29th International Australasian Winter Conference on Brain Research

2011 Programme and Abstracts

27-31 August 2011
Copthorne Hotel, Queenstown, New Zealand
www.awcbr.org

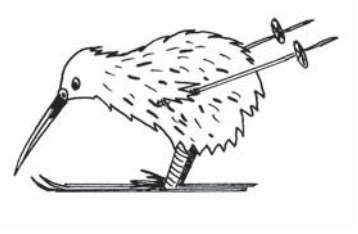
Saturday 27 August

3.00-6.00 pm	Registration, Copthorne Resort Hotel, Queenstown
5.00-6.00 pm	Student Meet and Greet, 1st Floor Bar
6.00 pm	Opening Reception, Cash Bar
7.00 pm	Opening Remarks

1. Molecular Mechanisms in Disease and Plasticity

Chair: Johanna Montgomery

7.15 pm	1.1	**Invited Speaker** **Craig Garner,** ***Stanford School of Medicine, USA*** Synaptic mechanisms underlying cognitive impairment in Down Syndrome
8.00 pm		Tea/Coffee break
8.15 pm	1.2	**Hollie Peacock,** ***University of Otago, New Zealand*** FEZF2 regulates projection maintenance in postnatal neurons *in vitro*
8.30 pm	1.3	**Ailsa McGregor,** ***University of Auckland, New Zealand*** Altered synapsin 1 and GluR1 immunoreactivity in the hippocampus of YAC128 Huntington's disease mice
8.45 pm	1.4	**Chantelle Fourie,** ***University of Auckland, New Zealand*** Alterations in postsynaptic density proteins in the human brain in response to neurodegenerative disease
9.00 pm	1.5	**Sarah Hulme,** ***University of Otago, New Zealand*** A role for astrocytes in hippocampal metaplasticity?



Sunday 28 August
Morning Session

7.30 am — Light Breakfast Available

2. Aging and Neurodegeneration

Chair: Stephanie Hughes

8.00 am	**2.1**	**Tracy Melzer,** ***Van der Veer Institute for Parkinson's and Brain Research, New Zealand*** Decreasing structural integrity with cognitive impairment in Parkinson's disease
8.15 am	**2.2**	**Nadia Borlase,** ***University of Canterbury, New Zealand*** Diffusion tensor imaging in the thalamus: An advanced method used to investigate cognitive decline in Parkinson's disease
8.30 am	**2.3**	**Jeff Bednark,** ***University of Otago, New Zealand*** Altered performance monitoring and enhanced outcome evaluation in medicated participants with Parkinson's disease
8.45 am	**2.4**	**Natalia Samorow,** ***University of Auckland, New Zealand*** The role of mood in facial emotional processing in pre-symptomatic HD gene-carriers
9.00 am		Tea/Coffee break
9.15 am	**2.5**	**Peter Thorne,** ***University of Auckland, New Zealand*** Circulation pathways in the cochlear lateral wall of aging mice
9.30 am	**2.6**	**Louise Parr-Brownlie,** ***University of Otago, New Zealand*** Globus pallidus neuronal activity does not underlie L-dopa induced dyskinesias in Parkinsonian rats
9.45 am	**2.7**	**Ping Liu,** ***University of Otago, New Zealand*** Pre-aggregated $A\beta_{25-35}$ alters arginine metabolism in the rat hippocampus and prefrontal cortex
10.00 am	**2.8**	**James McKearney,** ***University of Auckland, New Zealand*** Dopamine excites nigral dopaminergic neurons during blockade of D2 receptors – A comparison with L-DOPA-induced excitation

Sunday 28 August
Afternoon Session

AWCBR

3.15 pm Afternoon Tea Available

3. Drugs of Abuse

Chair: David Palmer

3.45 pm	**3.1**	**Judith Mandl**, *Victoria University of Wellington, New Zealand* Relationship between impulsivity, novelty seeking and MDMA self-administration in rats
4.00 pm	**3.2**	**Jennifer Do**, *Victoria University of Wellington, New Zealand* Self-administered MDMA produces dose- and time-dependent serotonin deficits in the brain
4.15 pm	**3.3**	**Joyce Colussi-Mas**, *Victoria University of Wellington, New Zealand* Acquisition of MDMA self-administration in rats: What has dopamine got to do with it?
4.30 pm	**3.4**	**Joanne Lin**, *University of Auckland, New Zealand* Quantifying metabolite changes in the brain due to methamphetamine addiction using proton magnetic resonance spectroscopy
4.45 pm		Tea/Coffee break
5.00 pm	**3.5**	**Colin Brown**, *University of Otago, New Zealand* Contribution of post-spike after-potentials to morphine withdrawal excitation of supraoptic nucleus neurons
5.15 pm	**3.6**	**Reem Jan**, *University of Auckland, New Zealand* The effect of methamphetamine on cognitive performance and grey matter structure in the human brain
5.30 pm	**3.7**	**Peter Bosch**, *Victoria University of Wellington, New Zealand* The cellular and behavioural investigation of KMS – a novel kappa opioid receptor agonist
5.45 pm	**3.8**	**Louise Curley**, *University of Auckland, New Zealand* Effects of an acute dose of triflurомethylphenylpiperazine (TFMPP) on human reward circuitry using functional magnetic resonance imaging (fMRI)

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 29 August
Morning Session

8.00 am		Light Breakfast Available

4. Neuroendrocrinology

Chair: Christine Jasoni

8.30 am	4.1	**Jenny Clarkson**, *University of Otago, New Zealand* Gpr54 in GnRH neurons is required for puberty and fertility in mice
8.45 am	4.2	**Victoria Scott**, *University of Otago, New Zealand* A hormonal action of kisspeptin activates supraoptic nucleus neurons in vivo
9.00 am	4.3	**Richard Piet**, *University of Otago, New Zealand* Electrical activity of two populations of kisspeptin neurons in the female mouse hypothalamus
9.15 am	4.4	**Siew Hoong Yip**, *University of Otago, New Zealand* Prolactin activates Stat5b but not Stat5a signaling in the mouse hypothalamus
9.30 am		Tea/Coffee break
9.45 am	4.5	**Robert Porteous**, *University of Otago, New Zealand* Kisspeptin neurons in the rostral periventricular area co-express galanin and met-enkephalin
10.00 am	4.6	**Tony Sapsford**, *University of Otago, New Zealand* Mechanisms of prolactin suppression of stress responsiveness
10.15 am	4.7	**Greg Anderson**, *University of Otago, New Zealand* Hypothalamic RFamide related peptide-3 (RFRP-3) neurons respond to the anxiolytic hormone prolactin and modulate the stress axis
10.30 am	4.8	**Simran Maggo**, *University of Otago, New Zealand* Cholesterol lowering through HMG CoA reductase inhibitors (statins) impairs long term potentiation and induces anxiety in guinea pigs
10.45 am		Tea/Coffee break for AGM attendees
11.00 am		**ANNUAL GENERAL MEETING** All conference participants are invited to attend

5. Afternoon Poster Session - Combined with MedSci

nb: Rydges Hotel, clancy's room, level 5

4.00 - 6.30 pm

Presenters will be in attendance during this time

Presenters for Posters A should be in attendance from 4.00 to 5.15 pm

Presenters for Posters B will be in attendance from 5.15 to 6.30 pm

The poster session will be followed by a student-only dinner to the held at Winnies at 8.00 pm; details to be provided.

5.1 - A **Simon Donaldson,** *Van der Veer Institute for Parkinson's and Brain Research, New Zealand*
Canterbury mild cognitive impairment study: Influence of different criteria

5.2 - B **Victor Borges,** *University of Auckland, New Zealand*
The effect of optic nerve neurodegeneration on functional activity in the human visual cortex

5.3 - A **Eng Toh,** *University of Otago, New Zealand*
Eye-hand coordination and relationship to cognition in Huntington's disease

5.4 - B **Carolyn Wu,** *University of Auckland, New Zealand*
Patients with Parkinson's disease show deficits in compensatory motor pathways during externally paced finger movements

5.5 - A **Mike Fleete,** *University of Otago, New Zealand*
Altered nitric oxide synthase and arginase activity and expression in Alzheimer's disease brain

5.6 - B **Katherine Hope,** *University of Otago, New Zealand*
Characterisation of neurons and processing of CLN5 in CLN5-deficient sheep

5.7 - A	**Dave Bergin,** ***University of Otago, New Zealand*** Learning and memory deficits following a single intracerebroventricular infusion of pre aggregated $A\beta_{25-35}$ in rats
5.8 - B	**Rena Jing,** ***University of Otago, New Zealand*** Regional specific changes of agmatine level in the presynaptic terminals in the aged rat brain
5.9 - A	**Gary D'Souza,** ***University of Auckland, New Zealand*** YAC128 transgenic Huntington's disease mice display motor, cognitive and affective symptoms
5.10 - B	**Aleisha Moore,** ***University of Otago, New Zealand*** Investigating steroid hormone feedback in a mouse model of polycystic ovarian syndrome
5.11 - A	**Shirley Douglas,** ***University of Otago, New Zealand*** GABA receptor subunit expression is altered during pregnancy and postpartum in mice with postpartum anxiety induced by low prolactin during pregnancy
5.12 - B	**Marc Matsas,** ***University of Otago, New Zealand*** Estrogen modulation of TrkA receptor signaling in PC12 cells
5.13 - A	**Thomas Kim,** ***University of Otago, New Zealand*** The role of maternal nutrition during lactation and leptin in the offspring on the neonatal projection from the arcuate nucleus
5.14 - B	**Janette Quennell,** ***University of Otago, New Zealand*** Gonadal steroids cause a region-specific enhancement of hypothalamic leptin signalling in male and female mice
5.15 - A	**Rachael Augustine,** ***University of Otago, New Zealand*** Effects of prolactin on signal transduction pathways in the supraoptic and paraventricular nuclei of diestrous and lactating rats
5.16 - B	**Stephanie Constantin,** ***University of Otago, New Zealand*** A new brain preparation to help understand the neuronal control of GnRH neurons
5.17 - A	**Andrea Kwakowsky,** ***University of Otago, New Zealand*** The role of CREB in estrogen negative feedback on GnRH neurons

5.18 - B **Xinhuai Liu,** ***University of Otago, New Zealand***
Dopamine inhibits GnRH neurons via D1- and/Or D2-like receptors in mouse

5.19 - A **Jayoung Shin,** ***University of Otago, New Zealand***
Is there a role for primary cilia in gonadotropin-releasing hormone (GnRH) neurons?

5.20 - B **Simon Stringer,** ***University of Otago, New Zealand***
Expression of GFP in kisspeptin neurons in a novel transgenic mouse line

5.21 - A **Anan Harbid,** ***University of Otago, New Zealand***
Characterisation of RFamide-related peptide-3 (RFRP-3) neurons in the brushtail possum brain

5.22 - B **Siobhan Kirk,** ***University of Otago, New Zealand***
Prolactin signaling in the tuberoinfundibular dopaminergic neurons of the lactating mouse

5.23 - A **Zin Khant Aung,** ***University of Otago, New Zealand***
Estradiol modulates cytokine signaling pathways within the brain

5.24 - B **Danielle Tranter,** ***University of Otago, New Zealand***
Interleukin-6 regulation of adrenal medullary chromaffin cells

5.25 - A **Hayden McEwen,** ***University of Otago, New Zealand***
Activation of the Wnt signalling pathway in the hypothalamus by metabolic parameters and its potential: possible involvement in glucose homeostasis?

5.26 - B **Charlotte Butler-Munro,** ***University of Auckland, New Zealand***
The role of TC10 in AMPA receptor dynamics at excitatory synapses

5.27 - A **Owen Jones,** ***University of Otago, New Zealand***
BCM-like metaplasticity independent of action potentials and changes in membrane properties

5.28 - B **Greig Joilin,** ***University of Otago, New Zealand***
Rapid down-regulation of a microRNA controller of gene expression, microRNA-132, following induction of long-term potentiation *in vivo*

5.29 - A **Rashi Karunasinghe,** ***University of Auckland, New Zealand***
Hypoxic spreading depression in the Substantia Nigra in acute brain slices

5.30 - B **Meghan McIlwain,** ***University of Auckland, New Zealand***
Genetic polymorphisms implicated in treatment resistant schizophrenia

5.31 - A **Ruwantha Munasinghe,** ***University of Otago, New Zealand***
Functional impact of novel migraine mutations in the $Ca_V2.1$ channel

5.32 - B **Siyi Chen,** ***University of Auckland, New Zealand***
MacGreen mice: A novel tool to investigate brain inflammation post stroke

5.33 - A **Elisabeth Pfister,** ***University of Auckland, New Zealand***
Neural progenitor cell proliferation is not altered in the subventricular zone of YAC128 mice

5.34 - B **Nishani Dayaratne,** ***University of Auckland, New Zealand***
The effect of oxygen and glucose deprivation on spontaneous optical activity in the developing cochlea

5.35 - A **Sangeeta Balabhadrapatruni,** ***University of Otago, New Zealand***
Effects of bilateral vestibular deafferentation on the dendritic morphology of CA1 pyramidal neurones -A Golgi study

5.36 - B **Lucy Stiles,** ***University of Otago, New Zealand***
The effects of D2 dopamine receptor antagonism on behavioural changes in bilateral vestibular deafferented rats

5.37 - A **Irene Cheung,** ***University of Otago, New Zealand***
Do rats with bilateral vestibular lesions experience anxiety?

5.38 - B **Jack Rivers,** ***University of Otago, New Zealand***
Cannabinoid receptor type II as a target for neuroprotection following hypoxia ischemia. Or is it an active vehicle in the driving seat?

5.39 - A **Phil Brownjohn,** ***University of Otago, New Zealand***
CB2 selective agonists have limited efficacy when delivered intrathecally in a rodent model of neuropathic pain

5.40 - B **Matthew Petoe,** ***University of Auckland, New Zealand***
On automated versus manual MRI analyses when evaluating corticospinal tract integrity for post stroke therapeutic interventions

5.41 - A **Hayley MacDonald,** ***University of Auckland, New Zealand***
Uncoupling response inhibition

5.42 - B **Haeme Park,** ***University of Auckland, New Zealand***
P50 sensory gating and schizotypal personality: Preliminary findings

5.43 - A **Gary Bird,** ***Victoria University of Wellington, New Zealand***
The role of eye gaze in decision making

5.44 - B **Matthew Gildersleeve,** ***Queensland University of Technology, Australia***
An indication that non-informative vision eliminates the Kinaesthetic Fusion Effect

5.45 - A **Laura Fogg,** ***University of Auckland, New Zealand***
Neuroscience public open days: evaluating Auckland Brain Day as a communication method

5.46 - B **Kevin Lee,** ***University of Auckland, New Zealand***
Association between bassoon and synaptic ribbons in developing mouse cochlea

5.47 - A **Manfred Oswald,** ***University of Otago, New Zealand***
Sublayer-specific colocalisation of corticospinal neurons with the lamina 5 pyramidal neuron marker *Fezf2*

5.48 - B **Suvimal Tantirigama,** ***University of Otago, New Zealand***
Projection neuron identity in the mouse motor cortex

5.49 - A **Rachel Sizemore,** ***University of Otago, New Zealand***
Rat striatal spiny projection neurons have markedly more synapses on their somata and primary dendrites compared to striatal cholinergic interneurons

5.50 - B **Yeri Kim,** ***University of Otago, New Zealand***
Nicotinic acetylcholine receptor subunit expression in mouse cerebellum

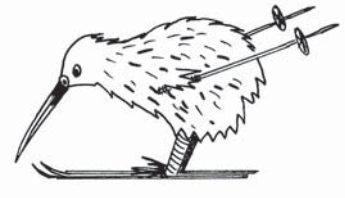
5.51 - A **Blaine Abraham,** ***Victoria University of Wellington, New Zealand***
Is 5-HT1A receptor supersensitivity a mechanism of serotonin deficit after MDMA exposure?

5.52 - B **Ana Holley,** ***Victoria University of Wellington, New Zealand***
Elucidating the cellular effects of MDMA on the serotonin transporter

5.53 - A **Daiichiro Nakahara,** ***Hamamatsu University School of Medicine, Japan***
Twenty-four hour access to intrathecal self-administration of cocaine results in a binge like behavior in mice

Poster Session

5.54 - B	**Grace Wang,** *University of Auckland, New Zealand* Cognitive function and methadone maintenance treatment
5.55 - A	**Sasa Peter,** *University of Auckland, New Zealand* Electrophysiological properties of sensory hair cells during type I fibre elimination
5.56 - B	**Vinthiya Paramanthasivam,** *University of Auckland, New Zealand* Age-related degeneration of supporting tissues in the mouse cochlea
6.30 pm	**Posters to be removed at this time**



Monday 29 August
Evening Events

6.30-7.00 pm	**Opening of Queenstown Research Week** **Rt Hon Wayne Mapp** Minister for Science and Innovation Venue: Rydges Hotel, Restaurant, Level 6
7.00-8.00 pm	**Queenstown Research Week Nobel Laureate Lecture** **Professor Barry Marshall,** ***University of Western Australia*** (2005 Nobel Prize in Physiology and Medicine) Title: **Helicobacter pylori in the post-genomic era** Venue: Rydges Hotel, Restaurant, Level 6
8.00 pm	**Social Mixer** **Combined QRW Welcome Function** Venue: Rydges Hotel, Trade Exhibition Area, Level 4
8.00 pm	**AWCBR Student Dinner** Venue: Winnies Gourmet Pizza and Bar, 7-9 The Mall, Queenstown

Tuesday 30 August
Morning Session

7.30 am Light Breakfast Available

6. Cognitive Neuroscience

Chair: Cliff Abraham

8.00 am	**6.1**	**Yvette Lamb,** ***University of Auckland, New Zealand*** Influence of Brain-Derived Neurotrophic Factor (BDNF) and Catechol-O-Methyltransferase (COMT) polymorphisms on recall
8.15 am	**6.2**	**Christopher Thompson,** ***University of Auckland, New Zealand*** The role of BDNF and COMT in frontal lobe functioning: The Tower of Hanoi
8.30 am	**6.3**	**Kate Sprecher,** ***University of Otago, New Zealand*** Are musical key and rhythm processed by distinct neural modules?
8.45 am	**6.4**	**Sarina Iwabuchi,** ***University of Auckland, New Zealand*** The spatial working memory network: Can we link structure and function?
9.00 am		Tea/Coffee break
9.15 am	**6.5**	**John Reynolds,** ***University of Otago, New Zealand*** Sensory reinforcement in the superior colliculus
9.30 am	**6.6**	**Jesicka Goei,** ***University of Otago, New Zealand*** A blue G and a G in blue – the involvement of associative memory in synaesthesia
9.45 am	**6.7**	**Daniel Spiegel,** ***University of Auckland, New Zealand*** Anodal tDCS decreases GABAergic suppression in primary visual cortex
10.00 am	**6.8**	**Jordan Searle,** ***University of Auckland, New Zealand*** Prior completion of left/right-facing rotated object discriminations facilitates use of a non rotation strategy during mirror/normal rotated letter discriminations

3.30 pm Tea and Coffee Available

7. Neurovascular Coupling

Chair: John Reynolds

4.00 pm	7.1	**Tim David,** *University of Canterbury, New Zealand* The challenge of multiple scales in the biological sciences: applications in cerebro vascular perfusion
4.15 pm	7.2	**Matthew Barrett,** *University of Auckland, New Zealand* Brain scans, blood flow, and how simulation might save the day
4.30 pm	7.3	**Hannah Farr,** *University of Canterbury, New Zealand* Models of neurovascular coupling—A tale of two (billion or so) astrocytes
4.45 pm	7.4	**Antonia Berretta,** *University of Otago, New Zealand* Sonic hedgehog signaling and post-stroke recovery
5.00 pm	7.5	**Simon Feng,** *Van der Veer Institute for Parkinson's and Brain Research, New Zealand* Correlations between ASL blood flow MRI and eye movement abnormalities in Parkinson's disease
5.15 pm	7.6	**Ben Smith,** *University of Auckland, New Zealand* Inferring causality using time-lag analysis of BOLD data

Tuesday 30 August
Evening Session

5.30 pm — Afternoon Tea Available

8. Disease Mechanisms

Chair: Peter Thorne

6.00 pm	**8.1**	**David Palmer,** ***Lincoln University, New Zealand*** In vivo intercellular correction in ovine CLN6 Batten disease
6.15 pm	**8.2**	**Suzanne Ackerley,** ***University of Auckland, New Zealand*** Priming sensorimotor cortex to enhance task-specific training after subcortical stroke
6.30 pm	**8.3**	**Kajsa Igelstrom,** ***University of Otago, New Zealand*** Anticonvulsant effects and sodium channel inhibition by selective serotonin reuptake inhibitors
6.45 pm	**8.4**	**John Ashton,** ***University of Otago, New Zealand*** The cannabinoid CB2 receptor controversy: a receptor with an identity crisis
7.00 pm	**8.5**	**Cliff Abraham,** ***University of Otago, New Zealand*** Secreted amyloid precursor proteins promote proliferation and glial differentiation of adult hippocampal neural progenitor cells
7.15 pm	**8.6**	**Prasanta Nayak,** ***University of Otago, New Zealand*** GYKI-52466 preconditioning preserves CA1 neuronal excitability and improves long-term potentiation in a rat model of hypoxic-ischemic brain injury
7.30 pm	**8.7**	**Emily McNamara,** ***University of Otago, New Zealand*** Memantine, a promising treatment for acoustic trauma-induced tinnitus

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Wednesday 31 August
Combined Day with MedSci

SESSION TO BE HELD AT THE RYDGES HOTEL, QUEENSTOWN

7.30 am		Light Breakfast Available Rydges Hotel, Clancy's, level 5
8.30		**Combined MedSci and AWCBR Plenary Lecture** Supported by the University of Otago
	9.1	**Professor Michael Cowley,** ***Monash University, Australia*** Leptin induced hypertension, the link between obesity and metabolic disease?
		Wakatipu Room, Level 5
9.30		Coffee Break
		Visualising brain function from networks to molecules (neuroendocrinology)
		Chairs: Allan Herbison and Rebecca Campbell
		Combined MedSci and AWCBR Symposium
		Wakatipu Room, Level 5
10.00 am	**9.2**	**Ulrich Boehm,** ***University of Hamburg, Germany*** Genetic approaches to understanding hypothalamic function in the mouse
10.30 am	**9.3**	**Lynn Enquist,** ***Princetown University, USA*** Viral tracing of neuronal networks
11.00 am	**9.4**	**Karl Iremonger,** ***University of Otago, New Zealand*** Initiation and propagation of action potentials in GnRH neuron dendrites
11.30 am	**9.5**	**István Abráhám,** ***University of Otago, New Zealand*** Single molecule imaging in living adult neurons
12.00 pm		Light lunch and Student Prize Presentation - Ben Lomond Restaurant

Acknowledgements
We are deeply indebted to Ms Norma Bartlett and Mrs Cara Duffy, Department of Psychology, University of Otago for their help with the conference organisation and secretarial assistance. We also thank William van der Vliet and Hadyn Youens, Department of Psychology, University of Otago, for their help with the AWCBR websites.We are very grateful to the Neurological Foundation of New Zealand for its generous financial assistance toward student travel and registration.

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1.1

Synaptic mechanisms underlying cognitive impairment in Down Syndrome

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Intellectual and developmental disability (IDD), defined by an IQ<70, affects 2-3% of the population in industrialized nations, resulting in enormous health, opportunity, and productivity costs and diminished quality of life for individuals and families. Data from our groups and others support a theory for cognitive dysfunction in IDDs based on imbalances between excitatory and inhibitory circuits in the brain. Specifically, we have found that cognitive deficits in mouse models of Down syndrome (DS) can be resolved in a long-lasting manner in adult mice by systemic delivery of drugs that target these imbalances. Specifically, we have found that excessive inhibitory tone within neuronal circuits that encode long-term memory consolidation are disrupted in the form most mouse model of DS and that low doses of several GABAA receptor antagonist fully normalize cognitive function. My presentation will cover the underlying mechanism of how these drugs improve cognition and our translational efforts that will soon see this strategy evaluated in the clinic.

1.2

FEZF2 regulates projection maintenance in postnatal neurons *in vitro*

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The development of cortical neurons depends on the expression of specific combinations of transcription factors. Many of these transcription factors are retained in the adult brain, however the functional significance of this expression remains unknown. Here, we tested the function of the layer V projection neuron gene, *Fezf2* in postnatal cortical neurons *in vitro*. Primary neural cultures from a transgenic mouse expressing GFP under the regulation of the *Fezf2* promoter (*pFezf2*GFP mice; postnatal day 2) were transduced with one of two *Fezf2*-shRNAs or non-silencing control viruses co-expressing red fluorescent protein. *pFezf2*GFP- positive neurons were analysed by time-lapse imaging or Sholl analysis to quantify projection complexity and length. *Fezf2* shRNA expression resulted in at least 53% knockdown of target mRNA, and a significant reduction in projection complexity and length (*Fezf2* shRNA mean maximum length 135 μm; non-silencing 250 μm; Wilcoxon Mann-Whitney test $p < 0.0001$). Using time-lapse imaging we found that the majority of cells demonstrating projection retraction died within 96 hours. The expression of several genes involved in projection maintenance was significantly altered in a microarray analysis of FEZF2-responsive genes. These results demonstrate that FEZF2 is required for the maintenance of a subset of FEZF2-positive postnatal cortical neurons *in vitro*. Testing this function in vivo will provide significant new information on the maintenance of cortical neurons in health and disease.

Supported by the Royal Society of New Zealand Marsden Fund and Otago School of Medical Sciences Bequest Funds.

1.3

Altered synapsin 1 and GluR1 immunoreactivity in the hippocampus of YAC128 Huntington's disease mice

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Predictive genetic testing of Huntington's Disease patients (HD) has shown that early changes in cognitive function occur in gene carriers before other clinical symptoms are apparent. These changes in working memory, executive function and recognition memory occur prior to any evidence of cell loss, suggesting that cellular dysfunction plays an important part in the early stages of the disease. We investigated the cognitive performance of 1, 2 and 6 month old YAC128 transgenic HD mice and age-matched wildtype littermates in the T maze. We then used an immunohistochemical approach to investigate whether the level and distribution of synaptic proteins (synapsin1 and PSD95) and glutamate receptor subunits (NR1 and GluR1) were altered in YAC128 mice compared to age-matched wildtype (WT) littermates. YAC128 mice showed a reduced ability to spontaneous alternate in the T maze from 1 month of age suggesting early deficits in working memory. Immunohistochemical analysis revealed an increase in synapsin 1 immunoreactivity in the hilus of YAC128 mice at 1 month of age compared to age matched wild type littermates. We also observed a decrease in GluR1 immunoreactivity within the entire hippocampus of YAC128 mice at 1 and 6 months compared to wild type littermates. No significant changes in PSD95 and NR1 immunoreactivity were observed between YAC128 and WT littermates at any age examined. Here we report for the first time that motor presymptomatic YAC128 mice display a very early cognitive deficit which correlates with alterations in key proteins involved in neuronal signalling and neurotransmitter release within the hippocampus. These results provide additional support to the hypothesis that cellular dysfunction may contribute to the onset of HD.

1.4

Alterations in postsynaptic density proteins in the human brain in response to neurodegenerative disease

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N-Methyl-D-Aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors and their bound synapse associated proteins (SAPs) are critical for normal brain function including synaptic transmission, plasticity, learning and memory. SAPs act as scaffolding molecules and are responsible for maintaining the structure of synapses, trafficking of receptors and activating signalling molecules. We hypothesise that these proteins could play an important role in the changes in synapse function that occur in response to the neurodegenerative diseases Huntington's disease (HD) and Parkinson's disease (PD). We performed immunohistochemistry in human brain tissue to determine changes in the expression of synapse associated protein (SAP97), postsynaptic density protein (PSD95), the GluR2 subunit of the AMPA receptor and the NR1 subunit of the NMDA receptor in normal, Huntington's and Parkinson's disease postmortem hippocampus and striatum tissue. We have found significant increases in SAP97 in the HD and PD hippocampus. PSD95 was differentially altered in the hippocampus (upregulated in HD and PD) and the striatum (downregulated in HD). We also found differential changes in NR1 and GluR2 expression levels in the diseased hippocampus. Interestingly, these changes are not consistent with previously reported data from HD and PD animal models, revealing that unique changes occur in the human brain with these diseases. The results provide insight into the altered subcellular mechanisms that could manifest into neurodegenerative diseases in the human brain.

1.5

A role for astrocytes in hippocampal metaplasticity?

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We have previously demonstrated a type of long-range metaplastic regulation of LTP/LTD in stratum radiatum (SR) of area CA1 in hippocampal slices following high-frequency priming stimulation of stratum oriens (SO) afferents. This communication between basal and apical dendritic compartments occurs even when somatic depolarisation is prevented. For this reason we predicted that an intercellular pathway, such as activation of the astrocytic network, may be involved in establishing the metaplastic state. In support of this hypothesis we found that delivering priming stimulation to SO (basal dendrites) in the presence of 30 μM carbenoxolone to block gap junctions prevented the induction of the metaplastic state in SR (apical dendrites). To further investigate a potential role for astrocytes in this effect, hippocampal slices from 3 week old male Wistar rats were bath-loaded with the fluorescent calcium indicator Fluo-4 AM and the specific astrocyte marker sulforhodamine for 2-photon imaging of astrocyte calcium responses. Astrocytes in SO responded robustly to SO priming stimulation. Critically, astrocytes in SR also responded, albeit with much smaller calcium increases. This suggests a long-range communication between astrocytes during priming. We also tested the possibility that SO priming altered the response of SR astrocytes to the subsequent SR LTP induction stimulus. We found however that there was no difference between primed and control slices in the proportion of SR astrocytes responding to the LTP induction stimulation or in the amplitude of responses. Taken together these results support the hypothesis that astrocytes play a critical role in the induction of a metaplastic state spanning dendritic compartments, via the spread of intracellular calcium elevations across the astrocytic network.

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2.1

Decreasing structural integrity with cognitive impairment in Parkinson's disease

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In addition to the characteristic motor impairments, Parkinson's disease (PD) is also associated with debilitating cognitive impairments. Characterizing neural changes associated with cognitive decline has important implications for patient prognosis and treatment. Diffusion tensor imaging (DTI) provides a non-invasive, *in vivo* magnetic resonance imaging technique to investigate microscopic structural integrity associated with cognition. This study characterized DTI-derived measures of fractional anisotropy (FA) and mean diffusivity (MD) from principal white matter tracts across the spectrum of cognitive impairment in PD. Ninety-six PD and 32 healthy control subjects completed comprehensive neuropsychological testing which was used to classify PD patients as cognitively normal (PD-N, n = 59), with mild cognitive impairment (PD-MCI, n = 21), or with dementia (PD-D, n = 16). An ANCOVA model was used to assess group differences across the whole brain with age, sex, and years of education as covariates. Both the PD-MCI and PD-D groups exhibited significantly abnormal FA and MD values in extensive white matter tracts relative to controls; MD was increased in PD-N relative to controls. PD-MCI and PD-D exhibited widespread, predominantly anterior MD increases relative to PD-N. Our findings suggest that PD is associated with initial white matter damage. As cognitive impairment worsens, FA and MD measures indicate further degradation beyond that associated with motor impairment. DTI provides a promising method to evaluate and potentially track anatomical substrates of cognitive decline in Parkinson's disease.

2.2

Diffusion tensor imaging in the thalamus: An advanced method used to investigate cognitive decline in Parkinson's disease

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As gross neurological abnormalities are only evident at the later stages of PD a tool is needed to identify and monitor early changes. We have previously shown that diffusion tensor imaging reveals a loss in microstructural integrity across the whole thalamus in Parkinson's disease patients, with increased mean diffusivity (MD, a measure of impaired structure) associated with increased cognitive impairment. Patients with relatively normal cognition (PD-N) had equivalent MD in the thalamus compared to healthy controls (HC) and those with mild cognitive impairment (PD-MCI) showed intermediate MD values between these groups and a group with dementia (PD-D). Here, k-means clustering was used to evaluate the integrity of individual thalamic nuclei/subregions. Twenty clusters were generated per hemi-thalamus and these were aggregated into 9 labelled "nuclei." Reduced fractional anisotropy (FA, a measure of fibre integrity) across groups, sample sizes: HC=24; PD-N=51; PD-MCI=18; PD-D=15 was found in the laterodorsal nucleus only (HC=N>MCI=D). Increased MD was evident in the PD-D group in all thalamic nuclei when compared to the HC group, whereas no HC vs PD-N differences were found. Increased MD in the PD-MCI group compared to the PD-N group was evident in the mediodorsal nuclei, laterodorsal nuclei and pulvinar nuclei. After adjustment of covariates, these three regions also showed an association with global cognitive score (aggregate Z-score), attention, memory and visuoperception, but not executive function. These findings extend our previous observations that the MD of the thalamus provides a sensitive measure of subtle brain changes associated with cognitive impairment in PD.

2.3

Altered performance monitoring and enhanced outcome evaluation in medicated participants with Parkinson's disease

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Learning the relationship between our movements and their sensory outcomes is dependent on the monitoring and evaluation of these outcomes. This learning process is thought to govern the formation of goal-directed movements. Recently, it has been proposed that patients with Parkinson's disease (PD) have an increased reliance on a goal-directed mode of movement, due to a loss of dopamine to dorsolateral striatal regions responsible for habitual movements. Additionally, dopamine medication in PD is proposed to accentuate associations between actions and positive outcomes. Event-related potential measures of performance monitoring and outcome evaluation were used to investigate whether there is an altered monitoring and evaluation of outcomes in dopamine-medicated persons with PD (n=8) compared to healthy age-matched (n= 8) controls. ERPs were recorded during movement-outcome learning and non-learning tasks, and during a stimulus-response task. Individuals with PD had a significantly larger P3 component of the ERP compared to controls in tasks requiring the updating of movement-related information for task performance ($p < .05$). Additionally, in the stimulus-response task the amplitude of the fCRP in PD patients was significantly larger than controls ($p < .05$), indicating altered performance monitoring. These results suggest that in dopamine-medicated persons with PD, unexpected sensory outcomes are monitored and evaluated like unanticipated outcomes of voluntary movement. Both altered performance monitoring and enhanced outcome evaluation may contribute to a heightened sense of control in dopamine-medicated participants with PD.

2.4

The role of mood in facial emotional processing in pre-symptomatic HD gene-carriers

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Huntington's disease (HD) is a neurodegenerative disease, primarily associated with motor dysfunctions, but also with cognitive and emotional problems which may precede motor symptoms. Deficits in recognition of emotional facial expressions, particularly in recognition of disgust, have been reported in pre-symptomatic HD gene-carriers (preHD), although findings have been inconsistent, calling for modification of the current methodology. This study investigated the facial emotional processing performance of preHD and matched controls; and the extent to which current mood levels mediate emotional recognition. Participants were administered a facial emotional recognition task which comprised both prototypical Ekman and Friesen (1976) faces and digitally-morphed faces with subtle expressions to increase likelihood of detecting subtle deficits (Buxton & Tippett, 2008). Current mood state was assessed with 4 scales, measuring anxiety, depression, inward- and outward-directed irritability. Our results indicate that preHD participants show an impairment in recognition of disgust ($p = .004$), but that deficits did not extend to other emotions. Furthermore, correlations between accuracy on the facial emotional task and mood measures indicated that, in the preHD group only, higher levels of anxiety ($p = .012$) and outwardly-directed irritability ($p = .047$) were related to a superior recognition of emotions. This study suggests that emotional impairments in pre-symptomatic HD are specific to recognition of disgust, and that the overall emotional recognition accuracy of pre-symptomatic HD gene-carriers may be mediated by exacerbated state levels of anxiety and outwardly-directed irritability.

2.5

Circulation pathways in the cochlear lateral wall of aging mice

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The spiral ligament and stria vascularis form the lateral wall of the membranous cochlea adjacent to the auditory sensory organ. An extensive network of fibrocytes, connected by gap junctions provides a circulation pathway particularly for buffering extracellular potassium. Degeneration of fibrocytes, has been observed in the C57/BL6 mouse and human cochlea with age. The impact of progressive loss of fibrocytes on intercellular communication pathways with age is unknown. This study investigated structural changes in lateral wall tissues and correlated these with expression of connexins (Cx26, Cx29, Cx30, Cx43), NaK-ATPase(α) and measurements of the endocochlear potential recorded from scala media in C57BL/6 mice. Tissue was collected at 1, 3, 6 and 12 months. Real time qPCR and immunohistochemistry were used to quantitate gene expression levels and to localise protein expression. Light and transmission electron microscopy was used to examine lateral wall structure. Progressive degeneration and loss of fibrocytes occurred in the spiral ligament area occupied by Type 3 and Type 4 fibrocytes mainly in the basal turn. The different connexins and NaK-ATPase hada distinct expression pattern within the cochlea, as described previously, with high levels of expression of Cx26, Cx30 and NaK-ATPase(α) in fibrocytes. No significant changes occurred in expression of Cx26, Cx30 and NaK-ATPase in Type 1 and Type 2 fibrocytes or the endocochlear potential with age. These data confirm the structural changes in the lateral wall of the C57BL/6 with age and show that remaining fibrocytes retain gap junction pathways and NaK-ATPase important for intercellular communication and potassium homeostasis.

2.6

Globus pallidus neuronal activity does not underlie L-dopa induced dyskinesias in Parkinsonian rats

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Levodopa (L-dopa) is the most commonly used treatment for Parkinson's disease (PD), but with prolonged use many patients develop dyskinesias. To elucidate the neurophysiology underlying L-dopa-induced dyskinesias we recorded single unit and local field potential activity in the globus pallidus (GP) of freely moving sham- and 6-hydroxydopamine PD model rats before and after administration of dyskinesia-inducing L-dopa (20 mg/kg p.o.). Preliminary data show that mean baseline firing rates are significantly reduced in PD model compared to control rats during both quiet rest (23.0 vs. 36.5 spikes/s, $p<0.05$) and walking periods (17.1 vs. 40.6 spikes/s, $p<0.05$). Baseline firing rates during spontaneous grooming and head movements did not differ between sham and PD model rats. However, firing rates of GP neurons were not affected by L-dopa in sham or PD model groups. In particular, GP firing rates during periods of L-dopa induced forelimb dyskinesia did not differ significantly with interspersed periods of quiet rest or natural grooming behaviour in PD model rats. These data indicate that while GP firing rates are lower in PD model rats, as predicted by standard models of basal ganglia dysfunction in PD, modulation of neuronal activity in the GP does not appear to be an important factor in the generation of dyskinesias.

This work was funded by grants from the Heath Research Council and Neurological Foundation of New Zealand. Thanks to Roseanna Smither for technical assistance.

2.7

Pre-aggregated $A\beta_{25-35}$ alters arginine metabolism in the rat hippocampus and prefrontal cortex

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Amyloid beta (Aβ) has been proposed to play a central and causative role in the development of Alzheimer's disease. There is increasing evidence suggesting that arginine and its metabolites may contribute significantly to the pathogenesis of AD. $A\beta_{25-35}$ is the neurotoxic domain of the full-length Aβ. A single central injection/infusion of pre-aggregated $A\beta_{25-35}$ has been shown to cause learning and memory impairments in rodents. The present study investigated how a single bilateral intracerebroventricular (i.c.v.) infusion of pre-aggregated $A\beta_{25-35}$ (30 nmol/rat) affected arginine metabolic enzymes and metabolites in the CA1, CA2/3 and dentate gyrus (DG) sub-regions of the hippocampus and prefrontal cortex (PFC) at the time points of 6-8 days post-Aβ infusion when compared to the rats that received the infusion of the reverse peptide $A\beta_{35-25}$ (30 nmol). $A\beta_{25-35}$ resulted in significantly decreased nitric oxide synthase (NOS) activity and endothelial NOS protein expression, but increased arginase activity, arginase II protein expression, and ornithine and putrescine levels, in hippocampal CA2/3. There were increased glutamate and putrescine levels in the DG, but decreased agmatine levels in the DG and PFC, in the $A\beta_{25-35}$ group relative to the $A\beta_{35-25}$ one. Cluster analyses were performed to determine if the 9 related neurochemical variables (arginine, citrulline, ornithine, agmatine, putrescine, spermidine, spemine, glutamate and GABA) formed distinct groups, and whether it changed as a function of $A\beta_{25-35}$. There were substantially different clusters between the two groups in the hippocampus and PFC. These results demonstrate that $A\beta_{25-35}$ affects animals' behavioural function and arginine metabolism, which further supports the prominent role of arginine and its metabolites in AD pathogenesis.

2.8

Dopamine excites nigral dopaminergic neurons during blockade of D2 receptors – A comparison with L-DOPA-induced excitation.

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We have recently demonstrated that the Parkinson's drug and dopamine precursor L-DOPA induces excitation of dopamine-sensitive cells in the Substantia Nigra pars compacta when applied in the presence of the D2 receptor antagonist sulpiride (1). This L-DOPA-evoked excitation consists of two phases, an early phase which can be attenuated by the AMPA/kainate receptor antagonist CNQX, and a prolonged phase. It remains unclear whether the excitation is mediated by L-DOPA itself, its oxidation products, or by dopamine (DA) produced from exogenous L-DOPA. The present study aimed to clarify whether DA evokes similar excitation as L-DOPA. Conventional extracellular recordings were made from nigral dopaminergic neurons in acute midbrain slices (300 µm) obtained from rats. DA (30 µM; 45 sec) evoked D2-receptor-mediated inhibition of firing when applied on its own. In the presence of D2-receptor block by sulpiride (30 µM) DA (50 µM; 4 min) produced excitation. This excitation was not attenuated by CNQX (20 µM) nor by CNQX and APV (50 µM). Our study demonstrates that excitation produced by DA is distinct from the ionotropic glutamate receptor component of L-DOPA-induced excitation. It also raises the possibility that the late phase of L-DOPA induced excitation is evoked by DA produced from L-DOPA.

(1) Yee et al. 2010. Proceedings of the 28th International Australasian Winter Conference of Brain Research. Abstract 6.4

3.1

Relationship between impulsivity, novelty seeking and MDMA self-administration in rats

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Several studies suggest that impulsivity and sensation seeking are two independent traits that might either predict or result from drug dependence. These two traits have been proposed to interact with different phases of drug-taking. Animal studies have suggested that response to novelty, as a measure of sensation seeking, has been linked to the acquisition but not the maintenance of self-administration. On the other hand, impulsivity has been linked to the maintenance but not the acquisition of self-administration. The aim of this study was to examine the relationship between impulsivity and novelty seeking in the acquisition and maintenance (drug seeking) of methylenedioxymethamphetamine (MDMA) self - administration. Rats were first screened for impulsivity, measured as premature responding, choice accuracy and omissions, on the 5-choice serial reaction time task (5-CSRTT), and for novelty seeking, measured as the locomotor response to a novel environment. Afterwards subjects were tested in the MDMA self-administration paradigm. Impulsivity did not predict acquisition of MDMA self-administration but was significantly correlated with MDMA (5.0 and 10.0 mg/kg, IP) produced drug-seeking. Choice accuracy was negatively correlated with the initial phase of MDMA self-administration (drug intake in the first 3 days). Omission was positively correlated with drug intake in the last 3 days of self-administration. Novelty seeking failed to correlate with any measures of MDMA self-administration. These findings suggest that impulsivity might be a risk factor for the development of compulsive drug-seeking following extinction of MDMA self-administration, as has been suggested for other drugs of abuse. Other studies have suggested a relationship between the response to novelty and cocaine or amphetamine self-administration but there was no relationship with any of the measures of MDMA self-administration. These findings suggest different underlying vulnerability mechanisms in the propensity to acquire and maintain MDMA self-administration.

3.2

Self-administered MDMA produces dose- and time-dependent serotonin deficits in the brain

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MDMA use and abuse have been increasing worldwide. Of concern, exposure to high doses of MDMA decreases several markers of 5HT neurotransmission and produces deficits in tissue levels of 5HT. Studies in laboratory animals have been conducted primarily following large doses (20.0-80.0 mg/kg) of experimenter-administered MDMA but it is unclear whether similar persistent deficits in tissue 5HT levels are produced following self administration. In this study, tissue levels of 5HT in frontal cortex, striatum and hippocampus were measured following different levels of self-administered MDMA. For both groups, responding was initially reinforced by an infusion of 1.0 mg/kg/infusion MDMA. The dose was reduced to 0.5 mg/kg/infusion once 90 infusions had been self-administered. For the two groups, testing continued until either a total of 165 or 315 mg/kg had been self-administered. Assays were conducted either 2 or 10 weeks following the last self-administration session. The lower dose exposure regimen failed to significantly decrease 5HT levels in any brain region. The higher dose exposure, however, decreased 5HT levels by 30-35% in all 3 brain regions 2 weeks, but not 10 weeks, following self-administration. Thus, MDMA self-administration produced dose and time-dependent deficits in tissue levels of 5HT suggesting that similar deficits would be produced in humans who use and abuse the drug.

3.3

Acquisition of MDMA self-administration in rats: What has dopamine got to do with it?

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(+/-)3,4-methylenedioxymethamphetamine (MDMA) is self-administered by laboratory rats but there is remarkable individual variability in the acquisition of MDMA self-administration. The basis for this variability is unclear. MDMA is a preferential serotonin agonist but also stimulates the release of dopamine. Because drug reinforcement has been attributed to dopaminergic responses, the present study aimed to evaluate whether the acquisition of MDMA self-administration was related to dopamine and/or serotonin responses to an initial exposure to MDMA. Drug naïve rats were given two injections of MDMA (1.0 mg/kg, i.v. followed 2 hours later by 3.0 mg/kg, i.v.) and synaptic dopamine and serotonin levels in the nucleus accumbens were measured via microdialysis. Two to three days later, animals were given daily access to MDMA self-administration until they earned a total of 240 infusions (total intake of 165 mg/kg MDMA). The initial MDMA-produced dopamine response of rats that acquired self-administration was not different from the response of rats that did not acquire self-administration. Interestingly, the initial MDMA-produced serotonin release was significantly lower in rats that acquired self-administration than in rats that did not acquire self-administration, indicating that rats that acquired MDMA self-administration had a higher dopamine/serotonin ratio than rats that did not meet the acquisition criterion. These results suggest that serotonin might prevent or delay the acquisition of MDMA self-administration and that the development of MDMA self-administration might not merely rely on the sensitivity of the dopaminergic system, but on the balance between the dopamine and serotonin systems.

3.4

Quantifying metabolite changes in the brain due to methamphetamine addiction using proton magnetic resonance spectroscopy

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Methamphetamine addiction is an epidemic of global proportion; the medical, social and economic consequences associated with its use have become a major problem worldwide. Magnetic resonance spectroscopy (MRS) studies of abstinent methamphetamine users have shown abnormalities relating to N-acetylaspartate (NAA) and choline-containing compounds (Cho), changes which may be indicative of reduced neuronal density and cell proliferation in response to neuronal injury. In order to investigate subtle metabolite changes in current methamphetamine users, absolute quantification of the metabolites – NAA, Cho and creatine (Cr) was carried out. Single-voxel proton MRS was performed in the anterior cingulate cortex (ACC), basal ganglia (BG) and visual cortex (VC) of 17 methamphetamine-dependent participants aged 22-46, and compared with 22 healthy controls. Imaging was undertaken using a 1.5 T Siemens Magnetom Avanto system. For quantification, a phantom model was constructed with known concentrations of brain metabolites. Results were analysed using jMRUI v4.0 software. Two-tailed independent t-tests between methamphetamine users and controls determined significant metabolite changes ($p<0.05$). Analysis revealed increases in Cho in the ACC but no metabolite changes in the BG and VC. It is possible that current methamphetamine use has different effects on these markers than those seen following abstinence, and abnormalities relating to NAA are only detected following drug cessation and withdrawal.

3.5

Contribution of post-spike after-potentials to morphine withdrawal excitation of supraoptic nucleus neurons

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Hypothalamic supraoptic nucleus (SON) oxytocin (OT) neurons develop morphine dependence when chronically exposed to this opiate, and undergo robust withdrawal excitation when morphine is subsequently acutely antagonized by naloxone. Morphine withdrawal excitation is evident as increased firing rate and is associated with an increased post-spike excitability that is consistent with the expression of an enhanced post-spike afterdepolarization (ADP). Here, we used sharp electrode recording from SON neurons in hypothalamic explants from dependent rats (administered 10 – 50 μg h^{-1} morphine, ICV, over five days from an Alzet 2001 mini-osmotic pump) to test the hypothesis that an increase in ADP amplitude contributes to morphine withdrawal excitation of OT neurons. Naloxone-precipitated morphine withdrawal increased ADP amplitude by 48 ± 11% in SON neurons; this represents a hyper-activation of ADPs because the basal amplitude of the ADP was similar in SON neurons recorded from explants prepared from morphine naïve and morphine treated rats. To determine whether an enhanced ADP could precipitate withdrawal-like increases in activity *in vivo*, we used intra-SON microdialysis administration of apamin (0.1 and 1 mM) to increase ADP amplitude (by inhibition of the concomitant medium afterhyperpolarization) in urethane-anaesthetized rats. Intra-SON apamin did not alter the firing rate of OT neurons recorded from morphine treated rats, or from morphine naïve rats, nor did intra-SON apamin affect the increase in firing rate precipitated by naloxone administration (5 mg kg^{-1}, IV). Hence, ADP enhancement does not trigger morphine withdrawal excitation of OT neurons but likely contributes to the withdrawal-induced increase in firing rate.

3.6

The effect of methamphetamine on cognitive performance and grey matter structure in the human brain

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The effect of methamphetamine (MA) on the structure of the human brain has not been extensively studied. Previous research has reported reductions in cortical grey matter density (GMD) in MA-dependent subjects relative to healthy controls, as well as an increase in striatal volumes suggesting the occurrence of a compensatory mechanism in the dopamine-rich basal ganglia. Seventeen active MA-dependent users and 20 healthy controls aged 18-46 years were scanned using a Siemens Magnetom Avanto 1.5T MRI scanner. Two high-resolution T1-weighted anatomical scans were acquired for each subject. Statistical analysis, controlling for age, gender and cumulative lifetime MA use, was conducted within FSL 4.1. A battery of neuropsychological tests was administered to MA-dependent participants outside the scanner. Normalised global brain volumes did not differ between groups. However, voxel-based morphometry results (using FSL-VBM) revealed significant GMD reductions in the left superior and right superior/middle frontal gyri in MA-dependent participants relative to controls, which were correlated with poorer performance on memory recall, sensorimotor and attention tasks. Moreover there were GMD gains in the bilateral putamen which were associated with improved performance on attention and executive function tasks. Results from the subcortical volumetric analysis were in agreement on the enlargement of the putamen. Additionally, there was a significant enlargement of the left accumbens. Cortical GMD deficits were associated with poorer cognitive function; in contrast striatal enlargement may occur as a compensatory response to maintain cognitive function.

3.7

The cellular and behavioural investigation of KMS – a novel kappa opioid receptor agonist

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Psychostimulant abuse represents a significant public health issue in New Zealand and around the world. In particular, the use of amphetamines in New Zealand and Australia is significantly higher than the rest of the world (2 – 2.8% compared with 0.2 – 1.4% worldwide prevalence, UNODC, 2010). Currently, there are no approved pharmacotherapies for the treatment of psychostiumulant addiction. This project is part of an ongoing collaboration investigating novel kappa opioid agonists, with the aim of designing compounds that reduce psychostimulant intake whilst having minimal side effects. This study investigated a new kappa opioid receptor agonist, KMS, and tested its ability to reduce reinstatement of extinguished cocaine-seeking behavior in rats. KMS showed a significant reduction in reinstatement at a dose of 1 mg/kg ($p<0.05$) when given prior to a priming injection of cocaine. The effect of KMS on dopamine transporter function in isolated cells was also investigated, showing a kappa-opioid receptor dependent increase in dopamine transporter function at 50 µM of KMS ($p<0.01$). As psychostimulant reinstatement and relapse has been linked to rises in dopamine in the nucleus accumbens, drugs that act to reverse this may be useful as future pharmacotherapies.

3.8

Effects of an acute dose of trifluromethylphenylpiperazine (TFMPP) on human reward circuitry using functional magnetic resonance imaging (fMRI)

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TFMPP is a non-selective serotonin (5-HT) agonist and a major constituent in a group of recreational designer drugs that have been consumed worldwide. Literature has indicated that 5HT influences reward modulation, and affects dopamine (DA) transmission via 5HT2C receptors. Currently there is no information regarding the effects of TFMPP on human reward circuitry. Eleven participants completed a randomised double blind cross-over trial using fMRI and a gambling task. Echo-planar images were collected 90minutes after an oral dose of TFMPP (participants <60 kg, 50 mg; >60 kg, 60 mg) or placebo. The gambling task required participants to guess whether the suit of a presented card would be red or black, for a monetary reward. Data were pre-processed and analysed using SPM8. Results indicate that the dorsal striatum, (caudate and putamen), showed greater activation when large monetary rewards were obtained, in the placebo condition ($p<0.001$ uncorrected). In large losses the results were mixed, activations were observed from the placebo condition in the thalamus and a small cluster in the posterior cingulate, however after TFMPP greater activation was found in the middle cingulate and a secondary small cluster was found in the thalamus ($p<0.001$ uncorrected). Literature suggests that $5HT_{2C}$ agonists, such as TFMPP, can reduce the firing rate of mesolimbic DA neurons. Reduced activation after administration of TFMPP suggests that both positive and negative feedback will not produce regular responses, leading to less reward, but also reduced aversive effects

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4.1

Gpr54 in GnRH neurons is required for puberty and fertility in mice

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Kisspeptin and its G-protein coupled receptor GPR54 are essential for the pubertal activation of gonadotropin-releasing hormone (GnRH) neurons, with Gpr54 mutations or deletion resulting in failed puberty and infertility in humans and mice. The critical site of kisspeptin action within the hypothalamic-pituitary-gondal axis has yet to be definitively identified. In the present studies we used Cre-loxP technology to create mice in which Gpr54 was deleted only from GnRH neurons in order to test the hypothesis that Gpr54 signalling in GnRH neurons is critical for puberty and fertility. Female mice were checked for vaginal opening (VO) from weaning until 5 months of age. Paraformaldehyde perfusion-fixed brains were collected from adult (>60 days) mice and immunocytochemistry conducted to examine the distribution of GnRH and Cre expression. Gonads were collected from adult mice and histological analysis was conducted on haematoxylin and eosin-stained tissue. The GnRH-Cre/Gpr54flox mice are viable and apparently normal apart from a complete lack of pubertal maturation. Mutant females do not exhibit VO, have thread-like uteri and small ovaries which lack corpora lutea. Mutant males have small external genitalia and testes and lack mature sperm in the testes. The GnRH-Cre/Gpr54flox mice exhibit normal numbers and distribution of GnRH neurons and Cre expression was restricted to GnRH neurons. These GnRH-Cre/Gpr54flox mice exhibit a severe reproductive deficit that is similar to global Gpr54 and kisspeptin knockout mice. These results demonstrate that Gpr54 signalling in GnRH neurons is absolutely necessary for the activation of GnRH neurons to induce pubertal development and fertility.

4.2

A hormonal action of kisspeptin activates supraoptic nucleus neurons in vivo

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Oxytocin and vasopressin are synthesized by magnocellular neurosecretory cells in the hypothalamic supraoptic and paraventricular nuclei, and released from the posterior pituitary gland into the circulation. Oxytocin stimulates uterine contractions during birth and is essential for milk ejection during suckling, while vasopressin regulates fluid balance through water reabsorption. Intravenous administration of kisspeptin-10, which is essential for puberty via its central actions on GPR54 receptors, increases plasma oxytocin levels and icv kisspeptin-10 increases vasopressin levels, indicating that kisspeptin might play a role in various physiological functions via stimulation of oxytocin and vasopressin secretion. Because posterior pituitary hormone secretion is dependent on action potential (spike) discharge, we used *in vivo* extracellular single unit recording to determine the effects of kisspeptin-10 on supraoptic nucleus neurons in urethane-anaesthetized female rats. Intravenous kisspeptin-10 (100 µg) increased the firing rate of oxytocin neurons from 3.7 ± 0.8 spikes s^{-1} to 4.7 ± 0.8 spikes s^{-1} (P = 0.0004), but only 25% of vasopressin neurons responded to iv kisspeptin-10, showing a short (<3 s) high frequency (>15 spikes s^{-1}) burst of firing. By contrast, icv kisspeptin-10 (2 and 40 µg) did not alter oxytocin or vasopressin neuron firing rate. To investigate the pathway involved in the peripheral action of kisspeptin-10, we used ip capsaicin to desensitize vagal afferents, and this prevented the iv kisspeptin-10 induced increase of oxytocin neuron firing rate. These experiments show that peripheral, but not central, kisspeptin-10 increases the activity of oxytocin neurons and a proportion of vasopressin neurons, and that endogenous kisspeptin regulation of supraoptic nucleus neurons is likely via vagal afferent input, with kisspeptin acting as a hormone in this system.

4.3

Electrical activity of two populations of kisspeptin neurons in the female mouse hypothalamus

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Kisspeptin has emerged as a crucial player in the regulation of the hypothalamo-pituitary-gonadal (HPG) axis, via its action on gonadotropin releasing hormone (GnRH) neurons. The two populations of hypothalamic neurons that synthesize kisspeptin, located in the rostral periventricular area of the third ventricle (RP3V) and in the arcuate nucleus (ARN), have been hypothesized to play distinct roles in mediating the feedback of oestrogen on the HPG axis in female rodents. Whether these two populations of neurons have different electrophysiological properties is currently not known. Here, we investigate the electrical activity of kisspeptin neurons in the RP3V and in the ARN by taking advantage of a recently developed mouse line which expresses Cre recombinase in these neurons (Kiss-Cre). Cross-breeding Kiss-Cre mice with a reporter mouse line expressing GFP in a Cre-dependent fashion allows for the targeting of kisspeptin neurons for electrophysiology in brain slices obtained from adult female mice (2-3 months old). On-cell loose patch recordings of GFP-expressing neurons reveal that kisspeptin neurons in the RP3V spontaneously fire action potentials at higher rates (2.19 ± 0.27 Hz, n = 35) than those in the ARN (0.08 ± 0.04 Hz, n = 11, p<0.0001). In addition, inspection of the firing patterns reveal that most RP3V kisspeptin neurons fired in a tonic or tonic/bursty fashion whereas most ARN kisspeptin neurons were bursty or silent. These preliminary results indicate that the two anatomically distinct populations of kisspeptin neurons display profoundly different spontaneous electrical activity in the female mouse.

4.4

Prolactin activates Stat5b but not Stat5a signaling in the mouse hypothalamus

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Prolactin exerts multiple functions throughout the mammalian body including mammary gland, heart, liver, muscle and brain. Prolactin binds to its receptors and coveys its action through the phosphorylation and thus activation of signal transducer and activator of transcription 5 (Stat5). There are two very similar widely expressed isoforms of Stat5 namely Stat5a and Stat5b. While expression of Stat5a in mammary gland is well known as the mediator of prolactin action, Stat5b is predominantly expressed in liver and muscle. It has been revealed that numerous brain regions including hypothalamus expressed prolactin receptors and responded to prolactin as indicated by phosphorylation of Stat5. However it is not known which Stat5 isoform is activated in these regions. Immunohistochemical and Western blotting analysis were used to determine the expression and activation of Stat5a and 5b throughout the hypothalamus in adult wild-type and Stat5b-deficient mice. Both groups (n=4) were pre-treated with 5mg/kg of bromocriptine to suppress endogenous prolactin levels followed by administration of 10mg/kg ovine prolactin for 45min. We demonstrated that Stat5a and Stat5b were expressed throughout the hypothalamus of wild-type mice. In contrast, only Stat5a was expressed in the Stat5b-deficient mice although there was a significant reduction in its expression compared to wild-type mice. When stimulated with prolactin, phosphorylated Stat5 was observed in hypothalamus of wild-type but not Stat5b-deficient mice. While the hypothalamus of Stat5b-deficient mice still expressed Stat5a, it did not respond to prolactin. This indicates that prolactin's pleiotropic hypothalamic actions are mediated exclusively by Stat5b. Despite the similarity between the two Stat5 proteins, Stat5a was unable to compensate for the absence of Stat5b suggesting that these two isoforms exhibit unique biological activities.

4.5

Kisspeptin neurons in the rostral periventricular area co-express galanin and met-enkephalin

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It is now well established that the kisspeptin neurons in rostral periventricular region of the third ventricle (RP3V) are implicated in the generation of preovulatory GnRH surge mechanism and puberty onset in female rodents. The present study set out to determine if other neuropeptides were co-expressed by this cell population. The neuropeptides met-enkephalin (mENK), galanin, neurotensin and cholecystokinin (CCK) where found to be expressed by neurons located in in a similar area in the RP3V of colchicine treated mice to that of kisspeptin neuron cell bodies. Further investigations with double label immunohistochemistry showed that 7% of kisspeptin cells co-expressed galanin and 28-38% of kisspeptin cells (depending on rostral to caudal location) expressed mENK. No co-expression was found for kisspeptin and neurotensin or kisspeptin and CCK. Examination of kisspeptin fibres in the vicinity of GnRH neuron cell bodies revealed co-expression of kisspeptin with both mENK and galanin particularly around the OVLT, a region of the POA previously shown to contain GnRH neurons activated during the preovulatory GnRH surge. Thus like the arcuate nucleus kisspeptin neurons, the RP3V kisspeptin population co-express a variety of neuropeptides. This will greatly enhance the ability of these kisspeptin neurons to modulate the activity of the neurons they innervate.

4.6

Mechanisms of prolactin suppression of stress responsiveness

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The anterior pituitary hormone prolactin is thought to dampen the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis to stress during lactation. We hypothesised that prolactin acts directly on corticotrophin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) through the long-form of the prolactin receptor, the predominant receptor isoform in the rat brain. Diestrous and lactating rats were injected with 100 ng or 500 ng of ovine prolactin, or vehicle, icv. Prolactin-induced cell signalling was examined by immunohistochemistry for phosphorylated STAT5 (pSTAT5), a marker of long-form prolactin- receptor activation. Dual-label *in situ* hybridisation was performed to investigate whether CRH neurons express prolactin receptors. Numbers of pSTAT5-labelled nuclei were increased ($p<0.05$) in the PVN in response to 100 ng or 500 ng ovine prolactin in both diestrous and lactating rats, and numbers of labelled cells were higher in lactating rats after the 100 ng dose ($p<0.05$). However, few (<5%) pSTAT5-labelled nuclei co-localised with CRH in response to prolactin during diestrus or lactation. This was consistent with *in situ* hybridisation data indicating that CRH mRNA and prolactin receptor mRNA was not co-expressed in the PVN. Furthermore, mRNA for the short-form prolactin receptor, an alternatively spliced isoform, was not detected in the PVN. These data suggest that prolactin does not regulate the HPA axis directly at the CRH neuron, but may act indirectly through other neuronal phenotypes.

4.7

Hypothalamic RFamide related peptide-3 (RFRP-3) neurons respond to the anxiolytic hormone prolactin and modulate the stress axis

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RFRP-3 neurons project from the dorsomedial hypothalamus to a wide variety of brain regions in rats including rostral aspects of the paraventricular nucleus (Rizwan et al 2009, Endocrinology 150: 1413-20) where they appear to contact corticotrophin-releasing hormone neurons (which drive the stress axis) (Qi et al 2009, J Neuroendocrinol 21: 690-7). Elevated circulating prolactin concentrations modulate the stress axis, such that during lactation stress responses are suppressed (Slattery and Neumann 2008, J Physiol 15: 377-85). However, the neuroanatomical pathway by which prolactin interacts with the stress axis is unknown. We therefore examined whether the hypothalamic RFRP-3 neurons act as a conduit between prolactin and the stress axis in female rats. In experiment 1, we tested if RFRP-3 neurons were responsive to prolactin. Acute prolactin treatment (2.5 ng icv) induced expression of pSTAT5 (an activated prolactin signaling molecule) in 93% of RFRP-3 neurons, identified using immunohistochemistry. Furthermore, chronic prolactin treatment (2 mg/kg ip twice daily for 2 days) or lactation both caused a marked suppression of RFRP mRNA levels ($P<0.05$). In experiment 2, lactating or diestrous rats (n=7-8) were acutely treated icv with combinations of prolactin, RFRP-3 or the RFRP-3 antagonist RF9. Ten minutes after central drug treatments, the rats were tested for anxious behavior using elevated plus maze (EPM) (5 minutes) and open field (OF) tests (5 minutes) followed by measurement of corticosterone secretion in response to acute restraint stress (30 minutes). RFRP-3 treatment increased measures of anxiety-related behavior and increased restraint stress-induced corticosterone secretion ($P<0.05$). Co-treatment with RF9 blocked these effects. Lactation or prolactin treatment decreased anxiety-related behavior and corticosterone secretion but co-treatment with RFRP-3 reversed this. Collectively, these findings suggest that prolactin's attenuating effects on stress responses are caused by inhibition of RFRP neuronal function.

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4.8

Cholesterol lowering through HMG CoA reductase inhibitors (statins) impairs long term potentiation and induces anxiety in guinea pigs

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Statins play a crucial role in reducing the risk of death from cardiovascular disease, and are prescribed to millions of people worldwide. Recent data shows that people taking statins have an increased risk of psychiatric adverse events such as amnesia, anxiety and even aggression. However, there is conflicting epidemiological data and a scarcity of direct experimental evidence that statins can alter neural functioning. This study aimed to investigate the effect of simvastatin (1mg/kg) and atorvastatin (0.5mg/kg) treatment on animal spatial memory and learning (Morris Water maze). Statin treatment increased time to platform over 5 days, though this result was not significant when compared with control animals. However, thigmotaxis and swimming speed were significantly ($p<0.05$ & $p<0.01$ respectively) elevated in the drug treated groups compared with control animals. Furthermore, to investigate the effect on synaptic plasticity, we conducted extracellular field recordings of synaptic transmission in area CA1 of freshly prepared hippocampal slices (400µm) to examine the effects of acute cholesterol lowering with lipid lowering drugs (bath administration). Long Term Potentiation (LTP), a key paradigm used to investigate memory changes within the hippocampus was significantly diminished in the presence of 5µM atorvastatin (62%), 5µM simvastatin (48%) and 0.5mg/ml methyl-β-cyclodextrin (MBCD) (30%) ($P<0.05$) when compared with vehicle treated slices. Deficits in water maze performance and hippocampal LTP demonstrated here are suggestive of statin induced changes in synaptic plasticity in the hippocampus. Further investigations into acute and chronic statin dosing and their effects on LTP, LTD and receptor populations will help elucidate the mechanism(s) of statin associated amnesia and anxiety.

Poster 5.1

Canterbury mild cognitive impairment study: Influence of different criteria

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Older volunteers in the Canterbury region, aged > 60yrs, were invited to participate in a longitudinal project to identify individuals who have mild cognitive impairment and who may be at risk of future cognitive decline. A preliminary analysis is provided concerning their neuropsychological scores on four tests (Rey-Copy; Rey-Immediate Recall; Trails A; pentagon drawing) and a self-report measure of cognitive impairment (AD-8) and the Montreal Cognitive Assessment (MoCA). Three hundred and ninety-two participants have been enrolled; 47 have been excluded from the current analysis due to existing neurological condition or undergoing current medication for a psychiatric condition. Employment of the recommended MoCA cut-off for neuropsychological impairment (<26/30) produced only moderate differences between an "impaired" and "unimpaired" group in terms of individual NP scores (area under the curve [AUC] for a receiver operating characteristic curve [ROC]: Rey-Copy, AUC=0.62 [95%CI=0.57-0.67]; Rey-Recall, 0.67 [0.60-0.71]; Trails A, 0.58 [0.53-0.63]; Pentagons, 0.56 [0.51-0.62]; and the AD-8, AUC=0.54 [95%CI=0.49-0.60]). Employing a stricter criterion for cognitive impairment (MoCA<23/30), substantially clearer differences emerged between "impaired" and "unimpaired" groups ([ROC]: Rey-Copy, AUC=0.77 [95%CI=0..72-0.82]; Rey-Recall, 0.73 [0.68-0.78]; Trails A, 0.61 [0.55-0.66]; Pentagons, 0.68 [0.63-0.73 and the AD-8, AUC=0.57 [95%CI=0.52-0.62]). Similarly, employing a neuropsychological criterion of an average Z-score across the Rey and Trails tasks, produced a MoCA Youden Index of <24/30, but with a sensitivity of only 67% (specificity = 85%). This analysis suggests that a lower MoCA (<23) than currently advised is more likely to identify individuals who have more robust cognitive impairments.

Poster 5.2

The effect of optic nerve neurodegeneration on functional activity in the human visual cortex

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Functional magnetic resonance imaging (fMRI) is a non-invasive technique that allows for the mapping of human brain areas based on patterns of neural activity. Using fMRI, we investigated the effects of glaucoma, a neurodegenerative disease of the optic nerve, on functional activity within the human visual cortex. Three patients with unilateral primary open-angle glaucoma underwent two fMRI scanning sessions. In the first session we mapped out the cortical representation of visual space for each eye using a technique known as retinotopic mapping. In the second session we recorded the response of the striate and extrastriate visual cortex to temporally modulated checkerboard stimuli of varying contrast, presented separately to each eye. Scotomata were readily identifiable in the retinotopic maps for the eyes affected with glaucoma within both primary and extrastriate visual areas. All three patients showed a more pronounced functional loss for high contrast checkerboard stimuli within these scotoma regions, consistent with a parvocellular loss. We also explored the activity in regions of cortex that corresponded to areas of the visual field with no clinically detectable visual deficits for either eye. We found a functional loss for low contrasts when stimuli were viewed through the eye with glaucoma in all three participants. This is indicative of a magnocellular loss. Our results demonstrate that fMRI is sensitive to visual deficits caused by neurodegeneration of the optic nerve. In addition our findings suggest that fMRI may be sensitive to disease related changes in visual cortex activity that cannot be detected by standard visual field measurements.

Poster 5.3

Eye-hand coordination and relationship to cognition in Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disease, characterised by triad of symptoms which consists of motor dysfunction, mood disorder and cognitive decline. Saccadic deficits have been recognized to be affected in those with the disease and abnormalities can even be seen prior to the development of motor symptoms. Studies in the past have only shown abnormal findings on saccadic function in HD but they failed to provide conclusive results in the relationship of such findings to hand coordination and cognitive functioning. In this study, two groups of participants will be recruited consisting of mild to moderately affected HD patients in the Canterbury region with no more than mild cognitive impairment (n=20) and a sex, gender and age matched normal controls (n=20). This study sets to investigate saccadic and hand coordination performance of HD patients in comparison to normal controls using high speed video-oculography and magnetic movement tracking system. This will be complemented by a comprehensive array of neuropsychological assessment tools to determine the performance of the two groups of participants in the different cognitive domains. Multi level regression modelling analysis will be used to determine the relationship between the different parameters tested. It is hypothesised that a relationship exists between saccadic deficits and movement disorders; and that this can be further correlated to cognitive decline in HD. Such findings may suggest that saccadic deficits can contribute to the development of motor and cognitive symptoms. Preliminary findings will be discussed.

Poster 5.4

Patients with Parkinson's disease show deficits in compensatory motor pathways during externally paced finger movements

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It is commonly observed that movement in Parkinson's disease (PD) can be improved with the use of external cues. Externally cued movement may recruit compensatory cortico-cerebello-thalamo-cortical pathways that bypass the cortico-basal ganglia-thalamo-cortical pathways which are dysfunctional in PD. Here, we employed fMRI to investigate network activations during externally paced movements in PD patients and age matched controls. We employed unimanual and bimanual simple and complex movements in order to examine the effects of hand use and complexity. Overall, PD patients demonstrated less activation relative to controls, despite continuing medication. Within a network differentially activated by differing degrees of complexity, differences in activation between the PD group and controls were observed bilaterally in the parietal regions (BA 40), supplementary motor regions (BA 6), precentral regions (BA 9), and the cerebellum. Within a network differentially activated by hand (left, right) the PD group had less activation in bilateral primary motor regions, occipital lobe, thalamus and cerebellum in patients. During bimanual movements, PD patients showed less activation bilaterally in the precentral gyri (BA 4), cerebellum and thalamus. These results suggest that although patients with PD may utilise a compensatory pathway, relatively lower levels of activation are also observed in the cortico-cerebello-thalamo-cortical pathway which is preferentially employed during externally paced tasks.

Poster 5.5

Altered nitric oxide synthase and arginase activity and expression in Alzheimer's disease brain

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and the presence of senile plaques and neurofibrillary tangles in the brain. A growing body of evidence suggests that arginine and its metabolites play a prominent role in AD pathogenesis. The present study, for the first time, investigated the activity and expression of two key arginine metabolic enzymes, nitric oxide synthase (NOS) and arginase, in the superior frontal gyrus and hippocampus in normal cases aged 60 (NC-60, n = 11) and 80 (NC-80, n = 12) years and in AD cases aged 80 years (AD-80, n = 12), with no significant differences between groups in the post-mortem delay or sample storage time. There were significantly decreased NOS and increased arginase activities in the AD-80 group relative to the NC-60 and NC-80 groups in both regions examined (all $p < 0.0001$). Inducible NOS activity was not detectable. Western blot revealed significantly decreased neuronal NOS (nNOS) and endothelial NOS (eNOS) expression, and increased arginase II (but not arginase I) expression in the AD-80 group in both regions when compared to the two control groups. These results suggest that the NOS (both nNOS and eNOS) and arginase (arginase II in particular) metabolic pathways of arginine are altered dramatically in the AD brain, which further supports the prominent role of arginine metabolism in AD pathogenesis.

Supported by Health Research Council of New Zealand.

Poster 5.6

Characterisation of neurons and processing of CLN5 in CLN5-deficient sheep

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The neuronal ceroid lipofuscinoses (NCLs), or Batten disease, are the most common inherited neurodegenerative disorders in children. Currently there is no cure and available therapies only treat the symptoms. CLN5, one of the eight genes associated with the NCLs, encodes a soluble lysosomal protein that is N-glycosylated. A naturally occurring sheep model of Batten disease is caused by a mutation at a consensus splice site in the CLN5 gene that leads to excision of exon 3 and a truncated protein. We have previously demonstrated that lentiviral vectors can be used to deliver transgenes to sheep neurons *in vitro* and *in vivo*. Here, we characterise a new neural cell culture model of CLN5 disease pathology and the expression and processing of CLN5 via a lentiviral vector in cultured neural cells. Primary neural cultures from foetal CLN5-deficient and normal control sheep were cultured and analysed for characteristic disease-associated autofluorescence. Wildtype myc-tagged CLN5 was cloned into a lentiviral vector and used to test the post-translational modification and trafficking in cells. Disease related fluorescent storage bodies accumulate in CLN5-deficient neural cells in culture over time. Using Western blot we have shown that wildtype CLN5 is post-translationally modified by EndoH- susceptible sugars in the ER and secreted into the cell culture media via exocytosis. These results demonstrate a new *in vitro* model of NCL. Our data also suggest the feasibility of CLN5 correction by lentiviral gene transfer in affected sheep, however future work is required to test the processing and secretion of CLN5 in affected primary cultures.

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Poster 5.7

Learning and memory deficits following a single intracerebroventricular infusion of pre-aggregated $A\beta_{25-35}$ in rats

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Amyloid beta proteins (Aβ) are central in the etiology of Alzheimer's disease. $A\beta_{25-35}$ is the neurotoxic domain of the full-length $A\beta_{1-42}$, and causes protein oxidation, lipid peroxidation, neuronal apoptosis and death. Previous research has shown that a single intracerebroventricular (i.c.v.) infusion of pre-aggregated $A\beta_{25-35}$ induces learning and memory impairments when tested at various time points, and that the first signs of neuronal changes become evident often at the time point of 1 month after the administration of peptide. Therefore the present study was designed to investigate the behavioural effects of a single bilateral i.c.v. infusion of pre-aggregated $A\beta_{25-35}$ at the time points of 4-8 weeks post-infusion. Rats with $A\beta_{25-35}$ i.c.v. infusion (30 nmol) were significantly impaired in the place navigation (but not cued navigation) of the reference version of the water maze task, the working memory version of the water maze and the object recognition memory task relative to those that received the i.c.v. infusion of the reverse peptide $A\beta_{35-25}$ (30 nmol). In a separate experiment, the $A\beta_{25-35}$ rats were significantly impaired in the standard working memory version, but not the reference memory vesrion, of the radial arm maze task as compared to the control $A\beta_{35-25}$ rats. These findings suggest that a single i.c.v. infusion of pre-aggregated $A\beta_{25-35}$ results in learning and memory impairments at the time points of 4-8 weeks after peptide administration.

Poster 5.8

Regional specific changes of agmatine level in the presynaptic terminals in the aged rat brain

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Age-related learning and memory deficits are associated with altered efficacy of synaptic neurotransmission. Agmatine is widely distributed in the mammalian brain and may directly participate in the processes of learning and memory as a neurotransmitter. It has been shown that the aging process significantly affects the tissue content of agmatine in the rat brain, with decreased levels with age in the prefrontal cortex (PFC) and increased levels in the temporal cortex (TE). The present study, using post-embedding immunogold electron-microscopy, investigated the effects of aging on agmatine levels in presynaptic terminals in the PFC and TE regions of male Sprague-Dawley rats (n=6). The rat had been implanted with a cannula into the right PFC for microdialysis sampling prior to the left PFC and TE being harvested for ultrastructural analyses. In total, 300 synapses were analysed for each brain region. Agmatine levels were not significantly altered with age in the PFC, with the average density of gold labelling in the aged rats (24 months) being 12.9 ± 0.67 gold/μm2 ± standard error of the mean (SEM) compared with 13.8 ± 0.68 gold/μm2 in young ones (3 months). In the TE region, however, agmatine levels were significantly increased with age by 60%, with the average density of gold labelling being 15.3 ± 0.72 gold/μm2 in the aged rats and 9.6 ± 0.40 gold/μm2 in young ones ($p<0.001$). This study, for the first time, demonstrates that the aging process may affect the levels of synaptic agmatine in the rat brain in a region-specific manner.

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Poster 5.9

YAC128 transgenic Huntington's disease mice display motor, cognitive and affective symptoms

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Huntington's disease (HD) is a fatal, inherited neurodegenerative disorder caused by an unstable polyglutamine expansion in the huntingtin gene. The symptomatic phase of HD is characterized by motor, psychiatric and cognitive deficits. An animal model that reproduces the triad of symptoms observed in human patients is essential to investigate underlying disease mechanisms and to validate new treatment strategies. YAC128 transgenic HD mice display progressive motor and cognitive deficits and comparable neuropathology to the human disease however affective symptoms have not been well characterised in this model. We investigated the performance of YAC128 mice and age-matched wild type (WT) littermates in the accelerod, T-maze, novelty suppressed feeding (NSF) and modified Porsolt tests at monthly intervals from 1 to 12 months of age. YAC128 mice show a significant decrease in fall latency in the accelerod test compared to WT littermates at all ages examined ($p<0.001$). YAC128 mice also show a decreased ability to spontaneously alternate in the T-maze from 1 to 3 months compared to WT littermates ($p<0.001$). Taken together, early deficits in accelerod performance in YAC128 mice may indicate impaired motor learning. We observed no difference in performance in the NSF test between YAC128 and WT mice at any age ($p=0.333$) suggesting no change in anxiety levels with disease progression. In contrast, YAC128 mice display a significant increase in floating time (reflecting learned helplessness) in the Porsolt test compared to WT animals from 4 to 8 months ($p=0.018$). Our results demonstrate that YAC128 mice are a clinically relevant model of HD and display early cognitive deficits, progressive motor impairment and a mid-stage depressive phenotype.

Poster 5.10

Investigating steroid hormone feedback in a mouse model of polycystic ovarian syndrome

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Polycystic ovarian syndrome (PCOS) is the most common cause of infertility among women of reproductive age worldwide. Although the aetiology is unclear, PCOS is identified as a state of impaired steroid hormone feedback to the brain. We employed a murine model of PCOS to investigate steroid hormone receptor expression in hypothalamic nuclei identified as important in steroid hormone feedback. We hypothesised that the expression of the progesterone receptor (PR), critical for regulating hormone feedback, would be altered. Prenatal androgen (PNA) exposure was used to generate a model of PCOS by delivering dihydrotestosterone to dams on days 16-18 of pregnancy. Female offspring were investigated as adults. Initial investigation of ovarian morphology was conducted to characterise the model. The ovaries of vehicle-treated (n=16) and PNA-treated (n=19) mice were stained with haematoxylin and eosin, and five sections per ovary examined. PNA treatment significantly reduced the area of the adult ovary containing corpora lutea ($p<0.01$). Investigation of antral follicles revealed the area of the granulosa cell layer was significantly reduced ($p<0.001$) and the area of the thecal cell layer significantly increased ($p<0.001$) in PNA-treated mice. This suggests impaired ovulation and altered hormone synthesis. Immunocytochemistry for PR was performed in PNA-treated (n=7) and vehicle-treated (n=7) mice in diestrus, and labelling was quantified in the anteroventral periventricular nucleus (AVPV) and the periventricular nucleus (PeN). PR positive nuclei were counted in unilateral nuclei from two representative sections from each animal. PR expression was significantly decreased in the AVPV ($p<0.001$) and the PeN ($p<0.001$) of PNA-treated mice. These results support that PNA exposure inhibits the ability of progesterone to relay feedback information to the brain, thus contributing to the endocrine and reproductive phenotype of PCOS.

Poster 5.11

GABA receptor subunit expression is altered during pregnancy and postpartum in mice with postpartum anxiety induced by low prolactin during pregnancy

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There is an increased risk of pathological anxiety in mothers after giving birth. Increased maternal anxiety adversely affects mother and offspring, and predisposes the mother to further episodes in subsequent pregnancies. Levels of neurogenesis are associated with anxiety, and there is an increase in maternal neurogenesis during pregnancy, and a further increase postpartum. In mice we have shown that low prolactin levels early in pregnancy decrease maternal neurogenesis in the subventricular zone (SVZ), which results in increased anxiety and impaired maternal behavior postpartum. These effects persist in the subsequent pregnancy, despite no further manipulation. There are no prolactin receptors in the SVZ, nor is there any pSTAT5 a marker of prolactin-mediated signal transduction, suggesting any effect on neurogenesis must be indirect. GABA regulates proliferation of neural stem cells, and expression of the GABA receptor subunits are influenced by hormonal fluctuations. Moreover, specific changes in GABA receptor subunits in the brain have been associated with expression of postpartum anxiety. Hence, we hypothesized that GABA receptor subunit composition would be differentially altered during pregnancy and postpartum in mice with low prolactin during pregnancy (anxious mice) compared to controls in the SVZ. Using Western Blotting, we analysed expression of $GABA_A$ $\alpha1$, $\alpha4$, $\alpha5$, δ and $GABA_B$ B1 and B2 receptor subunits in the SVZ during early pregnancy and on day 2 postpartum. There were no significant differences in levels of $GABA_A$ receptor subunit $\alpha4$, $\alpha5$, δ and $GABA_B$ B1 receptor subunits between control and anxious mice. However, levels of $GABA_A$ receptor subunit $\alpha1$ and $GABA_B$ B2 were significantly decreased in anxious mice compared to controls during pregnancy and postpartum. The data suggest that prolactin-induced changes in GABAergic activity may mediate prolactins action on neurogenesis in the SVZ. How prolactin alters GABA receptor subunit composition remains to be investigated.

Poster 5.12

Estrogen modulation of TrkA receptor signaling in PC12 cells

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While estrogens are known to have widespread and diverse actions within the brain the cellular mechanisms responsible for these effects are largely unknown. In addition to so-called classical genomic actions estrogens also mediate more rapid effects involving a variety of cell-signaling pathways. In this study we have used a combination of total internal reflection fluorescence microscopy (TIRFM) immunocytochemistry and immunoblotting to examine the ability of 17β-estradiol to interact with the TrkA signaling pathway in PC12 cells. TIRFM was used to track the movement of single TrkA receptors on the surface of the living cells. Preliminary immunocytochemical experiments validated that the rapid (5 min) incubation with anti-TrkA receptor antibodies, required for TIRFM, effectively labeled the cells. Immunoblotting was then employed to demonstrate that TrkA receptor stimulation by nerve growth factor (NGF 100 nM) activated the extracellular regulated kinase (ERK1/2) pathway (an index of TrkA receptor signaling) and that this response was not affected by antibody binding. TIRFM analysis of isolated PC12 cells demonstrated that NGF activation of antibody-labeled TrkA receptors resulted in increased periods of receptor immobility. Such periods of relative immobility are believed to coincide with enhanced intracellular signaling activity. In the context of this study it was significant to observe that the replacement NGF with low concentrations (100 pM) of 17-β estradiol also resulted in increased TrkA receptor immobility. This is important because it indicates that the estrogens are potentially able to modulate TrkA signaling events. On-going experiments will determine the influence of this TrkA receptor interaction on the downstream ERK1/2 activation.

Poster 5.13

The role of maternal nutrition during lactation and leptin in the offspring on the neonatal projection from the arcuate nucleus

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The nerve fibre innervation from the arcuate nucleus (ARC) to the paraventricular nucleus of the hypothalamus (PVH) is essential for the regulation of energy balance. Maternal undernutrition has been shown to alter energy balance in the offspring to predispose to obesity. Leptin in offspring during early neonatal period is critical for the development of innervation from the ARC to the PVH, and leptin levels in the offspring during this time can be disrupted by maternal undernutrition. This study investigated the effect of maternal undernutrition in the early neonatal period on the innervation from the ARC to the PVH on the offspring, and whether leptin administration is able to overcome maternal undernutrition. Pups were raised by either normal or 50% restricted-diet fed dams during early neonatal period, and received either saline or leptin injection during this time. The brains of the pups were collected post-puberty, DiI crystals were used to trace nerve fibre innervation from the ARC to the PVH, and the fibre innervation was quantified. The offspring raised by restricted-diet fed dams had a significant decrease in fibre innervation compared to the offspring of normal-diet fed dams (control) ($P<0.05$). Administration of leptin restored fibre innervation in the PVH ($P<0.05$), which was comparable to the control. Administration of leptin in the offspring of normal-diet fed dams did not significantly increase fibre innervation ($P>0.05$). In conclusion, restricted-maternal diet during lactation can disrupt the innervation from the ARC to the PVH on the offspring, but reversible by concomitant leptin treatment.

Poster 5.14

Gonadal steroids cause a region-specific enhancement of hypothalamic leptin signalling in male and female mice

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The adipocyte hormone leptin acts as an indicator of fat mass and is a key regulator of appetite, energy expenditure and fertility in the brain. Obesity is often referred to as a state of leptin resistance, as hyperphagia continues in the face of high levels of circulating leptin. Gonadal steroids (estrogens and androgens) have also been implicated in the regulation of energy balance. Estradiol inhibits feeding and weight gain, and may interact with leptin signalling pathways. To investigate the role of estrogens and androgens in modulating hypothalamic responsiveness to leptin, female and male mice were gonadectomised and given low dose implants of estradiol, non-aromatisable dihydrotestesterone (DHT), or placebo for one week. After a peripheral leptin challenge (1 µg/mouse), mice were perfused and brain tissue collected after two hours. Brains sectioned throughout the hypothalamus were subjected to immunohistochemistry for phosphorylated STAT3 (a leptin signalling molecule crucial for appetite regulation). Leptin receptive (i.e., pSTAT3 immunopositive) cells were counted in the arcuate (ARC) and ventromedial nuclei (VMN; where leptin acts to modulate energy balance) and the medial preoptic area (mPOA) and ventral premamillary nucleus (vPMN; where leptin may act to modulate fertility). The ARC and VMN showed no change in leptin sensitivity in response to sex or steroid treatment, suggesting that sex steroids do not alter leptin sensitivity in these regions. In contrast, untreated male mice had 73% less pSTAT3-immunoreactive cells than females ($p<0.01$) in the mPOA - both steroid treatments restored these levels to the female phenotype ($p<0.01$). Additionally, female mice displayed changes in leptin signalling in the vPMN in response to both hormones. These data show that gonadal steroids cause a region-specific enhancement of hypothalamic leptin signalling.

Poster 5.15

Effects of prolactin on signal transduction pathways in the supraoptic and paraventricular nuclei of diestrous and lactating rats

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Oxytocin secretion is essential for childbirth and lactation and oxytocin secretion is determined by action potential discharge of hypothalamic oxytocin neurons. We have shown that intracerebroventricular (ICV) administration of prolactin (1 µg) decreases oxytocin neuron firing rate in diestrous rats but not in lactating rats. Hence, prolactin actions on oxytocin neurons might ensure the needs and wellbeing of the mother and her offspring are being met. Prolactin acts directly on oxytocin neurons in the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN) via prolactin receptors (PRLR) and activates intracellular signalling cascades. We are particularly interested in whether prolactin activates the JAK/STAT5 and MAP Kinase signaling pathways upon binding to the PRLR, and whether differences in the activation of these pathways are evident between non-lactating and lactating rats, which might underpin the different firing rate responses of oxytocin neurons to prolactin in non-lactating and lactating rats. Rats were injected ICV with either vehicle or prolactin on diestrus or day 7 of lactation, and their brains were removed and frozen 15 min later. Coronal sections (300 µm) were cut through the hypothalamus and the PVN and SON were microdissected out and placed into lysis buffer. The amount of protein was measured in each sample using a protein assay. The ratio of phosphorylated STAT5 (pSTAT5), and phosphorylated ERK (pERK) to non-phosphorylated protein is currently being determined using western blots to assess the activation of the JAK/STAT pathway and MAPK pathway, respectively, and will be reported at the meeting.

Poster 5.16

A new brain preparation to help understand the neuronal control of GnRH neurons

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Gonadotropin-releasing hormone (GnRH) neurons are the ultimate effectors of the central nervous system upon reproductive function. Due to the scattered distribution of the GnRH neuron cell bodies across the rostral forebrain and the longitudinally spread dendrites/axons, most brain slicing techniques used for in vitro electrophysiological studies damage the GnRH neurons and severe incoming inputs to GnRH neurons. Our aim here is to investigate the potential benefit of a 600um-thick horizontal slice preparation that preserves the caudal GnRH neuron subpopulation with relatively long dendrites and its connection with the site of hormone release, the median eminence. Despite no change in overall firing properties, our data indicate a stronger bursting behavior in the new preparation compared to more conventional coronal brain slices. Because amino acids are the major regulators of neuronal activity, the responses evoked by AMPA and GABA were investigated. AMPA induced a robust excitatory response in ~80% of the cells regardless of the brain slice preparation used or the GnRH neuron subpopulation tested. In contrast with the typical excitatory response observed in coronal sections (~75%), GABA failed to induce firing in the new preparation and rather exerted a robust inhibitory effect on the AMPA-induced excitation, indicating a difference in the GABA-activated pathways in the new preparation. To test whether the excitation/inhibition were mediated indirectly, experiments were repeated by "isolating" GnRH neurons from their inputs using calcium-free medium. Our data suggest a direct modulation of GnRH neurons by both amino acids. Together, these results indicate the importance of maintaining cell integrity and network properties for acute brain slice experimentation.

Poster 5.17

The role of CREB in estrogen negative feedback on GnRH neurons

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Ovarian 17-beta-estradiol (E2) exerts homeostatic feedback actions upon gonadotropin-releasing hormone (GnRH) neurons of the hypothalamus to regulate fertility in all mammals. In females, estrogen has both negative and positive feedback actions. Current data suggests that rapid non-classical E2 actions on signaling molecules may comprise part of the negative feedback pathway and maintain a suppressive influence upon the activity of the GnRH neurons. However, the molecular mechanisms underlying these effects remain unclear. We have previously reported that E2 rapidly induces cAMP response element binding protein (CREB) phosphorylation in GnRH neurons in vivo. In the present study, we have used female mice with GnRH neuron-specific CREB deletion to investigate the role of CREB in estrogen negative feedback on GnRH neurons. Evaluation of GnRH neuron-specific CREB knockout (CREBKO) mice revealed normal puberty onset. The number of complete estrus cycles were not significantly different to those controls and knockout mice were found to be fertile. However, the percentage of time spent in diestrus and estrus was changed; CREBKO mice experienced longer periods of diestrus than the controls and spent significantly less time in estrus. Female CREBKO mice showed slightly elevated basal levels of luteinizing hormone (LH), and the increment in LH measured two weeks after ovariectomy (OVX) was normal. However, treatment with E2 for three hours was unable to restore elevated OVX LH levels to basal concentrations in CREBKO mice. In summary, our findings implicate CREB as an important component of the negative feedback actions of E2 on GnRH neurons.

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Poster 5.18

Dopamine inhibits GnRH neurons via D1- and/Or D2-like receptors in mouse

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Dopamine is involved in the control of various brain functions including reproduction. Anatomical studies have shown that dopaminergic fibers contact gonadotropin-releasing hormone (GnRH) neurons and those dopaminergic neurons are located in the rostral periventricular area of the third ventricle (RP3V), one key source of synaptic inputs onto GnRH neurons. In this study, we used a para-horizontal brain slice preparation of transgenic GnRH-GFP male and female mice and electrophysiology to examine how dopamine regulates GnRH neurons. Bath-applied dopamine (10 to 40μM) inhibited 50% of GnRH neurons (n=63) firing action potentials in a dose-dependent manner via both D1- or/and D2-like receptors subtypes. The action of dopamine was not affected (n=5) by inclusion of a cocktail of the amino acid receptor antagonists (10μM CNQX+20μM AP5+5μM GABAzine), suggesting that dopamine most likely acts directly on GnRH neurons. GnRH neuron responses to dopamine were blocked by SCH23390 (5μM, antagonist of D1-like receptors) alone (35%), by raclopride (4μM, antagonist of D2-like receptors) alone (35%), or by both SCH23390 and raclopride (30%). We also noted that ~30% of GnRH neurons (n=25) were tonically inhibited by endogenous dopamine, with D1-, D2-, or D1- and D2-like receptors mediating those actions. These studies show that dopamine exerts a potent inhibitory influence upon ~50% of GnRH neurons and this is mediated in a complex manner through both D1- and D2-like receptors.

Poster 5.19

Is there a role for primary cilia in gonadotropin-releasing hormone (GnRH) neurons?

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During embryonic development, gonadotrophin releasing hormone (GnRH) neurons make an extraordinary migration out of the nose and into the brain. In adulthoodhood, GnRH neurons in the brain drive the pituitary regulation of gonadal function and resultant fertility. Primary cilia are antennae-like immotile organelles projecting from the surface of virtually all cells, including GnRH neurons. While the role of primary cilia is not at all well understood in most cell types, links between defects in primary cilia and a variety of human pathologies have been discovered. Human ciliopathies can result in situs inversus and subfertility due to hypogonadotrophic hypogonadism suggesting a role for primary cilia in embryogenesis and reproductive function. Therefore, we aimed to investigate the role of GnRH neuron primary cilia, in their embryonic migration and adult control of fertility. To achieve this, we used a Cre-loxP approach to selectively disrupt GnRH neuron primary cilia. Kif3a is a member of the intraflagellar transport protein family, essential for primary cilia assembly and function. By crossing Kif3a 'floxed' mice with GnRH-Cre mice we were able to delete Kif3a in GnRH neurons exclusively. Confocal analysis revealed that 60% of the GnRH neurons in Kif3a $^{flox/flox}$GnRH-Cre $^{+/+}$ mice had complete absence of primary cilia. The remaining 40% had stunted primary cilia on GnRH neurons compared with controls. Kif3a$^{flox/flox}$GnRH-Cre$^{+/+}$ mice exhibited a normal adult distribution of GnRH neurons. Loss of primary cilia from GnRH neurons did not disrupt normal puberty onset or adult reproductive function measured by age of first estrus, age of vaginal opening, and estrous cyclicity (n=9/group). Together, these data suggest that primary cilia are not required for GnRH neuron migration or the regulation of fertility. However, because the onset of Cre activity in GnRH neurons during development is unknown, further study will investigate the timing of Cre activity and primary cilia loss over the embryonic GnRH migration time-line.

Poster 5.20

Expression of GFP in kisspeptin neurons in a novel transgenic mouse line

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Kisspeptin has emerged as a potent regulator of the hypothalamic-pituitary-gonadal axis. Neurons that synthesize kisspeptin reside in the rostral periventricular region of the third ventricle (RP3V) and in the arcuate nucleus (ARN). Recently, mice expressing Cre recombinase in kisspeptin neurons have been generated (Kiss-Cre). Kiss-Cre mice were crossed with mice carrying the GFP protein sequence following a floxed stop sequence to generate Kiss-Cre/GFP mice in which GFP should be expressed only in kisspeptin neurons. This study aimed to confirm that GFP expression is specific to kisspeptin neurons. Six adult Kiss-Cre/GFP mice (3 males, 3 females) received intracerebroventricular colchicine treatment to enhance cytoplasmic kisspeptin levels. Animals were anaesthetized and perfused with 4% paraformaldehyde 24 hours later. Coronal brain sections 30µm thick were incubated for 48 hours with a polyclonal kisspeptin-10 antiserum (1:10 000 dilution, AC566). The numbers of GFP and kisspeptin-expressing neurons were counted, and analyzed to determine the proportion of GFP-expressing neurons immunoreactive for kisspeptin. In the RP3V, 92±1% and 14±5% of GFP-positive neurons expressed kisspeptin in female and male mice respectively. In the ARN, 73±7% and 72±4% of GFP-positive neurons were immunoreactive for kisspeptin in female and male mice respectively. However, these percentages were improved by restricting analysis to the ventro-medial subregion of the ARN. Here, 93±1% and 79±6% of GFP-positive neurons were identified as kisspeptin neurons in female and male mice respectively. This study shows that the Kiss-Cre/GFP mouse is faithful in reporting kisspeptin neurons in the female RP3V and within a subregion of the ARN in both sexes. This region is currently being targeted for electrophysiological experiments.

Poster 5.21

Characterisation of RFamide-related peptide-3 (RFRP-3) neurons in the brushtail possum brain

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RFRP-3 neurons suppress reproduction by inhibition of gonadotrophin-releasing hormone neuronal function, and in some species they may also directly inhibit lutienising hormone release. In birds but not rodents, RFRP-3 neurons project outside the blood-brain barrier to act on the pituitary gland directly. There are no data available on marsupials, which have followed a divergent evolutionary path from placental mammals. The aims of this study were to characterise the seasonal fluctuations in neurons which produce RFRP-3 neuropeptide in the brushtail possum and to determine if these neurons project outside the brain, using the retrograde tract tracer Fluoro-Gold which cannot cross the blood-brain barrier. Adult luteal phase female possums were perfused with 4% paraformaldehyde prior to brain collection during the breeding season (June; n=5). Numbers of RFRP-3 neurons were assessed using immunohistochemistry and were compared to data that was collected during the non-breeding season (December; n=5). There was a significant 2-fold increase in the number of RFRP-3 cell bodies during the non-breeding season compared to the breeding season ($p<0.05$). As has been reported for other mammalian species, RFRP-3-immunopositive neurons were scattered throughout the dorsomedial hypothalamus. In the external zone of the median eminence (the neurosecretory zone) a small number of RFRP-3 fibers were observed. RFRP-3 neurons were found to accumulate Fluoro-Gold from a peripheral injection 1 week prior to perfusion, shown by 37% colocalization of Fluoro-Gold and RFRP-3. The presence of RFRP-3 fibres projecting outside the blood-brain barrier to the neurosecretory zone of the median eminence may be indicative of a direct inhibitory effect of RFRP-3 on pituitary gonadotrophin release, or on GnRH release from nerve terminals in this region.

Poster 5.22

Prolactin signaling in the tuberoinfundibular dopaminergic neurons of the lactating mouse

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Prolactin secretion from the anterior pituitary is tightly regulated by a short-loop negative feedback pathway. Dopamine secreted into the median eminence by the hypothalamic tuberoinfundibular dopaminergic (TIDA) neurons inhibits prolactin release from the lactotrophs. Circulating prolactin accesses the brain and interacts with specific receptors on the TIDA neurons. Receptor activation stimulates a number of intracellular signaling processes including the signal transduction and activator of transcription 5 (STAT5) pathway, leading to an increase in dopamine synthesis and release and thus suppression of prolactin secretion. It is hypothesized that prolactin levels rise during lactation due to modification of this feedback pathway. Dual-labeling immunohistochemistry was used to examine STAT5 activation (anti-phospho STAT5) within TIDA neurons (anti-tyrosine hydroxylase) in diestrous and lactating mice. While the number of TIDA neurons remained unchanged during lactation there was a marked rise in phospho-STAT5 dual-labeling. These data indicate that the STAT5 pathway in TIDA neurons is still responsive during lactation. Interestingly, lactating animals were less sensitive to exogenous prolactin. Endogenous prolactin secretion was suppressed in both diestrous and lactating groups (n=8) with 5mg/kg bromocriptine. Half of the animals from each group were then administered vehicle or 10mg/kg exogenous prolactin for 20min before being processed for immunohistochemistry. Both prolactin-stimulated groups showed a dramatic rise in the number of phospho-STAT5 positive cells compared to the vehicle-treated groups. However the magnitude of this increase was significantly lower in lactating compared to diestrous mice. These data suggest that while the STAT5 pathway in TIDA neurons is still responsive during lactation it may show reduced prolactin sensitivity. This proposal is currently being investigated by employing a range of exogenous prolactin concentrations.

Poster 5.23

Estradiol modulates cytokine signaling pathways within the brain

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The gonadal steroid estradiol has widespread and diverse actions within the brain although the cellular mechanisms responsible are largely unknown. This study extends our previous observations that estradiol can modulate signal transducer and activator of transcription (STAT) pathways within the hypothalamus. Such an interaction may be important in allowing estrogens to influence cytokine-mediated processes such as inflammatory events within the brain. Adult female mice were ovariectomized and then treated acutely (4 h) or chronically (1 week) with estradiol. Brains were removed, frozen and 300 m coronal sections prepared. Specific regions were collected by micro-punch and suppression of cytokine signaling (SOCS) mRNA levels measured by qRT-PCR. Acute and chronic estradiol treatment significantly ($p < 0.05$) increased SOCS1 and SOCS3 mRNA levels in the medial preoptic area. In contrast there were not significant changes in mRNA levels for either SOCS in the arcuate nucleus in response to acute or chronic estradiol. Changes in SOCS expression may alter STAT responses within affected cells. To investigate this possibility parallel experiments were conducted in which estradiol treated animals were injected with the STAT3-activator leptin (1mg/kg for 2h), perfused with paraformaldehyde and brain sections prepared and processed for immunohistochemistry. As expected STAT3 positive cells were seen throughout the hypothalamus. Interestingly, while this response was unaffected by acute estradiol, chronic treatment increased the number of STAT3 positive cells by approximately 25% in the medial preoptic area ($p<0.06$) but not other regions. These findings extend our previous observations made in rats. Chronic and perhaps acute treatment with estrogens may affect STAT-signaling pathways and thus potentially modulate inflammatory responses in specific brain regions.

Poster 5.24

Interleukin-6 regulation of adrenal medullary chromaffin cells

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The adrenal medulla helps coordinate the body's adaptation to stress by responding to various stimuli including neuronal, endocrine and paracrine signals. Recent evidence indicates that the adrenal medulla also responds to signals, including interleukin-6 (IL-6), interleukin-1 and tumor necrosis factor-α, which originate from the activated immune system. Such an interaction forms part of a bi-directional relationship believed to exist between the immune and neuroendocrine systems. We have shown that isolated bovine adrenal medullary chromaffin cells are directly responsive to IL-6. Acute exposure to this cytokine (5-60 min) selectively activates the signal transduction and activator of transcription 3 (STAT-3) and extracellular regulated kinase (ERK1/2) pathways. In this current study we have examined the effect of IL-6 on chromaffin cell gene expression. Isolated bovine chromaffin cells were exposed to IL-6 (10 nM), total RNA extracted and analyzed using a bovine-specific microarray (Affymetrix). A 24 h incubation with IL-6 increased the expression of around 300 identified transcripts by 2-fold or greater. Interestingly the mRNA for a number of neuropeptides (including galanin, vasointestinal polypeptide (VIP), gastrin releasing peptide and parathyroid hormone-like hormone) was notably increased. The effect of IL-6 on the expression of these neuropeptides is currently being verified by qRT-PCR and will be extended to examine the intracellular signaling pathways responsible. These data provide evidence that chromaffin cells are responsive to IL-6 and that this interaction may alter their neuropeptide synthesis profile. This is important because while the full physiological significance of adrenal medullary peptides is unknown some, including galanin and VIP, may act via the adrenal cortex to limit the inappropriate escalation of an inflammatory response.

Poster 5.25

Activation of the Wnt signalling pathway in the hypothalamus by metabolic parameters and its potential: possible involvement in glucose homeostasis?

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Diabetes is an ever-increasing epidemic, which, despite a growing body of research, shows no signs of abating. Only recently have we been able to gain new insights into the molecular mechanisms governing susceptibility to this disease. A recent genomic wide analysis of type-2 diabetics identified mutations in several genes that associated with susceptibility to the development of this disease. Surprisingly, genes typically thought of to be involved in the Wnt pathway, particularly T-cell factor 7-Like 2 (TCF7L2), showed some of the biggest genetic linkages with susceptibility to type-2 diabetes. Stabilisation of beta-catenin, a transcriptional co-factor involved with positive Wnt signalling, and binding to TCF7L2, up regulates genes encoding insulin receptor substrate (IRS1) in cell culture. Our study aimed to determine if this pathway is activated in the hypothalamus in response to metabolic parameters. Adult Sprague-Dawley rats were fasted overnight and re-fed for either 1, 4, or 6 hours. A group of fasted animals were also given a s.c. injection of 5mg exendin-4, a GLP-1 agonist, 1 hour before sacrifice, to mimic the effect of the normal release of GLP-1 during re-feeding. Brains were fixed and stained against beta-catenin, or RNA from micro dissections of various hypothalamic regions were collected and analysed for markers of downstream Wnt signal transduction using RT-qPCR. Both re-fed animals and GLP-1 treated animals showed an increase in beta-catenin immunoreactivity in specific metabolically-sensitive hypothalamic nuclei. These groups also showed increase mRNA for several Wnt-mediated genes, including axin-2 and cyclin D1 in the same nuclei. These data suggest an activation of the Wnt pathway in the hypothalamus following feeding, and potentially implicates the Wnt pathway in the hypothalamic regulation of glucose homeostasis.

Poster 5.26

The role of TC10 in AMPA receptor dynamics at excitatory synapses

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The levels of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors (AMPAR) at the post synaptic density (PSD) are highly dynamic, however, the molecules which control AMPAR endocytosis and recycling in the PSD are not well understood, especially under ambient conditions. This work investigates the role of TC10 in AMPAR endocytosis and recycling in the PSD. TC10 is a GTPase which regulates the exocytosis of a number of receptors and transporters. This work shows that disrupting TC10 expression by RNAi, or its function by TC10 dominant-negative (T31N) or constitutively active (Q75L) mutants, reduces AMPAR trafficking to the cell surface as assayed with surface fluorescent immuno-labelling. Consistent with this, paired recordings in dissociated hippocampal cultures showed decreased AMPAR mediated synaptic currents in both TC10CA and TC10DN expressing mutants. The decreased surface and synaptic expression of AMPARs correlated with increased AMPARs in dendritic intracellular pools, however, AMPARs and TC10 did not co-localise with recycling endosomes labelled with transferrin. AMPARs and TC10 did, however, co-localise with Arf-6, suggesting that under ambient conditions AMPARs enter an Arf-6 endocytotic pathway. AMPAR co-localisation with Arf-6 endosomal pools was increased by TC10DN while TC10CA decreased co-localisation but increased intracellular AMPAR in spines. This suggests TC10 mediates budding of vesicles from Arf6-contaning endosomal pools and trafficking to the cell surface. Interestingly paired electrophysiology recordings indicated a decrease in the ability to induce LTD in TC10DN mutants but no change in the ability to induce LTD in TC10CA mutants compared to controls. This suggests that TC10 activity at Arf6-contaning endosomal pools may be indirectly involved with the expression of synaptic plasticity, possibly through alterations in AMPAR dynamics and availability.

Poster 5.27

BCM-like metaplasticity independent of action potentials and changes in membrane properties

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Long-term potentiation (LTP) is a lasting increase in synaptic efficacy thought to underlie memory storage. However, LTP must be constrained or it will compromise further plasticity and lead to excitotoxicity. Regulation may come in part through metaplasticity, whereby prior neuronal activity influences later plasticity induction. The Bienenstock, Cooper and Munro (BCM) model proposes a plasticity threshold which shifts as a function of integrated postsynaptic action potential (AP) firing. The model predicts that strong postsynaptic activity will induce a *cell-wide* metaplastic increase in the LTP threshold. In our model, "priming" stimulation delivered to stratum oriens (SO) of rat hippocampal CA1 induces BCM-like changes such that LTP is inhibited at synapses in stratum radiatum (SR), *on the opposite side of the cell-body*. Somatic sharp electrode recordings were made to investigate the role of postsynaptic action potentials and depolarization in inducing this effect. EPSPs were elicited in SO and SR of impaled CA1 pyramidal cells. LTP in SR was significantly reduced in cells which received prior SO priming (3 x 100 Hz, 1 s, repeated after 15 min). Delivery of hyperpolarizing current to prevent action potentials and somatic depolarization during priming did not alter this effect (Control (n=8): 55.9 ± 6.8%; Primed (n=8): 24. 7 ± 5.0%; Hyperpol-primed (n=7): 26.3 ± 9.3%; $F(2,20)=6.36$, p= <0.01). Moreover, following priming there were no lasting effects on input resistance, the h current or the post-spike afterhyperpolarization. Thus, these data do not support the involvement of action potentials, postsynaptic depolarization or membrane mechanisms in mediating the long-range inhibition of LTP in this model.

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Poster 5.28

Rapid down-regulation of a microRNA controller of gene expression, microRNA-132, following induction of long-term potentiation *in vivo*

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Rapid up-regulation of gene networks is associated with the persistence of the long-term potentiation (LTP) model of memory, but how they are regulated is currently unknown. MicroRNA have recently been identified as negative regulators of gene expression that act through RNA degradation or translation inhibition. We hypothesized that the rapid LTP-induced up-regulation of gene networks is mediated in part by rapid down-regulation of microRNA expression. To test this hypothesis, Affymetrix GeneChip miRNA arrays were screened to identify LTP-regulated miRNA 20 min following LTP induction at perforant path synapses in awake adult male Sprague-Dawley rats (n=4). This screen identified 69 miRNA as differently expressed when compared to the non-tetanised control hemisphere using dual selection criteria (fold change ±0.15; $p<0.05$). One microRNA of particular interest showing differential expression with synaptic plasticity across a number of species was miR-132 (0.84±0.04, $p<0.05$). LTP-induced down-regulation of miR-132 was confirmed by reverse transcription quantitative PCR (RT-qPCR) using both the NCode (0.77±0.06, $p=0.03$) and TaqMan (0.23±0.11, $p<0.01$) platforms, with TaqMan showing greater sensitivity. Four mRNA, (EGR1, EGR4, NR4A2, and NR4A3) known to be up-regulated 20 min post-LTP were identified bioformatically as potential targets of miR-132. These data suggest that rapid down-regulation of miR-132 may result in release of translational arrest of these mRNA. Thus, microRNA appear to play an important role in regulating LTP-related gene expression, even at early time-points.

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Poster 5.29

Hypoxic spreading depression in the Substantia Nigra in acute brain slices

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Hypoxic spreading depression (HSD) is a profound depolarization of neurons and glia that spreads in a wave-like manner across susceptible gray matter in response to ischemia, modelled by oxygen-glucose deprivation (OGD) in vitro. Its occurrence influences the severity of acute ischemic damage. Although well characterized in cortical regions, little is known about HSD in the Substantia Nigra pars compacta (SNc), a dopaminergic nucleus involved in motor control and reward pathways. Transverse midbrain slices (250µm) from P21-25 rats containing the SNc were subject to OGD for 10 min (35.5°C). HSD developed at 5.2 + 0.2 min, as indicated by propagating changes in light transmittance and the occurrence of extracellular DC potential shifts. However, electrophysiological recordings conducted simultaneously from SNc neurons did not show signs of fast depolarization, typically observed in cortical neurons during the onset of HSD. Instead, an inhibition of cell firing associated with membrane hyperpolarization was observed, that persisted throughout OGD. Silencing of SNc neuron activity by the D2 receptor agonist quinpirole (2µM) did not influence the development of HSD, while dopamine (30µM) and L-DOPA (300µM) shortened the latency to HSD. The latter effect was abolished by the D1 receptor antagonist SCH23390 (3µM), but not the D2 antagonist sulpiride (2µM). Morphological and immunohistochemical (TH, MAP2 and GFAP) assessments were conducted in slices fixed after OGD and 10 min reperfusion. Compared to pyramidal CA1 neurons tested under similar experimental conditions in hippocampal slices, SNc neurons showed relatively mild somatic swelling and minimal changes to dendritic morphology. There was, however, an unexpected loss of nigral GFAP immunoreactivity. Our results indicate that SNc neurons are only minimally involved in the propagation of HSD, and that the initiation of nigral HSD is facilitated by D1 receptors.

Poster 5.30

Genetic polymorphisms implicated in treatment resistant schizophrenia

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Schizophrenia is a disabling mental illness with a lifetime prevalence of 0.7% worldwide and significant, often devastating, consequences on social and occupational functioning. There are a range of antipsychotic medications available however sub-optimal therapeutic response in terms of psychotic symptoms is common and affects up to one third of people with schizophrenia. Clozapine has been shown to be more effective than other antipsychotics in treatment-resistant populations however, only 30% to 50% of people experience clinically significant symptom improvement and the occurrence of adverse effects, some of which are potentially life-threatening, are important limitations. The ability to identify both treatment-resistant and clozapine-resistant patients early in the course of their illness using biomarkers such as genetic polymorphisms would enable the development of more effective treatment strategies and considerably improve patient outcomes. This study set out to examine the effects of polymorphisms in genes which may contribute to treatment resistance in schizophrenia. Blood samples were obtained from twenty clinically stable patients receiving antipsychotic treatment for schizophrenia. Participants were grouped by treatment; those taking first-line non-clozapine antipsychotics, clozapine monotherapy or a combination of antipsychotics. DNA was extracted using QIAamp Blood Midi Kit (Spin Protocol) and TaqMan® Pre-Designed SNP Genotyping Assays were used for genotyping. The participants' genotype was related to their history of treatment response or non-response in the case of the clozapine and combination antipsychotic groups. For instance, patients with suboptimal response to antipsychotics such as olanzapine were genotyped for the gene ABCB1 or multidrug-resistant protein-1 (MDR-1). This gene codes for P-glycoprotein and functions as an efflux transporter in many tissues including the blood-brain barrier which is thought to contribute to suboptimal treatment response.

Poster 5.31

Functional impact of novel migraine mutations in the $Ca_V2.1$ channel

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The neuronal voltage calcium channel Ca_V 2.1 is localised to presynaptic membranes where it plays a crucial role in regulating neurotransmitter release. Recently, several point mutations associated with migraine were identified in the intracellular loop of $Ca_V2.1$. This region is known as the synprint (synaptic protein interaction) site due to its involvement in SNARE protein interactions. In this study, we investigate whether synprint mutations could alter normal Ca_V 2.1 channel function to affect Ca^{2+} influx as a molecular mechanism underlying migraine pathophysiology. To test this hypothesis, we measured Ca_V 2.1 channel properties using whole cell (WC) patch clamp electrophysiology in HEK293 cells transiently transfected with wild type or mutant channels. Our results demonstrate that the synprint mutation, E1015K showed a significant ($p<0.05$) increase in WC current density (n=6) compared to wild type $Ca_V2.1$ channels (n=6). Furthermore, this mutation caused a significant ($p<0.05$) depolarising shift in voltage dependent inactivation while having no significant effect on voltage dependent activation. The increase in current density could be indicative of changes in channel conduction, open probability or the number of channels at the membrane. The observed shift in voltage dependent inactivation supports a possible effect of synprint mutations on Ca_V 2.1 channel gating. Overall, our results indicate that mutations of the synprint site can increase Ca^{2+} influx via Ca_V 2.1 which could have implications for neurotransmitter release and migraine pathophysiology.

Poster 5.32

MacGreen mice: A novel tool to investigate brain inflammation post stroke

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MacGreen transgenic mice carry a green fluorescent protein (GFP) reporter gene in activated monocyte and macrophage populations and provide a unique opportunity to directly visualise brain inflammation following experimental stroke. In order to evaluate MacGreen mice as a tool for experimental stroke studies we investigated the long term survival rate, volume of damage (in comparison to standard C57Bl6j mice) and level of GFP expression following transient middle cerebral artery occlusion (tMCAo). Following 45 min. tMCAo, both MacGreen and C57 mice show a reproducible pattern of ischaemic damage restricted to the ipsilateral striatum and cortex. The survival rate for both MacGreen and C57 mice at 35 days post stroke was 100%. Lesion volumes in the 2 strains were not significantly different at 24 hours ($p=0.499$) or 35 days ($p=0.450$) post stroke. Increasing the duration of occlusion to 60 min. was associated with an increase in lesion volume in C57 mice but not in MacGreen mice, suggesting lesion volume is already maximal following 45 min tMCAo. MacGreen mice show increased GFP expression 24 hours after stroke. Qualitative analysis shows regions with elevated GFP expression broadly correlate with regions of ischaemic damage outlined by thionin histology. GFP expression remained elevated 7 days post stroke but returned to contralateral levels at 35 days. This time course is consistent with the leukocyte recruitment timing in stroke patients and other rodent stroke models. These results demonstrate that tMCAo in MacGreen mice produces a reproducible area of brain damage and animals survive for up to 5 weeks post stroke. MacGreen mice are therefore a useful model in which to investigate new therapeutic strategies targeting sub-acute inflammation post stroke.

Poster 5.33

Neural progenitor cell proliferation is not altered in the subventricular zone of YAC128 mice

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Post mortem analysis of human Huntington's Disease (HD) brain has shown a increase in cell proliferation in the subependymal layer compared to control brains. The degree of proliferation increased with pathological severity and indicates the adult human brain has regenerative potential. Many transgenic HD models show high fidelity to the human condition in terms of disease progression. To date none have recapitulated the changes in proliferation and neurogenesis observed in the human brain. YAC128 transgenic HD mice develop late stage striatal and cortical atrophy from 9 months which is indicative of cell loss. This transgenic line therefore provides an opportunity to examine whether neurogenesis is altered in the subventricular zone (SVZ) in YAC128 brain in response to neurodegeneration. YAC 128 aged 6 and 15 months (n=6/group) and age matched wild type littermates (n=6/group) received 4 injections of 5-chlorodeoxyuridine (CldU) at 2 hour intervals to label proliferating progenitor cells. Animals were killed 2 hours after the final injection and brains were processed for CldU immunohistochemistry. Tile scan images of the entire SVZ were captured for each section and an estimated cell count per brain was calculated for each animal. The number of proliferating cells in the SVZ of YAC 128 mice and wild type littermates was not different at either 6 or 15 months of age ($p=0.325$ and $p=0.801$ respectively), however an age related decrease in the number of proliferating progenitor cells in the SVZ was observed in both genotypes ($p=0.036$). These results confirm that the cell loss in YAC128 mice is not sufficient to trigger an increase in neurogenesis in the SVZ of adult YAC128 brains.

Poster 5.34

The effect of oxygen and glucose deprivation on spontaneous optical activity in the developing cochlea

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Prior to onset of hearing, the developing auditory system undergoes spontaneous electrical activity to retain and refine neural connections important for development in the absence of sound. However, processes behind this are poorly understood. Research suggests the involvement of a transient structure known as the Kölliker's organ in depolarising inner hair cells (IHC) and supporting structures through ATP signalling. A correlation exists between such electrical events, Ca^{2+} transients, and optical changes within the Kölliker's organ. These optical changes reflect alterations in volume or shape of supporting cells adjacent to IHC, and acts as a surrogate index of the spontaneous electrical activity in the organ. This study explored the metabolic demands of the spontaneous activity using oxygen and glucose deprivation (OGD). The sensory hearing organ from apical turns of developing Wistar rat cochlea (P7-13) were studied by measuring changes in pixel intensity in real-time, under control conditions or following OGD (20min or 1hr) and reperfusion. OGD was induced by altering the composition of the bathing fluid (glucose to sucrose and oxygen to nitrogen). Shorter OGD experiments were conducted with higher resolution DIC imaging and faster rates of acquisition in order to study the frequency and amplitude of spontaneous activity. Optical activity significantly decreased following 1 hour OGD ($p<0.05$), recovering with reperfusion. Under higher resolution imaging, a significant decrease in the frequency and amplitude of optical activity was observed during at least one period of OGD ($p<0.05$). These results suggest that spontaneous morphological activity in Kölliker's organ is vulnerable to energy deprivation, either through reduced ATP signalling, and/or active processes involved in these optical changes.

Poster 5.35

Effects of bilateral vestibular deafferentation on the dendritic morphology of CA1 pyramidal neurones -A Golgi study

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Bilateral vestibular deafferentation (BVD) results in spatial learning and memory impairment. Neurochemical and electrophysiological changes in the hippocampus, part of the brain involved in learning and memory, have been reported following vestibular damage. Changes in the dendritic tree of hippocampal CA1 neurons may occur with BVD and underlie the functional changes. The aim of the current study was to investigate parameters of the dendritic tree, dendritic length and branching pattern, in CA1 pyramidal neurons of the rat hippocampus one month following BVD (n=8), sham surgery (n=8) and anaesthetic control (n=7). Animals were deeply anaethetised, perfused with 0.9% saline and brains impregnated with Golgi-Cox solution. Serial horizontal sections, 200µm thick, were collected through the entire hippocampus. Fully impregnated CA1 neurons, n=8-10 per animal, were identified under the light microscope and traced via a drawing tube using 40X objective lens. The number of intersections of the dendritic tree with Sholl radii was analysed. BVD resulted in a significant decrease in both the apical ($p<0.05$) and basal ($P<0.001$) dendritic length, dependant on the distance from the soma compared to both sham and non-surgery control animals. The dendritic length of the two control groups was not significantly different. The results of the present study demonstrate the dendritic atrophy of hippocampal CA1 neurones following BVD. This might be responsible for the spatial learning and memory impairment in rats as reported in earlier studies.

Poster 5.36

The effects of D2 dopamine receptor antagonism on behavioural changes in bilateral vestibular deafferented rats

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Increased locomotor activities as well as circling behaviours in animals with bilateral vestibular loss are well documented in the literature. However, the cause of these behavioural changes is still unknown. Dysfunction of the striatal dopaminergic system is responsible for a number of known movement disorders. The D2 dopamine receptor is known to be involved in the regulation of behaviours in these disorders. The aim of this study was to investigate the effects of the D2 receptor antagonist, eticlopride (0.02, 0.04 and 0.06 mg/kg; s.c), on locomotor behaviours in rats 5 months following bilateral vestibular deafferentation (BVD) surgery, using an open field maze. The levels of the D2 receptor protein expression in the striatum and frontal cortex were then measured using western blotting. BVD rats were found to show behaviours already reported in animals with vestibular loss, i.e. locomotor hyperactivity and circling. Treatment with eticlopride did not inhibit these behaviours. However, BVD rats did exhibit a decreased response to eticlopride compared to shams at the 0.02 mg/kg dose. There were no changes in the amount of the D2 receptor in the striatum or frontal cortex at one or six months post-surgery. These results suggest that while locomotor hyperactivity and circling behaviours following BVD are not due to changes in D2 receptor protein expression, there may be a change in the dopaminergic pathways in BVD rats.

Poster 5.37

Do rats with bilateral vestibular lesions experience anxiety?

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Vestibular dysfunction in humans is associated with a high rate of anxiety; however rats with bilateral vestibular lesions seem to exhibit similar behaviours to rats with reduced anxiety. This study aims to investigate whether changes in anxiety are directly linked to vestibular dysfunction or whether they are a product of sociological pressure that is only experienced by humans, by using anxiolytic and anxiogenic drugs. Eighteen male Wistar rats received either sham (n = 10) or bilateral vestibular deafferentation (BVD) surgery (n = 8). At one month post-op, baseline measurements of locomotor activity (open field; OF) and anxiety behavior (elevated plus maze; EPM and elevated T-maze; ETM) were taken prior to drug administration. Each rat was then given buspirone (an anxiolytic drug), FG-7142 (an anxiogenic drug), saline (vehicle for busprione) or DW/Tween20 (vehicle for FG-7142) using a Latin square design. The results were analysed using a linear mixed model analysis. Preliminarily results from the OF maze suggest that vestibular dysfunction reduced thigmotaxis, as BVD rats spent significantly more time in the inner zone than sham animals, which could not be modulated by anxiolytic or anxiogenic drugs (P = 0.000). No differences in time spent in the open arms (P = 0.157) of the EPM were seen between BVD and sham animals; indicating a similar anxiety level in both groups. On the ETM, BVD rats required more trials than sham animals to learn inhibitory avoidance during the predrug condition, however drug treatments modulated this behavior, including the control group (P=0.039). These results suggest that vestibular dysfunction can reduce "stress-induced inhibition of exploratory behaviour" but not associative fear conditioning.

Poster 5.38

Cannabinoid receptor type II as a target for neuroprotection following hypoxia ischemia. Or is it an active vehicle in the driving seat?

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Active marijuana extracts and synthetic analogues, referred to as cannabinoids, elicit their effects through two described cannabinoid receptors. Cannabinoid receptor type 1 (CBI) found ubiquitously throughout the central nervous system (CNS), and cannabinoid receptor type 2 (CBII) found primarily in systemic immune cells. Selective agonists of the CBII receptor produce an immunosuppressant effect without any of the psycho-active effects seen during CBI receptor activation. Some research suggests that administration of CBII agonists before neurological injury may offer some neuroprotection through an anti-inflammatory mechanism. Our research aimed to investigate whether a clinically significant paradigm, of post injury drug administration, would offer neuroprotection in a rat model of early childhood ischemic insult. The model Variable hypoxia ischemia (VHI) was established in our lab and involves a unilateral ligation of the left carotid artery, followed by a period of hypoxia (8%oxygen 72%nitrogen) until a clonic tonic seizure was induced. Drug administration began 30 minutes after VHI and infarction volumes were assessed 15 days after VHI. No neuroprotection was seen when a selective CBII partial agonist (GW 405833) or a selective CBII full agonist (HU 910) was administered using either a single dose of 3mg/kg or with 6 daily doses of 10mg/kg. Unexpectedly one of vehicles used in this study that contained cyclodextran 25% (w/v) was found to be neuroprotective with a 30.7% reduction in infarction volume when compared to a no vehicle control. This finding is consistent with research that suggests that cyclodextran reduces excitotoxicity by lowering cholesterol levels at the synaptic cleft, thereby altering glutamate receptivity.

Poster 5.39

CB2 selective agonists have limited efficacy when delivered intrathecally in a rodent model of neuropathic pain

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Damage to peripheral nerves can lead to neuropathic pain by central sensitisation of the pain pathway. Often accompanying this condition is a painful response to normally innocuous stimuli, otherwise known as allodynia. Clinical and anecdotal evidence has shown that cannabinoid receptor agonists, such as Δ^9-THC found in cannabis, are effective treatments for neuropathic pain. Limiting their use, however, are the associated psychoactive side effects due to activation of cannabinoid type 1 (CB1) receptors expressed on neurons. Compounds targeting the cannabinoid type 2 (CB2) receptor have been reported to relieve neuropathic pain in animal models, without these limiting adverse effects, especially when administered by intrathecal cannulation to the spinal cord. Using a rodent model of neuropathic pain, the chronic constriction injury model, we assessed the efficacy of a range of intrathecally delivered non-selective and CB2 selective cannabinoid receptor agonists at reducing mechanical allodynia. While a non-selective cannabinoid, WIN 55,212-2, was able to ameliorate mechanical allodynia, CB2 selective agonists were unable to produce a similar result. These findings indicate that despite initial promise for the treatment of neuropathic pain, CB2 selective agonists may have limited efficacy when delivered centrally to the spinal pain pathway.

Poster 5.40

On automated versus manual MRI analyses when evaluating corticospinal tract integrity for post-stroke therapeutic interventions

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When a stroke patient receives treatment for motor deficits (e.g. hand or leg weakness) it can often be difficult to predict their response to therapy. Modern MRI analysis techniques allow some prognoses to be made, based on the integrity of key pathways involved in motor control, and can assist in tailoring an appropriate intensity and duration of physiotherapy and rehabilitation. The post-stroke integrity of the descending white matter pathways, as measured by fractional anisotropy (FA) analysis of a diffusion-weighted MRI image, has been identified previously as a key indicator in the longer-term (3 month) prognoses of stroke patients. However, it is not yet clear whether computer-assisted means of delineating these structures in MRI analyses are robust enough for clinical use. This study aimed to test the efficacy of automated MRI analysis techniques by testing them against manually-administered analysis techniques. MRI images from 23 sub-acute stroke patients (< 14 days post stroke) were analysed by 4 independent examiners. The posterior limbs of the internal capsule (PLIC) were highlighted within each brain hemisphere as volumes-of-interest (VOI) before calculating the FA values. We report the variability in structural PLIC definition between each examiner and the automated methods, and the consequence on treatment prognoses. We found the automated techniques were faster to administer, but they were confounded by larger infarcts and/or poor image resolution. We therefore also trialled a human-assisted automated technique (the 'hybrid' method) that we propose may be more clinically useful when tailoring therapeutic interventions to post-stroke patients.

Poster 5.41

Uncoupling response inhibition

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The ability to inhibit action is fundamental to human behaviour and often impaired in neurodegenerative conditions. In situations where one of two prepared actions must be prevented from occurring, execution of the remaining response is markedly delayed in healthy subjects (Coxon et al., 2007; Aron and Verbruggen, 2008; Coxon et al., 2009; Cai et al., 2011). The reason for this delay is not clear. We hypothesized that it may reflect a cost associated with dynamic coupling and uncoupling of movement representations within the primary motor cortex. Fifteen healthy right handed participants performed a response inhibition task that required homogenous digit pairings involving bilateral index finger extension or thumb abduction, or a heterogeneous pairing of a combination of the two. We predicted that response delays would be greater for homogeneous pairings (same digit, homologous muscles) than for heterogeneous pairings (different digits, nonhomologous muscles), despite the apparent response complexity of the latter. Measures of response times (response time delay, variability and asynchrony between digits during action execution), stopping performance and electromyography (EMG) from EIP (index finger extension) and APB (thumb abduction) were analyzed. Remarkably, participants were able to perform all trial types successfully with heterogeneous digit pairings. Furthermore, selective stopping was better with heterogeneous pairs, indicated by shorter delays in response times and less asynchrony between responses on subsequent action execution trials. EMG indicated faster burst onsets during selective stopping compared to simple action execution with longer electromechanical delays for heterogeneous pairings. The results support the view that selective inhibition requires the uncoupling of responses and confers advantages from heterogeneous effector pairings. Future studies will determine if primary motor cortical networks underlie this process.

Poster 5.42

P50 sensory gating and schizotypal personality: Preliminary findings

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Schizotypy is defined as a cluster of subclinical symptoms and personality traits which are qualitatively similar to schizophrenia. Such characteristics are seen to be especially prevalent in non-affected relatives of those with schizophrenia and, due to the heritability of the disease, such persons are at a genetic high risk for developing the disease at a later date. Therefore, research into individuals with high levels of schizotypy has become increasingly important as it provides a valuable opportunity to investigate various phenotype traits associated with the schizophrenia spectrum without the confounding effects of medication and mental illness. A major finding that has been implicated in schizophrenia pathophysiology is sensory gating dysfunction, which is consistent with behavioural symptoms of the disease such as lack of attention and disordered information processing. Individuals with schizotypal personality disorder have also been shown to be deficient in their ability to filter out, or 'gate', irrelevant external stimuli. This can be assessed by testing the attenuation of the P50 event-related potential using an auditory paired stimulus paradigm, where two identical clicks are presented in quick succession. Using electroencephalography, we used this paradigm to test five neurotypical subjects with low levels of schizotypy. Preliminary results show a suppression of the P50 wave following the second click, indicating an intact sensory gating mechanism. Data is currently being collected for the next part of the study. This will include five highly schizotypic individuals who we expect will show a reduced P50 suppression, consistent with previous research showing an association between P50 suppression and schizotypal traits. Overall, this research will contribute to the idea that functional abnormalities are already present in clinically normal people who have a genetic vulnerability to schizophrenia.

Poster 5.43

The role of eye gaze in decision making

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Shimojo et al. (2003) provided preliminary evidence that gaze-duration (duration of fixation after a saccade) may have an active role in preference formation. As in Shimojo et al.'s experiment, the current study alternatively presented two faces (one for 900ms, one for 300ms) for six repetitions. In line with previous findings, subjects that were required to make eye movements to laterally presented faces and judge attractiveness were more likely to choose the longer presented face. This was also the case for eye movements and roundness judgements. However, subjects that were not required to make eye movements to centrally presented faces were also more likely to choose the longer presented face for attractiveness judgements, but not roundness judgements. The results suggest that a simple exposure effect is more likely to explain the gaze-duration effect for preference formation, whereas eye movements are a necessary component of the gaze-duration effect in roundness judgments.

Poster 5.44

An indication that non-informative vision eliminates the Kinaesthetic Fusion Effect

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This study investigated the Kinaesthetic Fusion Effect (KFE) first described by Craske and Kenny in 1981. The current study did not replicate these findings. Participants did not perceive any reduction in the sagittal separation of a button pressed by the index finger of one arm and a probe touching the other, following repeated exposure to the tactile stimuli present on both unseen arms. This study's failure to replicate the widely-cited KFE as described by Craske et al. (1984) suggests that it may be contingent on several aspects of visual information, especially the availability of a specific visual reference, the role of instructions regarding gaze direction, and the potential use of a line of sight strategy when referring felt positions to an interposed surface. In addition, a foreshortening effect was found; this may result from a line-of-sight judgment and represent a feature of the reporting method used. The transformed line of sight data were regressed against the participant reported values, resulting in a slope of 1.14 (right arm) and 1.11 (left arm), and $r > 0.997$ for each. The study also provides additional evidence that mis-perceptions of the mediolateral position of the limbs specifically their separation and consistent with notions of Gestalt grouping, is somewhat labile and can be influenced by active motions causing touch of one limb by the other. Finally, this research will benefit future studies that require participants to report the perceived locations of the unseen limbs

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Poster 5.45

Neuroscience public open days: evaluating Auckland Brain Day as a communication method

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Brain Awareness Week is an international initiative to highlight and communicate brain research. Neuroscience findings are especially relevant for public dissemination as they inform ethical decisions about human behaviour and health decisions in brain disease. In New Zealand, five annual 'Brain Days' are held nationally; these are public open days presented by universities with support from the Neurological Foundation of New Zealand. In 2011 it was estimated the Auckland Brain Day, featuring lectures and science demonstrations from neuroscientists and clinicians and community information stands, attracted around 3000 visitors. This study aimed to evaluate the effectiveness of the Brain Day communication method, and determine which sectors of public attended. A questionnaire was completed on the day by 233 attendees; 21% of these visitors had a neurological condition, and 10% were caring for someone with a neurological condition. The mean age was 47 years (SD 20), with a range from 8 to 84 years. Most people (79%) rated the lecture series as the reason they attended, however, many also visited the community expo (59%), and the laboratory demonstrations (33%). When asked to rate their agreement on a Likert Scale, the average response was 'strongly agree' for the statements 'I learnt something useful', 'Brain Day was a good day out for the whole family', and 'I would recommend Brain Day to my friends'. Participants also indicated they enjoyed finding out the latest brain research, and that they have learnt more about keeping their brain in optimum health. The open day format appears to be successful as a communication method, with a wide range of healthy general public members attending to learn neuroscience information.

Poster 5.46

Association between bassoon and synaptic ribbons in developing mouse cochlea

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Hearing depends on reliable and temporally precise neurotransmission established by a presynaptic specialization termed synaptic ribbon in cochlear hair cells. The number of synaptic ribbons reduces in the hair cells after birth, which is estimated as one of underlying causes of excess hair cell synapse elimination during the development, but the mechanism of how these synaptic ribbons are removed remain elusive. We hypothesized that a protein called Bassoon, essential for anchoring ribbons to synaptic membrane, may play a role in loss of synaptic ribbons in developing cochlea. The expression of Bassoon and synaptic ribbons were identified by performing fluorescent immunohistochemistry in mouse cochleae of postnatal day 0 (P0), 3, 6, 12 and adult (P38-42; n=3 for each age). Images were acquired using confocal microscopy and protein puncta were reconstructed into 3D in order to analyze. Bassoon and synaptic ribbons were well co-localized throughout development in inner hair cells (IHCs) and their patterns of expression were analogous to each other in terms of number, volume and intensity. However, there is a significant loss of co-localization between Bassoon and synaptic ribbons in OHCs at P6 ($p < 0.05$), just before onset of hearing starts. From the onset of hearing (P12), Bassoon undertakes a remarkable structural transition in to a shape of flower in OHCs while only few synaptic ribbons were identified. These results reveal that Bassoon undergoes different pathways of expression between IHCs and OHCs during the development, which in turn, may aid distinct patterns of synaptic ribbon anchoring in two types of hair cells.

Poster 5.47

Sublayer-specific colocalisation of corticospinal neurons with the lamina 5 pyramidal neuron marker *Fezf2*

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The principal pyramidal neurons of the cerebral cortex perform distinct functions within cortical microcircuits according to laminar location as well as their afferent and efferent connections. Cell-type specific functions within such microcircuits have been examined mainly for primary sensory and prefrontal cortical regions but remain poorly defined in the motor cortex. We have employed traditional retrograde tracing experiments in a BAC transgenic mouse line expressing GFP under the control of the promoter for the zinc-finger gene *Fezf2* (pFezf2GFP) as a marker for layer 5 pyramidal neurons projecting to subcortical structures and not across hemispheres. Corticospinal pyramidal neurons in p*Fezf2*GFP mice (n=9) were labelled by injection of micro-ruby into the lumbar (L1) spinal cord at P21. Mice were perfused with 4% paraformaldehyde at P28, and 60 µm coronal sections analysed by fluorescence microscopy. Retrograde-labelled neurons were situated in the primary motor and somatosensory hindlimb regions of the cerebral cortex at a depth of 742 ± 12 µm (mean ± SEM) from the pia. GFP expression within layer 5 was stronger in lamina 5a compared to 5b, and an intra-lamina border apparent at 671 ± 12 µm from the pia. Most retrograde-labelled neurons (66 ± 5 %) were found to be GFP-positive. GFP-positive neurons in lamina 5a had smaller soma (10 – 22 µm range) compared to corticospinal neurons in lamina 5b (14 – 26 µm range), whereas soma diameters of GFP-positive neurons in lamina 5b showed an overlapping distribution over the entire range. Thus the p*Fezf2*GFP mouse provides a useful model for further characterisation of functional and morphological properties of distinct subtypes of layer 5 neurons according to laminar location and projection target.

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Poster 5.48

Projection neuron identity in the mouse motor cortex

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In the primary motor cortex (M1), layer 5 projection neurons (L5 PNs) transmit motor commands to other motor systems, including the corticospinal and extrapyramidal targets. These motor commands rely on the morphological, molecular and electrical properties of PNs (or their identity). Previous attempts to classify the identity of L5 PNs have used unlabelled neurons in other cortical regions. Here, we define the identities of L5 PNs in M1 using a genetically encoded marker for cortical PNs (p*Fezf2*-GFP) combined with retrograde labelling following microRuby injections into the spinal cord and visually targeted whole-cell patch clamp recording in P21-28 mice. We observed a dense band of GFP+ PNs at a pial depth of 0.39 to 0.50 (fractional distance normalised to cortical thickness) and a second weaker expressing band at a depth of 0.51 to 0.67; defined as L5a and L5b, respectively. Features of L5a PNs (n=14) differed from L5b PNs (n=18) in the degree of spike frequency adaptation (adaptation index L5a 0.30 ± 0.09, L5b 0.07 ± 0.03, mean ± SEM, p<0.01, one-way ANOVA, Tukey's posthoc analysis), action potential half width (L5a 1.8 ± 0.10 ms, L5b 1.4 ± 0.06 ms, p<0.001), afterhyperpolarisation following high frequency firing (L5a -1.6 ± 0.60 mV, L5b -4.0 ± 0.46 mV, p<0.01) and soma size (L5a 15 ± 0.80 µm, L5b 19 ± 0.54 µm, p<0.01). Retrograde labelled corticospinal neurons (n=17) were located in L5b and displayed overlapping features with the GFP+ L5b PNs. The results revealed two distinct subpopulations of L5 PNs in the mouse M1. L5b PNs target the spinal cord, while L5a neurons may target extrapyramidal motor structures.

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Poster 5.49

Rat striatal spiny projection neurons have markedly more synapses on their somata and primary dendrites compared to striatal cholinergic interneurons

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Understanding the three-dimensional circuitry of neurons is essential for interpreting electrophysiological data as well as computer modeling of neurons and networks. This study measured the absolute number and type of somatic and primary dendritic synapses of spiny projection neurons and cholinergic interneurons in the rat dorsal striatum. Two adult, male, Wistar rats (Rats 1 and 2) underwent perfusion-fixation. Serial 50µm vibratome sections were cut through the dorsal striatum. Immunolabeling of sections from Rat 2 with choline acetyltransferase (ChAT) helped identify cholinergic interneurons. One 50µm section per rat was processed for transmission electron microscopy. Subsets of serial 80nm sections per rat were analysed to reconstruct three spiny projection neurons, two cholinergic interneurons (Rat 1) and two immunolabeled cholinergic interneurons (Rat 2). Neurons were identified by their ultrastructural anatomy, and in Rat 2, their ChAT-immunolabeling. Somata and primary dendrites were mapped for their synaptic input. The majority of synapses were symmetrical, thus presumably inhibitory. Spiny projection neurons had 3.5 times synapses on somata (130 ± 36, mean ± SD) than cholinergic interneurons (32 ± 10, Student's t-test, $p < 0.01$). There were four-times as many symmetrical synapses per µm of primary dendrite for spiny projection neurons (2.08 ± 0.42) compared to cholinergic interneurons (0.45 ± 0.03, $p < 0.04$). These data suggest that there is relatively weak inhibition of the larger somata and proximal dendrites of cholinergic interneurons. This is consistent with individual excitatory inputs generating action potentials in cholinergic interneurons. Greater inhibitory control of spiny projection neurons may contribute to their relative electrophysiological silence on stimulation.

Poster 5.50

Nicotinic acetylcholine receptor subunit expression in mouse cerebellum

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The role of extrinsic cholinergic inputs to the cerebellum is currently unknown. The diffuse nature of acetylcholine release requires specific nicotinic acetylcholine receptors (nAChR) that bind acetylcholine. In this study we examined the distribution of two nAChR subunits within the cerebellum using immunohistochemistry. The α4 subunit exists within heteromeric nAChRs that are permeable to Na^+ and exhibit a high affinity for agonist e.g. nicotine. In contrast, α7 subunits form homomeric nAChRs that exhibit a lower affinity for nicotine and are high permeability to calcium. Longitudinal cerebellar slices from mice (28-43 days old) were incubated with primary antibodies specific for α4 (Alomone) and α7 (Abcam) nAChR. Secondary fluorescent antibodies Alexa 488 and Alexa 594 (Invitrogen) were used to visualize the expression of α4 and α7 nAChR with fluorescence microscopy. We detected both α4 and α7 subunits of nAChR in neurons of the cerebellar cortex and deep cerebellar nuclei (DCN). Within the cerebellar cortex, we observed prominent homogenous expression of α4 nAChR in the Purkinje neuron soma, in Golgi cells and molecular layer inhibitory interneuron soma, but weak expression in the granule cell layer. In contrast, α7 subunits of nAChR displayed a punctate expression pattern throughout the cerebellum particularly in the granule cell layer and throughout the molecular layer and Purkinje neuron soma. Initial co-localization studies of α7 nAChR with synaptic marker proteins in the molecular layer indicated that α7 nAChR may be present at parallel fibre synapses. Our results indicate that α4 and α7 subunits of nAChR are present in the cerebellum. Their different patterns of expression could be significant for cerebellar processing and output following activation of extrinsic cholinergic inputs.

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Poster 5.51

Is 5-HT1A receptor supersensitivity a mechanism of serotonin deficit after MDMA exposure?

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+/- 3, 4-methylenedioxymethamphetamine (MDMA) decreases levels of serotonin (5-HT) in both human and animal studies. Decreased levels of 5-HT were produced by experimenter-administered as well as self-administered MDMA, but the mechanism for this deficit is currently unknown. Because the 5-HT_{1A} autoreceptor regulates release and synthesis of 5-HT, the current study examined effects of MDMA exposure on the response of this receptor. Rats self-administered 300 mg/kg of MDMA, or saline, in two hour daily sessions. Other groups were pretreated with four injections of 10.0 mg/kg MDMA or saline at 2 hour intervals (i.p.). Lower lip retraction was measured after injections of the selective 5-HT1A receptor agonist, 8-OH-DPAT (0.0-0.1 mg/kg, s.c.). Accumulation of 5-hydroxytryptophan (5-HTP) following decarboxylase inhibition was measured after an injection of 8-OH-DPAT (0 -0.06 mg/kg s.c.). There was no difference in the dose-response curve for lower lip retraction as a function of either self-administered or experimenter-administered MDMA. MDMA pretreatment induced a decrease in the accumulation of 5-HTP, suggesting decreased activity of tryptophan hydroxylase. The effect of 8-OH-DPAT on 5-HTP accumulation was, however, the same for MDMA and saline pretreated rats suggesting that this change in tryptophan hydroxylase was not related to a change in the 5-HT_{1A} autoreceptor.

Poster 5.52

Elucidating the cellular effects of MDMA on the serotonin transporter

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Serotonin (5-HT) is a neurotransmitter with an integral role in regulating mood; dysregulation of this system is implicated in disorders such as depression and withdrawal from drugs of abuse. 3,4- methylenedioxymethamphetamine (MDMA) or 'Ecstasy' is a commonly abused drug which primarily targets the serotonin transporter, SERT, and competes with 5-HT for uptake into the neuron. Using a sensitive technique called rotating disc electrode voltammetry (RDEV), changes in transporter function can be measured. Mouse neuroblastoma (N_2A) cells over-expressing GFP-hSERT have shown that exposure to MDMA induces a functional down-regulation of SERT within 5 minutes ($p<0.01$, 40 ± 3% decrease in 5-HT uptake compared to control). Human embryonic kidney (HEK-293) cells also show a rapid loss of cell-surface SERT following MDMA treatment (10µg/mL) using Total Internal Reflection Fluorescence microscopy (TIRF) ($p<0.05$, significant at 290s onwards). Cell surface biotinylation confirmed the rapid redistribution of SERT from the cell surface to the intracellular fraction in HEK-293 and N2A cells ($p<0.05$). Protein Kinase C (PKC) has been shown to regulate SERT function and cell surface expression. GFP-hSERT expressing N_2A cells were pre-treated with the selective PKC inhibitor Bisindolylmaleimide I (Bis I) to investigate a possible cell signalling mechanism. Preliminary data obtained using RDEV shows that Bis I prevents the MDMA-induced down-regulation of SERT function. This suggests that MDMA may regulate SERT via a PKC dependent mechanism.

Poster 5.53

Twenty-four hour access to intrathecal self-administration of cocaine results in a binge-like behavior in mice

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The long-term model of intravenous drug self-administration is well established to observe escalated, binge-like patterns in drug intake in rats. A similar long-term model in mice would allow the use of genetically modified animals to better understand the molecular mechanisms underlying drug addiction and relapse. However, attempts to date transferring this model to mice appear to have been less than successful, mainly because of technical difficulties with the long-term maintenance of the indwelling catheter implanted into the small jugular vein of mice. We devised an intrathecal probe implanted in the supracerebellar cistern as an alternative for intravenous drug administration to address this challenge and allow continuous, chronic drug self-administration in mice. Male C57BL/6 mice with an intrathecal delivery route were allowed to nose-poke for cocaine in consecutive 24 hrs a day. In experiment 1, mice, trained on a fixed ratio 1 schedule, were found to readily self-administer intrathecal infusions of cocaine and the number of self-administrations was related to the unit dose in an inverted U-shaped manner. Following extinction from self-administration, a priming infusion of cocaine evoked drug-seeking behavior in the absence of drug-associated cues. In experiment 2, mice, trained on a fixed ratio 1 schedule for first 10 days and then a fixed ratio 2 for last 10 days, were found to take about 90% of cocaine injections in the dark phase of the light/dark cycle. However, some of animals exhibited escalated, binge-like patterns, with increases of cocaine intake in both the dark and light phase. Following withdrawal from self-administration, presentation of cocaine-associated cues robustly increased drug-seeking behavior in the absence of drugs. This innovation enables a full analysis of long-term drug self-administration in mice not possible with intravenous administration. Long-access intravenous drug self-administration shows diurnal alterations in drug intake, with escalation and binge patterns, in rats. A similar long-access model in mice would allow the use of genetically modified animals to better understand the molecular mechanisms underlying drug addiction and relapse. However, attempts to transfer this model to mice have been less successful, mainly because of technical difficulties with long-term mainte- nance of the indwelling catheter implanted into small veins. We devised an intrathecal probe implanted in the supracerebellar cistern as an alternative for intravenous drug administration to address this challenge and allow continuous, chronic drug self-administration in mice. We found that mice readily self-administered intrathecal infusions of cocaine as a drug reward, and, under daily 24-h access conditions, animals exhibited a binge-like behavior comparable to rats. This innovation enables a full analysis of long-access drug self-administration behavior in mice not possible with intravenous administration.

Poster 5.54

Cognitive function and methadone maintenance treatment

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Methadone maintenance treatment (MMT) has been used to treat opiate dependency since the mid-1960s. It is well known that repeated or chronic exposure to opiates has a negative impact on cognitive function. Nevertheless, the cognitive deficits induced by methadone are poorly described in the literature. The findings vary between many studies. For example, some report a complete absence of deficits while others report a variety of cognitive impairments. Our research aims to investigate the effect of MMT on cognitive function by comparing the performance of patients currently enrolled in MMT (N= 23) to control subjects, using the IntegNeuro Test Battery (Brain Resource Company). The subjects comprised 11 females and 12 males, with mean age 39.22 ± 5.2 years and mean educational level 11.74 ± 1.8 years. They had been receiving MMT for at least one year (mean=7.5 years), and had been stablised on their current dose (mean=68.2 ± 44.5 mg/d) for a minimum of 2 weeks (mean = 16.2 ± 17 month). A deficit in any particular task was defined as two standard deviations below the mean for controls which is equivalent to a z-score of less than -2.00. Our results demonstrate that 65% of the patients exhibited specific cognitive deficits. Thirty nine percent of the subjects showed significant deficits in tests of recall and recognition memory (Immediate Recall Trials 1-4 and Memory Recognition Test), and 30% in sustained attention (Continue Performance Test). However, the subjects did not exhibit impairment in time estimation and verbal function. Notable was lack of a significant correlation between dose and cognitive deficits. These findings suggest that long term MMT may be associated with impaired cognitive function.

Poster 5.55

Electrophysiological properties of sensory hair cells during type I fibre elimination

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The electrophysiological and structural properties of hair cells in the mouse cochlea have been investigated thoroughly in recent years. In the current study we seek to extend this knowledge by looking at whole cell recordings of outer hair cells and the impact of eliminating type I fibre synapses on the structural and functional properties of the pre-synaptic hair cells and the post-synaptic afferent synapses. Using whole cell recordings of neonatal outer hair cells we have shown that these exhibit differential K+ currents at P0, P3 and P6. By establishing the healthy nature of the outer hair cells, the next step involving simultaneous recordings from pre-synaptic outer hair cells and post-synaptic afferent fibres can be made. This step will allow for further investigation of the functional properties of the synapses and their development in the neonatal ages (P0 to P6). We then examined the effects of preventing sensory stimulation of the hair cells by blocking sound conduction. In order to block sound stimulation of the cochlea, we have developed a conductive hearing loss in mice by puncturing the tympanic membrane and destroying the first ossicle in the middle ear, the malleus. This procedure has been successfully performed on 8 mice. The hearing sensitivity of these mice and their control littermates has been tested using the auditory brainstem response and shows an attenuation of hearing sensitivity by 35 to >50dB for frequencies 4 – 40kHz. Immunolabelling for the pre-synaptic protein CtBP2 and the postsynaptic marker for SGN, beta-tubulin, suggests structural changes at the synapse. Together these data suggest the temporary type I fibre synapses and sensory stimulation of hair cells alter the functional and structural properties of the hair cells.

Poster 5.56

Age-related degeneration of supporting tissues in the mouse cochlea

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Sensory hair cells of the cochlea transduce sound into activity in the auditory neurons. A network of supporting cells, comprising connective and epithelial tissues, play a large role in maintaining the ion and metabolic homeostasis within the cochlea essential for transduction. These are extensively connected through gap junctions which provide a circulation pathway necessary for buffering ions, especially extracellular potassium. Degeneration of these supporting structures has been observed with age, but the exact impact of these changes on the intercellular communication pathways and ion homeostasis is unknown. To provide a platform for subsequent physiological studies of intercellular communication, we have quantified and detailed the pattern and time course of these supporting tissue changes in the aging C57/BL/6 mouse cochlea. Tissue was collected at 1, 3, 6, 9 and 12 months of age and examined by light and transmission electron microscopy. Cell nuclei were also stained with DAPI and examined by fluorescence microscopy to enable quantification of cell loss. The predominant change occurred in the connective tissues with progressive degeneration and loss of fibrocytes, mainly Type 3 and Type 4 cells in the spiral ligament and interdental cells and fibrocytes of the spiral limbus as early as 1 month of age. These changes were first evident at the basal turn where it worsened and progressed apically with age. However, the Type 1, Type 2 and Type 5 fibrocyte pathways remain mostly intact with age. These data confirm the appearance of degenerative changes in the connective tissues alongside the loss of sensory cells and spiral ganglion neurons, but suggest that some intercellular communication pathways survive and continue to maintain essential ion homeostatic mechanisms.

6.1

Influence of Brain-Derived Neurotrophic Factor (BDNF) and Catechol-O-Methyltransferase (COMT) polymorphisms on recall

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Single nucleotide polymorphisms in the brain-derived neurotrophic factor (BDNF) gene and the catechol-O-methyltransferase (COMT) gene influence brain structure and function, as well as cognitive abilities. They are most influential in the hippocampus and prefrontal cortex (PFC), respectively. Recall is a form of memory proposed to be particularly dependent on these regions. This study aimed to determine whether the BDNF val^{66}met or COMT val^{158}met polymorphisms affect recall, and whether these polymorphisms interact. A sample of 20 healthy adults was genotyped and assessed on a standard test of recall. An omnibus factorial ANOVA was conducted on recall scores. Both the BDNF ($p<0.05$) and COMT ($p<0.01$) polymorphisms were associated with poorer recall ability. Of particular interest, there was a significant interaction between the two polymorphisms ($p<0.05$). Simple effects tests on this interaction revealed that only individuals carrying the polymorphism for both genes showed significantly impaired recall, suggesting that low BDNF and high dopaminergic activity are particularly detrimental on recall when coupled together. This may occur through the influence of BDNF and dopamine on neurodevelopment and long-term potentiation, a form of synaptic plasticity thought to underlie memory formation. Further investigation into how multiple genes interact to affect cognitive processes is warranted.

6.2

The role of BDNF and COMT in frontal lobe functioning: The Tower of Hanoi

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Two genes that have garnered significant attention due to their influence on cognitive processes are the brain derived neurotrophic factor (BDNF) gene and the catechol-O-methyltranferase (COMT) gene. A single nucleotide polymorphism (SNP) in the BDNF gene (val66met) has been shown to affect the release of BDNF. This polymorphism is associated with a variety of neurological disorders, and affects memory task performance. Similarly, a SNP in the COMT gene (val^{158}met) leads to differing frontal lobe functioning. The role of BDNF on memory has been extensively investigated, but its role in other cognitive domains is less certain. Here we investigated the effect of both BDNF and COMT SNP's on a test of frontal lobe functioning using the Tower of Hanoi (ToH). The results showed no effect of either SNP on overall measures of performance (total completion time, number of errors, number of moves). However, finer measures of performance (reaction time per move, trial difficulty and prior exposure) revealed that Val/Val genotypes for COMT were significantly slower at greater difficulty levels than participants with at least one copy of the Met allele. The results also showed a benefit for Val/Val genotypes for BDNF if there had been prior exposure to the ToH at both difficulty levels, but these individuals were slower at greater difficulty than participants with a copy of the Met allele when there wasn't any prior exposure. These results shed new light on the role COMT and BDNF have in executive ability.

6.3

Are musical key and rhythm processed by distinct neural modules?

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One prominent neuropsychological model of music processing proposes that musical key and rhythm are processed by distinct music-specific modules. The model is derived mainly from behavioural deficits in neurological patients whereas neurophysiological data are limited and conflicting. Therefore the purpose of this study was to investigate rhythm and key processing in neurologically intact individuals using electroencephalography (EEG). Furthermore the influence of musical expertise and attention was examined by comparing musicians and non-musicians using a mixed design with expertise as the between-subjects variable and the within-subjects factors of attention and deviant type. Participants listened to melodies and responded to occasional deviant notes that were out of key, out of rhythm, or both simultaneously. Each block contained 300 bars, 60 of which contained a deviant note. In the unattended condition participants ignored the music and watched a silent movie. Musicians were significantly more accurate than non-musicians in identifying out of key notes ($p=.024$). Accuracy was not significantly different between groups for rhythmic and double deviants. Both groups responded more quickly to rhythmic than key deviants ($p<.0005$) and slowest to double deviants, with no significant difference in reaction times between groups. This suggests that rhythm and key processing are differentially affected by expertise, supporting their separability. Unlike key, rhythm perception may be an essential biological function not specific to music. This modular model is currently being applied to variables derived from the EEG (data are forthcoming).

6.4

The spatial working memory network: Can we link structure and function?

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The involvement of the fronto-parietal regions in working memory have now been well-documented. However, few studies have directly linked the functional connectivity with measures of structural connectivity. With the use of functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) and tractography, we explored whether such a link could be established. Ten healthy right-handed participants completed a spatial 2-back task during fMRI, followed by a DTI scan. Participants were presented with 3-letter consonant-vowel-consonant words that could appear in one of eight locations, and instructed to memorise the location of the words. Peak bilateral activations in the frontal and parietal regions were used as seed points for both psychophysiological interaction (PPI) and tractography analyses, which were carried out for each hemisphere separately. Regions showing functional connectivity from the PPI analyses were used as regions of interest (ROIs), and as waypoint masks for the tractography. Parameter estimates were also calculated for these ROIs as a measure of functional connectivity. Mean fractional anisotropy (FA) was calculated for fronto-parietal pathways as an index of structural connectivity. So far, results have revealed a significant correlation between the two measures in the connection between the pre-motor cortex and the posterior parietal cortex (PPC) in the right hemisphere, suggesting that connections within the working memory network may be structured in an asymmetric manner. While other connections have yet to be considered, this is the first analysis of this kind using a more direct approach at investigating the relationship between structure and function

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6.5

Sensory reinforcement in the superior colliculus

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The response to a stimulus recorded in brain sensory areas habituates rapidly when not reinforced. An important property of reward is its ability to block sensory habituation or, indeed, potentiate sensory responsiveness. We recently reported that visual stimuli can activate neurons within the striatum via a pathway involving the superior colliculus (SC). These responses were only present following local blockade of GABA(A) receptors in the deep layers of the SC using bicuculline, suggesting that collicular inhibition may control sub-cortical sensory responsiveness. In the present study, we tested whether rewarding stimuli could attenuate inhibition in the rat SC, bypassing the need for bicuculline. Under urethane anaesthesia, light flashes were applied to the contralateral eye and measurements made of visual-evoked potentials (VEPs) within the SC. Rewarding stimuli consisted of substantia nigra (SN) stimulation known to induce dopamine release. We found that SN stimulation paired 1 sec after each light flash at 0.1 Hz for 10 minutes induced new collicular VEPs (mean amplitude ± SD: 76.3 ± 53.2 μV; n=9) that persisted for up to 10 minutes after SN stimulation. This new sensory responsiveness was greatly reduced when SN stimulation preceded the light flash by 1.0-1.5 sec (12.1 ± 44.8 μV; n=11) or followed it by 3 sec (20.0 ± 42.2 μV; n=11), suggesting that an optimal stimulus-reward timing exists for sensory reinforcement. Enhanced visual responsiveness was attenuated following local injection of a dopamine D1 receptor antagonist prior to pairing. These data indicate that rewarding stimuli can activate dopamine-dependent sensory reinforcement mechanisms within the SC, thereby rendering previously neutral or habituated stimuli as salient.

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6.6

A blue G and a G in blue – the involvement of associative memory in synaesthesia

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Synaesthesia is a neurological phenomenon associated with the unusual mixing of the senses. In grapheme-colour type synaesthesia the perception of letters, numbers and/or shapes (i.e. graphemes) induces automatic and involuntary perceptions of colour. This grapheme-colour synaesthesia is believed to be unidirectional: Only graphemes evoke the perception of colour, but not vice versa. However recent studies have shown evidence for bidirectional synaesthesia. We propose that associative memory may play a role in bidirectional synaesthesia. To investigate whether associative memory has a role in grapheme-colour synaethesia, one synaesthete (SI) was compared to 17 controls who learned synaesthetic associations of nine letter-colour pairings. Two synaesthetic associative priming tasks were used to determine if retrieval of letter-colour associations used an automatic process or a more controlled process. The synaesthetic associative priming tasks either used forward associative priming (letter prime —> word/non-word target) or backward associative priming (colour patch prime —> letter/symbol target) each with short (250ms) and long (750ms) stimulus onset asynchronies (SOA). Mean backwards reaction time (RT) was significantly faster than forwards RT for controls (444ms vs 538ms) and SMI (389ms vs 429ms). Interestingly significant condition vs SOA interactions were found in both groups: where in the forward conditions short SOA RTs were faster while conversely in the backward conditions long SOA RTs were faster. These results suggest that the same controlled processing was utilised by SMI and controls during the backward letter-colour priming. This may involve semantic matching through associative memory retrieval, where repeated forward or backward associative retrieval causes the controlled process to be more readily activated.

6.7

Anodal tDCS decreases GABAergic suppression in primary visual cortex

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Surround and overlay masking are two distinct suppressive mechanisms within the visual system that elevate the contrast detection threshold of a visual stimulus. Recent studies have indicated that surround masking may be driven by similar inhibitory interactions that contribute to decreased visual performance in amblyopia ("lazy eye"), for which there is currently no known treatment in adults. Neurophysiological studies have also suggested that while surround masking is cortical in origin, overlay masking occurs at the level of the lateral geniculate nucleus. In order to test the hypothesis that these two suppressive mechanisms have distinct neural loci, we used transcranial direct current stimulation (tDCS) to transiently modulate neural excitability in the human primary visual cortex while participants (n = 10) performed psychophysical tasks that allowed for the measurement of both surround and overlay masking. We found that anodal tDCS reduced the amount of suppression induced by surround masking by an average of 15%, $t(1,9) = -3.306$, $p = 0.01$, but did not affect overlay masking. These results support the hypothesis that surround masking has a cortical origin and provide further insight into the neural systems underlying human vision. Because anodal tDCS reduces suppression in the human visual cortex, it may be useful in the treatment of amblyopia ("lazy eye").

6.8

Prior completion of left/right-facing rotated object discriminations facilitates use of a non-rotation strategy during mirror/normal rotated letter discriminations

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Mental rotation (MR) is thought to underlie successful mirror/normal rotated letter discriminations and left/right-facing rotated object discriminations. Consistent use of MR should produce linear increases in response times (RTs) as a function of stimulus orientation from the upright. Mirror/normal discriminations typically produce curved RT functions. Based on group means, the "Mixture Model" (Kung & Hamm, 2010) specified that this curvature results from a mixture of trials employing MR and trials employing a non-rotation strategy. Kung and Hamm's mathematical model of RTs included a term for this mixture ratio. Searle and Hamm (unpublished data) included an exponent in the mixture ratio term and quantified individual differences in RT curvature. Moreover, exponents were larger (increased curvature) if left/right discriminations were completed before, compared to after, mirror/normal discriminations. Increased curvature is interpreted as decreased reliance on MR, and hence left/right discriminations reduce MR during mirror/normal discriminations. The current research investigated this task order effect further. Analogous to dose-response paradigms, participants were assigned to one of four conditions across which the number of left/right discriminations varied (0, 288, 576, or 864) prior to a constant number of mirror/normal discriminations (864). To ensure equal exposure (864 trials) to rotated objects, participants also made top/bottom discriminations which do not influence mirror/normal discriminations. Preliminary results indicate individuals' exponents for mirror/normal discriminations increase with more left/right discriminations. The non-rotation/MR mixture varies for mirror/normal discriminations depending on the amount of left/right discriminations completed beforehand. These novel findings have implications for interpreting performance on MR tasks and a wider range of visual imagery tasks.

7.1

The challenge of multiple scales in the biological sciences: applications in cerebro vascular perfusion

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In line with architectural advances in supercomputing science and engineering have each been posing more and more complex problems which are defined on complex geometric physical spaces. These physical spaces are themselves defined over vast ranges of scale lengths. In order to solve problems whose scale lengths vary substantially there are two possible solutions. Either discretise down to the smallest scale with the possibility of producing such large data sets and numbers of equations that the memory requirements become too large for the machine or divide the problem into a subset of appropriate length scales and map these discretised sub-domains onto appropriate machine architectures. The definition of "appropriate" here is determined on a case-by-case basis at present. There are a significant number of problems that exhibit a large range of physical scales but none so prominent in the 21st Century as that exemplified within the biological sciences. In the major arterial networks the blood flow dynamic scales are of the order of 1mm (cerebral vessels) up to 25mm (ascending aorta). Downstream of any major vessel exists a substantial network of arteries, arterioles and capillaries whose characteristic length scales reach the order of 10-20 microns. Within the walls of these cylindrical vessels lie ion channels consisting of proteins (100 nanometers and smaller) folded in such a way as to allow only certain molecules through the membrane. One can now of course ask the question as to why all these scales should be integrated into a single model. To investigate the way in which the brain responds to variations in pressure and yet maintains a virtually constant supply of blood to the tissue numerical models need to be able to have a representation of not only the vascular tree but also a dynamic model of how the small arteries constrict and dilate. Simulating this phenomenon as a "lumped" connection of arteries is insufficient since different parts of the arterial tree respond differently. Thus we have a range of scales from the major arteries down to the arteriolar bed. The combination of a 3D model taken from MR data coupled with an autoregulation model with a fully populated arterial tree able to regulate dynamically remains a relatively unexplored field. This particular talk will outline the reasons for investigating multiple scales and their particular constraints with special reference to the autoregulation of blood in the cerebro-vasculature simulated through the dynamics of large sets of coupled ordinary differential equations whilst outlining a possible solution.

7.2

Brain scans, blood flow, and how simulation might save the day

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Variations in local neural activity are accompanied by rapid, focal changes in cerebral blood flow (CBF) and volume (CBV). Although the purpose of these changes remains unclear, they are a major component of the widely-used functional Magnetic Resonance Imaging (fMRI) signal. A number of experimental observations have shown that significant dilation occurs in cerebral arteries and arterioles during neural activity; however, there is conflicting evidence about the presence and/or extent of volume changes in post-arteriole blood vessels. Here, we reconcile the competing observations using a mathematical model of the hemodynamic response. Initially, we followed a 'top down' approach, using experimental observations at progressively more detailed scales to constrain the model to physiological behaviour. Then, we then artificially blocked dilation of post-arteriole vessels and used the model to predict observations at progressively more aggregated scales (a 'bottom up' approach). Model predictions of changes in CBF, CBV, blood velocity, and vessel diameter were consistent with experimental observations. Interestingly, the model predicted slow increases in capillary and venule diameter that would be near indistinguishable from baseline noise, especially for brief stimulation. Blocking dilation of these vessels had a minimal effect on CBF, velocity and diameter, but led to CBV predictions that differed from experimental observations. The results suggest that arterial dilation represents the majority of regional CBV increases during functional activation. However, slow dilation of capillaries and venules is consistent with experimental observations, and becomes increasingly significant during extended stimulation. These are important considerations when interpreting results from different neurovascular imaging modalities.

7.3

Models of neurovascular coupling—A tale of two (billion or so) astrocytes

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Functional hyperemia is an important metabolic autoregulation mechanism by which increased neuronal activity is matched by a rapid and regional increase in blood supply. This mechanism is facilitated by a process known as "neurovascular coupling"—an orchestrated communication system involving neurons, astrocytes and arterioles. Important steps in this process are the production of EETs in the astrocyte and the release of potassium, via two potassium channels (BK and KIR), into the perivascular space. Using this model, we are able to achieve vasodilations (and vasoconstrictions) similar in magnitude to those seen in experiment. Constructing a model of sufficient physiological complexity has also allowed us to investigate the causes of experimentally observed observations, such as the paradoxical finding that vasoconstriction follows vasodilation when the astrocytic calcium concentration (or perivascular potassium concentration) is increased further. We suggest that the interaction of the changing smooth muscle cell membrane potential and the changing potassium-dependent resting potential of the KIR channel are responsible for this effect. A well-controlled mechanism of potassium buffering is potentially important for successful neurovascular coupling. Our model can investigate a number of varying situations easily and results will show the relationship between EET and Ca^{2+} dynamics. This project highlights the fact that mathematical modelling can be used as a tool to understand biological processes in a way that physical experiment cannot always do.

7.4

Sonic hedgehog signaling and post-stroke recovery

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Injury to the brain as a result of either stroke or traumatic head injury results in lasting functional impairments. The brain has a limited capacity to repair after an injury and this recovery is somewhat slow. Recent studies have shown that the formation of the glial scar surrounding the stroke is causally linked to this impaired recovery profile and modulating some of the secreted factors from these glial cells can aid in improved function. We aimed to assess the effects of modulating one of these secreted factors; sonic hedgehog (Shh), which is a morphogen that has been shown to play a critical role in neurogenesis and axon growth/guidance during development. Using an in vivo photothrombotic stroke model, Shh delivered via biopolymer hydrogel revealed no change in neurogenesis, however an increase in NG2+ oligodendocytes was observed. In addition, to investigate the putative effects of Shh on neurite sprouting, we established an in vitro model, whereby astrocytes grown on a flexible membrane were mechanically stretched to render them reactive and then cortical neurons plated on top. This model has been shown to impair neurite outgrowth, similar to what has been observed for reactive gliosis in vivo. Administration of Shh to the media following plating of cortical neurons resulted in a modified neurite response. Further studies are being undertaken to ascertain through which intracellular signaling pathway Shh is acting to mediate these changes.

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7.5

Correlations between ASL blood flow MRI and eye movement abnormalities in Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting the motor pathway in particular. There is a need to develop markers that determine Parkinson's disease progression. Eye movements provide useful information about changes in the motor system in PD. The aim of this study was to explore correlations between the MR imaging and eye movement abnormalities in Parkinson's patients with arterial spin labelling (ASL) blood flow MRI. ASL is a non-invasive technique for measuring cerebral blood-flow using magnetically-labelled endogenous blood water. The saccadic eye movement tasks investigated were the reflexive and predictive tasks with the latency (reaction time) and gain (accuracy) being the measures of performance. 59 PD and 27 controls had ASL MRI scanning data. The Parkinson's group represented a range of disease severity. The control group consisted participants matched by age, sex and years of education to the Parkinson's group.The analysis consisted of a voxel-wise correlation of blood perfusion in the brain and saccadic performance. The MRI scanning data was adjusted for multiple comparisons at 0.05 FDR (false discovery rate). Areas that were found to have positive correlation between saccadic gain and perfusion were the angular gyrus, cuneus and precuneus, occipital gyrus, posterior cingulate, superior parietal lobule and gyrus and the middle frontal gyrus. Building on previous experiments conducted by our lab group, these areas are characteristic of perfusion changes in PD. We conclude that reflexive gain is related to changes in perfusion experienced in PD and saccadic eye movement measures may provide novel markers of PD progression.

7.6

Inferring causality using time-lag analysis of BOLD data

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Interactions between brain regions have the potential to reveal much about the structure of cognitive systems that operate within the brain's neural structure, and may be measurable using time-lagged correlation of fMRI BOLD data. Previous researchers have described methods for detecting time-lagged correlation between region of interest (ROI) activation – primarily variants on, 'Granger causality' (GC), originally used in econometrics, as a proxy for causality. With appropriate caveats, GC can draw inferences from temporal precedence about effective connectivity between ROIs in a way methods like SEM and DCM do not. Some studies examined circumstances where time-lagged correlation between ROI activation can help draw causal inferences from BOLD data, and tested the limits of poor temporal resolution of fMRI on this method. The current project examines whether time-lag analysis can estimate the direction of causation in frontal and parietal areas known to act together in spatial working memory tasks. Independent Component Analysis (ICA) is used to identify independent spatial components, whose interactions are then examined using the Granger causality method. The method successfully identified causal relationships on replicated, artificially simulated data , but was not yet found to significantly detect Granger-causal relationships between ROIs in the spatial working memory task. There are several changes underway to better detect spatial working memory Granger-causal relationships: multivariate (rather than bivariate) Granger analysis can help to rule out false positives; adopting a frequency-domain approach could eliminate noise at irrelevant frequencies; and optimizing selection of components can ensure the current ICA and subsequent component selection does not accurately identify the ROIs. Additional data gathering utilizing a higher TR rate could potentially improve the detection of significant Granger-causal relationships.

8.1

In vivo intercellular correction in ovine CLN6 Batten disease

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Studies of chimeras comprised of cells from normal and CLN6 Batten disease affected sheep show that despite the CLN6 protein being cell intrinsic, the presence of some normal cells can lead to suppression of the disease. The extent of chimerism varied in individuals constructed by the fusion of affected and normal 16-32 cell embryos re-implanted into recipient ewes. CAT scanning and post-mortem examination revealed a range of responses. Two chimeras had brain volume changes that decreased with age, two maintained normal volumes even though genotyping indicated colonisation of affected cells within the brain and three recovered to reach normal volumes at ages beyond the life-span of affected sheep. Affected-like neuronal atrophy was observed in the affected like-chimeras whereas there was no neurons loss or disruption of cortical layers in the normal-like and recovering animals. Small storage deposits were found in some neurons in a normal-like chimera while the other normal-like the three recovering chimeras had no storage body accumulation in any brain regions. Astrocytosis was suppressed in the normal-like and recovering chimeras and GSB4 staining revealed no microglial activation in these animals. PSA-NCAM positive staining revealed extended neurogenesis along the SVZ in all the chimeric animals as well migrating positive cells within white matter. PSA-NCAM positive cells were present within the grey matter throughout all cortical layers in contrast to affected animals where newly generated cells are largely confined to cellular aggregates in upper cortical layers. This study shows that that gene therapy targeting neurogenic regions in the brain can work, if the right stem cells are corrected and if newly generated cells are born into the right environmental milieu.

8.2

Priming sensorimotor cortex to enhance task-specific training after subcortical stroke

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Combining theta burst stimulation (TBS) of primary motor cortex (M1) with training can improve task-specific motor performance in subcortical stroke patients. The aim of this study was to elucidate neurophysiological mechanisms that contribute to improvements in grip-lift performance after task-specific training primed with TBS. Thirteen patients at the chronic stage after subcortical stroke and with upper limb impairment were recruited to this blinded, cross-over, sham-controlled study. Standardised precision grip training with the paretic upper limb was primed with intermittent TBS of the ipsilesional M1 (iTBS$_{ipsiM1}$), continuous TBS of the contralesional M1 (cTBS$_{contraM1}$), or sham TBS, in separate sessions to examine effects on grip-lift kinetics, corticomotor excitability, sensorimotor integration, and sensation. Brain-derived neurotrophic factor (BDNF) genotyping was also performed, to identify Methionine (Met) allele carriers. Training after real TBS, but not sham TBS, improved grip-lift performance. After iTBS$_{ipsiM1}$ and training, ipsilesional M1 excitability and short latency afferent inhibition (SAI) increased. After cTBS$_{contraM1}$ and training, ipsilesional M1 excitability increased and contralesional SAI tended to decrease, but there was no effect on ipsilesional SAI. The pattern of modulation after TBS and training was similar in non-Met and Met carriers. In conclusion, priming M1 with TBS prior to motor training increased ipsilesional M1 excitability and enhanced paretic upper limb grip-lift performance, regardless of BDNF genotype. Increased sensorimotor integration between ipsilesional S1 and M1 may contribute, but was not necessary for improved grip-lift performance. The after-effects of cTBS$_{contraM1}$ were variable, and associated with stroke severity, and this requires further investigation.

8.3

Anticonvulsant effects and sodium channel inhibition by selective serotonin reuptake inhibitors

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Epilepsy affects ~1 % of the population and up to a third of patients do not achieve adequate seizure control with antiepileptic drugs. Many epileptic people suffer from comorbid depression, which is both underdiagnosed and undertreated. Part of the reason for the inadequate treatment of depression in epileptics is a widespread erroneous belief that antidepressant selective serotonin reuptake inhibitors (SSRIs) are proconvulsant and therefore potentially dangerous for seizure-prone individuals. Animal studies and uncontrolled human trials have, however, suggested that SSRIs may have anticonvulsant properties. While serotonin is not always anticonvulsant in the brain, SSRIs may have many non-serotonergic targets which could mediate anticonvulsant effects. In this study, we tested the effects of the SSRIs fluoxetine and citalopram in two brain slice models of acute seizures: the olfactory bulb low-Mg^{2+} model and the hippocampal low-Ca^{2+} model. Using field potential, single-unit, and whole-cell current clamp recordings, we found that SSRIs abolished seizure-like events at clinically relevant concentrations (10 µM). SSRIs also inhibited action potential generation in a manner consistent with Na+ channel blockade, and voltage clamp experiments revealed that SSRIs strongly inhibited the persistent Na^+ current in principal neurons. Na^+ channel inhibition is a major action of many antiepileptic drugs, and our findings suggest that SSRIs should be investigated as a potential treatment for some types of seizures. The relatively benign side effect profile of SSRIs, compared with current antiepileptic drugs, could significantly enhance the quality of life for epileptic patients.

8.4

The cannabinoid CB2 receptor controversy: a receptor with an identity crisis

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The endocannabinoid system includes at least two G-protein coupled receptors (GPCRs). The CB1 receptor is widely expressed on neurons in the central nervous system, whereas the CB2 receptor was first cloned and characterised in immune cells. The apparent absence of the CB2 receptor from neurons in the brain has made it a target for drug development. However, in recent years studies that have employed immunohistochemistry have reported widespread expression of CB2 in CNS neurons. Using in situ hybridization, we found no evidence for widespread neuronal expression of CB2 in the healthy rat brain or spinal cord. However, CB2 mRNA was expressed in the rat hippocampus 3 days following hypoxia-ischaemia. When we investigated the CB2 antibody used in recent published studies, we found that the antibody labelled cells not only in wildtype mouse spleen and spinal cord, but also in the same pattern in these tissues taken from CB2 knockout mice. We conclude that if the CB2 receptor is expressed in significant quantities in healthy rat brain neurons then it is at below the level of detection for in situ hybridibization and immunohistochemistry. We conclude that immunohistochemical studies claiming widespread expression of significant levels of CB2 in central nervous system neurons are in error. The problem may be widespread in the field of GPCR research, suggesting that published reports of GPCR protein distribution in native tissues may often be in inaccurate.

8.5

Secreted amyloid precursor proteins promote proliferation and glial differentiation of adult hippocampal neural progenitor cells

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Amyloid precursor protein (APP) is an integral membrane glycoprotein that is processed by two mutually exclusive proteolytic pathways to generate two soluble secreted forms, sAPPα and sAPPβ. sAPPα shows a range of neuroprotective, neurotrophic and memory-enhancing properties, in contrast to the generally less potent sAPPβ. sAPPα also increases proliferation of both embryonic neural stem cells and neural progenitor cells (NPCs) derived from the subventricular zone of the adult brain. Here, we examined the effect of both sAPPα and sAPPβ on the proliferation, survival and differentiation of adult NPCs isolated from the subgranular zone (SGZ) of the adult rat hippocampus in the presence or absence of depolarizing conditions. We observed that both sAPPα and sAPPβ increased the proliferation of SGZ-derived NPCs *in vitro*. Further, treatment of the differentiating cells with either sAPPα or sAPPβ increased the proportion of cells expressing the astrocytic marker GFAP, with a corresponding reduction in the proportion of cells expressing the neuronal markers MAP2 and calbindin, while increasing overall cell survival. The effect on differential fate was observed in both the presence and absence of depolarising conditions. These findings provide the first direct support for secreted forms of APP regulating SGZ-derived NPCs, and raise the possibility that some of the effects may have therapeutic benefit in models of neurological disease.

8.6

GYKI-52466 preconditioning preserves CA1 neuronal excitability and improves long-term potentiation in a rat model of hypoxic-ischemic brain injury

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Experimental preconditioning provides beneficial outcomes in conditions such as cardiac surgery, brain surgery and stroke. We found that prophylactic preconditioning with low-dose GYKI-52466 imparts significant protection against KA-induced seizures and hypoxic-ischemic brain injury in histological and behavioral paradigms. Here, we evaluated GYKI's efficacy on electrophysiological indices of hippocampal CA1 function after hypoxic-ischemic (HI) brain injury. Male Sprague Dawley rats (26 days old) were administered saline or GYKI-52466 (3 mg/kg, s.c.) 90 min before left common carotid artery ligation, and allowed to recover for 2 hr prior to placement in a hypoxia chamber (1 hr; 8% O_2/92% N_2; 33±1°C). On day 14, contralateral, and where possible, ipsilateral hippocampal slices were prepared, and population spikes and field EPSPs recorded in normal (2 mM Ca^{2+} and 2 mM Mg^{2+}) ACSF at 30-31°C. Low-dose GYKI-52466 preconditioning significantly ($p<0.05$) reversed the stroke-induced suppression of neuronal excitability and synaptic strength in both contralateral and ipsilateral hippocampi. In sham-operated controls, long-term potentiation was consistently induced after tetanus (42% increase in population spike amplitude from baseline; n = 3) in both contralateral and ipsilateral hippocampi. After stroke, LTP was markedly reduced (21%; n = 4; N.S.) in the contralateral hippocampus and completely absent ipsilateral to the carotid occlusion. In ischemic animals preconditioned with GYKI-52466, LTP was readily induced on both sides (contra: 35%; ipsi: 24%; n = 4). Similar results were obtained following LTD induction. The present results indicate that prophylactic preconditioning with low-dose GYKI-52466 preserves CA1 function, and improves synaptic plasticity processes contralateral, and more importantly, ipsilateral to the site of stroke.

8.7

Memantine, a promising treatment for acoustic trauma-induced tinnitus

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Chronic tinnitus is the frequent and persistent perception of sound in the absence of an external stimulus. For 8% of the general population, chronic tinnitus causes considerable anxiety and distress, and adversely affects quality of life. There is currently no specific pharmacological treatment for tinnitus. The most common cause of tinnitus is acoustic trauma, which initially damages the inner ear and later results in changes in the central auditory pathways, including neuronal hyperactivity and inhibition. Therefore, NMDA receptors could be a promising target for tinnitus treatment due to their known role in hyperactivity and NMDA receptor antagonists could have therapeutic benefits for chronic tinnitus. In the present study, memantine, an uncompetitive NMDA receptor antagonist, was tested in an animal model of acoustic trauma-induced chronic tinnitus. Male Wistar rats underwent unilateral noise exposure at 16 kHz for one hour at 110 dB (exposed, n = 8) or 0 dB (sham, n = 8). Auditory brainstem-evoked response thresholds were measured immediately before and after exposure, confirming hearing loss in only the ipsilateral ear of exposed animals. Using a conditioned lick suppression paradigm, psychophysical signs of tinnitus were confirmed in exposed animals and drug testing proceeded in three 18-day phases: vehicle, memantine (5 mg/mL in saline, s.c.) and washout. During memantine treatment, exposed animals no longer appeared to have signs of tinnitus, and tinnitus behaviour did not return in the subsequent washout period. Memantine may thus be an effective clinical treatment for chronic tinnitus. Further investigation into the longevity of memantine's effects is in progress.

9.1

Leptin induced hypertension, the link between obesity and metabolic disease?

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Obesity rates continue to rise, causing greater risks of diabetes, cancer, and cardiovascular diseases. Drugs to treat obesity have had very limited success, so we now seek to determine if we can break the link between obesity and metabolic diseases. We have previously described the phenomenon of leptin-resistance, where obese mice no longer lose weight in response to the adipocyte hormone leptin. We have discovered that leptin retains the ability to activate the sympathetic nervous system of obese mice, even though they are otherwise resistant to leptin, therefore leptin resistance is not global, rather it is selective. In response to leptin, obese leptin-resistant mice still show rapid activation of neurons in the dorsomedial hypothalamus, and rapid increases in brown adipose tissue temperature. Hyperleptinemic mice are hypertensive and tachycardic, conversely leptin deficient mice are bradycardic and hypotensive. Here I will describe the effects of chronic leptin treatment on cardiovascular tone in lean mice, and of leptin antagonism on cardiovascular tone in obese mice.

9.2

Genetic approaches to understanding hypothalamic function in the mouse

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An essential obstacle in neuroendocrinology is to understand how specific hormone-producing neurons in the hypothalamus are regulated by afferent pathways and how they impinge on downstream target cells to elicit behavioral and endocrine responses. A small subset of basal forebrain neurons that produce and secrete gonadotropin-releasing hormone (GnRH) controls reproductive physiology and behavior in mammals. To ensure reproductive success, the GnRH neuronal network has to process and integrate various cues. Likewise, it has to ensure that it selectively affects specific target cells in response to these cues. We developed genetic strategies to visualize neurons up- and downstream of GnRH neurons in the mouse brain and started to characterize these cells. Both the accessory and the main olfactory system relay information to GnRH neurons, revealing one afferent pathway by which chemosensory cues influence reproductive physiology and behavior. Target cells downstream of GnRH neurons are found in areas influencing sexual behaviors as well as in brain areas that process olfactory and pheromonal cues, revealing one efferent pathway by which the neuroendocrine hypothalamus may influence the sensitivity towards chemosensory cues. A subset of these cells expresses the GnRH receptor and responds to extracellular application of GnRH, suggesting that GnRH acts as a neurotransmitter in the brain and influences behavioral and endocrine responses to optimize reproductive success.

9.3

Viral tracing of neuronal networks

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To be inserted.

9.4

Exploring dendritic physiology with combined imaging and electrophysiology

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The morphology of gonadotropin-releasing hormone (GnRH) neuron dendrites is very different compared to other central neurons in that they are very long, thin and unbranched. In order to study the function of these dendrites, we have used Ca^{2+} and Na+ imaging in combination with dual soma and dendrite electrical recordings. Sagittal brain slices, 250 µm thick, were taken from adult male GnRH-GFP mice. Dual electrical recordings were performed from the soma and different dendritic locations of GnRH neurons. In the great majority of cells tested, action potentials were recorded first in the dendrite before the soma, indicating a dendritic site of spike initiation. We next loaded GnRH neurons with the Na^+ sensitive dye CoroNa Green (500 µM). The change in fluorescence of the Na+ indicator was measured at different soma and dendritic locations in response to a burst of action potentials. The site of the largest increase in fluorescence was in the proximal dendrite, on average 87 ± 15 µm from the soma. This suggests that the proximal dendrite has the highest density of functional Na^+ channels. Finally we loaded GnRH neurons with the Ca^{2+} sensitive dye Rhod2 (200 µM). Single action potentials could also reliably evoke Ca^{2+} rises in the dendrites of GnRH neurons. These Ca^{2+} transients could be observed for as far as the dendrite could be imaged in the brain slice (up to 458 µm from the soma). Together these findings suggest that the dendrites of GnRH neurons are highly excitable and that the site of action potential initiation is likely to be in the proximal dendrite of these neurons.

9.5

Single molecule imaging in living adult neurons

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Surface trafficking of receptors and interaction with second messenger molecules close to the membrane has emerged as major events in the regulation of synapse function and neuronal activity. In order to study the detail of these signaling processes the imaging field was searching for tools to investigate the microscopic behaviour of molecules with high spatio-temporal resolution. The recent development of the single molecule imaging technology opened a new avenue for wide range of applications in cellular biology and nanobiology unravelling of novel mechanisms related to molecular movements. In our experiments we isolate live adult neurons and label the receptor molecules with Quantum dot conjugated antibodies. Total internal refection fluorescence microscopy (TIRFM) is applied to visualize trafficking of single Qdot labelled receptor molecules such as TrkA or AMPA receptors on the plasma membrane of living adult neurons. Using appropriate mathematical tools diffusion parameters are extracted from the receptor molecule trajectory such as diffusion coefficient, period of immobility and confinement area. In addition the number of membrane compartment changes (synaptic versus extrasynaptic) are estimated and the interaction between different receptors or signaling molecules are identified. We also demonstrate how receptor ligands can alter these movement parameters in living neurons. Taken together, the TRIFM based single molecule imaging provides an effective platform to investigate signaling processes in the plasma membrane of living adult neuron with real-time single molecule-scale precision.