Investigating the effects of electrical stimulation modalities paired with cortical potentials generated by motor imagination

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Long-term potentiation (LTP) and long-term depression (LTD) have been associated with learning and memory through synaptic modifications. The function of these mechanisms may be altered from deficient homeostatic mechanisms and injury in the central nervous system such as a stroke. This can lead to abnormal increases or decreases in the excitability of cortical circuits. Artificial induction of LTP- or LTD-like plasticity may therefore be able to alleviate pathological conditions such as paralysis and spasticity after stroke. Recently, a synchronous BCI protocol was proposed to close the motor-control loop and induce LTP-like plasticity. This was accomplished by pairing the cortical activation from imaginary movements (Movement related cortical potential – MRCP) with timely correlated somatosensory feedback from peripheral ES. This protocol relied on exact timing of the arrival of afferent feedback in the cortex during the execution phase of the imaginary movement. The aim of this study was to investigate the effects pairing different cortical drives of TA contraction with different sensory feedback modalities. Through six sessions the effect of pairing two sensory feedback modalities; Peripheral nerve stimulation of CPN individually and together with NMES of TA, with three types of cortical drive; execution and imagination of a fast and forceful contraction of TA as well as a slow and moderate contraction. These were investigated and evaluated through MEPs elicited by TMS. Furthermore, a control session with both types of feedback modalities without a cortical drive was conducted. Significant difference between sessions including different cortical drives indicates that changing the cortical drive can affect the induction of plasticity. No significant difference was found between the different feedback modalities.

Poster 7.1

Neuroprotective role of *Centella asiatica* extract on hydrogen peroxide-induced SH-SY5Y cells

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Although numerous studies conducted have demonstrated the antioxidant properties of *Centella asiatica*, its neuroprotective mechanisms particularly via the Nrf/ARE signalling pathway is yet to be elucidated. Thus, this study aimed to explore the neuroprotective effects of methanol extract of *Centella asiatica* against hydrogen peroxide (H_2O_2)–induced SH-SY5Y cells. Firstly, the maximum non-toxic dose (MNTD) of the extract and IC_{50} of H_2O_2 towards SH-SY5Y cells was determined via 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay. Next, SH-SY5Y cells were subjected to treatments to determine the reactive oxygen species (ROS) and nitric oxide (NO) levels using dihydro-dichlorofluorescein-diacetate (DCFH-DA) and Griess reagent, respectively. Upon treatments, the expression of inducible nitric oxide synthase (iNOS) and heme oxygenase-1 (HO-1) were measured. The MNTD and half MNTD (½MNTD) determined in this study were 32.0±8.0 µg/mL and 16.0±4.0 µg/mL, respectively. The ROS induced by H_2O_2 was significantly reduced by 50 % when the cells were pre-treated with ½MNTD as compared to the cells subjected to H_2O_2 only. Results also revealed that pre-treatment with ½MNTD of *C. asiatica* extract reduced the levels of NO as well as down-regulated the expression of iNOS by 68 % and 27.2 %, respectively when compared to the H_2O_2-induced treatment group. In contrast, the HO-1 level increased but not significant by only 1.9% upon treatment with extract. Similar results were also observed when the cells were pre-treated with MNTD of *C. asiatica* extract. The findings indicated that *C. asiatica* extract, particularly at ½MNTD exerted neuroprotective effects against H_2O_2-induced SH-SY5Y cells via Nrf2/ARE pathway.

Poster 7.2

Anterior thalamic nuclei lesions, environmental enrichment and histone H3 acetylation in the extended hippocampal system

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In humans, dysfunction of the anterior thalamic nuclei (ATN) as a result of thalamic stroke or neurodegenerative disease is associated with severe anterograde amnesia. Supporting its role in an extended hippocampal system, ATN lesions in rats produce severe spatial memory impairments, and reduce immediate early gene (IEG) expression and dendritic complexity in both hippocampus and especially retrosplenial cortex (RSC). Housing rats in enriched environments following ATN lesions ameliorates spatial memory deficits and increases hippocampal dendritic complexity, but has no effect thus far on biomarkers of RSC function. Here, we used immunohistochemistry to examine histone H3 acetylation, a key epigenetic marker, in the hippocampus and RSC. ATN lesions, regardless of housing, reduced H3 expression in both the anterior CA1 and the caudal deep granular RSC, but increased expression in the caudal superficial granular RSC. In both sham and ATN rats, enrichment decreased expression of H3 acetylation in the caudal superficial dysgranular RSC. This first evidence of changes in the RSC after enrichment and ATN lesions directs attention to the epigenetic landscape of this limbic cortex and encourages future focus on the manipulation of specific genes within this brain region to facilitate improvements in episodic memory.

Poster 7.3

The selective D_2 dopamine receptor antagonist eticlopride prevents the development of MDMA-induced behavioural sensitisation in rats

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Repeated, intermittent exposure to MDMA results in behavioural sensitisation and cross sensitisation to both amphetamine and the D_2 agonist, quinpirole. These findings suggest a dopaminergic mechanism underlying the sensitised response. The present study investigated the effect of the selective dopamine receptor D_2 antagonist, eticlopride on the development of MDMA-induced behavioural sensitisation in rats. Eticlopride (0.0 or 0.3 mg/kg, IP), was administered 30 min prior to MDMA (0.0 or 10.0 mg/kg, IP) on each of five pre-treatment days. Following two days of withdrawal, the locomotor activating effect of MDMA (5.0 mg/kg, IP) was measured. MDMA pre-treatment produced a sensitised response that was blocked by eticlopride. These data suggest that activation of the D_2 receptor is critical to the development of sensitisation to the behavioural effects of MDMA. Studies are in progress to determine the role of sensitisation in MDMA self-administration.

Poster 7.4

Unequal effects of anterior thalamic nuclei and mammillothalamic tract lesions

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The mammillothalamic tract (MTT) is associated with diencephalic amnesia after stroke, whereas a combination of anterior thalamic nuclei (ATN) degeneration and mammillary body (MB) injury is associated with the amnesic Korsakoff's syndrome. Rat studies suggest that ATN lesions produce more severe spatial memory deficits than do MTT lesions. The current study, therefore, directly compared the effects of radiofrequency MTT lesions (n=9) and neurotoxic ATN lesions (n=8). Only ATN lesions produced reference memory deficits in the Morris water maze in rats. Both lesions produced working memory deficits in the water maze. The lesion deficit in the radial arm maze (RAM) was more pronounced in the ATN group. To compare effects of these lesions on immediate early gene (IEG; zif268) expression in the extended hippocampal system, a modified RAM task was used that is sensitive to retrosplenial cortex (RSC) lesions. Both lesions markedly reduced IEG expression in the RSC; there was a graded effect in hippocampal CA1 (ATN < MTT < Control); only ATN lesions reduced IEG expression in the anterior cingulate cortex. ATN lesions, and especially MTT lesions, reduced NeuN counts in the MB. This pattern of findings suggests that severe amnesia associated with MTT lesions in humans depends on the extent of direct additional injury to the ATN and/or other adjacent nuclei. Diaschisis in the retrosplenial cortex, in terms of IEG expression, may influence only a subset of memory tasks.

Poster 7.5

The effects of Autism Spectrum Disorder associated Shank2 mutations on excitatory glutamatergic synapses

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Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterised by deficits in social communication and interactions, and repetitive behaviours. ASDs have a strong genetic basis with many mutations involved in the development and function of neural circuitry. Shank proteins act as master regulators of excitatory glutamatergic synapses and isoform specific Shank mutations have been found in ASD patients. Here we have investigated the impact of ASD-associated Shank2 mutations at the synaptic level. Dissociated rat hippocampal cultures were transfected with plasmid control (EGFP-C1), EGFP-Shank2-Wildtype (WT), and Shank2 point mutations (EGFP-Shank2-S557N, -V717F, -A729T, -R818H, -G1170R, -D1535N and -L1722P). In comparison to wild type Shank2, all Shank2 ASD-associated mutations induced significant decreases in synaptic density (p-value<0.05) in hippocampal neurons. Chronic zinc treatment was found to prevent the development of synaptic deficits in a subset of ASD-associated Shank2 mutations. Furthermore, ASD-associated Shank2 mutations significantly increased postsynaptic and presynaptic protein expression, an effect that was not seen with the wild type protein. This may be a compensation for the reduction in synaptic density; but this could only be functionally significant if the increased protein level is translated to the receptor level. Analysis of glutamate receptor expression revealed differential reductions in the density of NMDA and AMPA receptor expressing synapses in neurons with ASD-associated Shank2 mutations. These ASD-associated reductions in synapse density accompanied with reduced surface receptor levels may have adverse consequences on synapse function and the overall hippocampal circuitry, causing impairments that may underlie the intellectual disabilities and behavioural deficits characteristic of ASDs.

Poster 7.6

Thalamic brain lesions, theta and memory

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Pathology within the medial thalamus is commonly associated with anterograde amnesia. The relative contributions of different thalamic structures and their distal effects on other brain systems have not been resolved. Effects of different thalamic lesions are usually assessed by behavioural tasks to determine dissociations between hippocampal (HF) and prefrontal cortex (PFC) function. However, neural interactions between the HF and PFC may be more relevant to memory. For example, phase coherence between PFC and HF theta rhythm may strengthen memory traces. The anterior thalamic nuclei have a large population of neurons entrained by theta oscillations and the anteroventral thalamic (AV) nuclei in particular have strong reciprocal connections with both the HF and PFC. The mediodorsal thalamic nuclei (MD) have reciprocal connections with the PFC that may influence interactions with the HF. We will describe the theoretical relevance of PFC-HF interactions to develop the rationale for comparing the behavioural and electrophysiological effects of contralateral AV+MD lesions with those produced by bilateral lesions of either the AV or the MD. This approach may explain why diencephalic amnesia is often associated with partial injury to these structures and point to new therapies based on augmenting HF-PFC interactions.

Poster 7.7

The distribution of DARPP-32 neurons in the normal and Huntington's disease human striatum

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The striatum is comprised principally of medium spiny neurons (MSNs) which are arranged into neurochemically distinct matrix and striosome regions. Previous animal studies have indicated that over 95% of MSNs are positive for DARPP-32, which has led to the assumption that for the human striatum DARPP-32 is also an accurate marker of MSNs. In addition calbindin is used as the standard MSN matrix marker. In the present human post-mortem tissue study, we have shown that DARPP-32 colocalises heterogeneously with calbindin, and that in the human striatum there are three neurochemically separate populations of MSNs: 1) DARPP-32 positive 2) calbindin-positive only 3) DARPP-32 and calbindin positive only. Preliminary qualitative investigations demonstrated that the great majority of DARPP-32 positive cells in the dorsal striatum were localised in the striosomes whereas scattered DARPP-32 positive cells were localised to the matrix. These findings were confirmed with triple immunofluorescence labelling with DARPP-32, calbindin and enkephalin. Overall the number of DARPP-32 positive neurons in the striatum is less than the number of calbindin-positive neurons. The results of the present study comparing the loss of DARPP-32 positive neurons in Huntington's disease striatum with normal striatum indicate that DARPP-32 positive neurons are more resistant to neurodegeneration than calbindin-positive neurons. These findings show for the first time that the MSNs form a heterogenous group of neurons in the striatum, and that sub-groups containing DARPP-32 are less affected in Huntington's disease.

Poster 7.8

Distribution of PSA-NCAM in the brain in neurodegenerative disease

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Polysialic acid-neural cell adhesion molecule (PSA-NCAM) is a regulator of cell-cell interactions and facilitates cell migration and plasticity. As such it is a popular marker of neurogenesis and neuroblast migration, however little is known of its function in wider brain areas. This study investigated the distribution of PSA-NCAM throughout the normal, Alzheimer's and Parkinson's disease brain with a focus on cortical regions and relevant subcortical structures. PSA-NCAM was labelled using DAB immunohistochemistry on 50 µm-thick sections from 10 normal, 5 Alzheimer's and 5 Parkinson's disease brains. The percentage of area stained per region was quantified using MetaMorph high-throughput image analysis software. PSA-NCAM+ cells were observed in the middle temporal gyrus, hippocampal formation, superior frontal gyrus, sensory-motor cortex and caudate nucleus. No staining was observed in the visual cortex, cerebellum or substantia nigra. PSA-NCAM load was highly variable between individuals and present on cell bodies and processes. Interestingly PSA-NCAM+ cells were identified in the caudate nucleus, a previously unreported finding. Using cell counting techniques we found the distribution of PSA-NCAM+ cells significantly increased in the ventral region relative to the middle and dorsal regions (control cases: mean = 49.92 ± 26.40 cells/mm^2 for ventral, 22.47 ± 14.53 cells/mm^2 for middle and 15.43 ± 13.61 cells/mm^2 for dorsal region. $P < 0.001$). No significant difference was identified between disease conditions and immunofluorescent double-labelling with calretinin indicates these cells are likely to be either immature neurons or interneurons. Together these data suggest neuronal plasticity is more widespread throughout the adult brain than previously thought in both health and neurodegenerative disease.

Poster 7.9

Characterising ventroanterior motor thalamus inputs to motor cortex

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The thalamocortical pathway connects the motor thalamus to the motor cortex and has an important role in controlling movements via development of a motor programme. To do this, it receives and integrates motor information from the basal ganglia (BG) and the cerebellum. The BG receiving motor thalamus comprises ventromedial (VM) and ventroanterior (VA) nuclei, and while the innervation pattern to the cortex has been well characterised for VM motor thalamus these data are lacking for VA. The aim of this study was to determine the laminar, cell phenotype and soma-dendritic targets of VA neurons in the primary motor cortex (M1). To do this we labelled glutamatergic VA neurons with mCherry by injecting the lentiviral vector (LV-CaMKIIa-mCherry) into VA thalamus and visualised their axon terminals in M1 using confocal microscopy. At low power, we observed VA terminals primarily in layers II/III and V. Immunohistochemical staining for GAD67 and VGlut2 revealed that mCherry tagged VA neurons innervated GABA and glutamatergic neurons in M1. High power microscopy revealed VA neurons appeared to synapse onto both the soma and primary dendrites of GABA and glutamatergic neurons in layers II/III and V. Currently we are immunostaining with a marker of glutamatergic post-synaptic densities (PSD95) to determine if synaptic proteins are in the region where VA inputs are closely associated with M1 neurons. Preliminary data show VA inputs are positioned to strongly influence pyramidal and GABAergic cell activity in M1 and therefore could play an important role in the development of a motor plan and control of movement.

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Poster 7.10

Enhanced uptake of drug into the brain when delivered in BBB-targeted cubosomes

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Limited permeability of therapeutic molecules across the blood-brain barrier (BBB) poses a major challenge in developing effective therapies for neurodegenerative disorders. A promising strategy to get therapeutic concentrations of drug into the brain is by incorporating them in nanoparticles that are targeted to and able to cross the BBB. The aim of this study was to investigate if the nanoparticle platform cubosomes: (1) can be formulated with BBB-targeting ligands and (2) if BBB-targeted cubosomes improve brain uptake of drugs with limited BBB permeability. Cubosomes were prepared with three different BBB-targeting ligands: Pluronic-F127, Poloxamer-188 or Polysorbate-80. Lissamine-rhodamine, a fluorescent molecule with limited BBB-permeability was used as the model drug. Size and structure of cubosomes were determined by dynamic light scattering (DLS), cryogenic transmission electron microscopy (Cryo–TEM) and small-angle x-ray scattering (SAXS). Brain uptake of lissamine-rhodamine *in vivo* was determined in our recently established zebrafish model of the BBB. All formulations were comparable in size (160-180 nm) and homogeneous (polydispersity index <0.2). SAXS and cryo-TEM confirmed formation of cubosomes. In vivo studies showed a 3- and 5-fold increase in brain uptake of lissamine-rhodamine when delivered in Polysorbate-80 and Poloxamer 188 cubosomes, respectively, as compared to unformulated control. Increased permeability of lissamine-rhodamine was not due to BBB toxicity. Here we demonstrate that; (1) BBB-targeted cubosomes can be formulated; (2) the type of ligand strongly influences the ability of cubosomes to deliver drug cargo into the brain. Future studies are in progress to determine the mechanism of cubosome-mediated uptake of drug into the brain.

Poster 7.11

Cognitive remediation interventions in learning disorders: Assessing the evidence with multiple Monte Carlo experiments

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Developmental learning disorders affect many children, impairing their experience in the classroom and hindering many aspects of their life. Once a bleak sentence associated with life-long difficulties, several learning disorders can now be successfully alleviated, directly benefiting from promising interventions. Here, we present an assessment of the current evidence for interventions programs to remediate learning disorders, based on multiple Monte Carlo experiments. Targeted simulations allow us to better understand frequent flaws in intervention studies, and help to identify underlying mechanisms and potential remedies. Our data clearly demonstrate that several flaws are prevalent and widespread in the literature on cognitive remediation, with significant influence on experimental outcomes. Based on this evidence, we discuss the features and components of effective intervention designs, and the appeal of recent ecological trends that implement multiple components within single regimens. Finally, we provide a reflection on the current shift toward individualized remediation programs, where the content of training regimens adapts to each individual to provide personalized interventions.

Poster 7.12

Correction of pathology in ovine CLN5 Batten disease neural cultures

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The neuronal ceroid lipofuscinoses (NCL, Batten disease) are a group of childhood neurodegenerative lysosomal storage disorders characterised by cortical atrophy, blindness, seizures, impaired mental and motor function and premature death. Naturally occurring CLN5 and CLN6 disease forms are found in New Zealand Borderdale and South Hampshire sheep, respectively, and neural cells isolated from these sheep are maintained in dissociated cell cultures, providing an invaluable tool for the study of early disease progression. The aims of this study were to identify early cellular pathologies in $CLN5^{-/-}$ cultures, and to test for pathological correction using NDD1. NDD1 is a compound previously shown to correct pathologies in $CLN6^{-/-}$ neural cultures including defects in autophagy, synaptic endocytosis and lysosomal pH. In comparison to healthy cultures, affected cultures showed a 27% reduction in the number of cells undergoing synaptic dextran uptake (33% normal vs. 6% $CLN5^{-/-}$; $p < 0.05$, two-way ANOVA), a 13% reduction in cells undergoing autophagic flux (27% normal vs. 14% $CLN5^{-/-}$; $p < 0.05$), and a decrease in acidic organelles, suggestive of increased lysosomal pH (average intensity/cell, 0.098 normal vs. 0.026 $CLN5^{-/-}$; $p < 0.05$). Addition of NDD1 restored these activities to at least 95% of those in healthy control cultures in each case. These results suggest a common molecular basis underlying CLN5 and CLN6 disease and suggest NDD1 as a potential treatment.

Poster 7.13

Facial recognition memory and the *BDNF* Val66Met polymorphism: Disentangling the neural bases of recollection and familiarity

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It has recently become apparent that Brain-Derived Neurotrophic Factor (BDNF) is a principal mediator of synaptic plasticity within the central nervous system, and a dynamic modulator of learning and memory. BDNF is coded for by the *BDNF* gene. Between 25-50% of the population carry a single nucleotide polymorphism on this gene which substitutes valine (Val) to methionine (Met) at codon 66. This substitution is associated with a reduction in the secretion of hippocampal BDNF, however, the impact of this reduction on hippocampal functioning and mnemonic performance remains heavily debated. Using a modified version of a standard recognition memory paradigm, the aim of the current fMRI study was to examine the impact of the *BDNF* Val66Met polymorphism on the neural circuits underlying recognition of famous and newly learnt non-famous faces. Based on the prolific (yet controversial) Dual Process Model of recognition memory, it was hypothesised that recollection- and familiarity-based recognition would activate distinct neural circuitry centred on the hippocampus and perirhinal cortex respectively. Additionally, these circuits would be differentially impacted by the Val66Met polymorphism. No behavioural differences between Val homozygotes and Met carriers were identified, however, the genotype groups did exhibit differences in BOLD activation. Val homozygotes demonstrated greater activation across various components of the hippocampal-based recollection circuit. Conversely, Met carriers unexpectedly demonstrated greater anterior temporal activation, which putatively overlaps with the familiarity circuit. Coupled with further significant clusters implicated in hippocampal-independent memory circuitry, it is suggested that Met carriers may employ compensatory activity to account for deficits in hippocampal BDNF secretion. Crucially, genotype differences were only revealed once recollection and familiarity were separated, thus supporting the qualitative distinction proposed by the Dual Process Model, as well as potentially accounting for disparate results from previous studies of the Val66Met polymorphism assessing recognition as a single construct.

Poster 7.14

Use of single-cell RNA-Seq to molecularly define human Cajal-Retzius neurons

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The human nervous system is composed of diverse cell types. Recently, next-generation single-cell RNA sequencing has enabled expression profiling of individual cells. Our group has performed whole-cell patch clamp electrophysiology followed by cytoplasm extraction and RNA sequencing for neurons from human adult neocortex and fetal brain and spinal cord of gestational weeks 10-20. We have applied a modified aRNA method (Van Gelder et al., PNAS 87:1663-7, 1990) and modified NuGen Ovation RNA-seq V2. The reads were mapped and assigned to genes using GT-FAR (Genome- and Transcriptome-Free Analysis of RNA-Seq). Heterogeneity of gene expression was evident between cells from different types of tissue when the data were analyzed for Principle Components (PC). Cajal-Retzius neurons are of special interest, as they are morphologically distinct and large cells sparsely located in the marginal zone of the developing fetal cortex, where they may play a role in defining the layered structure of the cortex. Defects in these cells have been implicated in schizophrenia and autism. PC analysis shows that the Cajal-Retzius neurons are molecularly distinct from fetal subplate neurons, and distinct sets of genes are significantly over- and under-expressed in these cells. Electrophysiological recording revealed for the first time that human Cajal-Retzius neurons have spontaneous synaptic activity and action potential firing. Pathway analysis of the gene expression data (using Ingenuity Pathway Analysis) suggests that the synaptic activity may be mediated by GABA, glutamate, serotonin, and dopamine. Our data illustrate the potential synergism of combining both functional and transcriptome analysis at single-cell level.

Poster 7.15

Interactive effects of *DAT1* genetic variants and the antenatal environment on childhood depressive symptoms

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According to the diathesis-stress model of behaviour, predispositional vulnerability in conjunction with certain environmental stressors can influence the occurrence of depression. Existing research on adolescents and adults indicates that this predisposition may be partly explained by variation in monoaminergic genes. However, research investigating the genetic determinants of depression in children and the moderating influence of early life stressors is limited. To address this gap in the literature, this study investigated whether single nucleotide polymorphisms (SNPs) from monoaminergic genes interacted with measures of early life stress to influence depressive symptoms in children from the Auckland Birthweight Collaborative cohort. Small for gestational age (SGA) and antenatal maternal stress were used as indicators of early life stress. When the cohort was at 11 years, depressive symptoms were measured using the Centre for Epidemiological Studies Depression Scale for Children (CES-DC) and DNA samples were collected for genotyping. Results revealed that SGA and two SNPs from the dopamine transporter gene *DAT1* had interactive effects on depressive symptoms in children. Specifically, children born SGA who are T homozygous for the rs1042098 SNP and C homozygous for the rs3863145 SNP had greater mean depressive symptoms at 11 years. These findings suggest that adverse intrauterine environments leading to a small birth weight for gestational age also seem to exacerbate the effects of certain *DAT1* variants on depression in children.

Poster 7.16

Immersive exer-gaming and cognitive function in sedentary young adults

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Exercise training interventions and cognitive training interventions have each been extensively studied in populations with cognitive impairments, such as mild cognitive impairment, dementia and Alzheimer's disease. This study aimed to determine the extent of the combined training effects of an immersive virtual reality exer-gaming intervention in sedentary young adults, on cognitive performance. The sedentary young adult population has been identified as being high risk for developing arteriosclerosis due to low cardio respiratory fitness levels. Arteriosclerosis has also been identified as a predictor of cognitive decline in later adult life. Participants were randomly allocated and counter balanced into one of two acute exercise conditions, an exercycle-only condition or an exer-gaming condition. The exercise protocols in each condition were matched for time duration and intensity; therefore the only difference in conditions was involvement in the immersive exer-game. Questionnaires and a battery of cognitive tasks were administered both before and after participation in each condition. The battery of cognitive tasks tested cognitive performance on planning, problem solving, set-shifting, executive function, organization, goal-maintenance and context processing. Hypotheses predict that cognitive performance will significantly improve after completing the exer-game condition, in comparison to the exercycle-only condition. The exer-gaming intervention involves cycling wearing an oculus rift, where participants are mentally immersed in a 3D virtual reality cycling world. Their aim is to physically and mentally maneuver throughout the cycle track collecting bonuses and avoiding obstacles. Preliminary data show both the exer-game and exercycling conditions improve motivation and cognitive function compared to baseline measures. However, the data also show that the exer-game condition heightens the cognitive functions and motivation factors tested, more so than exer-cycling alone. This study shows the combined effects of exercise cognitive training in immersive virtual environments are beneficial for cognitive performance in sedentary young adults.

Poster 7.17

Mutant huntingtin alters NMDA receptor distribution by changing the balance between SAP97 isoforms

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Huntington's disease (HD) is a neurodegenerative genetic disorder caused by an expansion of a CAG repeat tract in the huntingtin gene. Characteristics of the disease include decline in cognitive, motor, and psychiatric functions that originate predominantly from neuronal loss in the striatum and cortex. However, hippocampal abnormalities have also been reported. Multiple studies aiming to determine the source of synapse dysfunction in HD suggest that extrasynaptic NMDA receptors (NMDARs) drive neurodegeneration as transgenic HD mouse models exhibit an increased number of these receptors early in development. Extrasynaptic NMDARs when excessively stimulated can trigger cell death signaling pathways, whereas activity of receptors located within the synapse promotes neuronal survival. Several proteins are known to be responsible for trafficking and distribution of glutamate receptors within neurons. One of such proteins is Synapse-associated protein 97 (SAP97). Alternative splicing of SAP97 gives rise to its two main isoforms: αSAP97 and βSAP97. Our data have shown that βSAP97 isoform plays a major role in trafficking glutamate receptors to the extrasynaptic membrane while αSAP97 is located mainly in the post-synaptic densities (PSDs) where it acts as a scaffolding protein creating docking sites for the receptors within the PSD. In both animal and cellular models of the disease, our data also suggest that the maldistribution of glutamate receptors seen in HD is caused by changing the relative balance of alpha versus beta SAP97 isoforms. Moreover, while surface NMDAR levels in mutant huntingtin-expressing neurons increase, AMPA receptors seem to remain unaffected. Based on our results we hypothesise that reinstating normal SAP97 isoform balance may lead to recovery of synapse function in HD and prevent neurons from degeneration.

Poster 7.18

Regulation of MicroRNAs at dentate gyrus synapses after long-term potentiation induction *in vivo*

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Regulation of translation of synaptic messenger RNA (mRNA) is likely to contribute to the altered synaptic proteome necessary to consolidate long-term potentiation (LTP), a model of memory processes. MicroRNAs are non-coding RNAs that negatively regulate gene expression by suppressing translation and/or degrading mRNA. As specific microRNAs are synaptically located, we propose that they are ideally suited to couple synaptic activation, translational regulation, and LTP persistence. This study profiled LTP-regulated microRNAs at dentate gyrus synapses. LTP was induced unilaterally at perforant path-dentate gyrus synapses in awake adult male Sprague-Dawley rats using high frequency stimulation (400 Hz, 50 pulse trains). Five hours later, the dentate gyrus middle molecular layer, containing the potentiated synapses, was laser-microdissected from coronal cryosections. Total RNA, including microRNAs, was isolated (Norgen) from matched stimulated and control tissue. MicroRNA expression was profiled using TaqMan Low Density MicroRNA Microarrays (n = 4; Life Technologies). Comparison of eight normalisation strategies determined that normalisation using miR-301b decreased technical variance most successfully. One-sample t-tests identified eight differentially expressed microRNAs (fold change ± 15%; $p < 0.05$). Individual TaqMan assays confirmed up-regulation of miR-23a-3p (fold change = 1.30; $p = 0.015$) and miR-151-3p (fold change = 1.17; $p = 0.045$) in a second set of animals (n = 7). This is the first report of synaptically-localized microRNA regulation in response to LTP induction *in vivo*. These results support the hypothesis that synaptic, LTP-responsive microRNAs contribute to LTP persistence via regulation of the synaptic proteome.

Poster 7.19

16-Bromosalvinorin a modulates dopamine transporter function in a kappa opioid receptor and erk1/2-dependent manner

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Psychostimulant abuse is a major health, social, and economic burden worldwide, with no current FDA approved therapeutic available. The dopamine transporter (DAT) which primarily clears dopamine from the synapse following drug intake terminates the rewarding effects of drugs. Although the kappa opioid receptor (KOPr) modulates DAT function, traditional KOPr agonists present adverse side effects such as sedation and depression. The structurally novel non-nitrogenous KOPr agonist 16-bromosalvinorin A (16-brSal A), derived from Salvinorin A (Sal A), attenuates drug seeking behaviour with less side effects compared to traditional agonists. We therefore investigated the effects of 16-brSal A on DAT function. Live cell confocal microscopy studies with DAT and KOPr expressing Human Embryonic Kidney cells showed that 16-brSal A (10 µM, $p<0.05$) significantly increased DAT function (20%, one-way ANOVA with Bonferroni's post-test) without affecting cell surface expression of DAT measured using cell surface biotinylation methods. Prior incubation of cells with the selective KOPr antagonist nor-binaltorphimine or MEK1/2 inhibitor U0126 prevented this increase, showing that KOPr activation by 16-brSal A regulates DAT function in an ERK1/2- and KOPr-dependent manner. Modulation of DAT function by 16-brSal A is also observed in striatal rat brain tissue. Using rotating disk electrode voltammetry, 16-brSal A (500 nM) caused a significant KOPr-mediated increase in DAT function in the dorsal striatum (49%, $p<0.05$) and nucleus accumbens (50%, $p<0.01$) of rats. Studies investigating the modulation of DAT function by novel KOPr agonists will help elucidate cellular mechanisms underlying the anti-addiction effects of these compounds, and aid in the development of anti-addiction therapeutics.

Poster 7.20

Copper, zinc, iron, and manganese in the healthy and Parkinson's disease human brain

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Metals such as zinc, iron, copper, and manganese have essential roles in the brain and their levels are usually tightly regulated. In neurodegenerative diseases, concentrations of these metals are altered in affected brain regions. In the Parkinson's disease substantia nigra, zinc and iron are increased and copper is decreased compared to controls, and manganese neurotoxicity presents with Parkinson's-like symptoms. However, detecting metals in the human brain has long been a challenge on the basis of spatial resolution and accuracy of measurement. Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) allows quantitative measures of metal species to be acquired at a detailed anatomical level (30–40 µm resolution). In this study, LA-ICP-MS was used to compare zinc, copper, and manganese concentrations in the subventricular zone and caudate nucleus of both control and Parkinson's disease brains, and to show the distribution of these metals and iron in the olfactory bulb. Histological stains were also used for ferric iron and free zinc in these regions. Results from LA-ICP-MS showed that zinc was increased in the Parkinson's disease subventricular zone (24 ppm compared to 14 ppm in controls), but there were no significant changes in any other metals or regions. Clear regional differences in metal concentrations were observed using LA-ICP-MS, and histological stains showed similar patterns of metal distribution. This study highlights the use of LA-ICP-MS as a powerful method for measuring metal concentrations in specific brain regions, and points to possible entry sites in the brain for the metals that are implicated in the pathology of Parkinson's disease.

Poster 7.21

Characterisation of human brain pericytes *in situ* and *in vitro*

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Pericytes are a cell type that surrounds capillaries, and play important roles in maintaining vessel health and blood-brain barrier integrity in the brain. Pericytes tend to be identified by the expression of the proteins PDGFR-β or NG-2, but there has been speculation that brain pericytes occupy a wider range of phenotypes including more mature myofibroblast-like and immature mesenchymal stem cell phenotype. This research used immunohistochemistry of sections taken from the middle temporal gyrus and hippocampus of neurologically normal, post-mortem human brains (n = 3) and determined the expression of the proteins CD146, CD90, CD73, α-SMA and NG-2 in the vascular region. Expression patterns were similar in both brain regions. To determine if these were expressed in pericytes, sections were double-labelled with PDGFR-β and the other proteins. CD146 was found to be expressed in pericytes surrounding larger vessels, and to colocalise with smooth muscle cell marker α-SMA. CD90, CD73 and NG-2 were predominantly located in capillaries where they co-localised with PDGFR-β. These findings were reiterated in primary human brain pericyte cultures (n = 3, from the same cases studied *in situ*) *in vitro* where they were also found to express these proteins. Interestingly, CD146 and α-SMA expression was strongly co-localised *in vitro* as well as *in situ* validating our *in vitro* models. These results indicate that pericytes express a broad range of markers, many with unknown function, and that some of these, such as CD146, pick out specific populations of pericytes. In future studies I plan to use siRNA to knock-down these various markers and determine their functional roles in human brain pericyte biology.

Poster 7.22

Measuring the inner ear permeability using DCE-MRI

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Dynamic contrast enhanced MRI (DCE-MRI) is a methodological framework that can be used to characterize physicochemical properties of biological tissues and permeability of the vasculature. It relies on an intravacular bolus injection of a Gadolinium based contrast agent (GBCA, Dotarem©, dose: 0.1 mM/kg) and enables the concentration of GBCA in tissues to be quantified over the time. From such measures it is possible to use pharmacokinetic models to estimate vascular permeability. Taking this framework into consideration, we are studying the permeability of the blood labyrinth barrier (BLB) in the normal and diseased cochlea in animals and humans. Studying cochlear vascular permeability is challenging as it is a small organ with relatively large fluid spaces and a tight vascular barrier. Here we report on the use of a particular T1-weighted VIBE sequence (TR/TE=20/3.7 ms, matrix=512*512*44, FOV=1329*759*25mm, 5 minute acquisition time) in human subjects using a 3T MRI (Siemens Skyra). This sequence has the advantages of being sensitive to small enhancements, a high resolution (spacing= [0.3,0.3]mm, slice thickness=0.5mm). We compare results with a Fluid Attenuated Inversion Recovery (3D-FLAIR) pulse sequence (TR/TE=9000/122ms, matrix=324*384*12, FOV=1020*510*10mm, 5 minute acquisition time) which has been used to qualitatively assess cochlear vascular permeability. To verify pharmaocokinetic models the DCE-MRI sequences were also tested with GBCA phantoms to quantify noise sequences and validate GCBA concentration measurements. We measured changes in the cochlea and vestibule MRI signal using both sequences with a maximum signal intensity occurring about 4 hours after GBCA injection. The reported VIBE sequence allowed estimates of the uptake of GBCA in the different inner ear compartments and consistent quantification of the permeability of the BLB on human with and without hearing deseases respectively 3.6×10^{-4} min^{-1} and 0.8×10^{-4} min^{-1}.

Poster 7.23

Oleoylethanolamide incorporation into lipid nanoparticles for brain delivery: Physical characterisation and *in vitro* cytotoxicity

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Oleoylethanolamide (OEA) is an endogenous lipid with neuro-protective properties. However, rapid hydrolysis limits therapeutic applications. We propose that incorporating OEA into self-assembled lipid nanoparticles (cubosomes) may offer protection from hydrolysis and enable therapeutic concentrations to be reached and maintained in the brain. Nanoparticles were prepared by co-formulation of OEA (50% w/w) with the cubosome-forming lipid phytantriol, along with a surface stabiliser (Poloxamer 407, Poloxamer 188 or Polysorbate 80). Size and structure of the nanoparticles were characterized by dynamic light scattering (DLS) and cryogenic transmission electron microscopy (Cryo–TEM). *In vitro* cytotoxicity was evaluated using the human cerebral microvascular endothelial cell line, hCMEC/D3. Cells were incubated with cubosome formulations for two hours at concentrations ranging from 0-50 µg/mL total lipid, then stained with propidium iodide (PI) prior to flow cytometry analysis. DLS revealed an average particle size of less than 200 nm for all three formulations, with polydispersity indices (PDI) ranging from 0.1-0.3. Cryo-TEM images showed the presence of cubosomes with sizes corresponding to DLS measurements. Flow cytometry data showed cell viability similar to control up to lipid concentrations of 15 µg/mL for the Poloxamer 407 formulation and up to 20 µg/mL for the Poloxamer 188 and Polysorbate 80 formulations. This study demonstrates that OEA can be co-formulated with phytantriol and a variety of stabilisers to form cubosome nanoparticles, which can be incubated with hCMEC/D3 over a non-toxic concentration range. Future studies will investigate the *in vitro* uptake of the cubosomes by hCMEC/D3.

Poster 7.24

Targeting insulin-like Growth Factor-1 signalling for treatment of preterm brain injury

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Very preterm infants have high rates of life-long disability, which are strongly associated with exposure to infection around birth. The major of pattern of brain injury in preterm infants involves white matter damage, with selective death and impaired maturation of oligodendrocytes, the cells responsible for myelination. We examined the hypothesis that impaired white matter development following preterm infection is caused by altered insulin-like growth factor-1 (IGF-1) signaling, a neurotrophic factor critical for oligodendrocyte survival and maturation. Further, restoring IGF-1 signaling may be a therapeutic approach to promote normal brain development. Sprague-Dawley rat pups were randomly assigned to daily injection of saline (control), lipopolysaccharide (LPS; 0.3mg kg i.p.), cyclic glycine-proline (cGP; 0.1mg/kg i.p.), or LPS + cGP groups at postnatal day 1 (PND1) or PND1–3. Animals were recovered to PND2, 4, 7, and 14. Exposure to LPS was associated with a significant decrease in IGF-1 concentrations in the blood compared to controls ($p<0.0001$) at PND2, whereas in the brain, there was a significant increase in IGF-1 levels versus controls at PND2 ($p<0.0001$), which then resolved by PND4. By contrast, phosphorylated IGF-1 receptor-b protein expression was decreased in the brain at PND4. Acute treatment with cGP restored circulating IGF-1 levels in LPS animals, and significantly reduced cell death ($p=0.0023$), while delayed cGP treatment improved oligodendrocyte survival and maturation ($p=0.0022$). This study suggests that increasing IGF-1 signalling may be a therapeutic strategy to promote white matter development following preterm infection/inflammation.

Poster 7.25

White matter and cortical brain injury in the very immature rat following lipopolysaccharide-induced mild systemic inflammation

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Subclinical inflammation is a major cause of preterm birth and brain damage, often resulting in motor and cognitive disability. However, the precise mechanisms behind inflammation-mediated brain damage remain unclear. This study aimed to examine whether mild systemic inflammation causes white matter/cortical injury in the preterm-equivalent rat. Postnatal day (PND) 1–3 Sprague-Dawley rats received lipopolysaccharide injections (LPS; 0.3mg/kg/day) and were recovered until 4 hours, 12 hours, PND2, 4, 7, 14, or 21. Brains underwent analysis of the acute inflammatory response, oligodendrocyte/neuron survival/maturation, and white matter/cortical volume changes. LPS was associated with acute upregulation of cyto/chemokines in plasma and brain, and reductions in white matter (Sham, 24.6±0.9 *vs.* LPS, 17.0±0.3mm^3; $P<0.01$) and cortical (Sham, 321.3±9.6 *vs.* LPS, 287.0±8.6mm^3; $P<0.05$) volumes at PND21. Degenerating nuclei (Sham, 720±60 *vs.* LPS, 1164±126 cells/mm^3; $P<0.01$) and total olig2$^+$-oligodendrocytes (Sham, 93,334±5570 *vs.* LPS, 73,3044±4358 cells/mm^3; $P<0.05$) were increased and decreased respectively in the white matter after LPS at PND4. Total olig2$^+$-oligodendrocytes returned to control levels by PND14, corresponding with a decrease in PDGFRa+ oligodendrocyte progenitor cells (PND4: Sham, 52,488±3,226 *vs.* LPS, 34,133±2,930 cells/mm^3; $P<0.01$), and a proliferative response from PND7–PND21 (peak PND14: Sham, 34,070±1,988 *vs.* LPS, 58,526±9,287 cells/mm^3; $P<0.05$). By PND14 there was a decrease in the ratio of CC1$^+$ mature oligodendrocytes/total olig2$^+$-oligodendrocytes (PND21: Sham, 80±4% *vs.* LPS, 62±7%; $P<0.01$). LPS had no effect on numbers of cortical neurons (PND21: Sham, 2.22x10^7 *vs.* LPS, 2.15 x10^7 cells). Mild systemic inflammation in rats is associated with persisting alterations in white matter and cortical development. Studies examining cellular mechanisms of oligodendrocyte arrest and regenerative treatments are ongoing.

Poster 7.26

The neural mechanisms of encoding effortful space

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It is well established that the hippocampus plays a vital role in forming a representation of our world which aids in episodic memory formation and spatial navigation. To do this, the hippocampus associates aspects of an environment with when and where they occur. A majority of studies utilize flat, horizontal surfaces to investigate hippocampal coding of spatial information. Our environments are, however, rarely so simple and often contain elements, such as hills and valleys, with an effort cost associated with their traversal. The anterior cingulate cortex (ACC) is a prefrontal brain region known to anticipate and encode effort. We were interested, therefore, in how ACC and the hippocampus might communicate during navigation through a tilted, costly environment. Hippocampal and ACC single unit and local field potential activity was recorded in behaving rats as they ran back and forth in a shuttle box for a small, constant reward at each end. The shuttle box was tilted to different pitches, flat, 15 degrees, or 25 degrees, during recording sessions to introduce an effort-space Affordance-Engagement-Cost (AEC). Neurons in both the hippocampus and ACC responded to the tilted conditions by rate coding the amount of effort each condition required. Furthermore, during tilted conditions, significantly more hippocampal cells were phase locked to anterior cingulate theta (8-10Hz) oscillations than in the flat. The population of hippocampal cells phase locked to the ACC theta rhythm were also synchronised to a more similar phase angle for tilted conditions. These data indicate neurons in the ACC and hippocampus synchronise activity via theta rhythm entrainment during the experience of effort. This may serve to incorporate effort as an Affordance-Engagement-Cost within the hippocampus' representation of the world.

Poster 7.27

Interneuron loss in the cerebral cortex correlates with symptom heterogeneity in Huntington's disease

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Huntington's disease (HD) is characterized by variable symptoms and neuropathology in the basal ganglia and cerebral cortex. Our recent studies have shown that motor and mood symptoms of HD are respectively related to pyramidal cell loss in the sensori-motor cortex (primary sensory, primary and secondary motor cortices) and limbic cortex (anterior cingulate cortex) in the HD human. In the cortex, neural networks consist of two broad classes of neurons: excitatory pyramidal neurons and inhibitory interneurons. We have now extended these studies in the same HD cases to the cortical interneurons to determine whether interneuron loss also correlates with symptom profile, and is linked to pyramidal cell loss in these cortical regions. Stereological counting methods were used to quantify three major types of interneurons (calbindin-D28k, calretinin, parvalbumin) in four different cortical regions of 14 HD and 13 control cases of *post-mortem* human brain. The HD cases were grouped according to their predominant symptom profile ("motor", "mood", "mixed"). The results demonstrated a heterogeneous loss of interneurons across the four cortical regions, which was associated with the pattern of pyramidal cell loss in the same cortical areas. Most interestingly, the pattern of interneuronal loss in these cortical regions correlated with the variable symptom profiles in the HD cases. These findings extend our understanding on the role of the cerebral cortex in HD pathogenesis and symptom phenotypes by showing a precise correlation between cortical interneuronal loss and heterogeneous symptomatology in HD.

Poster 7.28

Prefrontal cortex stroke disrupts cholinergic pathways and impairs learning

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Cholinergic pathways have been shown to play a critical role in visual attention tasks and motor learning. Further disruption in cholinergic signaling has been linked to both dementia and impaired stroke recovery. We have recently reported that stroke to the prefrontal cortex results in delayed onset impairment in spatial memory similar to what is observed in human stroke patients. Using this newly established model of stroke, we aimed to further investigate the extent of the impairments using the reaching task for motor learning and the five-choice serial reaction time task (5-CSRTT) for assessing visual attention using operant-based touchscreens. Assessment of mice following prefrontal cortex stroke revealed a significant impairment in motor learning on the reaching task at 1 and 4-weeks post stroke ($P \leq 0.05$; n=15 per treatment group). As motor learning requires intact cholinergic signalling, we hypothesise that a disruption in cholinergic signalling is contributing to these impairments. Therefore, further studies are currently investigating changes in cholinergic cell populations and fibre densities, in addition to assessing impairments in attentional load using the 5-CSRTT. We suggest that this model will lead to a better understanding of stroke-induced cognitive impairments and can be used to investigate therapeutic interventions for translation into the clinic.

Poster 7.29

Vascular degeneration in Parkinson disease

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We have previously reported endothelial cell degeneration in Parkinson's disease (PD) brain. The current study examined the changes in various parameters including basement membrane, pericytes, angiogenesis, and their association with vascular and neuronal degeneration in PD. The present study used the grey matter of middle frontal gyrus from post-mortem human PD brain and age-matched control cases. Immunohistochemical staining of collagen IV, platelet-derived growth factor receptor-beta (PDGFβR), NeuN, proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), and phosphorylated insulin-like growth factor 1 receptor (IGF1Rp) were observed and quantified using image analysis programmes. Overall basement membrane density was similar between PD and controls. The density of string vessels increased in PD brains (p=0.0331). Compared to controls, the density of pericyte-associated blood vessels () and neurons) were reduced in PD (p=0.0416 and p=0.0101 respectively). The density (cells/mm^2) of VEGF-positive cells and capillary associated PCNA-positive cells) were also reduced in PD (p=0.0164 and p=0.0426 respectively). There was a reduction in average density of vascular IGF1Rp-positive cells in PD (approximately 30% reduced, although not statistical significant). Also there was a strong linear correlation with the density of vascular PCNA-positive cells which correlated with the pericytic changes. In conclusion, the results suggest that the basement membrane of the capillaries is retained in PD brains, but there is increased string vessel formation as a result of endothelial cell degeneration which might be caused by impaired vascular remodelling due to the loss of trophic support from IGF-1. Hypoperfusion may thus play a role in the neuronal degeneration of PD.

Poster 7.30

Characterising the target innervations of glutamatergic neurons in the reticular thalamic nucleus

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The reticular thalamic nucleus (RTN) is a thin band of neurons that receives inputs from the cortex and sensory and motor thalamic nuclei. The rostral RTN (rRTN) is the motor portion, which receives inputs from structures involved in the initiation and execution of movement, such as, basal ganglia nuclei (globus pallidus internus and externus and substantia nigra pars reticulata and compacta), the motor thalamus and the motor cortex. Historically, neurons in the RTN have been reported to be exclusively GABAergic, however, a recent study in our lab characterized a small novel glutamatergic population in the rRTN. To understand the role that these rRTN glutamatergic neurons may have in motor control, this study characterized their synaptic targets. A lentiviral vector (LV-CaMKIIα-mCherry) was injected into the rRTN to selectively label glutamatergic neurons with the fluorescent protein mCherry. Six weeks later, the specificity of mCherry expression was verified using double immunohistochemical staining and images were obtained using a confocal microscope. This confirmed a new functional population of glutamatergic neurons in the rRTN, and preliminary results suggest that they sparsely innervated the dorsolateral striatum and ventroanterior-ventrolateral (VAVL) motor thalamic nuclei, mostly to the proximal dendrites and soma of non-GABAergic neurons. Our study shows that the rRTN may have a complex role in motor control through its excitatory and inhibitory innervations to the striatum and the motor thalamus. This also raises a potential novel target for therapeutic strategies for movement disorders, such as Parkinson's disease.

Poster 7.31

TNFα mediated heterodendritic metaplasticity in the rat hippocampus

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Long-term potentiation (LTP) is an activity-dependent long-lasting increase in the efficacy of synaptic transmission. LTP is vital for learning and memory so must be regulated to keep within optimal boundaries. For example, LTP is regulated by *metaplasticity* which refers to activity-dependent changes in neuronal state that shapes the direction, duration or magnitude of future synaptic change. Previously we described heterosynaptic metaplasticity in the hippocampus in which strong high-frequency priming stimulation in stratum oriens (6x100 Hz) inhibits subsequent LTP elicited in the stratum radiatum of area CA1. Evidence to date indicates that this form of metaplasticity is independent of post synaptic depolarization and action potential firing and may instead be mediated by activation of nearby astrocytes. In this model, gliotransmitters (e.g. Tumour Necrosis Factor α or TNFα) released from astrocytes may signal back to neurons to inhibit future LTP. To investigate this, acute hippocampal slices were prepared from male Sprague-Dawley rats (6-8 weeks) and field excitatory postsynaptic potentials were recorded from area CA1 following stimulation of Schaffer collateral fibres. Bath application of TNFα antibody (50 µg/50 ml) prior to and during priming partially rescued the depression in LTP (control=141±6%, primed=123.6±4%, primed+drug=132.4±6%; N=7). However, slices preincubated with TNFα antibody (25µg/ml) completely rescued the reduction in LTP (control=142.3±3%, primed=126.8±5%, primed+drug=142.6±4%; N=7). Furthermore, bath application of thalidomide (blocks TNFα m-RNA synthesis; 5 µM) throughout the experiment also abolished the depression in LTP (control=150.4±4%, N=7; primed=127.6±6%, N=6; primed+drug=150.6±7%, N=5). Our findings validate the important role of TNFα, possibly released from astrocytes, in mediating heterosynaptic metaplasticity in CA1 region of rat hippocampus.

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Poster 7.32

Prefrontal cortex stroke induces delayed impairment in spatial memory

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Stroke is a leading cause of long-term disability. To date, experimental research has primarily focused on improving motor deficits. However, epidemiological evidence shows that memory is also affected after stroke and is more often observed at a delay, weeks to months after the insult. Here we have established a photothrombotic model of focal stroke that targets the medial prefrontal cortex (mPFC), in an effort to model the clinical setting of delayed impairment in memory. Assessment of stroke mice in the open-field showed a small increase in activity with no effects on gross motor tasks 1 and 4-weeks post stroke. Similarly, stroke to the mPFC had no effects on anxiety ($P \geq 0.05$). Assessment of stroke mice on the novel object task showed no differences at either 1 or 4-weeks compared to sham mice ($P \geq 0.05$). However, assessment of stroke mice on the object-location recognition task revealed a significant ($P \leq 0.05$) impairment in spatial memory by 4-weeks compared to sham controls. Preliminary evidence also suggests that mice trained using operant-based touchscreens for associative learning on a pairwise discrimination task; show a trend towards impaired learning, during the re-reversal phase 5-6 weeks post-stroke. This is the first experimental evidence that stroke to the mPFC result in a delayed onset impairment spatial memory, a finding that is similar to human epidemiological data. We suggest that this model may therefore be a useful tool in assessing potential rehabilitative/cognitive therapies after stroke.

Poster 7.33

Anxiolytic drug action in the stop signal task: α-asymmetry is not like goal conflict-specific rhythmicity

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Anxiolytic drugs have been proposed to act by changing rhythmicity in the Behavioural Inhibition System (BIS), which acts to resolve goal conflicts. Goal-conflict-specific rhythmic activation in the Stop Signal Task (SST) is decreased by all classes of anxiolytic drugs. A decrease in right, relative to left, frontal 8-12Hz rhythmicity (α-asymmetry) has also been suggested to reflect activation of the BIS but has alternatively been linked to active withdrawal. These alternate hypotheses would predict th[illegible]ics would increase or not change, respectively, α-asymmetry. Thirty-six participants, recr[illegible] Search, were administered double-blind with placebo, buspirone (10mg[illegible] pregabalin (25mg) and then performed the SST task. The placebo group showed [illegible]symmetry on Go trials consistent with having greater approach activation (left frontal) than avoidance activation (right frontal). A similar pattern was seen in the θ band (4-7Hz). Buspirone and triazolam each decreased both α- and θ rhythmicity on the right contrary to the postulated relationships of α-asymmetry to either behavioural inhibition or avoidance. However, unlike with conflict-specific rhythmicity, pregabalin had opposite effects on α- and θ-asymmetry to the other anxiolytic drugs. Thus, α-asymmetry in GO trials of the SST is pharmacologically unlike concurrently measured conflict-specific rhythmicity in STOP trials. It also appears to be functionally distinct from the α-asymmetry recorded in the resting state with eyes closed. One possible explanation of these results is that GO trial α- and θ-asymmetry could reflect right frontal rhythmic activation linked to strategic anticipatory slowing, the control of which shows only partial overlap with stopping and the control of goal conflict.

Poster 7.34

Interplay of spontaneous activity and metaplasticity in the computational model of the dentate granule cell

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Long-term potentiation (LTP) and long-term depression (LTD) are two well-known forms of synaptic plasticity. It has been shown *in-vivo* experiments that granule cells in the hippocampal dentate gyrus manifest *homosynaptic* LTP on the medial perforant path (MPP) and concurrent *heterosynaptic* LTD on the lateral performant path (LPP) due to medial high frequency stimulation (HFS). Another important factor revealed by experimental studies is the phenomenon of *metaplasticity*, which means that the history of previous pre- and postsynaptic activity affects the outcome of current synaptic plasticity. In this study we use a biophysically realistic model of granule cell to gain insight into the role of metaplasticity in heterosynaptic plasticity. Our synaptic plasticity model is based on spike-timing-dependent plasticity rule modified to include the metaplasticity term. In addition, we realistically simulate *in vivo* ongoing spontaneous activity, which we show to have a profound *homeostatic* impact on the meta- and synaptic plasticity of the granule cell model. First, the input spontaneous activity is applied to both MPP and LPP all the time and HFS is applied to MPP twice. We observe no further increase in the magnitude of LTP and LTD after the second HFS. Next, we turn the LPP spontaneous activity off during the first medial HFS. We observe no lateral LTD during the first medial HFS and virtually no LTD during the second HFS provided the frequency of the lateral spontaneous activity does not return to the pre-HFS level.

Poster 7.35

Investigating the neural mechanisms of analgesic properties of anaesthetic drugs with MEG

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The mechanism of action of anaesthetic-induced analgesia is poorly understood. Increasing this understanding could aid in the search for a reliable objective pain measure. Such a measure could decrease our reliance on the subjective self-reports of pain. There is currently no published research that involves analysing oscillatory magnetoencephalography (MEG)/electroencephalography (EEG) activity in sedated patients who are exposed to painful stimuli. In the current study, participants were administered either propofol, dexmedetomidine, or a placebo, in a cross-over design, and a cold pack was used to implement a cold pressor test (thought to resemble postoperative pain). The cold pack was left on for one minute past the participant's individual pain threshold in five trials, and was alternated with a warm pack as a recovery period. Oscillatory MEG activity was compared between the cold pain periods and the warm pack periods, using a nonlinear beamformer analysis to localise oscillatory power changes in the brain in pre-defined frequency bands. It was found that both propofol and dexmedetomidine administration resulted in a significant lessening of the decrease in alpha (8-13 Hz) and beta (13-30Hz) oscillatory activity seen during pain, in occipital, temporal, and parietal areas, as compared to placebo. There were no significant differences found between the two drugs. Further analysis will map the temporal evolution of the changes in regions of interest. This study confirms the usefulness of MEG in the study of pain and anaesthesia.

Poster 7.36

Electrophysiological components of attentional control predict individual performance on a concurrent working memory task

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While working memory and selective attention have traditionally been viewed as distinct processes in human cognition, there is now a growing body of literature which demonstrates significant overlap between these two constructs. One line of evidence for the presence of this relationship comes from between-subject designs in which individuals low in working memory capacity show greater interference in standard attention-based tasks. The specific neural mechanisms involved in this interaction are still unknown, however three lateralised ERP components have been identified as ideal candidates for studying the neural underpinnings of attention processes. N2pc, Ptc, and SPCN have been associated with object selection, attentional disengagement, and short term maintenance of target features respectively. In this study we measured these components during the delay period of a working memory task in order to see whether they could predict performance on the working memory task. The results showed that working memory accuracy and response times were consistently predicted by the amplitude of the Ptc component. In our analyses, individuals who produce a larger Ptc during visual search are predicted to perform faster and more accurately on the working memory task. These results provide direct neural evidence which is consistent with suggestions that a larger working memory capacity allows for more efficient disengagement from irrelevant objects during visual search.

Poster 7.37

Maternal cyclic-glycine-proline treatment during lactation enhances the growth and cognition of offspring in rats

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Cyclic-glycine-proline (cGP), an Insulin-like growth factor-1 metabolite, provides neuro-protection in rodents following brain injury. Either saline or cGP (3mg/kg/day) was gavaged into lactating Sprague-Dawley rats from postnatal (PN) d8-22. Concentrations of cGP, measured by High Performance Liquid Chromatography-Mass Spectrometry, significantly increased in the plasma and milk of dams ($P<0.01$) treated with cGP compared to control group. cGP concentration was also higher in the plasma of pups from treated dams on PNd23 but not on PNd77. Maternal cGP administration increased the litter growth rate between PNd7-14 ($P=0.06$), and enhanced the performance of pups on recognition (Novel Object Recognition; $P<0.05$) and spatial (Morris Water Maze; $P<0.05$) memory tasks conducted on PNd30 and PNd70, respectively. Brain samples were collected from dams on PNd23 and pups on PNd23 and PNd77. Immunohistochemical analysis of pup brains collected on PNd77 revealed that maternal cGP treatment did not cause any change in the mean intensity of staining for Synaptophysin and Glutamate receptor-1, average density of phosphorylated IGF1 receptor-labelled blood vessels and average density and length of blood vessels in all brain regions examined. However, an increase in average size and decrease in average density of astrocytes ($P<0.05$) was observed in frontal cortex, while a decrease in percentage of area occupied by astrocytes ($P<0.05$) was observed in CA1-2, CA3 and dentate gyrus sub-regions of hippocampus. Our data show the effective transfer of cGP to the offspring following maternal administration, leading to better growth and enhanced cognition in the offspring. The speculation that the biological plasticity which may underlie the cognitive enhancement may not be last-lasting is currently under investigation.

Poster 7.38

Reawakening adult-generated hippocampal granule cells: The effects of enriched environment on an established trend

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Adult neurogenesis occurs in the subgranular zone of the dentate gyrus, resulting in addition of functionally integrated neurons. These new cells go through a period of increased excitability around 4-6 week after cell division, but then attain more mature cell properties. Mature granule cells may become difficult to activate and essentially "retire". However, this hypothesis remains controversial. We addressed this controversy using a within-animal protocol for birth-dating two cohorts of adult born granule cells in 10 month old Sprague-Dawley rats. The thymidine analogues chloro-deoxyuridine (CldU) and iodo-deoxyuridine (IdU) were injected s.c. or i.p. to label cells born 4, 6, 12, or 35 week prior to death. Activation of adult-born cells was assessed post-mortem by quantifying co-expression of the immediate early gene Zif268, using double-label immunofluorescence techniques. The results produced a U-shaped curve with activation percentages of 3.6±0.5%, 1.6±0.4%, 1.1±0.2% and 3.9±0.8% corresponding to 4, 6, 12 and 35 week old cells. We then attempted to reawaken the less-active cells by exposing the animals to an enriched environment (EE) for 10 nights prior to death. Preliminary results showed that both the 12 and 4 week old cells were more active after exposure to EE (12 week (2.4±0.4%), 4 week (5.4±1.3%)). However, there was no difference between the level of increased activation, indicating that both groups of cells increased activity with EE, but the U-shaped curve remained representative of the activity of adult-born cells. Thus, the established trend appears unaltered by exposure to EE.

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Poster 7.39

The actin-binding protein moesin and memory formation in Drosophila

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Moesin is a cytoskeletal adaptor protein that plays an important role in modification of the actin cytoskeleton and the formation of dendritic spines, which may be crucial to long-term potentiation. Moesin has also been found to be overexpressed in brains affected by Alzheimer's disease. Despite being identified as a potential memory gene and linked to several neurological diseases, its role in memory has not been evaluated. The role of moesin in the *Drosophila melanogaster* brain was investigated by characterizing the impact of modulating moesin expression on several aspects of development and behavior. Moesin is involved in both brain and eye development. Knockdown and overexpression of moesin led to defects in the development of the mushroom body, a brain structure critical for memory formation and recall. Further, knockdown of moesin throughout development resulted in a significant deficit in long-term memory ($p<0.01$, ANOVA, post-hoc Tukey's HSD). Moreover, knockdown of moesin restricted to adulthood also resulted in a significant deficit in long-term memory ($p<0.01$), which suggests that moesin also has a non-developmental role in memory. Pan-neural expression of a phosphomimetic moesin mutant that mimics the phosphorylated, activated form of moesin disrupted photoreceptor development in the Drosophila eye and resulted in a novel sensorimotor phenotype characterized by a defect in stereotypical climbing behavior. Additionally, evaluation of a Drosophila Alzheimer's disease model involving coexpression of human APP (amyloid precursor protein) and BACE1 (β-site APP-cleaving enzyme) revealed increased activation of moesin. Moesin's involvement in brain and eye development as well as sensorimotor function suggests a critical role in general neurological functioning. It will be important to further investigate the molecular pathways involved in its activation due to its role in memory.

Poster 7.40

Brain derived neurotrophic factor genotype modulates recognition memory related event related potentials

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A common single nucleotide polymorphism (SNP) within the gene for brain derived neurotrophic factor (BDNF) is known to impact performance on recognition memory tasks. Previous research has identified two subcomponents of recognition memory, familiarity and recollection. While the neural circuits that underpin each of these processes are related, one major distinction is that recollection is dependent upon the hippocampus. Given that the highest concentration of BDNF is expressed in the hippocampus, it is of interest to examine how genotype for BDNF interacts with each aspect of recognition memory individually. Here we use EEG to dissociate the familiarity and recollection components of recognition memory using event related potentials (ERPs) gathered during a source recognition task. This task is comprised of an old-new discrimination and a source discrimination, allowing us to examine both familiarity and recollection processes. Familiarity has previously been associated with modulations to the N400, while recollection has been associated with a late positive component (LPC). Our preliminary results show significant differences between the genotype groups for the overall patterns of these two ERPs. During the old-new discrimination, both genotype groups show greater N400 positivity for old vs new items. However, during the source discrimination only val homozygotes show increased positivity for correct source judgements compared to incorrect source judgements. We therefore conclude that BDNF genotype has a greater impact on the recollection aspect of recognition memory compared to the familiarity aspect of recognition memory.

Poster 7.41

Optimisation of fluorescent activated cell sorting and RNA extraction from dissociated mature mouse cortex tissue for transcriptome profiling

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Pyramidal neurons of the mature cortex display diverse morphological and electrophysiological phenotypes. Identifying the molecular profiles that make these neuronal subsets distinct is critical for understanding the complexity of the healthy mature cortex. Fluorescently labelled retrograde tracers and fluorescent reporter mice, coupled with fluorescent activated cell sorting (FACS) provide the opportunity to tease out specific populations of cortical projection neurons from the adult mouse cortex for transcriptome profiling. Tissue fragility together with low numbers of neurons (<50,000), make this technically challenging. We have trialled several approaches to FACS-RNA isolation for downstream RNA sequencing. Addition of excitatory amino acid receptor antagonists during tissue dissociation improved cell membrane integrity post-sort. Trehalose also significantly increased the number of live neurons by >10% ($p=0.0212$, unpaired t-test, $n=3$), as well as the cell size post-sort. RNA from sorted neurons was of good quality (RIN>7), however the yield was 10-fold less when compared to RNA extracted from unsorted dissociated tissue, lysed at equivalent time points. With good quality RNA of between 300-400 pg, we generated libraries that demonstrated high complexity (duplication rates <10 %) and mapping rates of 84% ($n = 4$). Reducing the RNA amount to 90 pg lowered mapping rates to 55% ($n = 1$). Our results indicate that the sorting process affects RNA yield, regardless of health or size of the cell. Acquiring the optimum yield from low numbers of FACS-purified neurons is critical for successful RNA-sequencing and transcriptome analysis, if we are to distinguish the molecular basis for cortical projection neuronal diversity.

Poster 7.42

Regulation of HDAC1 and HDAC2 following long-term potentiation

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Long-term potentiation (LTP) is an enhancement of synaptic transmission, thought to underlie memory. LTP persistence critically requires gene expression. Histone deacetylases (HDACs) regulate gene expression and are implicated in LTP and memory. Inhibiting HDAC activity during LTP induction and learning enhances LTP persistence and memory. However, such HDAC regulation during LTP has only been investigated *in vitro* and thus only during early-phase. Previously, we reported that HDAC1 and HDAC2 are central to gene networks generated 5 h and 24 h post-LTP induction, and have temporally distinct mRNA expression and activity profiles. This suggests these HDACs act in discrete phases after LTP induction, potentially controlling specific groups of genes that stabilise LTP. Much of the memory work in this field has only investigated up until 24 h post-learning, therefore potentially missing these changes. In our latest work we have investigated protein expression of HDAC1 and HDAC2 in dorsal dentate gyrus of male Sprague-Dawley rats. We compared sham-stimulated control animals with the stimulated and contralateral hemispheres of animals in which LTP had been induced in awake, freely moving animals. Western blotting showed HDAC1 protein levels were increased in the stimulated hemisphere, compared to control animals 20 min (FC=2; $p<0.05$) and 12 h (FC=2.4; $p<0.01$) post-LTP induction. HDAC2 protein levels were decreased at 12 h (FC=0.66; $p<0.05$) and increased at 24 h (FC=2; $p<0.01$) in the contralateral hemispheres of the test animals. These results, in conjunction with the previous activity and mRNA results, identify temporally dynamic, subtype specific changes in HDAC regulation following LTP.

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Poster 7.43

In search of behavioural effects correlates of visual long-term potentiation

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Long-term potentiation (LTP) is a well-developed theory of synaptic plasticity, and a principal candidate for a neuronal underpinning of memory and learning. Although extensively studied in animals, the invasive procedures required for LTP are not easily adaptable for experiments with humans. In recent years the potentiation of the N1 component of the visual event-related potential (ERP) by high-frequency visual stimulation has been introduced as a possible analogue of LTP that can be recorded from human participants. This potentiation appears to be specific to the inducing stimulus, and to produce long-lasting modulation of N1 amplitude. In this study, we explore the hypothesis that visual LTP may also result in improved psychophysical detection or discrimination of the inducing stimulus. That is, that "visual LTP" may result in perceptual learning. We investigated the effect of high-frequency (8.6 Hz) presentation of Gabor patch oriented at either 45° or 135° on both the detection of low-contrast Gabor patches of the stimulated and non-stimulated orientation and on the amplitudes of visual ERPs evoked by these stimuli. Preliminary data suggest that high-frequency visual stimulation produces stimulus specific modulation of ERP amplitudes and improved behavioural discrimination for the Gabor patches that match the orientation and spatial frequency of the inducing stimulus. This pattern is consistent with visual LTP as a mechanism for perceptual learning.

Poster 7.44

Establishing the 3D distribution of synaptic proteins around sensory receptors in the mammalian cochlea during early postnatal development

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Inner hair cells (IHCs) in the mammalian cochlea transduce sound waves into electrical impulses and differential distribution of glutamatergic synapse structure around the base of the IHC appears to be important for encoding sound intensity information. This study examines the development of IHC innervation, including the pruning and changes in synapse structure prior to and after the onset of sound mediated stimulation of the IHC at postnatal day (P) 12. Cochlea mid-turns were dissected from P6 – 21 mice and the localization of RIBEYE and GluA2, components of the vesicle release machinery and AMPA receptor complexes respectively were examined using immunofluorescence and confocal microscopy. Custom written algorithms developed in Python where used for image analysis and mapped these synaptic proteins around the basolateral membrane of the IHC. These studies showed that the synapse distribution is established at birth and doesn't change through development. Additionally, synapse pruning is localized to specific regions of the IHC. Synapse structure was variable at birth, but this variability decreased through early development and by the onset of hearing synapse structure appeared established and consistent. These data suggest that the segregation of synapses around the IHC relies on intrinsic developmental signaling pathways and is not dependent on the onset of sensory stimulation of these receptors. They provide a blueprint of synapse development in the cochlea and will be used for future studies that examine how developmental insults affect synapse structure in the cochlea.

Poster 7.45

Steady-state evoked potentials of visual illusory flicker are modulated by concurrent auditory flutter frequency

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In auditory driving (Shipley, 1964), a flashing visual stimulus ("flicker") appears to flash synchronously with an auditory beeping ("flutter") presented concurrently but at a different frequency. Although neural correlates of a similar multisensory interaction have been observed in discrete event-related measures in the flash-beep illusion (Watkins, Shams, Tanaka, Haynes, & Rees, 2006), the sustained effect of auditory driving on conscious (mis) perception has yet to be shown. Here, we investigated how steady-state evoked potentials, known to closely track the frequency of rhythmic stimulation, would be altered by the cross-modal effects of auditory driving and whether hemispheric contrasts in spectral measures would encode veridical visual flicker or an illusory rate resulting from integration of visual and auditory rhythms. On each trial, participants were presented with a 15 Hz Gaussian luminance flicker in the left or right hemifield for three seconds, sometimes concurrently with a diotic square-wave flutter of 12 Hz, 15 Hz, or 18 Hz. When not accompanied by flutter, visual flicker induced an increased 15 Hz response in posterior electrodes contralateral to presentation. With flutter, participants reported that the flicker seemed faster or slower in synchronization with the auditory frequency, despite always occurring at 15 Hz. Although flutter was presented to both hemispheres, higher spectral power corresponding to the flutter frequency was observed contralateral to visual presentation, suggesting that hemifield-dependent visual processing was modulated by diotic stimulation. The findings show that auditory stimulation affects lateralized visual processing at early stages, and that electrocortical signatures encode conscious percepts, not just distal stimulus properties.

Poster 7.46

The urea cycle is induced in Alzheimer's brains

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The urea cycle is an essential pathway in the liver to dispose of toxic ammonia as the nontoxic form of urea. In normal brains, the urea cycle is incomplete (hence inactive) due to the lack of ornithine transcarbamylase (OTC) and carbamoyl phosphate synthetase 1 (CPS-1). Recent research has indicated that the urea cycle may be induced in Alzheimer's disease (AD) brains to dispose of excessive amount of ammonia. This study aimed to determine the presence of OTC and CPS-1 in AD brains using immunohistochemistry and quantitative PCR techniques. Both non-fixed frozen and formalin-fixed superior frontal gyrus (SFG) tissue from normal (mean age 60 (NC-60) or 80 (NC-80) years) and AD (mean age 80 years; AD-80) cases (n=6/group) were used. For OTC, immunoreactive cells were clearly seen in AD cases with some forming clusters (likely glial and/or endothelial cells). By contrast, OTC positive staining was hardly seen in the NC-80 and NC-60 cases. For CPS-1, there was a marked difference in the immunoreactivity between the AD and NC groups, with high intensity clustered positive astrocytes in AD cases relative to scattered labelling with much lower density in NC-80 cases. Moreover, there were about 30- and 2-fold increases in OTC and CPS-1 mRNA levels in AD cases relative to the controls. This preliminary work demonstrates that OTC and CPS-1 are indeed present in AD brains, hence suggesting the induction of the urea cycle to dispose of excessive ammonia during AD.

Poster 7.47

Role of glial-neuron interactions in central fatigue induced by alteration of tryptophan sensitivity

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Central fatigue is implicated in several clinical conditions including chronic fatigue syndrome, and leads to diminished cognitive function and disrupted social life. The expression of central fatigue is modulated by tryptophan (Trp), which activates 5-hydroxytryptamine (5-HT) and kynurenine pathways in the brain. Additionally, glia are involved in the synthesis of Trp metabolites and regulate the expression of several monoamine receptors. However, whether excessive brain Trp causes central fatigue in a confined neuronal network remains unclear. To clarify the mechanisms of glial-neuron interactions by which Trp sensitivity modulates central fatigue, we developed a rat model of central fatigue that is induced by chronic sleep disorder (CFSD). Moreover, we investigated the dynamics of monoamine metabolites, which is affected by changes in the Trp-kynurenine pathway, in both glial- and neuron-related central fatigue. Oligodendrocytic and presynaptic Trp, 5-HT, dopamine, noradrenaline, 3,4-dihydroxypheylacetic acid, 5-hydroxyindoleacetic acid, and homovanillic acid concentrations were measured in several brain regions of CFSD and control rats. Spatial memory and hyperactivity were measured with a Y-maze task, and impulsivity was measured with an elevated minus maze. Results showed that compared with the control group, presynaptic levels of Trp in the hypothalamus and hippocampus were 50% higher and those of 5-HT and monoamine metabolite concentrations were 30% lower in the CFSD group. Surprisingly, while hypothalamus- and hippocampus-derived oligodendrocytic Trp concentration was greater in the CFSD group, 5-HT and monoamine metabolites were absent in both groups. Moreover, behavioral tests showed that CFSD led to impairments in spatial memory accuracy and greater levels of hyperactivity and impulsivity. These findings suggest that central fatigue arises from dynamic changes in glial-neuron interactions in the hypothalamic-hippocampal circuit, with increased levels of Trp in this circuit leading to reduced cognitive function.

Poster 7.48

Investigating the analgesic properties of a novel mu-opioid receptor analogue of Salvinorin A

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Mu-opioid receptor agonists such as morphine are the gold standard treatments for surgical and cancer pain, although side effects, such as respiratory depression, addiction, nausea, tolerance, sedation and constipation hamper their use. Therefore, development of new pharmacotherapies to manage pain with fewer side-effects would significantly improve the quality of life of pain sufferers. Several compounds derived from the novel structure of Salvinorin A, isolated from the plant *Salvia divinorum* have been shown to activate the mu-opioid receptor. Using the intra-dermal formalin (2%) assay in mice, a model of acute inflammatory pain we have shown compound 2 (10 mg/kg/i.p.) significantly attenuates pain responses ($p<0.001$) in a mu-opioid dependent manner as these effects are absent following mu-antagonist pre-treatment (naloxone; 10 mg/kg/s.c.). Using the warm water tail-withdrawal assay in mice, a model of central nervous system mediated pain reflexes, we also show that compound 2 significantly attenuates tail-withdrawal latencies, similar to morphine following injections of both 5 and 10 mg/kg, with a peak maximal effect at 30 min ($p<0.001$). To screen for possible abuse potential we also performed conditioned place preference (CPP) tests in rats. Compound 2 (5 mg/kg/i.p.), showed significantly reduced place preference when compared to morphine (5 mg/kg/i.p.)($p<0.05$). Morphine significantly induced place preference ($p<0.001$), whereas, compound 2 showed no significant place preference compared to vehicle. Based on these preliminary results, compound 2 shows similar effects in modulating pain to morphine with less abuse potential. Future studies investigating the side-effects profile of compound 2 will evaluate its potential for development as an improved pain pharmacotherapy.

Poster 7.49

Fragments of amyloid precursor protein enhance rat hippocampal LTP

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Amyloid precursor protein (APP) is a transmembrane protein cleaved and modified to produce a variety of proteolytic fragments performing a range of roles in the development, maintenance and plasticity of the brain. Cleavage products of APP include soluble APP alpha (sAPPα), a molecule with established neuroprotective properties from which the fragments in this study were derived. The full sAPPα fragment, it's 16 amino acid C-terminal domain (DAEFRHDSGYEVHHQK), and the tri-peptide RER were screened in order to identify specific motifs that are beneficial for induction of LTP at Schaffer collateral synapses in area CA1 of rat hippocampal slices. After establishing a stable baseline of field EPSP's, fragments were superfused onto the slices for 30 min, at which time a brief theta-burst protocol was delivered to induce LTP. After a further 5 min, the fragment was washed out and recordings continued for another hour. The results demonstrated that sAPPα and each of the peptides improved LTP over no peptide controls, with controls exhibiting 15.2% LTP, the full length sAPPα fragment showing 38.97% LTP (at 1nM), the C-terminal 16 amino acid exhibiting 27.91% LTP (at 10nM) and 20.32% LTP (at 1nM), and the tri-peptide RER exhibiting 40.97% LTP (at 1nM) and 46.28% LTP (at 10nM). While all fragments appeared beneficial, 1nM sAPPα and both 1nM and 10nM concentrations of RER demonstrated statistically significant enhancement of LTP over controls. Results indicate that these APP fragments may have potential for improving neural plasticity and memory when they are impaired, such as in neurodegenerative disease.

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Poster 7.50

Self-administration of MDMA produces a sensitised response to the locomotor activating effect of MDMA

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Following a regimen of intermittent experimenter-administered MDMA we, and others, have demonstrated a sensitised response, as indicated by a leftward shift in the dose-effect curve for MDMA-produced hyperactivity. The present study was designed to determine whether behavioural sensitisation was also produced following MDMA self-administration and whether the sensitized response was comparable to sensitization produced following exposure to the same MDMA regimen administered non-contingently. Triads of rats were designated 'master', 'yoked MDMA', or 'yoked vehicle'. Responses produced by either the yoked MDMA or yoked vehicle rat were without programmed consequence. Responding by the master rat resulted in an intravenous infusion of MDMA for both the master rat and the yoked MDMA rat, as well as an equal infusion of vehicle for the yoked control rat. Therefore, the two MDMA rats in each triad received the same amount of MDMA exposure and the pattern of delivery was identical. The only difference was that for the master rat MDMA infusions were dependent on performance of a lever press operant, whereas the yoked rat received the drug infusion on the basis of performance by the master rat. Once a total of 350 mg/kg MDMA had been self-administered there was a two day withdrawal period, followed by a test day. On the test day, locomotor-activating effects of MDMA (5.0 or 10.0 mg/kg, IP), were measured. MDMA exposure shifted the dose-effect curve for hyperactivity to the left, suggesting a sensitized response. This sensitized response was comparable regardless of whether the drug was self-administered (master) or administered non-contingently (yoked MDMA). The basis for the differences between effects of repeated exposure to MDMA, and other drugs, is currently being investigated.

8.1

Measuring inner ear permeability using DCE-MRI in patients with Meniere's disease

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Ménière's Disease (MD) is a chronic, debilitating inner ear disease with bouts of severe dizziness, tinnitus and hearing loss. The causes and mechanisms of MD are largely unknown, but it is thought to be caused by disturbances of inner ear fluid homeostasis, possibly from an inflammatory reaction or immune response. Using a novel Magnetic Resonance Imaging approach we are investigating whether MD is correlated with disruptions in the blood-labyrinth barrier (BLB). Here we report preliminary findings on vascular permeability changes in a small group of MD patients compared with control subjects. Two MRI sequences were used, a VIBE T1-weighted and 3D-Flair sequence, to take images at intervals after the intravenous bolus injection of a Gadolinium based contrast agent (GBCA, 0.1 mM/kg). An increase in signal intensity was observed, particularly in the vestibule, eighth nerve and basal cochlear turn, only at 3-4 hrs after GBCA injection in both controls and MD patients. This was significantly greater in the MD patients and also was greater in the symptomatic ear. Using data from the VIBE sequence the concentration of GBCA in inner ear tissues was calculated and from this the vascular permeability constant, Ktrans, was calculated using a two-compartment pharmacokinetic model. The Ktrans (3.6×10^{-4} min^{-1}) was greater in MD than the control (0.8×10^{-4} min^{-1}) subjects. These preliminary findings suggest that the BLB is normally very tight and is disrupted in MD patients. Further studies are underway to increase the number of patients in the sample and to correlate these with blood cytokine measurements and clinical tests of vestibular and auditory function.

8.2

Encoding of virtual reality locomotion kinematics in the spinocerebellar vermis and lateral cerebellum

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The cerebellum has a well-established role in motor planning, execution and control. Recent imaging studies have shown that populations of cerebellar neurons are topically activated during locomotion and that optogenetic stimulation of Purkinje cells can affect the coordination of limb and trunk movements. However to date it is still not well understood how the cerebellar cortical circuit achieves movement control. We therefore aimed to characterize the activity of cerebellar neurons using high-density silicon electrode arrays in awake mice engaged in a locomotion task. We recorded the activity of over 500 single units in vermis lobule V-VI and 148 units in the lateral cerebellum, while mice navigated in a virtual reality environment. The cells were classified according to their electrophysiological properties (Hensbroek et al, J Neurosci Meth 232:173-80, 2014), identifying Purkinje cells, Basket or Stellate cells, and granule cells. We characterized the spiking activity of the cells in response to movement, finding three main response profiles: speed-sensitive neurons, yaw-sensitive neurons and step cells. Speed-sensitive neurons could be further divided into positively tuned, negatively tuned and preferred speed neurons. Yaw-sensitive neurons modulated (50-200%) their activity with respect to the clockwise or anticlockwise direction. Step cells displayed a bursting activity synchronized with quick acceleration events caused by the animal stride. By simultaneously recording a large population of cerebellar neurons in a behaving animal we were able to decode locomotion-related information from cerebellar neural populations. Further characterization of the cerebellar network with our approach will increase our understanding of how movement control is achieved through the cerebellum.

8.3

Effects of TMS coil orientation, posture and limb dominance on lower limb motor cortex excitability

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Transcranial magnetic stimulation (TMS) is used to examine the integrity of the corticospinal tract (CST) after stroke. The presence of a motor-evoked potential (MEP) in the target muscle indicates the CST is functionally intact, guiding expectations for recovery. Optimising TMS techniques may increase the likelihood of recording a MEP after stroke, while reducing patient discomfort. We investigated a TMS protocol in healthy adults (n=22), suitable for sub-acute stroke patients, and the effects of limb dominance on lower limb corticomotor excitability. TMS was delivered to induce a posterior-to-anterior (PA) cortical current and a medial-to-lateral (ML) cortical current, and MEPs were recorded from Tibialis Anterior (TA). Both coil orientations were used with the participant at rest and while activating the non-target leg. Corticomotor excitability was indexed with rest motor threshold (RMT), recruitment curve slope and MEP latency. ML current increased corticomotor excitability (lower RMT ($p<0.001$), steeper recruitment curve slope ($p=0.041$) and shorter MEP latency ($p=0.007$)). Activating the non-target leg reduced RMT in the target TA ($p=0.012$) and increased the slope ($p=0.001$). There was no effect of limb dominance on RMT, slope or MEP latency. A negative relationship was found between the degree of footedness and RMT ($p=0.017$) when inducing PA current, but not ML current. These results indicate that inducing ML cortical current while the participant is activating the non-target leg reduces RMT and latency, and increases recruitment curve slope, regardless of whether the dominant or non-dominant limb is tested. This has practical application for testing the integrity of the CST after stroke.

9.1

Arc expression in the mouse parabrachial nucleus following taste stimulation

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The parabrachial nucleus (PbN) is the second brain structure in the taste-processing pathway; it plays an important role in regulating autonomic and behavioural responses to food. Using the *Arc* (activity-regulated cytoskeleton-associated protein) catFISH method (cellular compartment analysis of temporal activity by fluorescent in situ hybridization) we aim to characterise the processing of gustatory information in the PbN. *Arc* expression is a marker for neuronal activity; its mRNA follows a strict temporal pattern of intracellular distribution. By stimulating C57BL/6 mice twice with tastants, the intracellular localization of the *Arc* mRNA allows us to infer which of the two stimulations activated which PbN neurons. Of the stimuli covering all five basic taste qualities only the three bitter stimuli showed a significantly higher rate of *Arc* induction in PbN neurons when compared to control stimulus, or any other taste quality. Animals stimulated twice with the same bitter stimulus showed a large increase in *Arc* expressing cells compared to animals stimulated only once with a bitter stimulus. Only a small portion (~15%) of neurons activated by the first bitter stimulation were reactivated by a second stimulation with the same stimulus. The portion of twice-activated neurons was not significantly lower in animals that were stimulated with two different bitter stimuli. It appears that this tastant-induced increase in *Arc* expression in the PbN is specific to bitter taste processing. We intend to further characterize the *Arc* expressing neurons in the PbN and their role in taste processing.

9.2

Bilateral vestibular lesions increase sensitivity to non-vestibular induced theta rhythm in rats

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Following bilateral vestibular loss (BVL), spatial memory and learning are impaired and hippocampal theta rhythm is reduced in freely moving animals. This study aimed to determine whether the reduction in theta was due to a loss of vestibular sensory stimulation, or whether the hippocampus is no longer able to generate theta, using a non-vestibular stimulus (tail pinch) in a chemical model of vestibular loss while under anaesthesia. Rats underwent transtympanic injections of sodium arsanilate to induce BVL or unilateral vestibular loss (UVL). Ninety days following lesioning, animals were anesthetized with urethane (1.5g/kg i.p.). A stainless steel recording electrode was inserted into the CA1 area of the hippocampus and field potential recordings were made. In order to induce hippocampal theta activity a clip was placed at the base of the animal's tail for alternating 60 second periods. Fast Fourier transforms were conducted on the raw traces and analysed with a linear mixed model analysis (SPSS 22). A significant increase in low frequency theta activity (3-5Hz) was found (Treatment $P \leq 0.05$; Treatment*Frequency $P \leq 0.05$) in all BVL and UVL animals, compared to sham controls; however, the increase was greater in BVL than in UVL animals. There was no significant group difference in the frequency associated with the maximum power ($P \geq 0.3$). These results indicate that the ability to produce hippocampal theta rhythm is retained following BVL or UVL. Unexpectedly, theta was increased following both BVL and UVL when generated through a tail pinch compared to sham animals, suggesting that a form of multi-sensory compensation or sensory substitution may have occurred.

9.3

Emotion-modulated force control: A multidisciplinary approach to investigate freezing reactions in humans

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Fearful or threatening emotional signals have been shown to modulate parameters of motor performance such as speed and force production, indexing engagement of the defensive activation system. We have previously shown facilitation of force control by aversive stimuli, mediated by the amygdala, right inferior frontal gyrus (rIFG), and periaqueductal gray (PAG). These data were interpreted as reflecting a freezing-like response, analogous to passive defensive behaviour observed in animals in response to threat. To test this notion further we examined whether modulation of motor behaviour and neural activity by aversive stimuli would be associated with physiological indices of freezing. Twenty-two participants performed a submaximal isometric precision-grip contraction while viewing unpleasant, pleasant, or neutral emotional images. Force magnitude was continuously recorded together with change in brain activity using fMRI, pupil dilation and eye movements, and cardiac responses. Enhanced force control during viewing of unpleasant images was associated with greater pupil dilation, more eye fixations of smaller duration, and greater scanpath length relative to pleasant and neutral images. Preliminary heart rate analyses revealed greater cardiac deceleration for unpleasant than pleasant images. Consistent with freezing responses in animals, unpleasant emotional signals during force maintenance elicited a higher state of alertness and arousal, orienting behaviour, and fear bradycardia. Critically, visual scanpath, a marker of controlled attention and threat reappraisal, significantly predicted force output, PAG and rIFG activity. This study presents a promising avenue to simultaneously explore motoric, autonomic and neural responses underpinning freezing reactions in healthy individuals and psychopathology.

9.4

Auditory attention with cochlear implants: The brief test of attention (Schretlen, 1997) in 2015

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The Brief Test of Attention (BTA) involves categorizing speech sounds into 'numbers' or 'letters', and reporting quantity of items in one category - assessing auditory divided attention. It has been standardized for normal hearing populations as well as clinical psychology populations (Schretlen, 1997). The purpose of this study was to investigate, via a cross-sectional pilot study, whether the BTA is a valid cognition test for adult cochlear implant (CI) recipients and establish whether re-standardisation is required for CI populations. Sixteen CI recipients aged 17.49 to 86.26 years (mean 57.68 ± 22.22) were tested. Ten participants had post-linguistic hearing loss onset, whereas six were pre-linguistic (*n*=4, <2 years) or "peri-linguistic" (*n*=2, 2-4 years). All participants received Cochlear™ devices (*n*=12 Nucleus24; *n*=2 Nucleus22) post-linguistically; 3 in childhood, ten after 40, and one at 21.The cohort's mean BTA score was 55% ± 22% (range 25% - 95%). Seven participants passed published age-standardized scores (percentiles and impairment categories). Of the remaining participants, two were "borderline impaired" (2nd - 9th percentile), and six were below 2nd percentile for their age ("impaired"). BTA scores do not correlate with speech-perception-in-noise scores (50% SRT for sentences) (*n*=10; r=-0.345; *p*=.330). Similarly, BTA score against time with CI showed non-significant correlation (*n*=15; r=0.208; *p*=.457). Lack of correlation between BTA and speech perception supports a divergent validity hypothesis i.e. the BTA is testing attention, not speech perception. The BTA does not seem to require high speech perception ability, making it a promising test of cognition for CI populations. However further data and subsequent re-standardisation is needed before the BTA could be used as a clinical test or screening tool.

10.1

Blood arginine metabolic profile is altered in male Sprague-Dawley rats

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Aging is a multi-factorial process leading to functional deterioration in body systems, and is a major risk for Alzheimer's disease (AD). L-arginine is a semi-essential amino acid with a number of bioactive molecules, and its metabolic profile in the brain is dramatically altered during aging and AD, hence it is a potential biomarker candidate. Blood serum and plasma are commonly used matrices for biomarker identification in both clinical and translational research. The present study measured the levels of L-arginine and its eight downstream metabolites in both matrices of male Sprague-Dawley rats at ages of 3 (young) and 22 (aged) months old, using liquid chromatography/mass spectrometry and high performance liquid chromatography. Present results show that higher arginine, citrulline, and g-aminobutyric acid (GABA), but lower spermidine and spermine levels were found in plasma when compared with serum. Only 4 and 2 out of 9 variables in the young and aged groups respectively showed significant positive correlations between plasma and serum. Furthermore, in both plasma and serum, citrulline, ornithine, putrescine, spermidine and spermine were significantly reduced in aged rats. Cluster analyses revealed that the related chemical variables formed distinct groups, which changed as a function of the blood compartments (young group only) or age. These results, for the first time, demonstrate that concentrations of arginine and its metabolites in serum and plasma differ in a chemical-specific manner. More importantly, aging has a similar effect on the arginine metabolic profile in both blood matrices. This study provides valuable information for future biomarker research on AD.

10.2

Impaired $GABA_A$ receptor function in Alzheimer's disease

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Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. GABA type A receptors ($GABA_A$Rs) are severely affected in Alzheimer`s disease (AD). However, which $GABA_A$Rs subunits exhibit most change remains controversial. AD is characterized by accumulation of neurotoxic beta-amyloid (Aβ) and impaired cognitive function. In this study, we have examined the effect of $A\beta_{1-42}$ treatment on the expression and subunit composition of $GABA_A$R subunits in the mouse hippocampus and consequences of these receptor changes on cognitive decline. Evaluation of aged wild-type mice that received bilateral $A\beta_{1-42}$ injection into the hippocampus just three days following hippocampal $A\beta_{1-42}$ injection, before any significant neuronal loss, showed significant increase of the $GABA_A$Rγ2 and decrease of the $GABA_A$Rα1 subunit expression in the CA1 region of the hippocampus. These mice demonstrated impaired learning skills compared to control groups revealed by the novel object recognition test. We also examined the expression of $GABA_A$R subunits in control and AD human hippocampal tissue samples. In contrast to the mouse, in human late-stage AD hippocampus we found a significant decrease of the $GABA_A$Rγ2 and increase of the $GABA_A$Rα1 subunits in the CA1 region. In conclusion, these findings suggest that alterations in $GABA_A$R signaling that occur in AD could be a primary mechanism contributing to cognitive decline and not secondary to neurodegeneration. Furthermore, the early molecular changes found in AD might be different compared to those seen in late-stage of the disease.

10.3

Protocadherin 19 (PCDH19) regulates estrogen receptor alpha (ERα)

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Mutations in Protocadherin 19 (PCDH19), one of the most frequently mutated genes in epilepsy, are responsible for Female-limited Epilepsy and Intellectual Disability (FE). The onset of PCDH19-FE is at 8 months of age, after an otherwise normal development. It often involves autism and other behavioural problems like ADHD. Cellular mosaicism, typical for females with random X-chromosome inactivation and rare in males with somatic mosaicism, has been speculated to drive the disorder. However, the mechanism remains elusive. We have identified p54nrb/NONO, a nuclear paraspeckle protein, as PCDH19 interacting partner and the two proteins are at least partly-localized to cell nucleus. We also show that PCDH19 is cleaved and positively regulates estrogen receptor alpha (ERα) activity. This regulation is facilitated and that could be enhanced by NONO. We show that PCDH19-FE mutations abolish ERα-mediated regulation and thus most likely represent loss of function mutations. This data is consistent with our findings that genes regulated by nuclear hormone receptors and those involved in the metabolism of neurosteroids in particular are dysregulated in PCDH19-FE girls and an affected mosaic male. Overall we define a novel mechanism of regulation of ERα and its downstream targets by cell adhesion molecule PCDH19. This signalling pathway is relevant not only to PCDH19-FE disorder, but potentially also to ERα-dependent cancers and offers opportunity for targeted therapeutic interventions.

10.4

Astrocytic response to low-intensity repetitive transcranial magnetic stimulation (rTMS)

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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of brain stimulation that has been used to treat a diverse range of neurological disorders. Most rTMS research to date has been neuron-centric and almost nothing is known about whether astrocytes respond to rTMS. We have characterised the astrocytic response to low-intensity rTMS by assessing intracellular calcium signalling, migration and proliferation in response to injury *in vitro* (repetitive magnetic stimulation-rMS). Primary murine astrocyte cultures (approximately 98% astrocytes, 2% neurons) were prepared. Fura-2 340/380nm ratiometic fluorescence was used to assess the calcium signalling response to 10 minutes of sham, 1Hz, 10Hz, cTBS and biomimetic high-frequency stimulation. In a separate set of cultures, a scratch assay was performed on confluent cultures to monitor the effect of rMS frequencies (10 minutes, once daily for 4 days) on astrocyte proliferation and migration. Data were analysed via one-way ANOVA (p £ 0.05). Stimulation at 1Hz resulted in a significant increase in cellular calcium that persisted up to 5 minutes post-stimulation. 1Hz stimulation also reduced astrocytic swelling in the 24 hours post-scratch injury. No significant changes were observed for other frequencies and rMS had no effect on the proliferation or migration of astrocytes *in vitro*. We conclude that astrocytes are indeed responsive to rMS. These data suggest that astrocytic-mediated effects need to be considered in determining the therapeutic benefit of rTMS. Further studies are underway to characterise gliomodulation by rMS in models of brain injury and plasticity.

10.5

Exploring the aversive and anxiogenic effects of novel kappa opioid receptor agonists

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Drug addiction is characterised by uncontrolled, compulsive drug use despite negative consequences. As this disease costs millions annually, greater attention is required in finding an effective treatment for sufferers. Kappa opioid receptor (KOPr) agonists demonstrate anti-addiction effects. Salvinorin A (SalA) has demonstrated reduced side-effects compared with traditional agonists. However, its short half-life and duration of action limits clinical development. The design of novel analogues with improved pharmacokinetics, anti-addiction effects and reduced side-effects is an important step towards pharmaceutical development of KOPr agonists. β-Tetrahydropyran SalB (β-THP), Mesyl SalB and ethoxymethyl (EOM) SalB have demonstrated anti-addiction effects but their aversive and anxiogenic properties have yet to be examined. The aim of this study was to investigate the aversive effects using the conditioned place aversion test, and anxiogenic effects in the light-dark and elevated plus maze tests in Sprague-Dawley rats. The parent compound SalA (0.3 mg/kg, $p<0.05$) and β-THP (1 mg/kg, $p<0.0005$) caused significant conditioned place aversion whereas Mesyl SalB (0.3 mg/kg) and EOM SalB (0.1 mg/kg) display no aversion. In both the light-dark and elevated plus maze tests, Mesyl SalB (0.3 mg/kg) showed no anxiogenic effects unlike SalA (1 mg/kg; $p<0.005$ and $p<0.05$ respectively). β-THP (1 mg/kg) and EOM Sal B (0.1 mg/kg) showed significant anxiogenic effects in the light-dark test ($p<0.05$) but not on the elevated plus maze. This study shows Mesyl SalB has a more desirable side-effects profile than its parent compound SalA. This demonstrates that the development of KOPr agonists with desirable effects and reduced side-effects is possible, providing a promising candidate for pharmacotherapy development.

10.6

SSRI antidepressants accelerate epilepsy development – role for 5-HT2 receptors?

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Due to the high comorbidity of epilepsy and depression, antidepressant treatment is commonly indicated for patients with epilepsy. Human and animal research suggests that selective serotonin reuptake inhibitors (SSRIs) may reduce epilepsy severity, but whether SSRIs impact the development of epilepsy has not been studied. We explored whether SSRIs influence epileptogenesis, and investigated neurobiological mechanisms. Wistar rats (n=46) underwent kainate-induced Status Epilepticus. Rats were then chronically treated with the SSRI Fluoxetine (10mg/kg/day sc) or vehicle. Animals were continuously monitored via video-EEG for 10 weeks, after which time the brains were processed for hippocampal mossy fibre sprouting. The onset of epilepsy, and total number of seizures were compared between treatments, as was the extent of sprouting. A second cohort underwent the same procedures, but was treated with a 5-HT2 receptor agonist DOI (1mg/kg/day/sc) or vehicle, and the same outcomes assessed. Fluoxetine significantly accelerated epileptogenesis, leading to a faster onset of epilepsy after SE, compared to control treatment ($p<0.0001$). Fluoxetine also resulted in greater disease severity, as evidenced by significantly more seizures than control ($p<0.0001$). Mossy fibre sprouting was more pronounced in fluoxetine-treated rats ($p<0.01$). In the second experiment, treatment with DOI also significantly enhanced epileptogenesis, accelerating the onset of epilepsy and increasing seizure frequency ($p=0.001$). We conclude that chronic treatment with fluoxetine accelerates epileptogenesis and magnifies disease severity following brain injury. Pathological reorganisation of hippocampal circuitry was also enhanced following fluoxetine treatment. The same effects were noted with an agonist at 5-HT2 receptors, suggesting that this receptor is responsible for the effects of fluoxetine. These findings may have relevance for people taking SSRIs at high risk of developing epilepsy, such as following brain injury.

11.1

A proof-of-concept human laboratory study of glucocorticoid receptor antagonism as a novel treatment for alcohol dependence

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Chronic heavy alcohol use and withdrawal are associated with abnormal HPA axis activity and glucocorticoid receptor (GR) feedback, and sensitization of CRF in the amygdala. We hypothesized that administering mifepristone (a GR antagonist) to recently abstinent alcoholics would normalize alcohol-related HPA axis dysregulation and thereby protect against relapse during protracted withdrawal. Fifty-six non-treatment-seeking paid volunteers (43 males, 13 females, 21-65 years of age) who met DSM IV diagnostic criteria for current alcohol dependence were randomized to 1-week of double-blind treatment with mifepristone 600mg/day or matched placebo. Alcohol abstinence was verified during the last 3 days of the 7-day dosing period by measurement of alcohol glucuronide in urine. Alcohol cue reactivity manipulations, followed by craving ratings, were conducted at the conclusion of the drug administration interval. Additionally, measures of drinking, liver functioning, general health and abuse potential were obtained pre and post treatment.Mifepristone was associated with significantly greater reductions than placebo in alcohol-cued craving, alcohol consumption and liver enzyme activity. There was no evidence of abuse potential, and no serious or unexpected adverse health events were observed. These proof-of-concept findings suggest that mifepristone may have therapeutic potential in alcohol dependence. A clinical trial in 150 outpatients seeking treatment for alcohol dependence is underway to replicate and extend these results.

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11.2

Pathophysiology of the cerebellothalamic pathway in a chronic rat model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder that presents with characteristic motor deficits. Despite the cerebellum being crucial for motor control, there is limited understanding of PD associated cerebellar changes. Imaging studies of PD patients report cerebellar hyperactivity and decreased volume. These changes may be a pathophysiological effect of hyperactivation of the subthalamic nucleus (STN), which has excitatory projections to the cerebellum via pontine nuclei. Supporting this, Purkinje neurons in the cerebellar cortex are hyperactive in a primate PD model. Purkinje neurons have inhibitory control of deep cerebellar nuclei (DCN), which generate cerebellar output. It remains unknown if there are PD associated changes in the DCN. Therefore, we recorded STN and DCN neural activity in a chronic rat model of PD, induced by unilateral lesioning of nigrostriatal dopamine projections with the neurotoxin 6-hydroxydopamine (6-OHDA). Consistent with previous studies, STN neurons in 6-OHDA-lesioned rats had significantly higher firing rates ($p = 0.013$) and were more bursty ($p < 0.0001$) than neurons in sham-lesioned rats. DCN neurons of 6-OHDA-lesioned rats exhibited a significant *decrease* in firing rate ($p = 0.041$) and *increase* in burstiness ($p < 0.010$). These data show for the first time that the cerebellothalamic pathway exhibits functional changes in neuronal activity in a PD model. The DCN provides important inputs to the motor cortex, via the motor thalamus. Thus, these changes may contribute to dysfunctional motor output in PD. Furthermore, our findings highlight DCN input to the motor thalamus as a potential novel drug therapy target for treating PD movement deficits.

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11.3

Improving longitudinal biomarkers of ovine batten disease: Neuroimaging and ventricular enlargement in sheep

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Batten disease (Neuronal ceroid-lipofuscinosis, NCL) is a group of fatal brain wasting diseases of children caused by mutations in at least 13 genes. Forms associated with mutations in two of these are being investigated in well-established sheep models. Brain atrophy is a defining feature of Batten disease. A longitudinal reduction of the intracranial volume (ICV) can be measured easily on computed tomography (CT) images, and there is a remarkable progressive enlargement of the cerebrospinal fluid (CSF) space, primarily the lateral ventricles, obvious on post mortem examination. There is evidence that viral mediated gene therapy inhibits these changes, indicating exciting therapeutic possibilities. Timely assessment of treatment trials will be empowered by accurate and rapid *in vivo* longitudinal monitoring of ICV and the CSF space. From previously obtained CT scans (n=202) the Hounsfield unit (HU) intervals for respectively ICV and CSF space were identified. Batten disease affected sheep (n=2x3) and unaffected age- and breed-matched controls (n=2x3) are being investigated for changes of ICV and CSF space. Their brains are scanned bi-monthly from 4 months to the present (aged approximately 10 months). The established thresholds are used to measure ICV and CSF space (ICV HU: [-12;56] and CSF HU: [-12;23]) followed by manual correction for scanning artefacts. Preliminary results support a reduction of ICV and an increase in the CSF space over time in Batten disease affected sheep brains compared to unaffected controls. Areas for refinement of the method have been identified.

11.4

Sniffing out the mechanism of seizure generalisation through the piriform cortex

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Recent human imaging studies have demonstrated the early involvement of the piriform cortex (PC) in the generalisation of focal seizures. However, little is known about the mechanisms involved. The normal role of the PC is to process odour information. Our aim was to elucidate the mechanism of the PC's involvement in seizure generalisation by studying neuronal activity in the PC in an *in vitro* epilepsy model. Experiments used 450 µm-thick slices of the PC from 18-30 day-old C57Bl6 mice. Two-photon imaging of the Ca^{2+} indicator OGB1-AM was used to monitor the simultaneous activity of 20-60 neurons in layer 2/3 of the PC. Hyperexcitability was generated by perfusing the slices with artificial cerebrospinal fluid containing no added Mg^{2+} and high K^{+} (0Mg/HK). We found that, before electrical stimulation, the neurons exhibited unsynchronised activity (n=49 slices), and after mild stimulation the synchrony increased dramatically ($p<0.001$, n=15 slices). Application of 50 µM D-APV to block NMDA receptors inhibited the induction of synchronous activity (n=4 slices), suggesting that some form of long-term synaptic plasticity is involved. All activity was also blocked by 10 µM DNQX (n=4 slices) or 1 µM TTX (n=4 slices), confirming the requirement for intact excitatory synaptic transmission. Finally, in contrast to the PC, we found that the neurons in the hippocampus (n=7 slices) and the neocortex (n=6 slices) were synchronised *before* electrical stimulation was applied, and electrical stimulation had no further effect. This suggests that the synchronisation phenomenon may be unique to the PC. In this study we have found a possible mechanism by which the PC becomes involved in epileptic seizure generalisation.

11.5

Synthetic cannabinoids: Unique formulations, chemical exposures and pharmacological consequences

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A wide variety of novel synthetic cannabinoids are being manufactured as designer drugs and distributed in herbal formulations that are combusted or heated during use. The first generation synthetic cannabinoids were derived from medicinal chemistry studies and contained molecular features demonstrated to be associated with cannabimimetic activity. However, as compounds were identified and banned by legislation, further structural elaboration occurred, such that compounds with unknown pharmacology and toxicology are currently being identified in a variety of formulations. These product may also contain degradants and impurities with unexpected pharmacological effects, or be exposed to variable conditions of heat, humidity, light, and other factors that can lead to the formation of degradation products over time. Information on the chemical exposures occurring during the combustion of these products is also scant, as is systematic study of their pharmacological and toxicological effects. Thermolysis and GC/MS analyses conducted in our laboratory demonstrate that heating or combustion of synthetic cannabinoids results in profoundly different degrees of degradation depending on structure, and converts some compounds to irritants and toxicants. Therefore, smoking or vaping of novel synthetic cannabinoid formulation clearly involves a high degree of uncertainty about the types and amounts of chemicals absorbed by the body and their pharmacological consequences.

11.6

Analgesic and anti-inflammatory effects of the bioactive lipid Docosahexaenoyl Ethanolamide (DHEA) in pre-clinical behavioural models of pain

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Pain is the most common reason to visit the doctor and is estimated to cost $635 billion annually in the United States alone. The standard treatment for pain is with mu-opioids, such as morphine, while effective, have side effects including nausea, constipation, respiratory depression, addiction, and long-term use leads to tolerance. As a potential therapeutic, conjugate compounds of fatty acids have been shown to have anti-inflammatory effects as a ligand for the cannabinoid-type receptors, CB1 and CB2. We have studied the N-acyl ethanolamine compound, docosahexaenoyl ethanolamide (DHEA) in pre-clinical behavioural models of pain and inflammation. Intraperitoneal administration of DHEA at 2 mg/kg in the formalin (2%) footpad model decreased both nociceptive ($p<0.005$) and inflammatory pain ($p<0.01$). DHEA also caused a 73.3 ± 21.8 % decrease in footpad oedema compared to formalin treated mice. In addition, intradermal administration of DHEA (2 mg/kg) decreased both nociceptive and inflammatory pain ($p<0.005$) in the formalin footpad model and lead to a decrease in footpad oedema ($p<0.05$), showing only a 1.1 ± 0.1 fold increase compared to vehicle. The tail withdrawal assay was used to measure the centrally-mediated analgesic properties, however, at 2mg/kg DHEA had no significant effect, suggesting effects are restricted to the periphery. DHEA showed a reduced side-effect profile at 2 mg/kg, with no decrease in the rotarod performance test and no change in core body temperature over 120 min. This study shows that DHEA has potential as an anti-inflammatory analgesic with a reduced side-effect profile and may be used as a scaffold for designing further therapeutics.

12.1

Direct reprogramming to model neurological disease

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Direct reprogramming of human fibroblasts to mature neurons by the introduction of defined neural genes has become well established and holds potential use in the areas of neurological disease modeling and drug development. However, use of induced neurons for large-scale drug screening and cell-based replacement strategies is limited due to their inability to expand once reprogrammed. To address this, we have developed a protocol which allows for the generation of expandable neural precursor cells directly from adult human fibroblasts. This was achieved by over-expression of the transcription factors SOX2 and PAX6 resulting in the generation of induced neural precursor (iNP) colonies expressing a wide range of neural stem and pro-neural developmental genes. Upon differentiation, iNP cells can give rise to GFAP+ astrocytes and electrophysiologically mature neurons expressing phenotypic markers for glutamatergic, GABAergic and dopaminergic neurons. We have recently advanced our direct-to-iNP reprogramming technology by using a novel chemically modified mRNA gene delivery system. The use of modified mRNA resulted in a substantial increase in co-transfect efficiency leading to an increased rate of iNP reprogramming of ~14-21 days compared with ~45-65 days required using cDNA plasmid transfection. Our direct-to-iNP reprogramming method has significant application for 'neurological disease modelling in a dish', and we have preliminary results demonstrating the potential for this technology to study Huntington's disease. Such research will provide novel insights into disease progression and cellular mechanisms not able to be examined using current models with potential for the identification of new therapeutic targets and high throughput drug screening.

12.2

HDAC4 and memory formation: Interaction with the actin cytoskeleton

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Haploinsufficiency of the histone deacetylase HDAC4 has been linked to intellectual disability and its presence is also essential for long-term memory (LTM) formation in rodents and Drosophila. However, HDAC4 is largely non-nuclear and the specific mechanisms through which it regulates memory, particularly in the cytoplasm, are unclear. In a genetic screen for genes that interact with HDAC4 in neurons, several regulators of the actin cytoskeleton were identified, which included Moesin (Moe) and Ankyrin2 (Ank2). Moe is a member of the ERM family that regulates actin polymerisation at the cytoskeleton and Ank2 links membrane proteins to the cytoskeleton. Remodelling of the actin cytoskeleton occurs during formation of LTM, however whether moesin and ank2 are required for LTM has not been investigated. In this study, we aimed to investigate the roles of Moe and Ank2 in brain development and LTM in Drosophila. RNAi-mediated knockdown of either gene in the brain resulted in severe growth and guidance defects including stalling and mistargeting of axons in the mushroom body, a key structure for memory formation in flies. Furthermore, knockdown of Moe in lobular plate tangential neurons, the spines of which closely resemble vertebrate dendritic spines, resulted in a severe disruption of dendritic architecture. Individual knockdown of both Ank2 and Moe also resulted in a significant impairment in LTM ($p<0.01$, ANOVA post-hoc Tukey's HSD). Ongoing analysis of these interactions in the brain will assist in understanding the mechanisms by which HDAC4 influences neurological processes.

12.3

Understanding how maternal obesity and fetal neuro-immune interactions modulate epigenetic regulation of neural development in the mouse

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In fetuses that develop in obese dams, the risk for later life dysregulation of body weight, and thus obesity, is increased. We have defined anomalies in the prenatal development of the neural circuitry that regulates body weight, when gestation takes place in an obese dam. Moreover, we have identified accompanying changes in gene expression that appear to underpin these morphological abnormalities; and we have begun to reveal that changes to epigenetic gene regulation may explain the pathological changes in developmental gene expression. Finally, we have observed that several classic immune regulators, including interleukin 6, are significantly elevated in the fetus in pregnancies complicated by maternal obesity; and preliminary experiments suggest that they may play a causative role in driving epigenetic change.

12.4

The role of extracellular vesicles in the spread of misfolded proteins associated with neurodegenerative diseases

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Neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD) and prion diseases are associated with proteins that misfold and deposit in the brain. Many cell types, including neurons, release extracellular vesicles (EVs) which include microvesicles and exosomes. EVs have been shown to be involved in processing of proteins such as APP, α-synuclein, and PrP which are those involved in AD, PD and prion diseases respectively. Roles for these vesicles include cell-cell signalling, removal of unwanted proteins, and transfer of pathogens (including prion-like misfolded proteins) between cells. Our group has shown that EV's contain distinct processed forms of these proteins and that, in the case of prion disease, they contain the transmissible form of the misfolded protein. In addition to their protein content these vesicles have recently been shown to contain genetic material in the form of protein coding (mRNA) and noncoding RNA species. We have analysed the protein and genetic cargo of EVs from a number of cell types and using deep sequencing, characterised the RNA cargo of these vesicles. As exosomes can be isolated from circulating fluids such as serum, urine, and cerebrospinal fluid (CSF), they provide a potential source of biomarkers for neurological conditions. This talk will review the roles these vesicles play in neurodegenerative disease and highlight their potential in diagnosing these disorders through analysis of their RNA content.