30TH
INTERNATIONAL AUSTRALASIAN
WINTER CONFERENCE ON BRAIN RESEARCH

2012
Programme and Abstracts

25-29 August 2012
Copthorne Hotel, Queenstown, New Zealand
www.awcbr.org

Supported by the
Neurological Foundation of New Zealand

Neurological Foundation of New Zealand

Saturday 25 August

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

1. Stem Cells

Chair: Richard Faull

7.15 pm	1.1	**INVITED SPEAKER** **Perry Bartlett,** ***University of Queensland, Australia*** Distinct neurogenic stem cell populations in the hippocampus: How are they regulated and what are their functions?
7.55 pm		Tea/Coffee break
8.10 pm	1.2	**Lachlan Thompson,** ***University of Melbourne, Australia*** Neurons derived from human embryonic stem cells extend long–distance axonal projections through growth along host white matter tracts after intra-cerebral transplantation
8.25 pm	1.3	**Bronwyn Connor,** ***University of Auckland, New Zealand*** Non-viral generation of neural precursor-like cells from adult human fibroblasts
8.40 pm	1.4	**Peter Mombaerts,** ***Max Planck Institute of Biophysics, Frankfurt, Germany*** Coding olfaction

Sunday 26 August
Morning Session

7.30 am		Light Breakfast Available

2. Cognition and Behaviour

Chair: Ian Kirk

8.00 am	2.1	**Philip Corlett,** ***Yale University, USA*** Formalizing aberrant salience: Prediction error and delusions
8.40 am	2.2	**Haeme Park,** ***University of Auckland, New Zealand*** P50 sensory gating and schizotypal personality
8.55 am	2.3	**Paul Corballis,** ***University of Auckland, New Zealand*** Competition for representation as a window into the functional architecture of extrastriate visual cortex
9.10 am	2.4	**Nadia Borlase,** ***University of Canterbury, New Zealand*** Thalamo-cortical circuitry in mild cognitive impairment and dementia in Parkinson's disease – combined diffusion tensor and fiber tractography study
9.25 am		Tea/Coffee break

Sunday 26 August
Afternoon Session

4.15 pm — Afternoon Tea Available

3. Drug Addiction and Reward

Chair: Sue Schenk

4.30 pm	3.1	**Andrew Lawrence,** ***University of Melbourne, Australia*** Neuropeptides and reward seeking
5.10 pm	3.2	**Brian Hyland,** ***University of Otago, New Zealand*** Tonic D2-dopamine receptor-mediated autoinhibition prevents amplification of reward-related cue responses by methylphenidate in normal rats
5.25 pm	3.3	**Sarah Bradbury,** ***Victoria University of Wellington, New Zealand*** The role of serotonin in the acquisition of MDMA self-administration
5.40 pm	3.4	**David Harper,** ***Victoria University of Wellington, New Zealand*** Effects of baseline training dose on the discrimination of saline versus 3,4-methylenedioxy-N-methylamphetamine (MDMA)

Sunday 26 August

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 27 August
Morning Session

8.30 am — Light Breakfast Available

4. Sensory and Motor Systems

Chair: Brian Hyland

9.00 am	4.1	**John Reynolds,** ***University of Otago, New Zealand*** Investigating the mechanisms of action discovery
9.15 am	4.2	**Yanfeng Zhang,** ***University of Otago, New Zealand*** Reinforcement of visual responses in the superior colliculus is dependent on timing and dopamine
9.30 am	4.3	**Mark Plenderleith,** ***Queensland University of Technology, Australia*** Expression of a galactose-containing membrane-associated glycoconjugate by physiologically-characterised primary sensory neurones in the rat
9.45 am		Tea/Coffee break
10.00 am	4.4	**Michael Lee,** ***University of New South Wales, Australia*** Unilateral high-frequency electrical nerve stimulation facilitates H-reflex transmission bilaterally: A threshold tracking study
10.15 am	4.5	**Jonathan Shemmell,** ***University of Otago, New Zealand*** Non-decussating portions of the corticospinal tract are not involved in stability-dependent modulation of the long latency stretch reflex
10.30 am	4.6	**Malinda Tantirigama,** ***University of Otago, New Zealand*** Diversity of layer 5 projection neurons in mouse motor cortex

5. POSTER SESSION

- COMBINED WITH MEDSCI

NB: BEN LOMOND RESTAURANT AND TRADES AREA, RYDGES HOTEL

4.00 - 6.30 pm	Presenters will be in attendance during this time Presenters for Posters A will 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 postgraduate dinner to the held at Winnies at 8.00 pm
5.1 - A	**Norman Ma,** ***University of Queensland, Australia***
	Developmental changes in expression of KCC2 and NKCC1 in normal and hypoxic-schemic neonatal piglet brain
5.2 - B	**Choo Peng Goh,** ***University of Melbourne, Australia***
	Ndfip1 regulates neuronal development and function via the MAP-kinase pathway
5.3 - A	**Samantha Murray,** ***University of Otago, New Zealand***
	Does the schizophrenia-inducing cytokine IL-6 alter neurite outgrowth in the developing brain?
5.4 - B	**Colin Mak,** ***University of Auckland, New Zealand***
	Progenitor cells in the thalamostriate subventricular zone of the adult human brain
5.5 - A	**Rachel Cotter,** ***University of Canterbury, New Zealand***
	Therapeutic-like properties of the trace amine-associated receptor 1 partial agonist, RO5203648, in animal models of methamphetamine abuse
5.6 - B	**Marcus Wilson,** ***University of Waikato, New Zealand***
	Electrical conductivity of mouse brain slices in seizing and non-seizing conditions

Poster Session

5.7 - A	**Sarah Poole,** ***University of Canterbury, New Zealand***
	Mathematical modelling of pH as a mechanism affecting vasoreactive response
5.8 - B	**Tatyana Vagner,** ***University of Auckland, New Zealand***
	Comparison of two gene regulation systems for use in gene therapy
5.9 - A	**Rui Liu,** ***University of Auckland, New Zealand***
	Direct generation of neural precursors from adult human fibroblasts using viral gene delivery
5.10 - B	**Yijia Li,** ***University of Melbourne, Australia***
	The function of Ndfip1 in regulating PTEN ubiquitination and localization
5.11 - A	**Chelsea Goulton,** ***University of Otago, New Zealand***
	Mechanisms of acute preconditioning with kainic acid in vitro: The role of extracellular calcium and Na+K+-ATPase
5.12 - B	**Paul McCarthy,** ***University of Otago, New Zealand***
	Effect of aging and dementia on functional connectivity: graph theoretical analysis of fMRI data
5.13 - A	**Prasanta Nayak,** ***University of Otago, New Zealand***
	GYKI-52466 preconditioning salvages ischaemia-induced deficits in long-term potentiation in rat hippocampal CA1
5.14 - B	**Vinod Suresh,** ***University of Auckland, New Zealand***
	'Extra permeability' is required to model dynamic oxygen measurements: Evidence for functional recruitment?
5.15 - A	**Emma Gowing,** ***University of Otago, New Zealand***
	Sonic hedgehog administration stimulates oligodendrogenesis and functional recovery in young and aged mice after stroke
5.16 - B	**Lucia Schoderböck,** ***University of Otago, New Zealand***
	Reversible Inactivation of primary neurons in vitro
5.17 - A	**Emmet Power,** ***University of Otago, New Zealand***
	Modification of glutamate uptake influences the properties of the cerebellar parallel fibre to purkinje neuron synapse
5.18 - B	**Rachel Sizemore,** ***University of Otago, New Zealand***
	Number and type of synapses on the somata and primary dendrites of dopaminergic neurons in the rat ventral tegmental area

Poster Session

5.19 - A	**Clementine Bosch,** ***University of Otago, New Zealand***
	New light-activated protein constructs to dissect the function of GABAergic neurons in the brain
5.20 - B	**Karen Parfitt,** ***Pomona College, USA***
	Mutations in palmitoyl protein-thioesterase 1 alter exocytosis and endocytosis at synapses in Drosophila larvae
5.21 - A	**Lucy Goodman,** ***University of Auckland, New Zealand***
	Super resolution imaging of hippocampal synapses
5.22 - B	**Hollie Peacock,** ***University of Otago, New Zealand***
	A role for FEZF2 in projection maintenance and cell survival
5.23 - A	**Greig Joilin,** ***University of Otago, New Zealand***
	N-Methyl-D-Aspartic acid receptor-specific down-regulation of mature microRNA, miR-34a, following induction of long-term potentiation in vivo
5.24 - B	**Bruno Galvão,** ***Pontifícia Universidade Católica do Rio de Janeiro, Brasil***
	Participation of rostral anterior cingulate cortex in conditioned and unconditioned fear eliciated by dPAG electrical stimulation
5.25 - A	**Fraser Putt,** ***Victoria University of Wellington, New Zealand***
	Comparisons between the effects of nicotine and other chemicals present in cigarette smoke on dopmaine and serotonin transporter function in rats
5.26 - B	**Paul Sowman,** ***Macquarie University, Australia***
	Temporally cued and self-initiated auditory stimuli evoke a reduced auditory N1/P2
5.27 - A	**Laura Boddington,** ***University of Otago, New Zealand***
	Using theta-burst stimulation to modulate functional recovery after stroke
5.28 - B	**Alice Lagas,** ***University of Auckland, New Zealand***
	Measurement of human visual cortex excitability using suprathreshold phosphene perception
5.29 - A	**Oliver Linsell,** ***University of Otago, New Zealand***
	Nanomiceller delivery of cannabinoids for neuropathic pain
5.30 - B	**Liam Farley,** ***University of Otago, New Zealand***
	Nitric oxide in the olfactory bulb in vitro
5.31 - A	**Bruce Harland,** ***University of Canterbury, New Zealand***
	Anterior thalamic lesions and recovery: Enriched environments restore spatial memory in the radial arm maze

Poster Session

5.32 - B	**Yvette Lamb,** ***University of Auckland, New Zealand***
	Influence of the catechol-O-methyltransferase (COMT) val158met polymorphism on magical ideation
5.33 - A	**Dion Henare,** ***University of Auckland, New Zealand***
	Distinct signatures of visual target selection and distractor suppression investigated using high-density electroencephalography
5.34 - B	**Susan Rapley,** ***University of Canterbury, New Zealand***
	Time-dependent changes in C-type natriuretic peptide in rat brain produced by enriched environments
5.35 - A	**Hannah Collins,** ***University of Auckland, New Zealand***
	Evoked potential correlates of object recognition memory and the influence of the BDNF val66met polymorphism
5.36 - B	**Chris Thompson,** ***University of Auckland, New Zealand***
	BDNF val66met polymorphism affects FN400 and LPC evoked potentials in human facial recognition memory
5.37 - A	**Jeremy Webster,** ***Victoria University of Wellington, New Zealand***
	The effect of the 5-HT1B antagonist GR-127935 on cocaine and MDMA seeking behaviour in rats
5.38 - B	**Anne Arola,** ***Victoria University of Wellington, New Zealand***
	The role of the dopamine receptor D1 in cognitive behaviour
5.39 - A	**Bridget Brox,** ***Victoria University of Wellington, New Zealand***
	The role of histamine H3 receptors in the behavioural effects of methamphetamine and 3,4-methylenedioxymethamphetamine
5.40 - B	**Dane Aronsen, V*ictoria University of Wellington, New Zealand***
	The effects of the 5-HT1B agonist RU-24969 on drug seeking in rats trained to self administer MDMA or cocaine
5.41 - A	**Kate Bray,** ***Victoria University of Wellington, New Zealand***
	Biochemical and pharmacological characterisation of the Drd1 mutant rat
5.42 - B	**Hanna Squire,** ***Victoria University of Wellington, New Zealand***
	A novel behavioural investigation of the dopamine D1 mutant rat
5.43 - A	**Alana Oakly,** ***Victoria University of Wellington, New Zealand***
	Amphetamine hyperactivity is enhanced in serotonin transporter knock-out rats

5.44 - B **Katharina Limbach, *University of Auckland, New Zealand***

EEG Alpha oscillations predict variability in visual signal detection

5.45 - A **Madihah Rushaidhi, *University of Otago, New Zealand***

Direct participation of agmatine in spatial learning: An in vivo microdialysis study

5.46 - B **Sarina Iwabuchi, *University of Auckland, New Zealand***

Structural and functional connectivity in language production and comprehension

5.47 - A **Nicole McKay, *University of Auckland, New Zealand***

Using diffusion tensor imaging to compare differences in the white matter tracts of right- and left-handed males

5.48 - B **James O'Leary, *University of Canterbury, New Zealand***

Effects of chronic unpredictable stress on adult neurogenesis: Behavioural consequences and similarities with hippocampal lesions

5.49 - A **Catherine Harrow, *Victoria University of Wellington, New Zealand***

Methamphetamine-induced disruption in Delay Matching to Sample is attenuated by the D1 antagonist SCH23390

5.50 - B **Takanobu Yamamoto, *Tezukayama University, Japan***

Involvement of tryptophan and kynurenine metabolites in central fatigue

5.51 - A **Dave Bergin, *University of Otago, New Zealand***

Age-dependent spatial learning and memory impairments in the APP/PS1 transgenic mouse model of Alzheimer's disease

5.52 - B **Angela Wu, *University of Auckland, New Zealand***

Astrocytes as a cell target of gene therapy for epilepsy

5.53 - A **Malvindar Singh-Bains, *University of Auckland, New Zealand***

Human globus pallidus volume reduction in HD with differential cell loss between external and internal segments

5.54 - B **Ann Jones, *University of Canterbury, New Zealand***

Supporting someone with Parkinson's disease: The influence of different cognitive status

5.55 - A **Samantha Ross, *University of Otago, New Zealand***

Behavioral effects of a double ethanol binge during brain development

Poster Session

5.56 - B	**Clare Parish, *University of Melbourne, Australia***
	Improving cell based therapy for Parkinson's disease
5.57 - A	**Eric Kim, *University of Auckland, New Zealand***
	Pyramidal and interneuron cell loss in the motor and cingulate cortex in HD human brain correlates with dominant symptom profile
5.58 - B	**Lily Boothman-Burrell, *University of Otago, New Zealand***
	Screening novel compounds as potential protectants after stroke
5.59 - A	**Junru Song, *University of Auckland, New Zealand***
	GABAA receptor subunit localisation in the human amygdala
5.60 - B	**Caine Smith, *University of Otago, New Zealand***
	Acute hippocampal cell death in the alcohol-exposed developing rat brain
5.61 - A	**Nicole Neverman, *University of Otago, New Zealand***
	Early pathology in Ovine CLN6 Batten disease – assays for testing therapies
5.62 - B	**Nasim Mehrabi, *University of Auckland, New Zealand***
	Changes in interneuron populations in the primary sensory cortex in Huntington's disease
5.63 - A	**Morgayn Read, *University of Otago, New Zealand***
	Atenolol attenuates cardiac and cortical electrographical changes during status epileticus
5.64 - B	**Hayden McEwen, *University of Otago, New Zealand***
	Phosphorylation of Akt by antipsychotic drugs is induced indirectly through dysregulation of glucose homeostasis
5.65 - A	**Kathie Overeem, *University of Otago, New Zealand***
	Aberrant expression of plasma microRNAs in the maternal immune activation model of schizophrenia
5.66 - B	**Stella Cameron, *University of Otago, New Zealand***
	Delayed post-treatment with mesenchymal stem cells affects progenitor cell proliferation in the subventricular zone after neonatal rat hypoxic/ischemic striatal injury
6.30 pm	**Posters to be removed at this time**

Monday 27 August
Evening Events

7.00 pm	Queenstown Research Week Social Mixer Venue: Rydges Hotel
8.00 pm	AWCBR Student Dinner Venue: Winnies Gourmet Pizza and Bar 7-9 The Mall, Queenstown

Tuesday 28 August
Morning Session

7.30 am — Light Breakfast Available

6. Novel Methods and Technology Development

Chair: John Reynolds

8.00 am	6.1	**Tim David, *University of Canterbury, New Zealand*** A computational model of oxygen transport in the cerebrocapillary-levels for normal and pathological brain function: An investigation on flow-metabolism coupling
8.15 am	6.2	**Jerusha Naidoo, University of Auckland, New Zealand** Characterisation of a novel gene regulation system in the rat brain
8.30 am	6.3	**David Baddeley, *University of Auckland, New Zealand*** Making sense of super-resolution data
8.45 am		Tea/Coffee break
9.00 am	6.4	**Cameron Gunn, *University of Canterbury, New Zealand*** A numerical model for understanding cerebral CO2 reactivity impairment in diabetes mellitus
9.15 am	6.5	**Janitha Mudannayake, *University of Auckland, New Zealand*** AAV5 vectors mediate efficient transgene expression in astrocytes in the rat substantia nigra
9.30 am	6.6	**Peter Bosch, *Victoria University of Wellington, New Zealand*** Investigation of methamphetamine self-administration in rats
9.45 am		**ANNUAL GENERAL MEETING** All conference participants are invited to attend

Tuesday 28 August
Afternoon Session

Session with QMB to be held at the Rydges Hotel, Queenstown

7. Imaging Excitable Cells

Chair: Ruth Empson

3.30 pm	7.1	**Thomas Knöpfel,** ***Knöpfel laboratory for Neuronal Circuit Dynamics, RIKEN BSI, Japan*** An optogenetic approach to voltage imaging
4.15 pm	7.2	**Christian Soeller,** ***University of Auckland, New Zealand*** Imaging cardiac ventricular myocytes – functional and structural aspects of contractile failure
4.40 pm	7.3	**Peter Jones,** ***University of Otago, New Zealand*** From dyes to proteins, imaging subcellular calcium events
5.05pm	7.4	**Peter Freestone,** ***University of Auckland, New Zealand*** Imaging techniques for neurotoxicity investigations

Tuesday 28 August
Evening Session

6.00 pm — Afternoon Tea Available

8. Disorders of the Nervous System: I

Chair: Cliff Abraham

6.30 pm	8.1	**Michael Pankhurst,** ***University of Otago, New Zealand*** Hormones in autism: The other side of the testes
6.45 pm	8.2	**Thomas Chen,** ***University of Auckland, New Zealand*** Human stroke patients develop autoantibodies to NR1 subunit of NMDA receptors
7.00 pm	8.3	**Nadia Mitchell,** ***Lincoln University, New Zealand*** Viral vector gene therapy for CLN5 and CLN6 batten disease in ovine models
7.15 pm	8.4	**Anthony White,** ***University of Melbourne, Australia*** Novel neuroprotective actions of biometal-complexes
7.30 pm	8.5	**Charlotte Thynne,** ***University of Auckland, New Zealand*** Autism associated mutations in ProSAP2/Shank3 impair synaptic transmission and neurexin-neurologin mediated transynatpic signaling

Wednesday 29 August
Morning Session

8.00 am		Light Breakfast Available

9. Disorders of the Nervous System: II

Chair: Stephanie Hughes

9.00 am	9.1	**Dorothy Oorschot,** ***University of Otago, New Zealand*** Spectrum of short- and long-term brain pathology and long-term behavioural deficits in male repeated hypoxic rats closely resembling human extreme prematurity
9.15 am	9.2	**Yu Jing,** ***University of Otago, New Zealand*** Pre-aggregated Amyloid Beta25-35 leads to prolonged alteration of arginine metabolism in the rat hippocampus and prefrontal cortex
9.30 am	9.3	**Jian Guan,** ***Liggins Institute, New Zealand*** Vascular degeneration of Parkinson disease
9.45 am	9.4	**Kevin Lee,** ***University of Auckland, New Zealand*** Molecular characterization of inhibitory synapses in autism related ProSAP2/Shank3 mutation
10.00 am	9.5	**Simran Maggo,** ***University of Otago, New Zealand*** The effects of chronic statin administration: Assessment of hippocampal spatial memory and long term potentiation in area CA1
10.15 am		Tea/Coffee break

Wednesday 29 August
Morning Session

10. Cognition and Behaviour

Chair: Paul Corballis

10.30 am	10.1	**Ian Kirk,** ***University of Auckland, New Zealand*** Theta-gating during a Sternberg working memory task
10.45 am	10.2	**Andrew Latham,** ***University of Auckland, New Zealand*** Speeded visual evoked potentials may reflect possible temporal underpinning of enhanced visuospatial performance in expert video game players.
11.00 am	10.3	**Karen Waldie,** ***University of Auckland, New Zealand*** The Catechol-O-methyltransferase (COMT) Val158Met polymorphism moderates the effect of antenatal stress on childhood behavioural problems
11.15 am		Closing Remarks
11.30 am		Light lunch and Student Prize Presentation - Copthorne Hotel

Acknowledgements

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2011	**Kajsa Igelstrom,** University of Otago, New Zealand
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ABSTRACTS

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ABSTRACTS

1.1

Distinct neurogenic stem cell populations in the hippocampus: How are they regulated and what are their functions?

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The production of new neurons in the hippocampus is thought to underpin aspects of learning and memory. Defining how neurogenesis is regulated is central to our understanding of the learning process and to the future development of neurogenic-based therapeutics aimed at ameliorating cognitive loss.Recently, we identified a large precursor pool in the dentate gyrus of the mouse hippocampus, including a small number of true stem cells, which is normally dormant but can be activated by depolarizing levels of K+ to produce large numbers of neurogenic neurospheres. *In situ* stimulation of the perforant pathway also activates this precursor population and leads to an increase in newly born neurons. Importantly, this population can be activated in the aged mouse, uncovering the potential for significant neurogenesis in the ageing brain.Further, synaptic activity stimulates precursor activity through the release of a number of soluble factors and the neurotransmitter, norepinephrine (NE). These factors act directly on the precursors with NE activating through a novel adreno-receptor pathway. Interestingly, different stimuli led to the activation of different pools of precursors and stem cells, suggesting production of hippocampal neurons in the dentate gyrus with distinct properties reflective of a specific stimulation process. This provides a mechanism by which the functional capacity and the number of newly generated neurons can be directly influenced by the type and complexity of environmental stimuli.

1.2

Neurons derived from human embryonic stem cells extend long–distance axonal projections through growth along host white matter tracts after intra-cerebral transplantation

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Human pluripotent stem cells have the capacity for directed differentiation into a wide variety of neuronal subtypes that may be useful for brain repair. While a substantial body of research has lead to a detailed understanding of the ability of neurons in fetal tissue grafts to structurally and functionally integrate after intra-cerebral transplantation, we are only just beginning to understand the *in vivo* properties of neurons derived from human pluripotent stem cells. Here we have utilised the human embryonic stem (ES) cell line *Envy*, which constitutively expresses green fluorescent protein (GFP), in order to study the *in vivo* properties of neurons derived from human ES cells. Rapid and efficient neural induction, followed by differentiation as neurospheres resulted in a GFP+ neural precursor population with traits of neuroepithelial and dorsal forebrain identity. Ten weeks after transplantation into neonatal rats, GFP+ fibre patterns revealed extensive axonal growth in the host brain, particularly along host white matter tracts, although innervation of adjacent nuclei was limited. The grafts were composed of a mix of neural cell types including differentiated neurons and glia, but also dividing neural progenitors and migrating neuroblasts, indicating an incomplete state of maturation at 10 weeks. This was reflected in patch-clamp recordings showing stereotypical properties appropriate for mature functional neurons, including the ability to generate action potentials, as well profiles consistent for more immature neurons. These findings illustrate the intrinsic capacity for neurons derived from human ES cells to integrate at a structural and functional level following transplantation.

1.3

Non-viral generation of neural precursor-like cells from adult human fibroblasts

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Recent studies have reported direct reprogramming of human fibroblasts to mature neurons by the introduction of defined neural genes. This technology has potential use in the areas of neurological disease modeling and drug development. However, use of induced neurons for large-scale drug screening and cell-based replacement strategies is limited due to their inability to expand once reprogrammed. We propose it would be more desirable to induce expandable neural precursor cells directly from human fibroblasts. To date several pluripotent and neural transcription factors have been shown to be capable of converting mouse fibroblasts to neural stem/precursor-like cells when delivered by viral vectors. Here we extend these findings and demonstrate that transient ectopic insertion of the transcription factors Sox2 and Pax6 to adult human fibroblasts through use of non-viral plasmid transfection or protein transduction allows the generation of induced neural precursor (iNP) colonies expressing a range of neural stem and pro-neural genes. Upon differentiation, iNP cells give rise to neurons exhibiting typical neuronal morphologies and expressing multiple neuronal markers including tyrosine hydroxylase and $GAD_{65/67}$. Importantly, iNP-derived neurons demonstrate electrophysiological properties of functionally mature neurons with the capacity to generate action potentials. In addition, iNP cells are capable of differentiating into glial fibrillary acidic protein (GFAP) -expressing astrocytes. This study represents a novel virus-free approach for direct reprogramming of human fibroblasts to a neural precursor fate.

1.4

Coding olfaction

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Each olfactory sensory neuron in mouse chooses one of 1,200 odorant receptor genes for expression. Odorant receptor genes are chosen for expression by greatly varying numbers of neurons. The mechanisms that regulate the probability of odorant receptor gene choice remain unclear. We have applied the NanoString platform of fluorescent barcodes and digital readout to measure RNA levels of 577 mouse odorant receptor genes in a single reaction, with probes designed against coding sequences. In an inbred mouse strain with a targeted deletion in the P element (ΔP mice), we find that this element regulates odorant receptor gene choice differentially across its cluster of 24 odorant receptor genes. Importantly, the fold changes of NanoString counts in ΔP or ΔH mice (mice with a deletion in the H element) are in very close agreement with the fold changes of cell counts, determined by in situ hybridization. Thus, the P and H elements regulate the probability of odorant receptor gene choice, not odorant receptor transcript level per neuron.

2.1

Formalizing aberrant salience: Prediction error and delusions

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The salience hypothesis of psychosis rests on the simple but profound observation that subtle alterations in the way that we perceive and experience stimuli have important consequences for how important these stimuli become for us, how much they draw our attention, how they embed themselves in our memory and, ultimately, how they shape our beliefs. The original hypothesis went on to explore the putative neurobiology of incentive salience attribution and how excessive dopamine function in the striatum could lead to inappropriate salience attribution and ultimately to positive psychotic symptoms.

Whilst the theory is appealing in its simplicity and elegance, empirical work related to the salience hypothesis paints a more complex picture. Specifically, dopamine is, of course not the only neurochemical mediator of salience attribution, the basal ganglia are not the only site of salience processing and salience itself can be parsed into numerous sub-processes. Whilst the cognitive neuropsychiatry of delusions is much indebted to the aberrant salience hypothesis, the devil is in the details. This talk will focus on one alternate view of the neurochemistry, neurobiology and phenomenology of psychosis related to but different from salience attribution; this view focuses on prediction error.

Prediction error represents the mismatch between what we expect in a given context and what we actually experience. Normally this mismatch acts as a teaching signal for belief updating. However, if prediction error is registered inappropriately, attention is driven toward irrelevant stimuli, thoughts, and percepts; and delusions are constructed to explain away such unpredictable experiences. The empirical data in favor of this hypothesis will be presented. Furthermore, novel predictions related to this aspect of aberrant salience processing will be outlined, and data pertaining to these predictions will be discussed. Crucially, key aspects of delusions hitherto unaddressed by aberrant salience; the fixity and elasticity of delusions in the face of contradictory evidence will be addressed.

2.2

P50 sensory gating and schizotypal personality

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Sensory gating is the ability to filter out, or 'gate', irrelevant stimuli from the environment. Individuals with schizophrenia consistently demonstrate deficits in this ability leading to sensory overload and cognitive fragmentation. Recently, a dysfunction in sensory gating has also been found in those with schizotypy. Schizotypy is defined as a manifestation of subclinical symptoms and personality traits which are qualitatively similar to those found in schizophrenia. Sensory gating may 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. In the present study, we used this paradigm to test seven schizotypic individuals and ten control participants. We found a robust suppression of the P50 wave following the second click in the control group, indicating an intact sensory gating mechanism. In contrast, this attenuation of the second P50 wave was reduced in those with schizotypy, consistent with previous research showing an association between poor P50 suppression and schizotypal traits. These data suggest that schizotypic individuals may have early sensory gating deficits similar to schizophrenia patients. As they do not exhibit overt psychotic symptoms, it is likely that such deficits represent an underlying core cognitive dysfunction within the schizophrenia spectrum. This may indicate a vulnerability to schizophrenia at a later date.

2.3

Competition for representation as a window into the functional architecture of extrastriate visual cortex

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The ventral stream of the extrastriate visual system has been long been associated with the representation and recognition of objects. Neurons in this stream have large receptive fields, but only appear to be able to encode the properties of a single object at a time. When multiple objects fall into a single receptive field there appears to be "competition" between objects to control the response of the neuron. Desimone and Duncan (*Ann. Rev. Neurosci.*, 1995) have suggested that this competition and its resolution may be the basis for visual selective attention. I will present evidence for competition for representation from a series of event-related potential (ERP) studies. Visual stimuli – images of faces, houses, trees, shoes, butterflies, words, or letter strings – were presented on a monitor flanked by context stimuli that were either members of the same category, members of a different category, or phase-scrambled control images. In each case the amplitude of the N1 component of the ERP was attenuated when the flanking stimuli were drawn from the same category as the critical stimulus compared to either different-category or phase-scrambled context stimuli. These results are consistent with the suggestion that stimuli from the same perceptual category compete with one another for representation, but not (or less so) with stimuli from other categories. Competition for representation – manifested in the amplitude modulation of the N1 and possibly other ERP components – offers a simple and potentially powerful new paradigm to explore the functional architecture of the human extrastriate visual system.

2.4

Thalamo-cortical circuitry in mild cognitive impairment and dementia in Parkinson's disease – combined diffusion tensor and fiber tractography study

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Due to reciprocal connectivity with areas of the neocortex known to affect cognition, the thalamus is a likely neurocorrelate of cognitive dysfunction in Parkinson's disease (PD). Diffusion tensor imaging (DTI) was used to investigate microstructural degeneration in segmented thalamic nuclei in 84 Parkinson's disease patients – 51 classified as having normal cognition (PD-N), 18 with mild cognitive impairment (PD-MCI) and 15 with dementia (PD-D) - compared to 24 healthy age and education-matched controls. The lateral dorsal (LD) and mediodorsal (MD) nuclei show altered microstructure in PD-MCI relative to control and PD-N groups. In PD-D, all nuclei showed disruptions relative to controls with alterations also evident relative to PD-N in all nuclei except those affiliated with motor dysfunction. The thalamo-cortical fiber tracts originating from these regions remained intact in the PD-MCI group and only tracts originating from the LD and MD were altered in PD-D. In PD participants, after excluding the influence of age, education and UPDRS motor score, DTI parameters of the LD were associated with cognition beyond the expected relationship with learning and memory; LD parameters were also significantly associated with attention, visuospatial/perception and an aggregate global score, but not executive function. Diffusion parameters of MD were associated with learning and memory dysfunction only. There was no association between integrity of the fiber tracts and any aspect of cognition. The microstructure of the thalamic nuclei rather than the thalamo-cortical connectivity influences cognitive dysfunction in Parkinson's disease.

3.1

Neuropeptides and reward seeking

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For over 15 years one of the interests of my laboratory has been examining the role that neuropeptides play in natural and drug rewards, including relapse. We established that isolation rearing of rats resulted in a CRF-driven anxiety phenotype that facilitated high ethanol consumption. Subsequent molecular studies suggested the effect was likely mediated via modulation of dopamine D2 receptors throughout the extended amygdala. CRF has also been implicated in relapse, particularly that elicited by stressors. By using viral knockdown of CRF1 receptor expression in mice, we have identified that CRF1 receptor signalling in the ventral tegmental area regulates relapse to cocaine-seeking, but not cocaine self-administration. We were the first to demonstrate a role for orexins in both alcohol consumption and cue-induced reinstatement of alcohol-seeking. These effects were specific, and we demonstrated a differential effect of orexin1 receptor antagonism on the motivational strength of ethanol compared to sucrose. Moreover, in a model of reinstatement following extended abstinence, we also found evidence for a role of orexin1 receptors in this behaviour. Fos studies suggested that the prelimbic and orbitofrontal cortices were potential loci where ascending orexinergic input could modulate relapse-like behaviour. Subsequent microinjections confirmed that antagonism of orexin1 receptors in the prelimbic cortex can dramatically attenuate ethanol-seeking, with no effect on sucrose-seeking. In contrast to the orexin1 receptor system, which is implicated in both ethanol-seeking and consumption, our studies to date on the orexin2 receptor suggest a role in ethanol consumption but not ethanol-seeking. Collectively, these data provide strong evidence that orexins are implicated in both appetitive and consummatory drives for rewards.

3.2

Tonic D2-dopamine receptor-mediated autoinhibition prevents amplification of reward-related cue responses by methylphenidate in normal rats

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Methylphenidate (Ritalin) is a dopamine transporter (DAT) blocker used in the treatment of attention deficit hyperactivity disorder. There are contrasting theories of the effect DAT blockers have on task-related dopamine release as part of their therapeutic action. Some suggest DAT will amplify phasically released dopamine, to correct a presumed deficit in such signalling in ADHD children (Levy (1991) Aust NZ J Psychiat 25:277-283). However, others propose that increased tonic levels of dopamine would suppress phasic dopamine responses, through autoinhibition via presynaptic dopamine D2 autoreceptors (Seeman & Madras (2002) Behav Brain Res 130:79-83). To investigate this, we monitored striatal dopamine using fast scan voltammetry in free-moving Wistar rats performing a conditioned approach task in which an auditory cue predicted delivery of sweetened water reward. Rats received either saline, methylphenidate (5 mg/kg, i.p.), the selective dopamine D2 antagonist raclopride (0.3 mg/kg), or methylphenidate plus raclopride prior to task performance. Results showed clear phasic dopamine responses to reward-predicting cue onset in saline treated animals. Methylphenidate treatment did not enhance the release, and raclopride alone had no effect. However, co-administration of raclopride and methylphenidate produced a very large increase in amplitude of the dopamine response (significant Time x Treatment interaction ($F_{6,32}$ = 6.85, $p < 0.0001$), significantly larger than the response following all other treatments ($p < 0.001$ all contrasts, Bonferroni post-hoc tests). These data support the autoinhibition hypothesis, in rats with normal behavioural phenotype. Further work is addressing whether this is different in an animal model of ADHD.

Supported by the Marsden Fund and the Health Research Council of New Zealand.

3.3

The role of serotonin in the acquisition of MDMA self-administration

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Our previous studies have shown that the acquisition of MDMA self-administration is relatively slow and a larger number of rats fail to meet acquisition criteria compared to other drugs of abuse. During the initial sessions, only a small number (1-2) of infusions are self-administered. With repeated testing, however, there is an escalation of intake over days and eventually some rats self-administer 20-30 mg/kg/day during 2 or 6 hr test sessions. We have suggested that the preferential effects of MDMA to increase synaptic serotonin (5HT) initially limit its self-administration. Experiment 1 measured MDMA-produced extracellular levels of 5HT and dopamine (DA) in the nucleus accumbens (NAc), prior to the commencement of MDMA self-administration. Of the 18 rats tested, 10 met the criterion for the acquisition of MDMA self-administration. The initial MDMA-produced 5HT response was lower for rats that acquired MDMA self-administration but there was no difference in the DA response. Experiment 2 experimentally examined the role of 5HT in the acquisition of MDMA self-administration by determining the effects of neurotoxic 5,7 DHT lesions on the acquisition of MDMA self-administration. Intracerebroventricular administration of 5,7 DHT produced a 65% decrease in tissue levels of 5HT in a number of brain sites. Acquisition of MDMA self-administration in control rats proceeded with a protracted time course and about half the rats failed to acquire self-administration within a 25 day cut-off period. The lesioned rats, however, acquired self-administration more rapidly and all of the rats met the criterion for self-administration. These data support the idea that MDMA self-administration is, at least initially, limited by 5HT effects.

3.4

Effects of baseline training dose on the discrimination of saline versus 3,4-methylenedioxy-N-methylamphetamine (MDMA)

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At relatively low doses (less than 3mg/kg) acute 3,4-methylenedioxy-N-methylamphetamine (MDMA) produces relatively greater enhancement of serotonin activity compared to dopamine activity across a range of brain regions. Previous evidence using the Drug Discrimination procedure suggests that at doses high enough to produce significant elevation in extracellular levels of dopamine (greater than 1.5mg/kg) MDMA is subjectively experienced as being more 'amphetamine-like' than 'MDMA-like' by rats. In the current study we examined whether the baseline training dose of MDMA is an important variable in determining the subsequent subjective experience of MDMA. Using a 2-way Drug Discrimination paradigm rats were either initially trained to discriminate 1.5mg/kg i.p. MDMA vs. saline or 3.0mg/kg i.p MDMA vs. saline. Both groups were able to reliably discriminate between MDMA and saline during initial training. Contrary to expectations, however, neither group generalised to novel untrained dopamine agonists (*d*-amphetamine and SKF81297). Similarly, the D1 antagonist (SCH23390) had little effect on discrimination performance. These results are consistent with the possibility that the tendency to generalise from MDMA to other dopamine agonists is not an automatic product of being exposed to high doses of MDMA, and is possibly reliant on prior experience with those dopamine agonists themselves.

4.1

Investigating the mechanisms of action discovery

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The timing between an action and a sensory event is critical for discovering which of our actions caused a specific event to occur. In our experiments we are investigating this 'action discovery' by measuring the effects of a light stimulus on learning and associated synaptic plasticity. We have developed a behavioural paradigm where a rat discovers the movements of a joystick required to locate a hidden target, to activate a light stimulus followed by electrical brain stimulation reward (BSR). By 'switching' the target location during a session we can measure learning during action discovery. Behaviour during acquisition, switching and extinction were similar whether the light was reinforced by food or BSR, although the time to achieve each learning milestone was shorter with BSR, probably through lack of satiation. In order to investigate the synaptic plasticity that might underlie this learning, we made extracellular recordings from neurons in the striatum, an area specialised for reinforcement learning. Under urethane anaesthesia, we measured the effect of delivering a light flash on the efficacy of inputs from the cerebral cortex, after first rendering the light flash 'salient' by disinhibiting the superior colliculus with a local bicuculline injection. We found that corticostriatal responses were only potentiated when the light flash followed the cortical input within 1 second, with no net synaptic change induced when the light was delayed by 2 seconds or preceded the cortical input. Thus, corticostriatal plasticity *in vivo* occurs within a behaviourally-relevant time scale when reinforcement is provided by a normal sensory stimulus. Ongoing work will test the correlation between plasticity and measures of action discovery.

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4.2

Reinforcement of visual responses in the superior colliculus is dependent on timing and dopamine

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The response to visual stimulation in brain sensory areas is only maintained if the stimulation becomes 'salient' (ie, behaviourally significant), e.g., by association with reward. Without reinforcement, responses quickly habituate. The deep layer of the superior colliculus (SC), which relays sensory signals to dopaminergic neurons in the substantia nigra (SN) and glutamatergic neurons in the thalamus, is a candidate brain structure for forming visual stimulus-reward associations.

We tested whether rewarding stimuli can potentiate visual responses in the rat. Under urethane anaesthesia, light flashes were applied to the contralateral eye and visual-evoked potentials (VEPs) measured within the SC. Rewards consisted of SN stimulus trains known to induce dopamine release. We found that rewarding stimulation paired 1 sec after each light flash (0.1 Hz for 10 min) induced a new VEP component (mean amplitude ± SD: 81.2 ± 46 μV; n = 15) that persisted for 10 min after SN stimulation. This new sensory responsiveness was greatly reduced when SN stimulation preceded the light flash by 3 s (14.8 ± 18.2 μV; n = 6), 1.0 - 1.5 s (15.3 ± 44.2 μV; n = 12) or followed it by 3 s (16.9 ± 41.5 μV; n = 12), suggesting that reinforcement of visual signals is dependent on stimulus-reward timing. Enhanced visual responsiveness was attenuated following local injection of SCH23390, a dopamine D1/D5 receptor antagonist, before pairing.

These data indicate that pairing rewarding stimulation with a visual stimulus within behaviourally relevant timing can activate dopamine-dependent sensory reinforcement mechanisms within the SC, thereby rendering previously neutral or habituated stimuli as salient.

Supported by the RSNZ Marsden Fund.

4.3

Expression of a galactose-containing membrane-associated glycoconjugate by physiologically-characterised primary sensory neurones in the rat

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Previous work in our laboratory has led to the suggestion that binding sites for the plant lectin *Bandeiraea simplicifolia* isolectin B4 (IB4) are expressed by nociceptive primary sensory neurones. IB4 has a high affinity for galactose and because binding sites for this lectin are expressed by the plasma membrane and Golgi apparatus of neurones it has been proposed that a galactose-containing membrane-associated glycoconjugate may be selectively expressed by nociceptors. However there is some debate regarding the classes of nociceptors that express this glycoconjugate. In order to help resolve this, we have screened different functional classes of primary sensory neurones for IB4 binding in the rat. Intracellular recordings were made from neurones in the sacral dorsal root ganglia of deeply-anaesthetised rats. Following physiological-characterisation, selected cells were labelled with neurobiotin. These cells were subsequently visualised in histological sections using a rhodamine-avidin conjugate and the presence of lectin binding determined using an IB4-fluorescein conjugate. To date a total of 27 primary sensory neurones were intracellularly stained and 19 of these were subsequently recovered and screened for IB4 binding. Of these, 14 were low threshold muscle or cutaneous sensory neurones and none of them expressed IB4 binding sites. The remaining five cells were activated by high intensity mechanical, thermal and chemical stimuli and had conduction velocities of 0.5 - 2.0 $m.sec^{-1}$. All 5 cells of this class of neurone were found to bind the lectin IB4. Collectively these findings suggest that a galactose-containing membrane-associated glycoconjugate may be selectively expressed by nociceptive primary sensory neurones in the rat.

4.4

Unilateral high-frequency electrical nerve stimulation facilitates H-reflex transmission bilaterally: A threshold tracking study

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The H-reflex is commonly used to examine the excitability of spinal circuitry. Conventional techniques measure the reflex amplitude evoked by a fixed stimulus, and interpret amplitude changes to reflect alteration in spinal excitability. However, such interpretation is over-simplistic because the H-reflex is influenced by changes in the recruitment gain of the motoneuron pool and intrinsic motoneuronal properties. These confounding factors can be minimised by using the "threshold tracking" technique which measures the stimulus current required to produce a fixed reflex amplitude and ensures that the reflex response involves a constant population of α-motoneurons. Therefore, the change in threshold becomes a surrogate marker for the level of synaptic drive to the motoneuron pool. The aim of the study was to investigate the effects of high-frequency (100-Hz) tibial nerve stimulation on soleus H-reflex transmission using threshold tracking. Stimulus-response curves and threshold intensity needed to generate an H-reflex of 10% Mmax were recorded bilaterally in 10 healthy adults (mean age of 30.1±4.5 yrs) before and after unilateral tibial nerve stimulation via a portable TENS unit (Neurotrac™) at 2sec on/off duty cycle. Thirty minutes of stimulation increased the maximal H-reflex amplitude and H/M ratio in the stimulated leg ($p=0.031$ and 0.049 respectively). Mmax remained unchanged. H-reflex threshold decreased by 20% in the stimulated leg ($p=0.026$) and 24% in the non-stimulated leg ($p=0.011$). Our results demonstrated that high-frequency electrical stimulation can increase α-motoneuron excitability and enhance synaptic drive to the motoneuron pool. High-frequency stimulation may be used to reverse maladaptive spinal plasticity that occurs following CNS injury.

4.5

Non-decussating portions of the corticospinal tract are not involved in stability-dependent modulation of the long latency stretch reflex

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When operating in the physical world, the posture and stability of our body and limbs are continuously regulated by our central nervous system to compensate for variation or instability in the environment. As humans, the most rapid neurophysiological mechanism we have available to stabilise limb posture is the stretch reflex. While decussating corticospinal tract neurons have been implicated in the regulation of stabilising stretch reflex responses, it remains unclear whether non-decussating fibres also contribute. We used transcranial magnetic stimulation (TMS) to suppress each primary motor cortex while stretch reflexes were elicited in a wrist extensor muscle with the wrist in stable and unstable mechanical environments. The amplitude of the transcortical portion of the stretch reflex was significantly decreased in both mechanical environments by TMS applied over the motor cortex contralateral to the target arm (-23%, $p = 0.025$) but not altered by TMS applied over the ipsilateral motor cortex ($p > 0.05$). These results indicate that, in a healthy nervous system, rapid muscular responses designed to maintain postural stability in the upper arm are regulated by supraspinal circuits contralateral, but not ipsilateral, to the destabilised limb.

Supported by the NZ Neurological Foundation.

4.6

Diversity of layer 5 projection neurons in mouse motor cortex

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In the primary motor cortex (M1), layer 5 projection neurons (PNs) signal directly to distant motor structures to drive movement. Distinct PN types have been described in sensory cortices but surprisingly little is known about the diversity of M1 PN types. Here, we compare the electrophysiological and morphological properties of corticospinal, corticothalamic, corticostriatal and corticocallosal PNs in mouse M1. PNs were retrogradely identified by stereotaxic injection of Alexa647-tagged cholera toxin into the lumbar spinal cord, ventrolateral thalamic nucleus, contralateral striatum or contralateral M1, respectively. After 3 to 12 days (postnatal day 22-32) labelled PNs were visually targeted for whole-cell recording in vitro, and filled with biocytin for subsequent morphological reconstruction. Input resistance, firing threshold, action potential decay, hyperpolarisation-induced inward rectification and dendritic tuft size of commisural corticostriatal (n=16) and corticocallosal (n=16) PNs were similar (all $P>0.05$, one-way ANOVA, Tukey's post-hoc analysis) except for higher spike frequency adaptation and smaller action potential amplitude and rate of rise in corticostriatal PNs (all $P<0.05$). Compared with commisural neuron types, corticospinal (n=11) and corticothalamic neurons (n=16) exhibited lower input resistance, lower spike frequency adaptation, prominent hyperpolarisation-induced inward rectification and larger dendritic tufts (all $P<0.05$). Action potentials in corticothalamic PNs overall had the fastest kinetics, and a higher threshold compared with cortiospinal PNs (all $P<0.05$) and mostly fired as doublets. An unsupervised cluster analysis of all parameters from the 59 PNs verified a separation of four phenotypes based on projection identity. In conclusion, we identified four distinct PN phenotypes within layer 5 PNs of M1 each specialized to communicate unique information to their downstream motor structures.

Poster 5.1

Developmental changes in expression of KCC2 and NKCC1 in normal and hypoxic-schemic neonatal piglet brain

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Background: In the neonatal brain over activation of excitatory neurotransmitter systems secondary to hypoxic ischaemia (HI) causes significant neuronal cell damage and seizure generation. These neurotransmitter systems include (but are not limited to) the GABA receptor, and the chloride (Cl-) co-transporters NKCC1 and KCC2 The principle function of the GABA system is inhibition in the adult brain whilst in the neonatal brain GABA provides much of the excitatory drive. It is thought that during early postnatal development changes in NKCC1 and KCC2 expression drive the switch in function of the GABA system from excitation to inhibition through regulation of the intracellular concentration of Cl-. Thus administration of GABA enhancing drugs (antiepileptic), that in adult brain promote inhibition, may in neonates potentially worsen HI brain injury.

Object:To characterise the normal developmental expression of NKCC1 and KCC2 in 4 cortical brain regions of neonatal piglets around the time of birth. To compare expression of NKCC1 and KCC2 in neonatal piglets following a hypoxic ischemic insult.

Methods: For the developmental expression studies piglets were obtained at several gestational time-points (Premature -23, -17, -14, -10, birth and one week old) by caesarean section or spontaneous vaginal delivery. For the HI experiments newborn piglets were placed through our established HI animal model. Brain tissues from all 4 cortical regions were collected and prepared for Western Blotting. KCC2 and NKCC1 protein expression was assessed using specific antibodies and visualised in different brain regions using ECL and measured by densitometry.

Result and Conclusion: There were clear temporal and regional differences in developmental expression of KCC2 compared with relatively stable expression of NKCC1 in all cortices. There was marked upregulation of KCC2 around birth which may constitute the 'switch' in GABAA function; this was different between regions. Changes in expression of the KCC2 and to a lesser extent the NKCC1 co-transporter may play an important role in HI brain injury and seizures.

Poster 5.2

Ndfip1 regulates neuronal development and function via the MAP-kinase pathway

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Receptor tyrosine kinase (RTK) signalling pathways are vital for neuronal development and function. In this study, we demonstrate that ubiquitination pathways involving the Nedd4 E3 ligase are important for transmitting growth factor receptor signaling. This process is mediated by Ndfip1, an adaptor and activator of Nedd4 function. Specifically, Ndfip1 regulates Sprouty 2 (Spry2) by ubiquitination leading to reduction of Spry2 and consequently increasing pErk following EGF receptor activation. In the developing cortex, Spry2 is co-expressed with Ndfip1 in similar cells; and deletion of Ndfip1 results in Spry2 upregulation in these cells. Conversely, over-expression of Ndfip1 in a neuronal cell line (SY5Y cells) results in reduction of Spry2, suggesting that Ndfip1 can regulate Spry2 levels. These results point to Ndfip1/Nedd4 ubiquitination as an important mechanism for gating pErk signaling in the EGF-R pathway.

Poster 5.3

Does the schizophrenia-inducing cytokine IL-6 alter neurite outgrowth in the developing brain?

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Maternal infection during pregnancy is a risk factor for schizophrenia. Maternal immune activation (MIA) in rodent models causes up-regulation of cytokines that can access the fetus, leading to schizophrenia-like behaviours in adult offspring. Pro-inflammatory cytokines, especially Interleukin-6 (IL-6), are strongly implicated in development of this schizophrenic phenotype, however little is known about what effect cytokines may be having in the brain during development. The growth of neurites and formation of neuronal connections are essential for development of functional neural circuits in the brain. Therefore, the present study aimed to investigate the effect of IL-6 on neurite outgrowth in the developing hippocampus. Explants of hippocampal tissue were obtained from gestational day 17.5 (GD17.5) and postnatal day 0 (P0) mice, and plated in a 3D collagen gel containing either 10 ng/ml IL-6 or vehicle (phosphate-buffered saline). The plated explants were incubated for 24 or 48 hours, then fixed and stained with the neuron-specific antibody TuJ1. Images were obtained using confocal microscopy and analyzed using computer software ImageJ. A ratio of outgrowth was calculated using number of pixels outside the explant divided by number of pixels inside the explant. At P0, outgrowth of IL-6 treated explants (n = 6) was 95.9% of control outgrowth (n = 5) at 24 hours, however at 48 hours outgrowth in the treated group (n = 21) was significantly reduced to 35.3% of control outgrowth (n = 15, $P < 0.05$, Student's *t*-test). At GD17.5, outgrowth of IL-6 treated explants was not significantly different from controls at either 24 or 48 hours. These results suggest that exposure to elevated IL-6 found in MIA can disrupt hippocampal wiring, forming a mechanism for schizophrenia risk in offspring.

Poster 5.4

Progenitor cells in the thalamostriate subventricular zone of the adult human brain

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Although it was long thought that no new neurons were born after development, it has recently been found that the adult human brain harbours progenitor cells in the subventricular zone (SVZ) and hippocampus, and that these early cells are able to differentiate into functioning new neurons and glia. In humans, most studies have examined the rostral SVZ over the caudate nucleus (CN). However, it has been alluded to by some researchers that there is a substantial increase in thickness of the SVZ caudal to the CN. The present study aimed to map out the boundaries of the large thickening of the SVZ in the caudal part of the ventral lateral ventricle, namely in the thalamostriate region (tsSVZ). Immunohistochemistry was performed on 50-µm-thick serial section in five formalin-fixed human brains, using proliferating nuclear cell antigen (PCNA) a marker of proliferating progenitor cells. In the sagittal plane, the tsSVZ, centred around the dip between the CN and thalamus, began to thicken at about 4.5 mm from midline, became most prominent at 9 mm from midline, and tapered off at 11.5 mm from midline. At the thickest point it was nearly 40 times thicker than the normal human SVZ over the CN. Further analyses of the histological organisation of the cellular layers of the tsSVZ were performed using hematoxylin and eosin, and luxol fast blue staining. This study describes for the first time in detail, the massive enlargement of the SVZ in the caudal region between the CN and thalamus of the human brain, and may represent a large reservoir of progenitor cells destined for neurogenesis.

Poster 5.5

Therapeutic-like properties of the trace amine-associated receptor 1 partial agonist, RO5203648, in animal models of methamphetamine abuse

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The abuse of stimulant drugs, such as methamphetamine (METH), has become a major source of public concern in New Zealand. Specific medications for treating METH addiction are not available at present. The newly discovered trace amine-associated receptor 1 (TAAR1) constitutes a novel receptor target for medication development in neuropsychiatry. TAAR1 regulates monoamine systems in the brain, especially dopamine, and is activated directly by psychomotor stimulants, including METH. We examined the effects of the newly developed TAAR1 partial agonist, RO5203648, in rat models of METH abuse. In experiment 1 rats were administered different doses of RO5203648 (0, 1.67, 5mg/kg i.p.) followed by METH (0, 0.75, 2mg/kg i.p.). Locomotor activity was monitored via automated video tracking system in an open field. The results revealed that RO5203648 dose-dependently reduced acute METH-induced stimulation and prevented long-term sensitization following chronic exposure. Paradoxically, RO5203648 potentiated METH-induced c-Fos protein expression in the nucleus accumbens. In experiment 2 rats were trained to consistently self-administer METH (0.5mg/kg/infusion) and were then pre-treated with RO5203648 (0, 3, 10mg/kg i.p.). The data showed that RO5203648 drastically reduced METH intake. We next substituted RO5203648 (0.25, 0.5, 1.0 mg/kg/infusion) for METH in the same paradigm. Remarkably, RO5203648 exhibited no reinforcing efficacy compared with METH. Taken together, these observations showed that RO5203648 is able to attenuate methamphetamine-related behaviours, including locomotor stimulation, sensitization and self-administration, and highlight the great potential of TAAR1-based medications for the treatment of METH addiction.

Poster 5.6

Electrical conductivity of mouse brain slices in seizing and non-seizing conditions

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There is a considerable literature on electrical conductivity of brain tissue in vivo. However, measuring *in vitro* causes difficulties because the tissue must be bathed in artificial cerebrospinal fluid (ACSF). We have successfully measured the electrical conductivity of mouse cortex *in vitro* using the method of van der Pauw [1] in seizing and non-seizing conditions. Mouse brain slices were prepared with standard procedures and placed in either normal ACSF or ACSF with all magnesium ions removed. The latter generates seizures in the slice; these were confirmed by monitoring the local field potential. Slices were removed from the ACSF, small (2mm square) sections of cortex were cut, and four silver-silver chloride electrodes were placed at the corners. These electrodes were connected to an Agilent E4980A impedance monitor. Excess ACSF was removed with filter paper. The conductivity of each sample was calculated based on measurements of injected current and potential difference between electrodes. The mean conductivity at 10 kHz of the non-seizing and seizing samples was 0.37 S/m and 0.33 S/m respectively. The distributions are statistically different (p=0.005 with a non-parametric t-test). Results suggest a link between electrical conductivity and seizure activity. We have not investigated the causes of these differences but explanations consistent with the literature are a change in chemical environment during seizure or a reduction in gap junction connectivity.

[1] Van der Pauw, L. J. (1958). A method of measuring specific resistivity and Hall effect of disks of arbitrary shape. *Philips Research Report, 12*(1):1-9

Poster 5.7

Mathematical modelling of pH as a mechanism affecting vasoreactive response

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Vasoreactivity is the change in radius of blood vessels to regulate the concentrations of oxygen and carbon dioxide in the tissue. Hypercapnic conditions are known to cause vessel dilation via a decrease in smooth muscle cell (SMC) calcium levels; however the precise mechanism by which this occurs has not been identified. We propose that changing pH levels in the blood and tissue are responsible for vessel radius changes. An existing SMC and endothelial cell (EC) coupled model was combined with an existing vessel wall model, creating a comprehensive tool for simulation of vasoreactivity. Experimental data was used to define a tissue pH dependency of the modelled SMC voltage operated calcium channel (VOCC). Simulations showed that this dependency caused a 2% change in vessel radius over the normal blood pH range of 7.35 to 7.45. This corresponds to around a 16% change in flow through the vessel. Following experimental findings, a blood pH dependency was also added to the EC non-selective cation channel. This dependency was simulated to determine the magnitude of the change in flux required to give a significant change in vessel radius. The change in flux required was found to be of a similar magnitude to the experimentally verified VOCC flux change, although the settling time was found to be longer due to the need for calcium to diffuse through to the SMC. These results indicate that pH could indeed be the mechanism by which blood flow is regulated in response to changes in breathing conditions.

Poster 5.8

Comparison of two gene regulation systems for use in gene therapy

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Constitutive transgene expression poses a problem for clinical applications of gene therapy because of potential side-effects from excessive levels of transgene protein. We developed two novel autoregulatory gene expression systems, which might allow for physiological regulation of transgene expression such that transgene expression is only produced when required. In this concept, transgene expression is driven by a regulatory protein (RP): either a transcription factor (ARF5), or a recombination enzyme (CRE). The RP is fused with a dominant nuclear export signal (NES) via a linker containing cleavage sites for caspase-3 or calpain, which are activated in response to apoptotic stimuli. Under basal conditions, NES restricts RP distribution to the cytosol; when caspase-3/calpain is activated, NES is cleaved from RP, allowing it to translocate to the nucleus to drive expression of the transgene. The aim of this study was to conduct an *in vitro* comparison of the functionality of the two regulatory systems under basal and cell stress conditions. HEK293 and Neuro2A cells were transfected with plasmids expressing a green fluorescent protein (GFP) reporter gene linked to the ARF5 or CRE regulation system, and expression of GFP assessed under basal conditions and following exposure to 20-40 nM okadaic acid, 0.3-1 M staurosporine or 48 h co-expression A35T mutant α–synuclein, agents that induce caspase-3/calpain activation. We observed up to a 5-fold increase in GFP fluorescence following neurotoxin exposure with the ARF5 system by Western blot analysis, but significantly lower GFP expression under basal conditions with the CRE compared to the ARF5 system. Current studies are investigating the application of this system for gene therapy of Huntington's disease.

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Poster 5.9

Direct generation of neural precursors from adult human fibroblasts using viral gene delivery

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Somatic cell reprogramming is an innovative field with considerable potential to enhance our understanding and treatment of a wide range of neurological disorders. We have recently demonstrated that adult human dermal fibroblasts (HDFs) can be directly converted to neural precursors in one step, by-passing an intermediate pluripotent embryonic stem cell stage. We have shown that induced neural precursors (iNPs) express a wide range of neural precursor and pro-neural genes and can be differentiated into mature, functional neurons expressing $GAD_{65/67}$ and tyrosine hydroxylase. For future clinical application this was achieved by over-expression of the transcription factors Sox2 and Pax6 using a non-viral transfection method. However, due to the low efficiency of cell transfection the current study aimed to optimize and assess the ability to directly generate neural precursors from adult HDFs using lentiviral transduction. Lentiviral vectors expressing Sox2-zsGreen (LV-Sox2-zsGreen) or Pax6-tdTomato (LV-Pax6-tdTomato) were constructed. Lentiviral transduction of HDFs was optimized and FACS analysis established that efficiency of lentiviral transduction (~40%) was higher than for non-viral transfection (~10%). Further, ~9.3% of HDFs exhibited co-expression of Sox2 and Pax6. Following co-transduction of adult HDFs with LV-Sox2-zsGreen and LV-Pax6-tdTomato, we observed an increase in the rate of iNP colony formation (~20 days) compared to the non-viral gene method (~65-85 days). PCR analysis confirmed high expression of Sox2 and Pax6 following transduction with no expression detected in control HDFs. We have also characterised the transcriptional profile of lentiviral-induced neural precursors. Our results suggest viral induction of neural precursor cells from adult HDFs is more efficient and potentially better suited for research purposes than non-viral methods.

Poster 5.10

The function of Ndfip1 in regulating PTEN ubiquitination and localization

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Background: Ubiquitination is a post-translational modification used to target proteins for either trafficking or degradation. E3 ligases conjugate ubiquitin following target recognition and binding. This targeting can be enhanced by adaptor proteins such as Ndfip1 that recruit Nedd4 E3 ligases. Recently we have shown that Ndfip1 plays an important role in the ubiquitination and translocation of PTEN, a well-known tumor suppressor protein with multiple roles including synapse development.

Methods: Interactions between Ndfip1 and PTEN, as well as PTEN and ubiquitin were investigated using Bimolecular Fluorescence Complementation (BiFC). This method is based on the complementation between fragments of the GFP protein Venus, which have been attached to target proteins. PTEN and Ndfip1 BiFC constructs and various subcellular markers were transfected into MEF cell lines. BiFC signals indicating protein interactions and protein ubiquitination were imaged using confocal microscopy.

Results: 1) Ubiquitinated PTEN has a different distribution pattern compared to PTEN in general, ubiquitinated PTEN was found to localize mainly in peri-nuclear and nuclear regions. 2) Ubiquitinated PTEN was found to co-localize with early endosomes (containing Rab5), recycling endosomes (containing Rab11), but not late endosomes (containing Rab7 and 9), indicating it may use the endosomes pathway to travel from plasma membrane to the nucleus. 3) Ndfip1 binds with PTEN in the cytoplasm, also co-localizing with early endosomes, recycling endosomes. 4) Ndfip1 promotes monoubiquitination of PTEN, which accumulates in the nucleus.

Conclusion: Using BiFC, we observed an interaction between Ndfip1 and PTEN that is associated with PTEN ubiquitination. Ubiquitinated PTEN was found to change subcellular location and distribution towards nuclear and peri-nuclear regions. These findings suggest that PTEN ubiquitination is a major regulator of PTEN subcellular localization, with major implications for PTEN function during development and disease.

Poster 5.11

Mechanisms of acute preconditioning with kainic acid in vitro: The role of extracellular calcium and Na^+K^+-ATPase

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At low concentrations, kainic acid (KA) has been shown to be an effective acute preconditioning agent against excitotoxic challenge *in vitro* (Hesp *et al*, 2004). The mechanism behind this protective effect is not yet known. The current study aimed to address two potential contributing factors: the presence of extracellular calcium during preconditioning induction and a change in Na^+K^+-ATPase activity following induction. In the first experiment, hippocampal slices were preconditioned for 30 min with 500nM KA in ACSF containing low (0.5mM), normal (2.5mM) or high (4mM) extracellular calcium and compared to untreated controls (normal ACSF only). Extracellular recording from CA1 neurons was then conducted during a 4µM KA excitotoxic challenge. Preconditioning in normal calcium conditions protected slices against the population spike suppression observed in controls ($p<0.05$ at t=20 min; n=7-8). This effect was not significantly altered by low or high calcium conditions ($p>0.05$ vs. normal calcium; n=7-8). For the second experiment, 6-8 hippocampal slices were preconditioned with 500nM KA or left untreated (controls). One slice was examined with electrophysiology, while the remaining slices were homogenized for Na^+K^+-ATPase activity assay. Extracellular recordings again showed that preconditioning was protective against a 4µM KA challenge ($p<0.05$ vs. control; n=11). In preconditioned slices, the Na^+K^+-ATPase activity was also significantly increased ($p<0.01$ vs. control; n=11). The current findings support the possibility that an increase in Na^+K^+-ATPase activity may contribute to ability of hippocampal neurons to resist a depolarizing insult by directly opposing the influx of positive charge. Further, the minimal effects of manipulating extracellular calcium, suggests that calcium influx is not essential for the induction of preconditioning protection.

Poster 5.12

Effect of aging and dementia on functional connectivity: Graph theoretical analysis of fMRI data

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Functional magnetic resonance imaging allows us to measure blood flow throughout the brain over time; from these measurements, we may infer neural activity, and gain insights into the functional connectivity of the brain: how different regions interact with each other over time. How can we analyse these interactions, and how do they change with age and onset of neurological disorders? Networks provide an ideal model to analyse functional connectivity; voxels are modeled as nodes in a network, and strong temporal correlations between voxels modeled as edges between nodes. We present results from such an analysis, comparing healthy young and aged subjects with subjects suffering from mild Alzheimer's diesase. We have found several differences between each of these three groups using various techniques and network measures. In particular, regionally specific declines of connectivity are present in subjects suffering from Alzheimer's disease and, perhaps counter-intuitively, increased areas of connectivity are found in healthy aged brains when compared with healthy young brains.

Poster 5.13

GYKI-52466 preconditioning salvages ischaemia-induced deficits in long-term potentiation in rat hippocampal CA1

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Global ischaemia during cardiac surgery, brain surgery and stroke frequently leads to lasting neuropsychological dysfunction including cognitive impairment. Here, we evaluated the efficacy of low-dose GYKI-52466 against ischaemia-induced reduction in long-term potentiation (LTP) in area CA1 of hippocampus. Male Sprague Dawley rats (26 days old, n = 8/group) were administered saline or GYKI-52466 (3 mg/kg, s.c.) 90 min before left common carotid artery ligation, and allowed to recover 2 hours prior to placement in a hypoxia chamber (1 hr; 8% O_2/92% N_2; 33±1°C). On days 14 and 90, contralateral, and where possible, ipsilateral hippocampal slices were prepared, and field potentials were recorded in balanced (2 mM Ca^{2+} and 2 mM Mg^{2+}) artificial cerebrospinal fluid at 31±1°C. Slices with >3 mV maximal population spikes and >1 mV field EPSPs were considered acceptable for LTP studies. In addition, a scoring scale was used to quantify the extent of brain injury on the ipsilateral hemisphere. On days 14 and 90, LTP was consistently induced in sham-operated controls in both contralateral and ipsilateral hippocampi. In contrast, LTP was significantly reduced ($p<0.05$) in the contralateral and completely abolished in ipsilateral hippocampi at 14 and 90 days ischaemia. In comparison, LTP was readily induced on both sides in ischemic animals preconditioned with GYKI-52466. A negative correlation ($p<0.05$) was observed between ipsilateral brain injury score and contralateral maximal population spike amplitude. This contralateral diaschisis was dependent on the magnitude of ipsilateral injury in our study. The present results indicate that prophylactic low-dose GYKI-52466 preserves LTP contralaterally, and more importantly, ipsilateral to ischaemic injury.

Poster 5.14

'Extra permeability' is required to model dynamic oxygen measurements: Evidence for functional recruitment?

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Neural activation triggers a rapid, focal increase in blood flow and thus oxygen delivery. Local oxygen consumption also increases, although not to the same extent as oxygen delivery. This 'uncoupling' enables a number of widely-used neuroimaging techniques, such as functional magnetic resonance imaging; however, the physiological mechanisms that govern oxygen transport under these conditions remain unclear. Here, we explore this dynamic process using a new mathematical model. Motivated by experimental observations and previous modelling, we hypothesised that *functional* recruitment of capillaries – where previously under-perfused vessels become rapidly perfused – plays an important role during neural activation. Using only conventional mechanisms, the model predictions were not consistent with *in vivo* measurements of oxygen partial pressure. However, dynamically increasing net capillary permeability, a simple description of functional recruitment, led to predictions consistent with the data. Increasing permeability in all vessel types had the same effect, but two alternative mechanisms were unable to produce predictions consistent with the data. These results are further evidence that conventional models of oxygen transport are not sufficient to predict dynamic experimental oxygen measurements. Our results suggest that it is necessary to include a mechanism which dynamically increases net vascular permeability. While the model cannot distinguish between the different possibilities, we speculate that functional recruitment could have this effect *in vivo*.

Poster 5.15

Sonic hedgehog administration stimulates oligodendrogenesis and functional recovery in young and aged mice after stroke

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The mechanisms of reorganization and repair after stroke are not well characterized. Recent evidence has shown that a number of processes involved in neuronal development are reactivated after a stroke. 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 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-impregnated biopolymer hydrogel was infused into the stroke cavity of young (3-month old) and aged (24-month old) C57Bl6 male mice and changes in oligodendrogenesis and functional recovery assessed out to 8-weeks post stroke. Shh triggered an increase in NG2+ oligodendocytes in both young and aged mice. This increase in oligodendrogenesis was blocked following co-administration of either PP2 or cyclopamine, blockers for the non-canonical and canonical pathways of Shh signaling. Shh administration also resulted in a significant improvement in functional recovery; both foot placement on the grid-walk and improved asymmetry on the cylinder; in both young and aged. These studies demonstrate that direct administration of Shh to the site of injury can overcome the reactive glial response and alter mechanisms associated with repair i.e., increased oligodendocyte response and improved recovery of function.

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Poster 5.16

Reversible Inactivation of primary neurons *in vitro*

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To study the function of specific neuronal subtypes in cell culture models or within the brain, technologies are needed that allow the silencing of subsets of cells within a population. Ideally, this would be reversible and in a cell-type and developmentally specific manner. The properties of ligand-gated ion channels are important in the modulation of neuronal excitability and function and are attractive targets for silencing cells. Here we use an ivermectin-gated chloride channel, delivered by a lentiviral vector, for cell silencing. To restrict expression, our constructs are expressed under the synapsin promoter, inverted and flanked by two sets of loxP sites, restricting the chloride channel to cells expressing Cre recombinase; mCherry serves as a transfection and transduction marker. We are currently testing the constructs in primary mouse neurons, with the aim to continue in transgenic Cre-expressing animal models. Our results show that mCherry and the chloride channel are expressed in a Cre-dependent manner in neurons. The functional verification of the constructs was assessed by monitoring the effects of ivermectin on gabazine-induced expression of the immediate early gene (IEG) Zif268. Treatment of cells expressing the ivermectin-sensitive receptor led to a decrease in gabazine-induced expression of the IEG Zif268, while ivermectin failed to decrease gabazine-induced Zif268 expression in cells expressing an ivermectin-insensitive variant of the receptor. This technique with its multiple layers of regulating the expression of the ivermectin-gated chloride channel will in future allow us to address not only questions of basic research *in vivo* but also its potential usefulness in gene therapy for disorders involving excitotoxicity.

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Poster 5.17

Modification of glutamate uptake influences the properties of the cerebellar parallel fibre to purkinje neuron synapse

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Glutamate uptake transporters of the excitatory amino acid transporter family (EAAT) are critical for controlling glutamate levels at synapses. Of the five mammalian EAATs, EAAT3 (EAAC1) and EAAT4 are found on Purkinje neurons (PNs) the sole output neurons of the cerebellar cortex, whilst EAAT1 (GLAST) and EAAT2 (GLT1) are on Bergmann glia, the most abundant cerebellar astrocyte. Mutations in EAAT1 accompany human episodic ataxia.

We used sagittal slices of mouse (25-28 days old) cerebellum to record PN excitatory postsynaptic current (EPSC) responses to single (1x) and high frequency (10x at 200 Hz) PF stimulation whilst inhibiting EAATs with DL-TBOA. We compared peak amplitudes of fast 1x EPSCs, paired pulse facilitation (PPF) and recovery time constants (tau) using paired t-tests, values are means ± sem.

High frequency PF stimulation increased EPSC tau from 31.1 ± 1.9 ms (1x) to 51.1 ± 5.6 ms (10x) $P < 0.01$, $n = 10$. 100 µM TBOA significantly and reversibly increased both 1x and 10x tau values, $P < 0.001$, $n = 6$ and the peak amplitude of fast 1x EPSCs, $P < 0.05$, $n = 6$, it also enhanced PN spike firing. 10 µM TBOA did not alter tau values, $P > 0.7$, $n=4$, or spike firing but increased the peak amplitude of fast 1x EPSCs from 318 ± 51 pA to 394 ± 59 pA $P < 0.05$, without influencing PPF, $P = 0.6$, both $n = 4$.

These results suggest that fast excitatory synaptic transmission at PFs needs rapid, high affinity glutamate uptake whereas a burst of high frequency PF activity recruits a slower, lower affinity mechanism that also helps control PN spike firing output.

Poster 5.18

Number and type of synapses on the somata and primary dendrites of dopaminergic neurons in the rat ventral tegmental area

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Understanding the morphological bases of behavioural control requires characterisation of the afferents that regulate firing patterns of midbrain dopaminergic neurons, including those that suppress activity during aversive non-rewarding events. This study measured the absolute number and type of synapses on the somata and primary dendrites of two dopaminergic neurons in the ventral tegmental area (VTA). One adult, male, Sprague Dawley rat was perfusion-fixed and serial 50µm vibratome sections were cut through the VTA. Dopaminergic neurons in the VTA were verified by immunolabelling with an antibody to tyrosine hydroxylase and processed for transmission electron microscopy. One 50µm section was selected and serial 80nm sections were analysed to reconstruct the synaptic input of approximately 75% of two tyrosine hydroxylase-positive dopaminergic somata and all of two proximal primary dendrites. Synapses were categorised as symmetric, asymmetric or unclassifiable. The mean number of somatic synapses analysed was 98 $\pm$ 44 (mean $\pm$ SD). Of these synapses, 69 ± 0.4% were symmetrical, presumably inhibitory. The mean number of synapses per µm of proximal primary dendrite was 0.80 ± 0.19. Of these synapses, 78 ± 15% were symmetrical, presumably inhibitory. These number data are within the range for rat striatal neurons previously analysed. Yet, the average percentage of symmetrical synapses is remarkably low compared to rat striatal spiny projection neurons and cholinergic interneurons (i.e. somata 98 ± 2%, 95 ± 5%; dendrites 98 ± 3%, 92 ± 3%). Hence, the timing of activation, and the development, of relatively fewer symmetrical inhibitory synapses onto dopaminergic neurons of the VTA may be exquisitely important in suppressing activity during aversive non-rewarding events.

Poster 5.19

New light-activated protein constructs to dissect the function of GABAergic neurons in the brain

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Optogenetics is a powerful tool enabling excitation or inhibition of specific neuronal populations in the brain. Optogenetics requires expression of light-activated excitatory (channelrhodopsin, ChR2) or inhibitory (halorhodopsin, NpHR) proteins, under the control of a specific promoter in the target neuronal population. While GABAergic inhibitory neurons represent ~35% of neurons in the brain, previously available optogenetic constructs only targeted a subset of these GABAergic neurons, for example, those expressing the calcium binding protein parvalbumin. The aim of the current study was to develop, package and express *in vivo* two new light-activated proteins constructs specific for GABAergic neurons.

First, using standard cloning techniques, we ligated the rat promoter for the enzyme GAD67, which controls synthesis of GABA, into a lentiviral backbone plasmid containing either ChR2 fused to mCherry or NpHR fused to eYFP. DNA sequencing confirmed that the GAD67 promoter had been successfully ligated to ChR2-mCherry and NpHR-eYFP plasmids. Second, we packaged the newly created GAD67-ChR2-mCherry and GAD67-NpHR-eYFP plasmids into lentiviral particles. We estimated that the two purified lentiviral constructs LV-GAD67-ChR2-mCherry and LV-GAD67-NpHR-eYFP were highly concentrated (1.2 to $4.3x10^{13}$ viral particles/ml). Finally, we performed *in vivo* injections of the two lentiviral constructs and confirmed by immunostaining their specificity for GABAergic neurons.

These new LV-GAD67-ChR2-mCherry and LV-GAD67-NpHR-eYFP lentiviral constructs constitute useful tools to investigate physiology and pathophysiology of the brain as they permit optogenetic excitation or inhibition of any GABAergic pathway in the brain.

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Poster 5.20

Mutations in palmitoyl protein-thioesterase 1 alter exocytosis and endocytosis at synapses in *Drosophila* larvae

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Infantile-onset Neuronal Ceroid Lipofuscinosis (INCL) is a severe pediatric neurodegenerative disorder produced by mutations in the gene encoding palmitoyl-protein thioesterase 1 (Ppt1). This enzyme is responsible for the removal of a palmitate group from its substrate proteins, which may include presynaptic proteins like SNAP-25, cysteine string protein (CSP), dynamin, and synaptotagmin. The fruit fly, *Drosophila melanogaster,* has been a powerful model system for studying the functions of these proteins and the molecular basis of neurological disorders like the NCLs. We have examined Ppt1's involvement in synaptic function at the *Drosophila* larval neuromuscular junction (NMJ). Mutations in *Ppt1* genetically interact with temperature sensitive mutations in the *Drosophila* dynamin gene *Shibire,* accelerating the paralytic behavior of *shibire* mutants at 27°C. Electrophysiological work in NMJs of *Ppt1*-deficient larvae has revealed an increase in miniature excitatory junctional potentials (EJPs) and alterations in response to repetitive (10 hz) stimulation. In particular, synapses in *Ppt1* mutant larvae exhibited a significant increase in vesicle depletion in response to 10 hz stimulation, and impairment in vesicle recovery. Similar results were obtained in larvae containing a point mutation in Ppt1 within the substrate binding site. *Ppt1*-mutant larvae also demonstrated significantly less FM1-43 uptake as compared to WT larvae. In addition, *Ppt1*-deficient and *Ppt1* point mutant larvae display defects in locomotion; these defects were not observed in *Df(1);UAS-PPT1*-rescued larvae. Taken together, our genetic, cell biological, and electrophysiological analyses suggest a direct role for Ppt1 in synaptic vesicle exo- and endocytosis at motor nerve terminals of the *Drosophila* NMJ.

Poster 5.21

Super resolution imaging of hippocampal synapses

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The postsynaptic density (PSD) is a dense region of protein that lies beneath the postsynaptic membrane of excitatory glutamatergic synapses. Understanding the 'molecular architecture' of the PSD may reveal whether structural changes in architecture are correlated with synaptic plasticity. Of particular interest are the scaffolding proteins responsible for transporting glutamate receptor components to the postsynaptic membrane and thus regulating the excitability of the neuron. However, the ~200 nm resolution limit of traditional optical microscopy has greatly complicated detailed study of protein arrangements within the densely packed PSD. Recently developed super resolution imaging techniques have overcome these limitations so that optical fluorescence studies can now complement traditional electron microscopy protocols. We have applied a single molecule localisation method of super resolution imaging known as dSTORM (Baddeley et al., 2011; Heilemann et al., 2008) to image the distribution of synaptic proteins in cultured rat hippocampal neurons. Dual-colour super resolution imaging of the respective pre and postsynaptic proteins Homer and Bassoon reveals two physically discernible protein distributions separated by the synaptic cleft. 3D super resolution imaging has allowed us to align synapses into the same orientation, providing a stable reference point from which to measure the relative locations of other protein distributions. Transient overexpression of the MAGUK scaffolding protein SAP97 alters synapse morphology and protein distribution, a process thought to underlie synaptic plasticity. We are currently investigating the spatial distribution of SAP97 relative to other key synaptic proteins, including Homer, Bassoon, and PSD95. This study illustrates how new super resolution imaging techniques can be used to study the molecular architecture of the synapse in unprecedented detail.

Poster 5.22

A role for FEZF2 in projection maintenance and cell survival

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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.

FEZF2 is a transcription factor which is required for the maintenance of FEZF2-positive postnatal cortical neurons *in vitro*, with *Fezf2* knockdown resulting in a significant reduction in projection complexity and length. Time-lapse imaging revealed that the majority of neurons demonstrating projection retraction died within 96 hours.

To identify genes that contribute to FEZF2 function, Affymetrix GeneChip Human Genome U133 Plus 2.0 microarrays were used to identify genes differentially expressed after *FEZF2* knockdown in a neural precursor cell line. Using a threshold fold change cutoff (≤ 0.4 and ≥ 1.6) and a LIMMA-moderated paired t-test derived FDR ($P < 0.05$) a list of differentially expressed *FEZF2*-regulated genes (FRG) was obtained. The FRG set contained 764 differentially expressed genes. Of the 764 differentially expressed genes, 52 genes were downregulated and 712 genes were upregulated in the *FEZF2*-knockdown samples.

Network analysis suggested roles for FEZF2 in neuron maintenance and cell survival. Genes involved in actin cytoskeleton regulation, axon and dendrite maintenance (including CRMP4, TIMP4, BICD1, MAP-2 and RHOC) and cell survival (including RAD18, CUL1) were upregulated after FEZF2-knockdown.

This work highlights an active network of FEZF2 signaling which will help unravel the functional role of this transcription factor. Examining these pathways in postnatal cortical neurons will advance our understanding of FEZF2 in the adult brain.

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

Poster 5.23

N-Methyl-D-Aspartic acid receptor-specific down-regulation of mature microRNA, miR-34a, following induction of long-term potentiation *in vivo*

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The persistence of long-term potentiation (LTP) is crucially dependent on both activation of N-methyl-D-aspartic acid receptors (NMDARs) and regulation of complex gene networks. Interestingly, our bioinformatics analysis of LTP-regulated gene networks found that microRNA, small non-coding regulatory RNA derived from larger primary transcripts, may act as high-level regulators of these networks. As microRNA are negative regulators of gene expression, we hypothesised that the early phase of up-regulated gene expression would be associated with a rapid down-regulation of microRNA. We confirmed that microRNA miR-34a was indeed down-regulated 20 min post-LTP. To advance this work, we investigated whether the observed down-regulation of microRNA was dependent on NMDAR activation or concurrent down-regulation of primary transcripts. High-frequency stimulation (HFS) of the perforant path of awake adult male Sprague-Dawley rats resulted in robust potentiation (excitatory postsynaptic potential (EPSP): 39% from baseline; population spike (PS): 411%, n=10), which was blocked by the NMDAR antagonist, CPP (EPSP: 3%, PS: 21%, n=4; 7.5mg/kg, IP; 90 min pre-HFS). Using TaqMan microRNA quantitative RT-PCR and normalisation to the geometric mean of miR-16, Y1, and U6 control sequences, we confirmed that HFS decreased levels of miR-34a (0.59±0.14, p=0.01, average fold change stimulated vs. control ± SEM, Student's t-test) and found that it was blocked by CPP (1.26±0.21, p=0.51). Furthermore, using TaqMan pri-miRNA probes and normalising to HPRT, we found no significant regulation of the primary transcript pri-miR-34a by HFS (1.02±0.25, p=0.94) or HFS+CPP (1.25±0.23, p=0.40). These data suggest that LTP-inducing HFS activates NMDARs to directly regulate mature miR-34a expression, without affecting levels of the primary transcript.

Poster 5.24

Participation of rostral anterior cingulate cortex in conditioned and unconditioned fear eliciated by dPAG electrical stimulation

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Electrical stimulation of the dorsal periaqueductal gray (dPAG) induces a repertoire of defense: dPAG-evoked freezing, escape reaction and Post-dPAG-stimulation freezing. This work studied the effect of electrolytic lesions on rostral anterior cingulated cortex (rACC) in conditioned and unconditioned fear eliciated by dPAG-electrical stimulation. The results of electrolytic lesions on rACC suggest that although rACC lesions did not change the dPAG-evoked freezing and escape threshold, it might exert an inhibitory effect on the dPAG post-stimulation freezing, reinforcing the hypothesis that dPAG-evoked freezing and dPAG post-stimulation freezing are modulated by two independent circuitry of defense. As additional data, we studied pain sensibility of rACC lesioned animals submitted to formalin test on conditioned analgesia paradigm. The results suggest that rACC lesions might exert an inhibitory effect on conditioned analgesia and consequently exacerbates recuperative behaviour.

Poster 5.25

Comparisons between the effects of nicotine and other chemicals present in cigarette smoke on dopmaine and serotonin transporter function in rats

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Cigarette smoking results in over 5000 deaths per year in New Zealand alone. There are over 4000 compounds present in cigarette smoke, some of which may contribute to smoking addiction. Despite this, the majority of smoking addiction research to date has focused on nicotine alone. Smoking causes the release of neurotransmitters in the brain including dopamine and serotonin. Dopamine activates the brain's natural reward pathway and serotonin is involved in the regulation of mood, memory and motivation. The dopamine transporter (DAT) and serotonin transporter (SERT) function to remove dopamine and serotonin from the synapse, thus terminating their signalling. This study has investigated the effects of total particulate matter (TPM) from cigarette smoke and nicotine (0.35 and 3 mg/kg i.p.) on the function of DAT and SERT in discrete brain regions of rats. Dopamine uptake by DAT and serotonin uptake by SERT was measured using rotating disk electrode voltammetry. In vivo TPM treatment resulted in an increase in DAT function in the striatum; whereas nicotine alone produced no change compared to control. In vitro treatment of the striatum with TPM caused a significant decrease in SERT function whereas nicotine alone caused no change. These changes were not entirely attenuated by the nicotinic receptor antagonist mecamylamine, which indicates non-nicotinic components of TPM may be responsible for these changes. This work has increased our understanding of the non-nicotinic effects of cigarette smoke on DAT and SERT and in the future may lead to the development of novel smoking cessation therapies.

Poster 5.26

Temporally cued and self-initiated auditory stimuli evoke a reduced auditory N1/P2

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Event related potentials (ERPs) to tones that are self-initiated are reduced in their magnitude in comparison to ERPs to tones that are externally generated. This phenomenon has been taken as evidence for an efference copy of the motor command acting to suppress the sensory response. However, self-initiation provides a strong temporal cue for the stimulus that might also contribute to the ERP suppression for self-initiated tones. The current experiment measured the amplitude of the N1/P2 complex evoked in auditory cortex source waveforms extracted from 64 channels of EEG during a task that presented 1kHz tones triggered either by a button press, externally following a timed cue, or externally with no cue. We sought to investigate the suppression of monaural tones by temporal cueing and also whether the addition of self-initiation enhanced this suppression. Lastly, the experiment sought to investigate the lateralisation of the ERP suppression via presenting these monaural tones to each ear respectively. Both cueing and self-initiation reduced the auditory N1/P2 amplitude significantly for stimuli presented to the right ear. Only self-initiation significantly reduced the auditory N1/P2 amplitude when stimuli were presented to the left ear. On average the auditory N1/P2 amplitude reduction was larger, but not significantly larger, for self-initiation compared to temporal cuing. The auditory N1/P2 amplitude was significantly larger for stimuli presented to the right ear during the control condition but this ear advantage was no longer evident when the auditory stimulation was temporally cued or self-initiated. We conclude that a significant proportion of ERP suppression by self-initiation is a result of inherent temporal cueing.

Poster 5.27

Using theta-burst stimulation to modulate functional recovery after stroke

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Stroke is a leading cause of disability with many survivors showing some degree of motor impairment. Functional recovery is often limited and this may be due to changes in neuronal excitability. We hypothesise that application of theta-burst stimulation (TBS) protocols to the contralesional hemisphere after stroke may modulate functional recovery, via its effects we have previously observed on interhemispheric inhibition. To test this hypothesis, focal lesions were created in the forelimb motor cortex of four rats using suction aspiration. Cortical stimulating electrodes were implanted in the contralesional motor cortex for delivery of either intermittent (iTBS) or continuous TBS (cTBS). Before and after application of TBS, forelimb co-ordination was assessed using a grid-walking task and asymmetry in exploratory forelimb use determined using a cylinder task (% preference for unaffected limb).

After lesioning, all rats showed an 8-9% increase in stepping errors with the contralateral paw and up to 40% bias for using the ipsilateral paw in the cylinder. Rats receiving iTBS (n=3) showed improvement of forelimb co-ordination to 4.7% at twenty-four days. The rat receiving cTBS (n=1) displayed marginal improvement to 7.4% after twenty-four days. Curiously, the same treatments appeared to induce opposite effects in terms of recovery of forelimb symmetry using the cylinder test (50.2% iTBS, 11.3% cTBS). Calculated lesion sizes (1.4-6.2% of hemispheric volume) were unrelated to initial behavioural deficits.

Possible explanations for these data include the extent and placement of the lesions. These preliminary data involve aspiration lesions. Further research will extend the data set and investigate photochemical induction of cortical lesions.

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Poster 5.28

Measurement of human visual cortex excitability using suprathreshold phosphene perception

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Human visual cortex excitability can be measured by using single-pulse transcranial magnetic stimulation (TMS) to induce the percept of a phosphene. The standard technique involves varying the intensity of TMS delivered to the occipital pole, until an intensity that produces phosphenes on 50% of pulses is identified. Here we investigated the perception of phosphenes induced by single-pulse TMS delivered at varying suprathreshold intensities. The aim was to assess whether suprathreshold phosphene perception could provide an additional measure of visual cortex excitability. Seven healthy adult males completed measurements of threshold and suprathreshold phosphene perception on three separate occasions. Phosphene thresholds were determined using standard techniques. Perception of suprathreshold phosphenes was assessed with single-pulse TMS across a fixed range of five stimulator output strengths. Participants rated the intensity of each phosphene relative to the percept induced by the maximum TMS strength used within a session. A logistic function was fitted to the average intensity ratings which provided a 50% intensity threshold. Phosphene intensity ratings were correlated with phosphene thresholds (Pearson's $R = 0.84$, $p<0.02$) and did not vary systematically across sessions, $F(2,12) = 0.33$, $p=0.7$. In contrast, phosphene thresholds declined significantly across sessions, possibly due to task learning $F(2,12) = 6.18$, $p=0.014$. These results suggest that measurements of suprathreshold phosphene perception may provide a useful additional measure of human visual cortex excitability.

Poster 5.29

Nanomiceller delivery of cannabinoids for neuropathic pain

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Cannabinoids are drugs that are either derived from or mimic the effects of cannabis. Cannabinoids are moderately effective at reducing neuropathic pain, but only at doses that cause unacceptable levels of psychoactive side effects. We investigated the potential of a nanomiceller delivery system to target a cannabinoid to inflamed neural tissue whilst reducing penetration into the brain, and thus reduce the side effects associated with cannabinoids. Further a nanomiceller delivery system could achieve extended action due to prolonged half-life in the plasma. We hypothesized that this could be achieved with the cannabinoid WIN55,212-2 (WIN) formulated as styrene-maleic acid (SMA) nanomicelle . Following chararcterisation of the loading, size, and release profiles of SMA WIN micelles we employed the chronic constriction injury (CCI) model of neuropathic pain in rats to assess the ability of WIN micelles to reverse neuropathic pain whilst minimizing psychoactive side effects, comparing results of these tests with free WIN. Both formulations were delivered by the i.v. route. A 21% loading of WIN to SMA resulted in the abolishment of acute sedation following administration compared to free WIN, and resulted in moderate but sustained reversal of neuropathic pain over 24 hour.

Poster 5.30

Nitric oxide in the olfactory bulb *in vitro*

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Nitric oxide (NO) is a ubiquitous gasotransmitter implicated in physiological and pathological processes throughout the brain, including synaptic plasticity and seizure generation. The olfactory bulbs (OB) of the brain contain among the highest levels of the NO producing enzyme, nitric oxide synthase, but no study has yet looked at the effects of NO on synaptic processing in the mammalian OB. We aimed to determine the acute effects of NO on responses of OB principal neurons (mitral cells) to synaptic glutamate released from the olfactory nerve (ON), using single-unit recording from OB slices *in vitro*. In response to electrical stimulation of the ON *in vitro*, mitral cells produce long-lasting depolarisations (LLDs) associated with action potential generation. LLDs are generated by mutual excitation among OB output neurons, mediated principally by NMDA receptors. LLD duration depends on the frequency of ON stimulation: repetitive stimulation (0.2 Hz) elicits LLDs lasting several hundred ms, while a single ON stimulus elicits an LLD lasting up to several seconds. The NO donor sodium nitroprusside (SNP, 10µM, 50 µM) decreased LLD duration evoked by repetitive ON stimulation, and decreased spontaneous action potential frequency. Another NO donor, S-Nitroso-N-acetyl-DL-penicillamine (20 µM, 100 µM), or the NO synthase substrate L-arginine (0.1 mM, 2 mM) did not have these effects, consistent with a NO-independent mechanism of SNP, possibly mediated by effects of ferrocyanide (a SNP end-product) on NMDA receptors. L-arginine did, however, reversibly reduce LLD duration following a single ON stimulus. The effect of NO in the OB may therefore be dependent on the frequency of synaptic input: NO may selectively reduce the duration of resposes to low frequency synaptic input mediated by glutamate receptors.

Poster 5.31

Anterior thalamic lesions and recovery: Enriched environments restore spatial memory in the radial arm maze

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Postoperative enrichment in rats with anterior thalamic nuclei (ATN) lesions has been shown to ameliorate deficits in forced choice spatial working memory in a cross maze and reference memory in the water maze, but failed to promote recovery of spatial memory in the radial arm maze (Loukavenko et al., EJN, 2007; Wolff et al., Hippocampus, 2008). The current study re-examined the influence of enrichment (Enr) in ATN rats in the radial arm maze. ATN lesions produced severe impairment in spatial working memory in the cross maze immediately after surgery ($F=31.4$; $df=1,36$; $p<0.0001$), which was substantially reduced by 40 days of subsequent enrichment (Enr vs Standard housing [Std]; ATN-Std < ATN-Enr [$p<0.03$, post-hoc Newman-Keuls]; ATN-Enr was not different to Sham-Std and Sham-Enr [$p>0.15$]). We also replicated the improvement in the ATN-Enr rats when tested on "alternate-arm" trials in the cross maze, a test of allocentric memory. The four groups were subsequently trained in a standard 8-arm radial maze, but with one arm never baited. In the radial arm maze, the ATN-Std group made more errors than each of the other groups ($p<0.001$; Sham-Std worse than Sham-Enr, $p<0.05$, no other significant pair-wise differences). Also, all ATN-Std rats failed to reach criterion within 35 days of radial arm maze testing. The current study confirms that enrichment promotes recovery from severely impaired spatial memory after ATN lesions in rats and extends this influence to spatial memory in the radial arm maze. Histological analysis of CA1 morphology is being examined to determine whether changes in these neurons are associated with impairment and recovery after ATN lesions.

Poster 5.32

Influence of the catechol-O-methyltransferase (COMT) val^{158}met polymorphism on magical ideation

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A frequent single nucleotide polymorphism in the catechol-O-methyltransferase (COMT) gene influences levels of extracellular dopamine in the prefrontal cortex (PFC). The presence of the COMT wild-type allele has been linked to a number of psychiatric disorders, including schizophrenia, in clinical populations, as well as with various non-pathological personality traits in healthy samples. Magical ideation is a semi-serious consideration of the possibility of causal relationships between events that are conventionally deemed to be unrelated. Research suggests that high levels of this tendency may indicate a predisposition to schizophrenia that is linked to PFC dysfunction. This study aimed to determine whether the COMT val^{158}met polymorphism affects performance on the Magical Ideation Scale. A sample of healthy young adults was genotyped and assessed on the Magical Ideation Scale. A one-way between-groups ANOVA run on preliminary data suggests an overall effect of COMT genotype on Magical Ideation scores that is approaching significance ($p<0.1$). Further testing of participants will help elucidate any relationship between COMT genotype and magical ideation in healthy individuals.

Poster 5.33

Distinct signatures of visual target selection and distractor suppression investigated using high-density electroencephalography

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A typical visual scene includes many objects, but we are only aware of a small subset at any given time. In order to function in the world in spite of this limitation, we must selectively attend to objects which are relevant to our goals while ignoring or suppressing distracting or irrelevant information. Previous research has used electroencephalography (EEG) to isolate brain potentials related to the selection of visual "targets" and the suppression of "distractors". Target selection is associated with the N2pc component of the visual evoked potential. N2pc typically occurs 180-250ms post-stimulus and manifests as increased negative voltage at posterior scalp electrodes contralateral to visual targets. A later potential with a more temporal scalp distribution, the Ptc, has been associated with the suppression of distractors. Here, we employ high-density EEG to provide further evidence for the dissociation of N2pc and Ptc, and to provide estimates of their likely cortical generators. Participants respond to the orientation of a coloured target in amongst a circle of grey fillers while ignoring a coloured distractor. In half of the trials the target is lateralised while the distractor is on the midline while in the remaining trials this is reversed. This allows us to dissociate the effects of targets and distractors on N2pc and Ptc. Preliminary results provide more precise scalp distributions of N2pc and Ptc than were previously available, and suggest that N2pc is evoked by all salient stimuli, while Ptc is only evoked by lateralised distractors. These results confirm previous indications that the N2pc and Ptc are distinct components of the VEP which index attentional selection and distractor suppression respectively.

Poster 5.34

Time-dependent changes in C-type natriuretic peptide in rat brain produced by enriched environments

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C-type Natriuretic Peptide (CNP), the third member of the cardiac family of natriuretic peptides, is found throughout the CNS. CNP elevates cGMP, but its role in brain function is unknown beyond in vitro studies showing that CNP has neurotrophic properties for sensory neurons and influences hippocampal plasticity. We therefore examined CNP concentrations (fmol/gram tissue) in six brain regions (snap-frozen fresh tissue) in 8-month old male rats housed in an enriched environment (EE) for either 14 or 28 days (Ns=12) compared to those of standard-housed controls (Ns=6). CNP was significantly increased in medial prefrontal cortex, occipital cortex, and mammillary bodies after 14 days, but not 28 days, of EE (Housing x Time, all $F > 4.78$, $p < .036$). In the rostral retrosplenial granular cortex and hypothalamus, significant main effects of Time (F's >7.56, $p < .01$; higher at 14 days) and Housing (F's > 7.24, $p < .011$; higher in EE) were found, but no interactions (Housing x Time, F's < 1.52). In the hippocampus, significant main effects of time were found in both hemispheres (F's>4.51, p's<.042), and a significant main effect of Housing was found only on the right ($F=5.33$, $p=.028$; Housing x Time, F's <1). In contrast to CNP, NTproCNP was unchanged, suggesting that the increased CNP reflected reduced degradation (e.g. by neprilysin, IDE) and clearance (eg NPR-C receptor). This study provides the first evidence that CNP in intact brain is modulated by a behavioural manipulation. Time-limited influences of EE suggest CNP contributes to the initial cascade of neural changes associated with enriched environments.

Poster 5.35

Evoked potential correlates of object recognition memory and the influence of the BDNF val66met polymorphism

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Recognition memory involves the contribution of two distinct retrieval processes, recollection and familiarity. Recollection is generally assumed to reflect the retrieval of qualitative information associated with previously encountered stimuli, while familiarity reflects a measure of the memory strength of an item. They have been shown to be functionally dissociable and to rely on partially distinct neural networks. Recollection processes are thought to require the hippocampus and prefrontal cortex, whereas familiarity incorporates the perirhinal cortex and mediodorsal thalamus. Furthermore, recent evidence has shown that recollection and familiarity are associated with different event related potential (ERP) modulations: familiarity with an early onset FN400 effect, and recollection with a late positive component (LPC). A single nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene (val66met) affects the release of BDNF and memory task performance. In the present study we tested the effect of the val66met polymorphism on recognition memory performance and the associated ERP modulations. Pilot results suggest that individuals with the met allele substitution exhibit poorer performance on object recognition tasks. They exhibit a significantly lower FN400 during familiarity tasks and a lower LPC during recollection tasks. These data support previous suggestions that BDNF polymorphisms affect human memory performance, and that these performance differences can be indexed by underlying physiological signals.

Poster 5.36

BDNF val66met polymorphism affects FN400 and LPC evoked potentials in human facial recognition memory

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Recognition memory is thought to involve two processes, familiarity and recollection. These processes have been shown to be functionally dissociable and show different neural activity. Recent evidence has shown these two processes are associated with two seperate event related potential (ERP) modulations: familiarity with a early positive component centred around the frontal midline called the FN400, and recollection with a late positive component which is lateralized to the left, called the LPC. BDNF has been shown to be an important modulator of synaptic plasticity and memory in humans. A single nucleotide polymorphism in the BDNF gene resulting in a valine-to-methionine substitution at codon 66 (val66met) affects activity-dependent secretion of BDNF and is associated with lower performance in memory tasks. In the present study, we tested whether the val66met polymorphism was associated with electrophysiological changes in facial recognition memory, either immediately after training (familiarity) or a day after training (recollection). Preliminary results show that the two memory tasks do evoke the two different ERPs (FN400 for familiarity and LPC for recollection) and that individuals with the met allele (Val/Met, Met/Met) have significantly lower ERP amplitudes. Behavioural data also show these individuals perform more poorly on the memory tasks. These results add further weight to the suggestion from earlier studies that BDNF plays a critical role in human memory processes, and that this is reflected in modulations at the physiological level.

Poster 5.37

The effect of the 5-HT1B antagonist GR-127935 on cocaine and MDMA seeking behaviour in rats

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The serotonin 1B (5-HT1B) receptor is a terminal auto-receptor responsible for modulating the release and synthesis of serotonin. Serotonin regulates several other neurotransmitters including dopamine (DA) which is thought to contribute to the reinforcing properties of addictive drugs such as cocaine and MDMA. A role of DA in MDMA-seeking behaviour, a model of relapse, has been demonstrated by our group, but the role of serotonin is less clear. Rats were trained to self-administer cocaine or MDMA followed by an extinction phase during which responding was no longer reinforced. An MDMA priming injection reinstated extinguished drug-seeking behaviour, but the effect was greater for MDMA- than for cocaine-trained rats. The role of the 5-HT1B receptor was then investigated by pre-treating rats with the selective 5-HT1B antagonist, GR-127935. Preliminary results are consistent with previous findings which suggest that GR-127935 has minimal effect on cocaine-seeking behaviour. The effect of GR-12935 on MDMA trained rats is under investigation. These findings may provide support to the theory that MDMA dependence is driven by reduced inhibition of dopaminergic pathways due to the depletion of 5-HT levels following chronic exposure.

Poster 5.38

The role of the dopamine receptor D1 in cognitive behaviour

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The dopamine receptor D1 (Drd1) has been linked to cognitive functioning in various human, pharmacological and animal studies. In human studies the evidence is often only correlational, and pharmacological studies use agonists and antagonists that are not selective to the Drd1, but also influence the dopamine receptor D5. Therefore, it is unclear to what extent a dysfunction in the Drd1 really causes cognitive impairments. In order to investigate this we developed a rat with a single point mutation in the Drd1, leading to a functional inactivation of the receptor (the Drd1-/- rat). In the novel object recognition task rats explored two objects in a circular open field. After a delay (20 minutes or 60 minutes) a novel object replaced one of the objects that the rats had explored previously. Rats have a natural tendency to spend more time exploring the novel object, indicating that they still hold a representation of the first object in memory. Preliminary findings showed that the Drd1-/- rats were slightly impaired after a 20 minute delay. After a 60 minute delay this impairment was no longer found. In the standard version of the Morris Water Maze (MWM) female Drd1-/- rats were slightly but significantly slower at finding a hidden platform. When external cues were removed and the rats had to rely on their own body coordinates to find the hidden platform (egocentric learning), the Drd1-/- rats were drastically impaired. Together these results suggest that the DD1R is necessary for normal cognitive functioning. Currently, both egocentric and allocentric learning is being investigated in a novel star maze task using both positive (chocolate cereals) and negative (ice) reinforcement.

Poster 5.39

The role of histamine H3 receptors in the behavioural effects of methamphetamine and 3,4-methylenedioxymethamphetamine

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Whereas the histamine H1 and H2 receptors occur in both the brain and the periphery, the histamine H3 receptor is primarily located within the central nervous system. While there are no selective H3 agonists or antagonists currently on the market there exists a great deal of research interest in H3 receptor antagonists because they are thought to have therapeutic effects in a variety of disorders: cognitive and attentional deficits, schizophrenia, sleep disturbances and eating disorders. Recent studies in animals have suggested that H3 ligands may also be relevant for the treatment of addiction. However, traditional H3 imidazole antagonists, like thioperamide, reduce the metabolism of most addictive drugs, such as amphetamine and methamphetamine, thus making it difficult to study their effect on the actual rewarding properties of these drugs of abuse. The current study compared the effects of a traditional H3 imidazole antagonist (thioperamide) and a novel H3 non-imidazole antagonist (Compound-A) on the behaviour induced by either methamphetamine (MA) or 3,4-methylenedioxymethamphetamine (MDMA). The results demonstrated that both Compound-A and thioperamide caused a significant decrease in the number of lever presses on self-administered MA; whereas, preliminary data showed that Compound-A had no clear effect on self-administered MDMA, although only a small number of animals were tested. Additionally, neither thioperamide nor Compound-A had an effect on MA induced locomotor activity. In sum, both thioperamide and Compound-A seem to have an inhibitory effect on MA self-administration, most likely caused by an increase in dopamine release. These results confirm the role of H3 receptors in the psychomotor and the rewarding effects of addictive drugs.

Poster 5.40

The effects of the 5-HT1B agonist RU-24969 on drug seeking in rats trained to self administer MDMA or cocaine

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The serotonin(5-HT)1B receptor is a terminal autoreceptor that regulates the synthesis and release of 5-HT. Serotonin release in terminal regions has been shown to modulate tissue levels of dopamine, suggesting an important role of 5-HT in drug addiction. Rats were trained to self-administer cocaine or MDMA, followed by an extinction phase in which operant responding was no longer reinforced. The ability of MDMA to reinstate extinguished drug seeking behaviour was subsequently investigated. MDMA was found to be more effective at reinstating MDMA seeking than cocaine seeking, as has been shown in previous research. The 5-HT1A/1B agonist RU-24969 produced a marked dose-dependent suppression of MDMA produced cocaine seeking, similar to previous research. The results are being followed up with rats trained to self-administer MDMA, and these data will also be presented. Together, these results will elucidate the role played by the 5-HT1B receptor in relapse to drug taking, and also have important implications for research into MDMA induced 5-HT depletion.

Poster 5.41

Biochemical and pharmacological characterisation of the Drd1 mutant rat

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There is increasing support for the involvement of the dopamine D1 receptor (Drd1) in several symptom domains of schizophrenia, especially the cognitive and negative symptoms. We recently created a novel rat model by target-selected N-ethyl-N-nitrosourea (ENU)-driven mutagenesis, which resulted in rats with a Drd1 point mutation, leading to an isoleucine – serine mutation in the third transmembrane domain. If the point mutation has functional consequences in the rat it may represent a novel model for the negative and cognitive symptoms of schizophrenia in humans. The aim of the present study was to provide a first behavioural, biochemical and pharmacological evaluation of the *Drd1* mutant rat. A first assessment showed that general behaviour and health measures were similar for the WT and mutant animals, with the exception of the mutants having a lower body weight and more vocalisations when being handled. [^{3}H]SCH23390 autoradiography was used to examine mutant *Drd1* expression. Binding was reduced by 20-50% in the rats homozygous for the Drd1 mutation. cAMP levels, which were increased as a result of *Drd1* activation in WT rats, were unaltered in the mutant rats, indicating that the Drd1 is non-functional in the homozygous mutant rats. This was also observed in a motor task (the paw test), where a Drd1 antagonist increased hindlimb retraction time in the WT but not in the homozygous *Drd1* mutant rat. In summary, these results suggest that the point mutation in *Drd1* leads to a significantly reduced functioning of the *Drd1*. Research is currently underway to investigate the localisation of the mutant receptor in a cellular system, and to study whether the Drd1 mutation influences morphology and connectivity between neurons.

Poster 5.42

A novel behavioural investigation of the dopamine D1 mutant rat

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The dopamine (DA) D1 receptor (D1R) has been shown to play a central role in the successful execution of numerous cognitive and behavioural tasks, including working memory function, locomotor output, and motivational processes. Researchers, to date, have relied on pharmacological means, such as the administration of D1R agonists and antagonists, to investigate the function of the D1R. However, such pharmacological agents do not distinguish between the D1 receptor and the D5 receptor. Recently, a novel strain of mutant rat was generated, using N-ethyl-N-nitrosourea (ENU)-driven target selected mutagenesis, rendering D1 receptor function down-regulated whilst leaving D5 receptor function intact. The current study is a preliminary investigation into the behavioural attributes of homozygous DA D1 mutant (DAD1-/-) rats. A battery of experiments were conducted in which DAD1-/- rats were compared to heterozygous (DAD1+/-) littermates in regards to motivation to consume sugar pellets, locomotion in an open field, autoshaping to press a lever for reinforcement, balance beam performance and working memory performance in the T-maze. In comparison to the DAD1+/- rats, the DAD1-/- rats were severely impaired in terms of balance beam performance, did not autoshape to press a lever for sucrose reinforcers, and were slower to consume sugar pellets when they were freely available. On the contrary, there was no difference between the DAD1-/- and DAD1+/- rats in terms of working memory performance in the T-maze and in terms of locomotor tendencies in the open field. It was concluded that the DAD1-/- rats display reduced motivation to work for reward. Future research that aims to characterise the DAD1-/- rats further could examine these motivational differences in more detail, which would ultimately provide a greater understanding of the D1R's role in motivation.

Poster 5.43

Amphetamine hyperactivity is enhanced in serotonin transporter knock-out rats

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While it is known that (±)-3-4-methylenedioxymethamphetamine (MDMA) exerts influence over both the serotonin reuptake transporter (SERT) as well as the dopamine reuptake transporter (DAT), it is not known what role each of these play in determining the behavioural properties of MDMA. One way to elucidate this matter is to use SERT knock-out rats. Due to the inability of MDMA to exert any influence on the SERT in knock-out animals it was predicted that, while wild type animals would be able to discriminate between amphetamine and MDMA (as previously shown) SERT knock-out rats would perceive them as similar. Accordingly, a two-lever drug discrimination paradigm was implemented. Rats were trained to respond on different levers following an injection of amphetamine (0.5 mg/kg, IP), or saline. Once all animals could reliably discriminate amphetamine from saline, testing was planned to ascertain whether the animals could discriminate amphetamine and MDMA. However, at low doses no animals could reliably discriminate amphetamine and saline, and at higher (1.0 mg/kg, IP), many animals failed to respond, of which a significantly higher proportion were SERT knock-out. In order to determine whether this difference was due to increased sensitivity to amphetamine in SERT knock-out animals, locomoter response to amphetamine (0.75 mg/kg, IP) was tested. It was found that SERT knock-out animals indeed showed a higher amount of hyperactivity in response to the drug. The results suggest the SERT knock-out animals exhibit enhanced sensitivity to amphetamine compared to wildtype animals.

Poster 5.44

EEG Alpha oscillations predict variability in visual signal detection

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Perception is highly variable - we sometimes miss a stimulus that we can easily perceive at other times, even though nothing changes about the stimulus itself. Recent research has indicated that variation in the peristimulus amplitude and phase of the alpha rhythm of the electroencephalogram (EEG) can predict this variability (Busch, Dubois, & VanRullen, 2009; Mathewson, Gratton, Fabiani, Beck, & Ro, 2009).

Here, we extend this research by both including resting alpha activity as a potential predictor and expanding the analysis to frequency bands outside the alpha range. EEG was recorded while participants performed a backward-masking task requiring the detection of a near-threshold visual stimulus. Analysis of the EEG data focused on three possible predictors of detection performance: (1) oscillatory power during the 4 min resting periods before and after the experimental task, (2) oscillatory power in the 200 ms interval directly preceding stimulus presentation, and (3) the phase angle and the amount of inter-trial coherence at the time of stimulus presentation. Each of these measures was compared for trials in which participants successfully detected the stimulus and for trials in which they failed to detect the same stimulus. Although this remains a work in progress, our preliminary results suggest that low resting alpha power, in addition to low peristimulus alpha power, is predictive of better detection performance. There is also evidence for a systematic relationship between oscillatory alpha phase at the moment of stimulus presentation and detection performance, confirming previous reports.

These results are consistent with the idea that alpha oscillations index the momentarily excitability state of the cortex and can thereby predict perception performance.

Poster 5.45

Direct participation of agmatine in spatial learning: An in vivo microdialysis study

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Agmatine, decarboxylated arginine, is widely distributed in mammalian brains and is considered as a novel putative neurotransmitter. Recent research demonstrates spatial learning-induced increases in agmatine in memory-related structures at the tissue and presynaptic terminal levels. By using the in vivo microdialysis technique coupled with highly sensitive liquid chromatography/mass spectrometry assay, we investigated dynamic changes of extracellular agmatine in the rat dorsal hippocampus before, during and after water maze training for a fixed hidden platform. Water maze training resulted in approximately 2-6 folds rapid and sharp increases in extracellular agmatine in the dorsal hippocampus on the first and fourth day of testing, whereas swimming per se had no effect. Learning-induced net agmatine release was dramatically decreased across the 3 blocks of training on day 1, but was significantly increased in the later training block containing a probe trial on day 4. Furthermore, the baseline level of extracellular agmatine was significantly shifted upwards after 30 trials of training. The present study provides a direct evidence for the participation of endogenous agmatine in the processes of learning and memory as a neurotransmitter. Endogenous agmatine in the dorsal hippocampus appears to be involved in the encoding and retrieval of spatial information processing.

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Poster 5.46

Structural and functional connectivity in language production and comprehension

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The brain structure-function relationship has been one of the most fundamental issues in neuroscience. Previous work has demonstrated associations between the degree of language laterality and white matter asymmetries of language pathways. However, many studies show these relations indirectly where fractional anisotropy measures are correlated with laterality indices based on group average activation. Here, we used functional MRI and diffusion tensor imaging (DTI) to directly investigate the link between structure and function by using functionally-defined language sites to perform tractography. Nineteen participants were scanned during verb generation and sentence comprehension tasks and also underwent DTI. Using psychophysiological interaction analyses, we mapped the two language networks and measured the degree of functional connectivity. This was correlated with various diffusion measures to explore the existence of anatomo-functional relationships. We found significant structure-function correlations in the fronto-motor connection for verb generation only. This pathway may be specific to the role of generating verbs, due to the recruitment of the motor cortex in processing action-related words. Interestingly, connectivity was stronger in the fronto-temporal portion of the arcuate fasciculus compared to the fronto-motor pathway, despite the lack of a significant anatomo-functional correlation. The fronto-temporal pathway may be involved in a more diverse range of functions than can be represented at the anatomical detail available with DTI. The sentence comprehension task revealed two pathways connecting the frontal and temporal language regions: a ventral and dorsal pathway. This is in line with the previously proposed dual-route theory of reading. Our results demonstrate that a direct, individualistic approach can be used to investigate structure-function associations in the language network, but also that these relationships may be more complex than once thought.

Poster 5.47

Using diffusion tensor imaging to compare differences in the white matter tracts of right- and left-handed males

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Information regarding connectivity in the human brain can be gathered using diffusion tensor imaging (DTI). Fractional anisotropy (FA) is the most commonly derived value, and reflects how strongly directional the underlying tracts are. Differences in FA are thus associated with differences in the underlying microstructure of the brain. The relationships between FA values and microstructure and functional differences in corresponding regions have also been examined. Previous studies have found an effect of handedness on functional lateralisation in the brain and its corresponding microstructural differences. Here, using tract-based spatial statistics (TBSS) to analyse DTI-derived FA values, we build on previous studies to compare the structural differences of white matter in the brains of right- and left-handed males. We found significantly higher FA values for left-handed individuals (n=13) when compared to right-handed individuals (n=16) in all major lobes, and in the corpus callosum. In support of previous suggestions, we find that there is a difference in the microstructure of white matter in left- and right-handed males that is associated with less lateralisation of function in left-handed individuals.

Poster 5.48

Effects of chronic unpredictable stress on adult neurogenesis: Behavioural consequences and similarities with hippocampal lesions

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The brain continually produces new neurons into adulthood. In the hippocampus, adult derived progenitor cells are generated in the subgranular zone of the dentate gyrus (DG). Surviving cells become integrated into the hippocampal circuitry as granular neurons; however, the functional contribution of these young neurons remains poorly understood. The present study investigated how chronic mild stress impacts adult hippocampal neurogenesis and a range of behavioural tasks in hooded rats. The effects were compared with those induced by colchicine-induced lesions of the DG. Mild chronic stress reduced the acquisition rate of a stimulus-response task ($p=0.04$), but facilitated the acquisition of a discrimination between a small and a large reward ($p=0.02$). In locomotor activity assays, chronic stress did not shift the dose-response to methamphetamine. Analysis of 2,5-bromodeoxyuridine incorporation showed that, overall, chronic mild stress decreased the survival of neuronal progenitors ($p=0.03$). However, learning of the tasks had a positive influence on cell survival in stressed animals ($p=0.03$). On the other hand, colchicine produced significant lesions of the dentate gyrus and surrounding CA1, CA3 and neocortex. Colchicine lesions impaired reference memory performance in a cross-maze ($p=0.05$), while sparing simple discrimination learning. In a delay discounting procedure, the lesions did not induce impulsive-like behaviour when delay associated with a large reward was introduced. The present experiments showed both facilitatory and inhibitory effects of chronic mild stress on learning. These effects were for the most part dissimilar to those produced by hippocampal lesions in related tasks. Furthermore, stress exposure reduced survival of adult-born neurons in the hippocampus, with learning acting as a buffer to mitigate the negative effects of stress on neurogenesis.

Poster 5.49

Methamphetamine-induced disruption in Delay Matching to Sample is attenuated by the D1 antagonist SCH23390

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Previous studies (e.g. Harper et al 2005, Behavioral Neuroscience 119: 455-63) have indicated that a number of different drugs of abuse (cocaine, d-amphetamine, MDMA) disrupt performance in the delayed matching-to-sample (DMTS) task that is best characterised as an overall decrease in discriminability in rats. More recent work (Harper 2011, Addiction Biology 43: 2015-23) has indicated that a D1 antagonist (SCH23390) can attenuate the disruptive effects of such drugs of abuse. The current study extended this work by looking at the effects of methamphetamine (0.3, 0.6 & 1.0 mg/kg i.p) on DMTS performance on its own and in combination with SCH23390. Consistent with previous work, methamphetamine produced an overall decrease in discriminability with no change in response bias. Similarly, SCH23390 (0.04mg/kg) administered 15mins prior to methamphetamine significantly attenuated the disruption to discriminability. This finding is consistent with the conclusion that methamphetamine's disruptive effects on memory are related to its action as a dopamine agonist at the D1 receptor site.

Poster 5.50

Involvement of tryptophan and kynurenine metabolites in central fatigue

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Purpose: Serotonin, a neurotransmitter synthesized from tryptophan, has been proposed to play a key role in central fatigue. In this study, we examined whether tryptophan itself and/or its two metabolites, kynurenic acid (KYNA) and quinolinic acid (QUIN), were involved in central fatigue. Materials and Methods: Experiments were conducted using Sprague-Dawley rats (SDR) and analbuminemic rats (NAR). Central fatigue was assessed with use of treadmill running and a Morris water maze test. Microdialysis was used to collect samples for measurement of extracellular concentration of tryptophan, serotonin and 5-hydroxyindoleacetic acid (5-HIAA) and to infuse test agents. To examine the kinetics of release, synaptosomes in the striatum were prepared in vitro to measure intra- and extrasynaptosomal concentration of tryptophan, serotonin and 5-HIAA. Results: The concentration of tryptophan secreted into the extracellular space of the striatum was higher only during fatigue and returned quickly to basal level with recovery from fatigue. Running time to exhaustion was reduced by activating the tryptophan receptor. Time to exhaustion was shorter in NAR, which maintain a high extracellular level of striatum tryptophan, than do SDR. Impaired memory performance in a water maze task after tryptophan treatment was attributable to high levels of KYNA and QUIN in the hippocampus acting synergistically on N-methyl-D-aspartic acid receptors. When branched-chain amino acids were administered, tryptophan transport to the extracellular space of the striatum was drastically inhibited. Conclusion: Our findings demonstrate that the increase in fatigue which occurs because of excessively elevated brain tryptophan can be further amplified by the use of synthetic KYNA and QUIN.

Poster 5.51

Age-dependent spatial learning and memory impairments in the APP/PS1 transgenic mouse model of Alzheimer's disease

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AD is a common neurodegenerative disease among the elderly characterised by behavioural alterations and the hallmark symptom of progressive cognitive decline. Transgenic mice (Tg) bearing mutant human amyloid precursor and presenilin proteins (APP/PS) are experimental models for investigating the underlying mechanisms and therapeutic interventions in AD. Studies using the APPswePS1ΔE9 transgenic mouse have demonstrated amyloid plaques and behavioural alterations that develop with age, but are present from as early as 6 months of age. In the majority of time-course behavioural studies a combination of both female and male mice have been used, with females demonstrating a greater impairment. The present study compared the behavioural performance of 7 and 13 month old male APPswePS1ΔE9 mice in the elevated plus maze (EPM), open field and two versions of the Morris water maze task. At 7 months of age, APP/PS1 mice spent significantly more time in the enclosed arms of the EPM and showed a mild impairment in the working memory version of the water maze task relative to WT mice, with no significant differences in the open field apparatus and the reference memory version of the water maze task. In comparison 13 month old APP/PS1 mice were significantly impaired in both the reference and working memory versions of the water maze task, but not in the EPM or open field. These results demonstrate that APPswePS1ΔE9 transgenic mice display spatial learning and memory deficits in an age-dependent manner, a finding representative of the progressive cognitive decline found in AD.

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Poster 5.52

Astrocytes as a cell target of gene therapy for epilepsy

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To date, gene therapy strategies for neurological disorders have focused on the manipulation of neuronal physiology. Given that many neurological disorders are associated with neuronal loss and reactive gliosis, astrocytes, prevalent and dysfunctional in the diseased brain have emerged as attractive cellular targets for new therapies. Recent advances in adeno-associated viral (AAV) vector technology have enabled the specific targeting of transgenes to astrocytes. The aim of this study was to determine whether AAV-mediated overexpression of excitatory amino acid transporter 2 (EAAT2), glutamine synthetase (GS) or knockdown of adenosine kinase (ADK) expression by microRNA (miR) sequences in hippocampal astrocytes has anticonvulsant efficacy in the kainate model of temporal lobe epilepsy (TLE). Male Sprague Dawley rats (250-300g) received a bilateral hippocampal infusion of AAV9 vectors expressing luciferase, EAAT2, GS, luciferase, miR-negative control, or miR-ADK (n=10-15 per treatment). Immunohistochemical analysis of the brains of subgroups of rats at 3 weeks post-vector injection showed each transgene was expressed predominantly in hippocampal astrocytes at high levels with minimal inflammation and neurotoxicity. To assess therapeutic efficacy, rats (n=8-10 per treatment) were implanted with a cannula and electrode 3 weeks after vector infusion. Seizures were induced 1 week later by unilateral intrahippocampal injection of kainic acid (40ng), and electroencephalographic and motor seizures were recorded for 90 minutes. Overexpression of EAAT2 or GS did not produce anticonvulsant effects relative to luciferase-injected controls. However, ADK knockdown significantly reduced the duration of electrographic seizures by 51% ($p=0.02$) compared to miR control rats. These results provide additional support for ADK as a therapeutic target for TLE.

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Poster 5.53

Human globus pallidus volume reduction in HD with differential cell loss between external and internal segments

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In Huntington's disease (HD), there are major pathological changes in the basal ganglia, with major loss of striatal neurons. However, there have been no studies using design-based stereology to assess cell and volume changes in the globus pallidus (GP), the target of striatal output. In our study, 8 HD and 8 normal cases were analysed in detail using unbiased stereological counting methods and 3D volume analysis, to quantify pallidal neurons and investigate volume changes in all segments of the GP. Pallidal neurons were morphologically identified on Nissl-stained 70 µm serial sections, with external (GPe) and internal (GPi) segment boundaries identified using enkephalin and substance-P immunoreactivity.

The results show a major reduction in total GP volume in HD, with GPe volume loss being greater than GPi. Preliminary findings show a 54% reduction in GPe volume, with greater reduction corresponding with increasing HD grade (grade 1, 45% decrease; grade 3, 56% decrease). In the GPi, there is an overall 38% reduction in volume, with greater reduction with increasing grade (grade 1, 29% decrease; grade 3, 40% decrease). Pallidal neuron quantification (in progress) shows greater cell loss in the HD GPe compared with GPi. GPe quantification shows a 64% loss of pallidal neurons, with greater cell loss corresponding with increasing grade (grade 1, 40% loss; grade 3, 80% loss). GPi quantification shows a 20% decrease in pallidal neurons. These findings show that there is a greater volume and cellular reduction in the GPe compared to GPi in HD, consistent with neurochemical studies showing that enkephalinergic striatal-GPe fibres degenerate in advance of substance-P striatal-GPi fibres.

Poster 5.54

Supporting someone with Parkinson's disease: The influence of different cognitive status

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Cognitive impairment in Parkinson's disease (PD) can impact negatively on caregivers and is associated with carer distress and feelings of burden. To investigate this relationship we examined level of burden, coping strategies, depression, anxiety and potential positive aspects of caregiving in the caregivers of 106 PD patients. The PD patients were classified as either showing normal cognition (PD-N; n=55), with mild cognitive impairment (PD-MCI; n=37) or with dementia (PD-D; n=14). The mean Zarit burden score increased between carers of PD-N (M=13.7, SD=1.6) through to PD-MCI (M=21.3, SD=1.9) and PD-D (M=28.3, SD=3.2); F (2,103) =10.6, p<0.0002. Post hoc test (Newman-Keuls) identified significant Zarit burden scores between: PD-N and PD-MCI, p<0.03, PD-N and PD-D p<0.0002, and PD-MCI and PD-D, p<.05. The proportion of carers showing significant levels of burden (Zarit >21) was 23% for PD-N, 49% for PD-MCI and 85% for PD-D. Time spent providing care and type of coping strategies, such as engaging in self-distraction and seeking instrumental support, increased with the extent to which caregivers experienced burden. The level of burden experienced was independent of whether the caregiver lived with the person with PD, whether the caregiver was a spouse, family member or friend and whether the caregiver felt positively about their role in providing care and support. There was no difference in depression and anxiety between the three groups suggesting that the emotional response of caregivers was independent of burden. The study highlights the impact of Parkinson's disease on those providing care when the patients' cognition is poor, including those with MCI. Caregiver well-being has important implications for nursing home placement and disease course.

Poster 5.55

Behavioral effects of a double ethanol binge during brain development

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For women who continue to drink during pregnancy, periodic binge drinking is more prevalent than daily drinking. This study investigated the effects of a 'double binge', on a range of behaviors in the offspring. On PN6 and PN8 Long Evans rat pups in treatment groups; E4, 4.5g/kg/day; E5, 5.25g/kg/day or E6, 6.0g/kg/day, received ethanol in an artificial milk solution via intra-gastric intubation in two feeds two hours apart. A sham intubation (SI) group acted as a control for the effects of ethanol and pups reared normally by the dam were suckle controls (SC). Testing in the Morris Water maze and elevated plus maze was carried out in young adult rats during the 'dark cycle' of the animals' day. In the water maze there was a significant effect of treatment [$F(4,348 = 24.95$, $p<0.0001$) and day [$F(3,348) = 23.95$, $p<0.001$] on path-length but no significant interaction. A range of water maze performance parameters also indicate key factors impacting on the performance of E6 animals. Ethanol treatment also had a significant effect on avoidance ($F[4,128]=7.206$, $p<.0001$) but not the escape component in the T-maze. This data shows a dose dependent effect of a double binge-like ethanol exposure on behavior in the mature animal. This has possible implications for the intermittent drinking during the third trimester of human pregnancy resulting in human behavioral dysfunction.

Poster 5.56

Improving cell based therapy for Parkinson's disease

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Parkinson's disease is characterized by the progressive degeneration of midbrain dopamine (DA) neurons, resulting in motor function disturbances. Whilst current therapies are limited, clinical trials have demonstrated that new DA neurones transplanted directly into the brain can structurally and functionally compensate for those lost in PD. Whilst providing proof-of-principle, these trials have also shown extensive variability amongst patients and exposed a number of caveats in the technology, including: limited tissue availability; poor cell survival; and insufficient reinnervation of target tissue. These hurdles highlight the need for further research, and provide the foundation for our research. Our focus is on optimising donor material, improving graft survival and promoting integration of grafted neurons.

In order to tackle these problems we rely heavily on knowledge of developmental biology. How are DA neurones normally born in the foetus and what regulates the growth and guidance of their axons to appropriate targets? Understanding these processes and exploiting them in a stem cell transplantation context could significantly improve this technology. This presentation will focus on a recent birth dating study to identify optimal tissue for transplantation. This work includes classical ectopic transplantation into Parkisonian rodents to restore DA transmission as well as efforts to restore normal circuitry through homotypic grafting and delivery of trophic cues.

Poster 5.57

Pyramidal and interneuron cell loss in the motor and cingulate cortex in HD human brain correlates with dominant symptom profile

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Huntington's disease (HD) is characterised by variable symptoms and neuropathology in the basal ganglia and cerebral cortex. Our recent studies have shown that motor and mood symptoms of HD were related to pyramidal cell loss in the primary motor (BA 4) and anterior cingulate (BA 24) cortex in the HD human, respectively (Thu et al., Brain, 133; 2010). We have extended these studies in the same HD cases to the cortical interneurons to determine whether interneuron loss also correlates with symptom profile, and is linked to pyramidal cell loss. A double-blind study was conducted in 13 HD and 14 matched control cases using unbiased stereological cell counting methods to quantify three major types of interneurons immunoreactive for calbindin-D28k (CB), calretinin (CR), and parvalbumin (PV). Detailed data on symptomatology of HD cases was collected from family members and clinical records, and were categorised into dominant symptom groups ("motor" and "mood" symptoms) (Tippett et al., Brain, 130; 2007). Overall, the pattern of interneuron loss showed a significant association between pyramidal cell loss and HD symptomatology. The HD cases which were dominated by "motor" dysfunction showed a significant loss of both CB+ interneurons (57% loss) and pyramidal cells (45% loss) in the motor cortex but no cell loss in the cingulate cortex. By contrast, cases with major "mood" dysfunction showed a significant major loss of all three interneuronal populations (71% loss CB+; 60% loss CR+; and 80% loss PV+ cells) and pyramidal cells (40% loss) in the cingulate cortex but no loss in the motor cortex. The findings in this study show that interneuron loss is associated with pyramidal cell loss in the HD motor and cingulate cortex and the loss is significantly associated with the dominant symptom profile, suggesting that pyramidal-interneuron loss is closely linked in the pathogenesis and symptomatology of HD.

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Poster 5.58

Screening novel compounds as potential protectants after stroke

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Despite decades of active research, stroke remains a significant cause of mortality and profound morbidity. The vast majority of strokes are ischemic, generating a core of rapid cell death surrounded by a penumbral region that remains at-risk. However, with the failure of so many stroke studies to translate into the clinic, there is a need to find new potential therapeutics. We have tested two new drug compounds as potential neuroprotectants. Young (3-month old) male C57Bl6 mice underwent photothrombotic stroke to the motor cortex and were then treated with drug or vehicle 1hr after stroke and then again 24hrs later. Stroke volume (n=5 per group) was analysed histologically 7-days post-stroke using cresyl violet staining and functional recovery assessed behaviourally on both the grid-walking and cylinder tasks. Drug X showed a small yet significant decrease in infarct volume for all three doses tested (0.1, 1 & 10mg/kg i.p.: $P<0.05$). Drug Y resulted in a marked decrease in stroke volume at the low dose (0.1mg/kg i.p.: $P<0.001$), however this protection was lost at the highest dose (10mg/kg i.p.). These are the first studies testing these compounds as potential neuroprotectants with the initial screening showing some promise for at least two of the drugs tested to date. Further studies are being done to test their potential protection in aged 24-month old) mice and to also assess whether this protection also translates into functional improvements.

The work is supported by an HRC Sir Charles Hercus Fellowship.

Poster 5.59

$GABA_A$ receptor subunit localisation in the human amygdala

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$GABA_A$ receptors are inhibitory ionotropic heteropentamers assembled from 19 different subunits. Receptor pharmacology and physiology is determined by subunit configuration, and receptors containing α2- and α3-subunits are of interest for their involvement in anxiety. Rodent studies demonstrate $GABA_A$ receptor expression throughout the brain, notably in the amygdala. The amygdala, which is composed of a heterogeneous cluster of distinct subnuclei, has many functions, ranging from neuropsychological to behavioural. However, few studies have characterised its chemoarchitecture in the human. This study aimed to localise major GABAA receptor subunits in the subnuclei of the normal human amygdala, and identify cell types that express them. Perfusion-fixed amygdala sections from 8 normal post-mortem human brains were stained immunohistochemically using antibodies against GABAA receptor subunits α1, α2, α3, β2,3 and β3. Immunofluorescent double-labelling was used to localise GABAA receptor subunits with calcium-binding proteins, parvalbumin and calbindin. The α1- and β2,3-subunits had similar distributions, with higher neuropil and cellular immunoreactivity in the lateral nucleus, and cellular immunoreactivity in the basal nucleus. The α2-subunit showed high neuropil immunoreactivity in all subnuclei, particularly the lateral, central and cortical nuclei. High α3-subunit immunoreactivity was seen in the neuropil of the intercalated nuclei while the β3-subunit was only expressed on few cells throughout the subnuclei. A subset of α1- and β2,3- but no α2-subunit immunoreactive cells colocalised with parvalbumin and calbindin. Thus, comparable to the rodent, $GABA_A$ receptors feature prominently in the human amygdala. The heterogeneous localisation of $GABA_A$ receptor subunits in the human amygdala subnuclei reflects the diversity of amygdala function. Furthermore, the prevalent expression of the α2-subunit suggests a role in anxiety for the amygdala.

Poster 5.60

Acute hippocampal cell death in the alcohol-exposed developing rat brain

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Alcohol consumption during pregnancy can result in fetal defects, especially in the brain, with consequent memory and learning deficits. The risks of a single or repeat binge drinking are unclear. This study aimed to quantify ethanol-induced apoptotic cell death in the hippocampus after a single binge-like exposure to ethanol on PN8, and if this was altered by an early binge exposure on PN6. Long-Evans rat pups from three litters were pseudorandomised into ethanol-exposed (EE) or intubation control (IC) groups. EE pups were administered 6 g/kg of ethanol either on PN6 and PN8, or on PN8 only. IC pups received sham intubations at equivalent times. Rat pups were deeply anaesthetised (sodium pentobarbitone, i.p.) and perfusion-fixed (4% paraformaldehyde) 12 hours after the last ethanol delivery. Brains were removed, cryo-protected, frozen, sectioned in the coronal plane at 40µm, and stained with Cresyl Violet. The optical fractionator was used to determine the total number of apoptotic bodies within the CA1, CA3, and DG hippocampal regions. Initial results indicate 15,400 apoptotic cells in CA1 with ethanol exposure on PN6 plus PN8 with 31,100 after PN8 exposure alone, compared to less than 5,000 apoptotic cells in ICs. There was no significant cell death in the CA3 and DG regions. These results show that a prior exposure to ethanol affects subsequent acute apoptotic cell on a particular day. This data may reflect that a subpopulation of CA1 cells are vulnerable to ethanol's neurotoxic effect. This study increases our understanding of the potential consequences of binge drinking during the third trimester equivalent of human fetal development.

Poster 5.61

Early pathology in Ovine CLN6 Batten disease – assays for testing therapies

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The neuronal ceroid lipofuscinoses (Batten disease) are a group of severe, fatal, and incurable childhood lysosomal storage diseases characterised by cortical atrophy, blindness and seizures, culminating in premature death. Mutations in one of 11 genes have been shown to cause NCL. Naturally occurring forms of Batten disease are seen in three breeds of sheep, CLN6 in New Zealand South Hampshires and Australian Merinos, and CLN5 in New Zealand Borderdales.

This study used primary sheep neural cells obtained from foetal South Hampshire sheep (embryonic day 60; mid-gestation) deficient in CLN6 (CLN6-/-) and unaffected Coopworth controls to study early changes in cellular pathology.

A significant decrease in lysosomal acidity was observed in CLN6-/- primary neural cultures compared to healthy controls using the dye LysoTracker Red ($P < 0.0001$ $n = 3$ animals per group, ANOVA).

Confocal analysis of calnexin immunostained sheep neural cells revealed a reduction in endoplasmic reticulum staining in CLN6-/- cells compared to control cells. Analysis showed this difference to be statistically significant ($P = 0.036$ $n = 3$, unpaired t-test).

These findings highlight the importance of intervention at the earliest possible stage and provide an assay in which to test the success of potential treatments in CLN6 disease. The second phase of the study will test the effectiveness of lentiviral mediated gene therapy. Specifically, examining reversal of pathology in the cells after lentiviral transduction. CLN6-/- neural cells will be transduced with wild-type CLN5 or CLN6 containing lentivirus and LysoTracker and endoplasmic reticulum assays will be used to test correction after gene therapy treatment.

Poster 5.62

Changes in interneuron populations in the primary sensory cortex in Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disorder with variable symptoms including choreiform movements, cognitive, mood and neuropsychological changes. According to our recent studies, variable symptomatology of HD is associated with variable pyramidal cell loss in the cerebral cortex. To further extend these results, we are now investigating the correlation between the pattern of GABAergic interneuron loss in the cerebral cortex and the phenotypic variability in HD. The GABAergic interneurons are inhibitory neurons that modulate the activity of pyramidal neurons in the cerebral cortex, thereby determining the cortical output. This study is being carried out using unbiased stereological cell counting to quantify three major types of GABAergic interneurons in the primary sensory cortex of 10 HD and 12 neurologically normal post-mortem human brains. Three different calcium binding proteins, calbindin-D28k, calretinin and parvalbumin, are used to label interneurons. The HD cases are categorized into three dominant symptom groups ("mood", "motor" and "mixed") based on detailed data of their symptomatology, which was collected from family members and clinical records. According to our preliminary data, there is a heterogeneous loss of Calbindin-positive interneurons in the sensory cortex of the HD cases compared to control cases, with parvalbumin-positive interneurons being preserved in all HD cases. We have observed a significant loss of calbindin-positive interneurons (67% loss) in HD cases with major "motor" disorder, but not in cases with mainly "mood" or "mixed" symptoms. Therefore, these preliminary results suggest an important association between the pattern of interneuronal loss in the sensory cortex and the variable symptomatology in HD.

Poster 5.63

Atenolol attenuates cardiac and cortical electrographical changes during status epileticus

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Status epilepticus has been increasingly associated with cardiac injury in both clinical and animal studies. The current study examined the effect of kainic acid (KA, 10 mg/kg) induced seizures on EEG and ECG activity. It was hypothesised that atenolol, a peripheral β_2 antagonist, would attenuate cardiac arrythmias and structural damage caused by status epilepticus induced injury. Sprague-Dawley rats (male, 300-350g) were implanted with EEG and ECG electrodes to allow simultaneous telemetric recordings of CNS cortical and cardiac responses during and after seizures. Animals were randomised into saline controls, and saline vehicle-pretreated and atenolol-pretreated KA groups. Bradycardia, with decreased P wave amplitude coinciding with low level seizure activity, was observed within the immediate period following KA administration. Heart rate decreased maximally by 27.6 ± 5.9% in the saline-KA group. As high level seizure behaviours and EEG spiking progressively increased, tachycardia developed, with a maximum heart rate increase of 33.1 ± 7.4 % coinciding with QTc prolongation and T wave elevation over the remainder of the 3 hour recording period. Maximal increases in EEG spiking were observed 125 min post-KA with increases occurring across all frequency bands (delta-gamma). Pretreatment with atenolol attenuated KA-induced changes in heart rate, QTc interval and P wave amplitude observed during both bradycardic and tachycardic phases. Pre-administration of atenolol also successfully reduced seizure activity across all frequency bands and decreased seizure behaviours. These results suggest that the modulation of sympathetic activity by atenolol in status epilepticus provides a promising therapeutic approach to seizure-induced cardiomyopathy as well as decreasing seizure severity.

Poster 5.64

Phosphorylation of Akt by antipsychotic drugs is induced indirectly through dysregulation of glucose homeostasis

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The second-generation antipsychotic drugs (SGA) clozapine and olanzapine is believed to promote positive outcomes in Schizophrenic patients through increasing neuronal survival and dendritic alterations via activation of the Akt (PKB) signaling pathway in the brain. Incidentally, schizophrenia has been associated with higher incidences of genetic defects in the Akt pathway, suggesting that alterations in Akt activation by antipsychotic drugs may be linked to recovery. Common side effects of SGAs are diabetic like symptoms, notably higher glucose and insulin levels, which is a known activator of the Akt pathway in the brain. We propose this increase in serum insulin levels by SGAs is causing the phosphorylation of Akt in the hippocampus and cerebral cortex. Male Sprague-Dawly rats were injected i.p. with clozapine, then perfused trans-cardinally with paraformaldehyde after one hour. Brains were sectioned and stained against serine-473 phosphorylated Akt. Another group were pretreated with octreotide, an inhibitor of insulin and glucagon secretion, for one hour before injection of clozapine. Rats treated with clozapine had increased cellular and dendritic Akt phosphorylation in the cerebral cortex and hippocampus. These effects were reversed in animals pretreated with octreotide. This data suggests that the diabetic side effects of these SGAs may be contributing to alterations in Akt phosphorylation, which would result in the increased cognitive outcomes in patients suffering from schizophrenia.

Poster 5.65

Aberrant expression of plasma microRNAs in the maternal immune activation model of schizophrenia

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Recently microRNA have been identified extracellularly within the circulatory system. They have been proposed to act as biomarkers for disease states and disorders, including those with a neurological basis such as schizophrenia. The aim of this study was to investigate whether maternal immune activation (MIA) in rodents, an animal model of enhanced risk for schizophrenia development, would alter microRNA levels in the plasma of adult offspring. MIA was induced in dams by administering poly(I:C) mid gestation. We isolated RNA from plasma derived from adult MIA (n = 9) and Control (n = 10) offspring and used TaqMan low density microarrays to conduct high throughput quantitative-real time-PCR analysis of 754 microRNA within the plasma of our animals. Differential expression of individual microRNA was assessed using moderated (empirical Bayesian) *t*-tests with Benjamini-Hochberg corrections for multiple testing and a $\log_2$ fold change (LFC) cut-off set at +/- 1.0. Three microRNA were found to be significantly reduced in the MIA group: miR-106b (LFC = -1.10, $P = 0.005$), and miR-15a (LFC = -1.19, $P = 0.01$), miR-451 (LFC = -1.54, $P = 0.0005$). Previous reports have indicated that the expression of miR-106b is decreased and miR-15a is increased in the schizophrenic brain. MiR-451 synthesis requires a novel microRNA biosynthesis pathway, while canonical microRNA biosynthesis is increased in the schizophrenic cortex. This study has shown that a prenatal insult can alter the expression profile of plasma microRNA in adulthood. Our data suggests that circulating microRNA can reflect a predisposition to a schizophrenic state.

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Poster 5.66

Delayed post-treatment with mesenchymal stem cells affects progenitor cell proliferation in the subventricular zone after neonatal rat hypoxic/ischemic striatal injury

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Neonatal hypoxic/ischemic (H/I) striatal injury can lead to cerebral palsy. In our laboratory the absolute number of striatal medium-spiny neurons is restored at one week after delayed treatment with bone marrow-derived mesenchymal stem cells (MSCs). The adjacent subventricular zone (SVZ) is a source of progenitor cells that may restore these neuronal numbers. Whether treatment with exogenous MSCs facilitates neurorestoration via progenitor cell proliferation, migration, survival and differentiation is unknown. Here we investigated whether MSCs affect progenitor cell proliferation in the SVZ. Postnatal day (PN) 7 male Sprague-Dawley rat pups underwent ligation of the right common carotid artery, followed by exposure to 8% oxygen/92% nitrogen for 1.5 hours. On PN14 a subcutaneous injection of cultured bone marrow-derived MSCs (126,000 cells), or saline, was administered to four H/I rats, respectively. After perfusion on PN21, serial cerebral sections were incubated with Ki-67 primary antibody, a specific marker of cellular proliferation, followed by biotinylated secondary and streptavidin-peroxidase antibodies and aminoethylcarbazole as the end label. Stereological methods were used to measure the absolute number of Ki-67-positive cells in the SVZ. There was a statistically significant reduction in the absolute number of Ki-67-positive cells in the SVZ of H/I animals treated with MSCs (1380 ± 120, mean ± SEM, n = 3) compared to H/I diluent-treated animals at one week after treatment (3390 ± 536, n = 4, $p<0.035$). This decrease in the number of proliferating progenitors in the SVZ suggests that MSCs were effective in stimulating the migration, survival and differentiation of SVZ progenitor cells into nearby striatal neurons. Experiments investigating migration, survival and differentiation are underway.

6.1

A computational model of oxygen transport in the cerebrocapillary-levels for normal and pathological brain function: An investigation on flow-metabolism coupling

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The oxygen exchange and correlation between the cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption ($CMRO_2$) in the cortical capillary-levels for normal and pathological brain functions remain the subject of debate. A 3D realistic mesoscale model of the cortical capillary network (non-tree like) is constructed using a random voronoi tessellation in which each edge represents a capillary segment. The hemodynamics and oxygen transport are numerically simulated in the model which involves rheological laws in the capillaries, oxygen diffusion and nonlinear binding of Hb to oxygen, respectively. The findings show that cerebral hypoxia due to a significant decreased perfusion (as can occur in stroke) can be avoided by a moderate reduction in oxygen demand. Oxygen extraction fraction (OEF) can be an important indicator for the brain oxygen metabolism under normal perfusion and misery perfusion syndrome (leading to ischemia). The results demonstrate that a disproportionately large increase in blood supply is required for a small increase in the oxygen demand which in turn, is strongly dependent on the resting OEF. The predicted flow-metabolism coupling with respect to maintaining the tissue oxygen tension in the realistic model supports the experimental studies of spatiotemporal stimulations in humans by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

6.2

Characterisation of a novel gene regulation system in the rat brain

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A common gene therapy strategy involves continuous, long-term overexpression of a transgene with therapeutic potential in a target tissue. Unregulated transgene expression poses a problem clinically due to potential side-effects from excessive transgene levels. The aim of this study was to characterise the functionality of a novel gene regulation system developed in the lab that relies on activation of caspase-3 or calpain, proteases that are activated in response to cell stress, to selectively switch on transgene expression only when required in “at-risk” neurons but not in healthy neurons. Adeno-associated viral vectors (AAV) vectors expressing green fluorescent protein (GFP) under the control of a caspase-3 or calpain “switch” were injected into the striatum or substantia nigra pars compacta (SNc) of male Sprague-Dawley rats (200-300g). Three weeks later, brains from a subgroup of rats were taken for analysis of basal GFP expression. Additional subgroups received an intrastriatal infusion of either quinolinic acid (QA) (n=10 per vector) or 6-hydroxydopamine (6-OHDA) (n=5 per vector) before rats were perfused 48 hours later and brains removed for immunohistochemical analysis. Under basal conditions, AAV-mediated gene transfer was not associated with any toxicity as assessed by immunohistochemistry to cell death markers, and small numbers of GFP-positive cells were observed in the injected hemisphere. QA injection increased GFP-positive cell numbers surrounding the lesion site and similarly, GFP-positive cell numbers appeared to be increased in the SNc relative to the uninjected hemisphere following 6-OHDA-injection. Our results suggest that our gene regulation system has a low basal expression and toxicity profile and initial findings provide proof-of-principle of its functionality in two models of neurodegeneration.

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6.3

Making sense of super-resolution data

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Super-resolution optical techniques such as PALM, STORM and STED are becoming both increasingly mature, and increasingly widespread. This means that even if you don't use the techniques in your own research, you are likely to encounter super-resolution images in your subject literature. The data produced by super-resolution methods is however quite different in both scale and nature to that obtained using conventional imaging methodologies, with the result that many established metrics such as colocalisation have limited usefulness. In the last 4 years we have applied super-resolution to a wide range of samples covering both neuronal and cardiac nanostructures. Drawing on this data I will discuss a number of the challenges we have encountered, and the solutions we have developed to them. These challenges include the lack of appreciable colocalisation at 30 nm resolution, a surprising degree of variability in the nanostructure of cellular signalling domains such as synapses which appear relatively uniform at the diffraction limit, as well as the difficulty of ensuring that the labelling accurately reflects the underlying structure. In addition to establishing a basis on which to assess published super-resolution images, I will discuss the implications of our findings for conventional confocal imaging.

6.4

A numerical model for understanding cerebral CO2 reactivity impairment in diabetes mellitus

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Cerebral CO2 reactivity is impaired in those suffering from diabetes mellitus. A potential source of this impairment is the stiffening of blood vessels in cerebral tissue by hyperglycaemia-induced glycosylation of arterial walls. A mathematical model of cerebral CO2 reactivity is developed to investigate the effect of these alterations, and whether they agree with experimental results. Modelled elements include the transport of CO2 from cerebral tissue into arterial blood; MLCK phosphorylation and smooth muscle stress development; a viscoelastic model of a vessel wall; and the relationship between interstitial CO2 and cytosolic Ca2+. Alterations in wall stiffness and thickness are investigated as sources of discrepancies between diabetic and control data.

By choosing parameter values such that the model output corresponded to experimental data, the model predicted mean arteriole stiffness of (3.2 +/- 1.8) kPa in control patients and (4.6 +/- 1.7) kPa in diabetic patients; and wall thicknesses of (11.8 +/- 7.7) um and (5.9 +/- 3.5) um respectively. Both of these results are statistically significant ($p < .05$). These results provide evidence that the impairment in cerebral CO2 reactivity observed in diabetes mellitus patients is contributed to by altered mechanical properties of vessel walls.

6.5

AAV5 vectors mediate efficient transgene expression in astrocytes in the rat substantia nigra

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Adeno-associated viral (AAV) vectors have become the gene delivery vehicles of choice for human gene therapy to the central nervous system (CNS). Given that astrocytes play key roles in supporting neuronal function, and reactive astrocytes in neurodegenerative diseases have the potential to evolve into dysfunctional cells that promote neurodegeneration, astrocytes may be a better cellular target for gene therapy. The aim of this study is to develop and validate an optimised AAV vector for targeting "resting" and reactive astrocytes in the rat substantia nigra. An AAV serotype 5 (AAV5) vector expressing a green fluorescent protein (GFP) under control of the glial fibrillary acidic protein (GFAP) promoter, with incorporation of target sequences (miR124T) for the neuronal specific miR124 to silence off-target GFP expression in neurons (rAAV5-GFAP-GFP-miR124T) was injected into the substantia nigra pars compacta (SNc) of naïve adult male Sprague Dawley rats (2×10^8 genomes in 2uL; n=5). Additional rats received rAAV5-GFAP-GFP-miR124T in the SNc at 1 or 4 weeks (n=5 per timepoint) following an intrastriatal infusion of 6-hydroxydopamine which causes progressive dopamine cell loss and reactive gliosis in the SNc. Three weeks following vector infusion, brains were taken for immunohistochemical analysis. In the naïve brain, high levels of GFP was found in astrocytes in the SNc, whereas GFP was found predominantly in astrocytes at a more dorsal aspect to the SNc in the 1 week lesion group. The 4 week lesion group is currently being analysed. These results suggest that rAAV5 vectors target both healthy and reactive astrocytes, and could be used to genetically manipulate nigral astrocyte function as a therapeutic approach for Parkinson's disease.

Supported by the Marsden Fund

6.6

Investigation of methamphetamine self-administration in rats

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The use and abuse of psychostimulant drugs represents a growing social and economic problem in New Zealand. The latest world drug report lists New Zealand and Australia as higher users of amphetamines than the rest of the world (UNODC, 2010). There is a large body of research into the effects of high-dose "binge" methamphetamine injections in animal models. However, a relatively small body looks at changes associated with methamphetamine self-administration. Addiction proteomics is a growing field with great promise for researching different stages of the addiction process in a wide variety of reward-related brain regions. Dopamine is an important neurotransmitter that is involved in reward and motivation in the brain; however, many other factors in the brain contribute to the development of drug addiction. This project aims to investigate self-administration of methamphetamine in rats, and to determine the change in the striatum and nucleus accumbens after long-term exposure. Rats received methamphetamine self-administration training for 20 days followed by 2 weeks of forced abstinence. There is no significant change in dopamine uptake in the striatum or nucleus accumbens after this period of time, and no change in total dopamine transporter protein using western blots. Shotgun proteomics of synaptosomes prepared from striatum tissue show 19 significantly down-regulated proteins and 11 up-regulated proteins among the 453 proteins identified. The differentially-expressed proteins are involved in glycolysis, vesicle trafficking, cytoskeleton, protein folding and mitochondrial dysfunction. Global analysis of the proteome in a complex disorder such as drug abuse provides the means to identify future therapeutic targets and a greater understanding of the mechanism of drug addiction.

7.1

An optogenetic approach to voltage imaging

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Protein-based fluorescent probes of neuronal activity are at the core of emerging approaches to study the dynamics of neuronal circuits that are composed of heterologous cell types [1]. The rationale behind our large effort to develop genetically encoded voltage indicators lies in the fact that these probes allow us and others to move beyond the electrophysiological analysis of individual or small numbers of cells without neglecting cellular diversity or compromising temporal resolution. Work in our and other laboratories during the last 15 years resulted in a new generation of voltage-sensitive fluorescent proteins (VSFPs) based on the voltage-sensing domain (VSD) of *Ciona intestinalis* voltage sensor-containing phosphatase (Ci-VSP). To this end, our laboratory explored different design principles for these engineered proteins and characterized numerous mutational variants for each facility. We demonstrated that recent versions of VSFPs can report membrane voltage signals in isolated neurons, brain slices and living mice [2,3]. The most advanced probes enable the optical recording of action potentials from individual neurons in single sweeps and voltage imaging of population activity, including synchronized activities in the gamma frequency band, from defined cell populations in acute brain slices. In living mice, VSFPs afford sufficient SNR for probing sensory-evoked responses and enables univocal detection of spontaneous electrical population activity in somato-sensory cortex during light anesthesia or quiet alertness.

Along with the ability to target specific genetically-defined cell populations, VSFPs open a new experimental window for the study of the interaction dynamics of neuronal assemblies, facilitate the investigation of information processing mechanisms of the brain, such as the circuit operations involved in sensing our environment and generation of body movements, but will also be applicable to directly visualize cognitive functions.

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2. Akemann, W., et al. Nat Methods 7, 643-649 (2010).
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7.2

Imaging cardiac ventricular myocytes – functional and structural aspects of contractile failure

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The amplitude and time course of the cytosolic Ca^{2+} transient in cardiac muscle cells is one of the major regulators of cardiac contractility. The rapid, cell- wide increase in cytosolic Ca^{2+} is caused by the summation of elementary Ca^{2+} release events called Ca^{2+} sparks. During the cardiac action potential, these elementary events are triggered by voltage-gated Ca^{2+} channels in the cell surface membrane. We have visualized these microscopic Ca^{2+} release events in intact heart cells with fast confocal scanning and studied their relationship to the distribution of key Ca^{2+} handling proteins. Our data shows that elementary release events occur via clusters of ryanodine receptors (RyR) in the intracellular Ca^{2+} store, the sarcoplasmic reticulum (SR) and are opened by a process known as Ca^{2+} induced Ca^{2+} release. Using a combination of confocal microscopy and novel optical super-resolution imaging techniques we have started to dissect the mechanistic changes underlying contractile dysfunction in heart failure. Our results show that extensive remodelling of the t-tubular network (an extension of the cell membrane) and associated excitation-contraction coupling proteins occurs in the failing heart which may contribute to abnormal calcium handling in heart failure. We have developed novel quantitative approaches to characterize these changes, including new fluorescent imaging methods that have single molecule resolution. These super-resolution techniques can detect protein proximity with ~20 nm resolution, similar to electron microscopy, but with the molecular specificity of fluorescence approaches. Compared to previous estimates obtained with thin-sectioned electron microscopy our data reveals a more complex distribution of proteins compatible with a stochastic protein cluster assembly process. Our structural data suggests that these clusters are altered in failure suggesting that structural changes at the nanoscale may contribute to contractile failure.

7.3

From dyes to proteins, imaging subcellular calcium events

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Intracellular calcium signalling is one of the most widely used signalling pathways and is used to control a vast range of cellular events. Given the diversity of calcium signalling, each signal cascade must be carefully regulated and compartmentalised to prevent crosstalk. This leads cells to having multiple calcium microdomains. A major challenge in the calcium imaging field is to separate these domains both spatially and temporally. With the advent of high speed line scanning microscopy and rapidly responding calcium dyes such as Fluo and Rhod, capturing high temporal cytosolic calcium signalling became possible. However, the use of these dyes beyond cytosolic calcium measurements has been limited, primarily due to the lack of subcellular targeting mechanisms and difficulties in loading these dyes into subcellular membrane enclosed organelles. More recently many of these obstacles have been overcome with the development of rapidly responding, easily expressed, genetically encoded calcium indicator proteins. Calcium indicator proteins can be developed to have a range of calcium affinities to accommodate the dynamic range of subcellular calcium concentrations, ranging from nM to mM. They can also be targeted to specific subcellular structures giving unrivalled spatial resolution. These calcium sensing proteins can be broadly categorised into two types; (i) those based on a single green fluorescent protein (GFP) and (ii) those based on a pair of fluorescent proteins (Förster/Fluorescence Resonance Energy Transfer, FRET). Irrespective of the type, these sensors report calcium levels by coupling the conformational change of a calcium sensing protein, calmodulin, to conformational changes in the fluorescent moieties. These new classes of calcium indicator proteins give unrivalled capabilities for observing the rapid and exquisitely spatially organised subcellular calcium signalling events which control a host of cellular functions.

7.4

Imaging techniques for neurotoxicity investigations

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Live imaging techniques are essential to answering questions relating to mechanisms of neurotoxicity, offering real-time monitoring of many cellular and sub-cellular events. One such technique is calcium imaging using fluorescent ratiometric dyes such as Fura-2. Whilst this approach is well established, it is a relatively simple technique and capable of addressing many unanswered questions. Understanding intracellular calcium dynamics are critical for studies of neurotoxicity – in addition to precise involvement in specific intracellular pathways, wide-spread calcium overload is often a precursor to cell death. Mitochondrial dysfunction is another key factor in many neurotoxic mechanisms. Data will be presented on the real-time monitoring of mitochondrial membrane potential, and mitochondrial superoxide production using the fluorescent dyes Rh-123 (de-quenching mode) and MitoSox respectively. Intrinsic optical signalling is a non-fluorescent imaging technique utilizing changes in light transmittance and scattering to infer alterations in neuronal morphology (e.g. swelling and dendritic beading) in a whole brain slice preparation. Applications of these techniques will be presented in the context of Parkinson's disease (rotenone) and stroke (oxygen glucose deprivation) animal models in *in vitro* brain slice preparations. Whilst these techniques are well established, they continue to offer valuable insight to cellular dysfunction in neurotoxicity investigations.

8.1

Hormones in autism: The other side of the testes

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Autistic spectrum disorders (ASDs) are developmental disorders characterised by the presence of stereotyped behaviours as well as impairment in social interaction, communication and language. Autistic pathology in the brain causes an altered trajectory early in development. ASDs have an unexplained male bias, with incidence estimated to be 3 times higher in males than females. There is little evidence to show that excessive testosterone causes ASDs and little information available for the testicular protein hormones, inhibin B (InhB) and anti-Müllerian hormone (AMH, also known and Müllerian inhibiting substance) in children with ASDs. We measured InhB and AMH levels in 82 autistic boys by ELISA and found no differences with respect to the mean concentrations of normal boys. InhB correlated with the autism diagnostic interview-revised (ADI-R) score for the social interaction (R=0.29, p=0.009) and communication domains (R=0.29, p=0.022). Sub-analysis revealed that the correlation was not due to increased severity of individual symptoms but rather the number of symptoms that an autistic individual displayed. In a sub-section of the participants with milder symptoms, InhB showed stronger correlations with ADI-R score for the social interaction and communication domains (R=0.42, p=0.012 & R=0.50, p=0.030, respectively) and AMH showed a significant negative correlation (R=−0.44, p=0.018 & R=−0.39, p=0.039, respectively). ASD was thought to involve abnormal levels of male hormones, but the data suggests that the primary initiating causes of ASDs are equal in boys and girls but hormones like InhB and AMH could modify ASD severity. The male bias in autism may be due to sexually dimorphic hormones that modulate a non-dimorphic pathology.

8.2

Human stroke patients develop autoantibodies to NR1 subunit of NMDA receptors

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We previously showed that rats immunised with the NR1 subunit of the NMDA glutamate receptor (NMDAR) developed circulating NR1 antibodies, and were protected against experimental stroke and epilepsy. NR1 antibodies were found at low-levels in the brains of NR1-vaccinated rats under normal resting conditions, and were able to bind to NMDARs. This resulted in chronic low-level NMDAR antagonism and a compensatory up-regulation of NMDARs leading to downstream events including the up-regulation of cell survival genes. Breaches in the blood-brain-barrier that occur in neurological conditions such as stroke may lead to development of immune responses against brain proteins including NR1. The aims of this study were to determine whether human stroke patients develop specific anti-NR1 antibodies, to regions on the NR1 protein. Sera were collected from a cohort of 48 stroke patients at five days after admission and diagnosis of cortical, subcortical or brainstem lesions following ischaemic stroke, with pooled sera from age-matched healthy individuals used as control. Sera (n=12) that showed the strongest reactivity to the full-length NR1 protein, were screened for specific reactivity against a panel of 74 overlapping peptides spanning the extracellular domain of the NR1 subunit by enzyme-linked immunosorbent assay. Control sera showed no reactivity against NR1 peptides. However, 10 out of 12 stroke sera showed significant reactivity to at least two NR1 peptides, with 33.2% ± 7.4% of reactive epitopes located within the NMDA receptor ligand-binding site. Current studies will assess whether anti-NR1 antibodies from stroke patients can bind to NMDA receptors and alter neuronal function.

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8.3

Viral vector gene therapy for CLN5 and CLN6 batten disease in ovine models

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The causative genes of Batten disease (neuronal ceroid lipofuscinoses, NCLs) code for two classes of proteins, soluble lysosomal proteins or intramembrane proteins, which might differentially influence gene therapy strategy requirements. Large brains require targeted injections as all neurons cannot be reached.

Lentiviral vectors were packaged with the gene sequences and an expression tag for two representative forms of Batten disease in sheep. These were for a soluble protein defect, CLN5 in Borderdales, and an intramembrane protein defect, CLN6 in South Hampshires. Specific areas of the brain were surgically targeted, particularly the subventricular zone from which extended neurogenesis continues to supply migrating neurons, thus allowing for corrected cell replacement of dying affected cells.

Following the brain injections, the sheep were monitored for amelioration of disease via brain CT scans to monitor brain atrophy, simple behavioural tests, and for evidence of blindness. No differences were found in any of these parameters between the injected animals and untreated affected controls. However immunohistochemical analyses at *post mortem* showed persistent transduction of the ependymal cells lining the lateral ventricles and transduced cells apparently migrating from the sites of injection.

This study shows the lentiviral system stably transduces neuronal cells *in vivo* and that direct injection into the lateral ventricles is a satisfactory route for targeting the subventricular zone and the consequent migration of transduced cells. The likelihood of efficacy will be increased by refinement to improve vector spread, removal of the expression tag, much higher doses, and treatment of younger animals to maximise the chances of functional correction.

8.4

Novel neuroprotective actions of biometal-complexes

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Neurodegenerative illnesses such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are characterized by altered biometal metabolism in the brain. This has led to the development of novel therapeutic strategies designed to restore biometal homeostasis. We have investigated the effect of lipid soluble biometal-complexes on neuronal function in models of neurodegeneration. Models of AD, PD and ALS have been treated with bis(thiosemicarbazone)-metal complexes (CuII(gtsm), CuII(atsm) and ZnII(atsm)). The biometal-complexes inhibited amyloid beta accumulation and tau phosphorylation in cell cultures and an animal model of AD (APP/PS1) and improved cognition in the animal model. The biometal-complexes also induced robust neuroprotection in three animal models of PD and delayed disease onset and extended lifespan in two murine models of ALS. We are currently using a range of techniques to map the sub-cellular trafficking and mechanism of action of the biometal-complexes. We have identified unique cell-type specific patterns of biometal-complex uptake and localization associated with ER and vesicle-associated pathways. The biometal-complexes induce up-regulation of a number of important neuroprotective pathways in astrocytes together with improved neuronal function and survival. We have extended these findings to show that biometal-complexes modulate accumulation of neurotoxic TDP-43 in motor neuron disease models and rectify a number of abnormal processes in a murine model of lysosomal storage disorders. The basis of these broad protective effects is associated with modulation of basal brain biometal homeostasis and the cell signaling pathways affected by these metals. Our studies provide the first evidence that biometal-complexes delivered to neurons or glia can stimulate broad neuroprotective pathways and may provide the basis for treatment of neurodegenerative diseases.

8.5

Autism associated mutations in ProSAP2/Shank3 impair synaptic transmission and neurexin-neurologin mediated transynatpic signaling

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Mutations in several postsynaptic proteins have recently been implicated in the molecular pathogenesis of autism and autism spectrum disorders (ASDs), including Neuroligins, Neurexins and members of the ProSAP/Shank family, suggesting that these genetic forms of autism may share common synaptic mechanisms. Initial studies of ASD associated mutations in ProSAP2/Shank3 support a role for this protein in glutamate receptor function and spine morphology, however these synaptic phenotypes are not universally penetrant, indicating that other core facets of ProSAP2/Shank3 function must underlie synaptic deficits in patients with ASDs. We have examined the ability of ProSAP2/Shank3 to coordinate pre/postsynaptic signaling through the neurexin-neuroligin signaling complex. We find that synaptic levels of ProSAP2/Shank3 regulate AMPA and NMDA receptor-mediated synaptic transmission and induce widespread changes in the levels of pre- and postsynaptic proteins via neurexin-neuroligin transsynaptic signaling. ASD-associated mutations in ProSAP2/Shank3 disrupt not only postsynaptic AMPA and NMDA receptor signaling, but also interfere with the ability of ProSAP2/Shank3 to signal across the synapse to alter presynaptic structure and function. These data indicate that ASD associated mutations in a subset of synaptic proteins may target core cellular pathways that coordinate the functional matching and maturation of excitatory synapses in the central nervous system.

9.1

Spectrum of short- and long-term brain pathology and long-term behavioural deficits in male repeated hypoxic rats closely resembling human extreme prematurity

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Brain injury in the premature infant is associated with a high risk of neurodevelopmental disability. Previous small animal models of brain injury due to extreme prematurity typically fail to generate a spectrum of pathology and behaviour that closely resembles that observed in humans, even though they provide initial answers to numerous cellular, molecular and therapeutic questions. We tested the hypothesis that exposure of rats to repeated hypoxia from postnatal days (PN) 1-3 models the characteristic white matter neuropathological injury, gray matter volume loss, and memory deficits seen in children born extremely prematurely. Male Sprague-Dawley rats were exposed to repeated hypoxia or repeated normoxia from PN1-3. The absolute number of O4-positive pre-oligodendrocytes, the surface area of myelin, the absolute volume of cerebral white and gray matter, and the absolute number of cerebral neurons, was quantified stereologically. Spatial memory was investigated on a radial arm maze. Rats exposed to repeated hypoxia had a significant loss of: (i) O4-positive pre-oligodendrocytes at PN4, (ii) cerebral white matter volume and myelin at PN14, (iii) cerebral cortical and striatal gray matter volume without neuronal loss at PN14, and (iv) cerebral myelin and memory deficits in adulthood. Decreased myelin was correlated with increased ADHD-like hyperactivity. This is a new small animal model of extreme prematurity that generates a spectrum of short- and long-term pathology and behaviour that closely resembles that observed in humans. This new rat model provides a clinically relevant tool to investigate numerous cellular, molecular and therapeutic questions on brain injury due to extreme prematurity.

9.2

Pre-aggregated Amyloid Beta$_{25-35}$ leads to prolonged alteration of arginine metabolism in the rat hippocampus and prefrontal cortex

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Accumulating evidence suggests that arginine metabolism is critically involved in the pathogenesis of Alzheimer's disease (AD). L-arginine can be metabolized to form L-citrulline, L-ornithine and agmatine respectively. L-ornithine and agmatine are precursors of the polyamines putrescine, spermidine and spermine. L-ornithine can be channelled to generate glutamate and g-aminobutyric acid (GABA), the major excitatory and inhibitory neurotransmitters in the central nervous system, respectively. Amyloid beta fragment 25-35 ($A\beta_{25-35}$) is the neurotoxic domain of the full-length $A\beta_{1-42}$. It has been shown that a single bilateral intracerebroventricular (i.c.v) infusion of pre-aggregated $A\beta_{25-35}$ leads to learning and memory deficits in rats when tested several weeks post-infusion. The present study measured the levels of L-arginine and its eight downstream metabolites in the CA1, CA2/3 and dentate gyrus sub-regions of the hippocampus and prefrontal cortex (PFC) in male adult Sprague Dawley rats at 42 days after the infusion of either $A\beta_{25-35}$ or its reverse peptide $A\beta_{35-25}$ (30 nmol/rat, n = 8 in each group) using liquid chromatography/mass spectrometry and high performance liquid chromatography. $A\beta_{25-35}$ resulted in significantly decreased L-arginine, L-citrulline, L-ornithine, GABA and agmatine levels in the CA1 sub-region of the hippocampus. Moreover, significantly decreased GABA and agmatine levels were found in the PFC region in rats treated with $A\beta_{25-35}$. These results, for the first time, demonstrate that a single bilateral i.c.v infusion of pre-aggregated $A\beta_{25-35}$ leads to a prolonged alteration of arginine metabolism in the hippocampus and PFC in a region-specific manner, which may underlie the long-lasting behavioural deficits induced by this toxic peptide.

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9.3

Vascular degeneration of Parkinson disease

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Vascular degeneration plays a significant role in contributing to neurodegenerative conditions such as Alzheimer disease. Our understanding of the vascular components in Parkinson disease is however limited. We have examined the vascular morphology of human brain tissue from both Parkinson disease and the control cases using immunohistochemical staining and image analysis. The degenerative morphology seen in Parkinson's disease cases included the formation of endothelial cell 'clusters', which may contribute to the fragmentation of the capillaries. When compared to the control cases, the capillaries of Parkinson diseases were less in numbers ($p<0.001$), shorter in length ($p<0.001$) and larger in diameters ($p<0.01$) with obvious damaged to the capillary network evidenced by less branching ($p<0.001$). The vessel degeneration associated with Parkinson disease was found in multiple brain regions, but particularly in the substantia nigra, middle frontal cortex and brainstem nuclei, but less in the caudate nucleus. The degeneration seen in the caudate nucleus was also seen in the age matched control cases. The data suggest that vascular degeneration could be an additional contributing factor to the progress of Parkinson disease. Thus treatments that prevent vascular degeneration and improve vascular remodeling may be a novel target for the treatment of Parkinson disease.

9.4

Molecular characterization of inhibitory synapses in autism related ProSAP2/Shank3 mutation

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Autism spectrum disorders (ASDs) comprise a range of neurodevelopmental disorders characterized by deficits in social interaction and communication, and by repetitive behaviour. Mutations in synaptic proteins such as neuroligins, neurexins, and ProSAPs/Shanks have been identified in patients with ASDs. ProSAP/Shank is a postsynaptic protein that is core to regulating both function and structure of excitatory synapses and its gene mutation is associated with cognitive impairment in ASDs. Here we have characterised the molecular changes in inhibitory GABAergic synapses following changes in the expression of the ASD candidate gene, ProSAP2/Shank3. Rat hippocampal dissociated cultures were transfected with EGFP-C1 control, GFP-ProSAP2-Wt, GFP-ProSAP2-RNAi, and 4 rat ASD-related ProSPA2 mutant forms (point mutations: GFP-ProSAP2-R87C, GFP-ProSAP2-R375C and GFP-ProSAP2-Q396R; frameshift mutation: ProSAP2-InsG), corresponding to human ASD mutations of ProSAP2/Shank3 (R12C, R300C, Q321R, InsG2). Cultured neurons were then stained with primary antibodies against $GABA_A$ β2/3 and glutamic acid decarboxylase 67 (GAD67). The density of GAD67 showed a significant increase when three ASD-related point mutant forms of Shank3 were expressed (p-value < 0.005) as well as when ProSAP2 genes were overexpressed or knock-downed (p-value < 0.005; p-value < 0.05), indicating an increase in reception of inhibitory input when ProSAP2 expression is altered. However, only ProSAP2-R375C and ProSAP2-Q396R, which contain point mutations within the domain of ankyrin repeats, showed a significant increase in $GABA_A$ β2/3 density (p-value < 0.05; p-value < 0.005), demonstrating unsynchronised changes between input and output of inhibitory signals, and also the disparity between different forms of ASD-related mutations. This study revealed a change in inhibitory synapses when ASD-related ProSAP2/Shank3 expressions were altered at excitatory synapses indicating that the excitation inhibition balance may be altered in ASDs.

9.5

The effects of chronic statin administration: Assessment of hippocampal spatial memory and long term potentiation in area CA1

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Statins lower the risk of death from cardiovascular disease in millions of people worldwide. Recently, data shows people taking statins have an increased risk of psychiatric adverse events such as amnesia, anxiety and even aggression. This study aimed to investigate the effect of simvastatin (2mg/kg) and atorvastatin (1mg/kg) treatment on memory in an animal model of spatial memory and learning; the Morris water maze (MWM). Furthermore, to assess the effect of chronic statin treatment on synaptic plasticity, we conducted extracellular field recordings in area CA1 of hippocampal slices prepared from animals completing behavioural assessment. In the MWM, statin treatment did not show any deficits in the first five days of reference memory testing. However, statin treated animals took significantly ($p<0.05$) longer to find the platform on days 1 and 2 in the working memory phase (platform is changed to a different location daily). Previously, we reported a dose dependent decrease in LTP with statins bath applied (1-10μM). In the present study, assessment of hippocampal LTP in area CA1 in statin treated animals did not show a significant difference compared with control animals. However, irrespective of treatment group, LTP declined over 5 days of electrophysiological testing and therefore may suggest an enviromental enrichment effect of the MWM in masking the effects of chronic statin treatment. Deficits in water maze performance and hippocampal LTP are suggestive of statin induced changes in hippocampal plasticity. Statin effects on membrane expression of glutamate receptor populations are currently underway and will help elucidate mechanisms of statin associated amnesia and anxiety.

10.1

Theta-gating during a sternberg working memory task

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Sternberg (Science, 153: 652-654 (1966)) found that the time taken (RT) to decide whether a given "probe" item was, or was not, in a memorized set was a linear function of the number of items in the set. This function was not influenced by whether the probe was in the set, or the position of the "probe" in the set. Sternberg concluded therefore, that subjects scan the set serially and exhaustively in order to find a match for the probe. We have argued previously (Kirk et al, 2009: http://psy.otago.ac.nz/awcg/Abstracts/Abstracts2009.htm#Kirk) that the duration of theta gating during a reference memory task reflects the position of the probe in list, suggesting a serial self-terminating working memory search. Here, wavelet analysis was performed on scalp-recorded EEG data collected during the performance of the classical Sternberg task to determine if our previous result holds. The duration of theta gating over frontal electrodes was measured as subjects decided whether a probe letter was a member of a set of previously displayed letters (4, 5 and 6 letter sets). Again, contrary to the predictions of the Sternberg hypothesis, the position of the probe in a set was found to be linearly related to the duration of the gated theta activity. These data are consistent with a serial self-terminating rather than a serial exhaustive search.

10.2

Speeded visual evoked potentials may reflect possible temporal underpinning of enhanced visuospatial performance in expert video game players

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Behavioural evidence is accumulating to suggest that individuals with video game expertise show a generalized enhancement in a range of visuospatial tasks, extending beyond the context of video game play. It remains unclear what underlies these enhancements. In this study, we used electro encephalography (EEG) to measure occipital N1 latencies and amplitudes accompanying visual stimuli in the Poffenberger paradigm. This methodology also allows for estimation of interhemispheric transfer time (IHTT) across the corpus callosum in both directions. Participants comprised 16 right-handed male expert video game players (VGPs) and 16 matched controls. VGPs began playing before the age of 10, had a minimum of 8 years' experience and maintained a playtime of at least 20 hours per week over the previous 6 months. Participants were required to respond by pressing the spacebar as soon as they detected a black and white checkerboard circle presented to the left or right visual field. Evoked potentials were recorded using a 128-channel EEG system. The latency of occipital N1s in the VGPs were significantly earlier than controls (p = .028). While VGPs showed no significant directional difference in IHTTs, neither did control participants. No significant group differences were observed for amplitude. Occipital N1s are thought to reflect the visual processing of attended stimuli suggesting that expert VGPs may detect and begin processing visual information before controls.

10.3

The catechol-*O*-methyltransferase (COMT) Val158Met polymorphism moderates the effect of antenatal stress on childhood behavioural problems

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The functional polymorphism Val158Met in the *COMT* gene was analysed to determine its association with maternal perceived stress and childhood behavioural problems. Data is presented from the Auckland Birthweight Collaborative (ABC) study, where data was collected at birth and at 1, 3.5, 7 and 11 years of age. A total of 546 DNA samples were collected at age 11. The main independent variable was perceived maternal stress at birth, 7, and 11 years and the outcome was the Total Difficulties score at both 7 and 11 years of age from the Strength and Difficulties Questionnaire. IQ was assessed at age 7. Met/Met homozygotes were at increased risk of behavioural and emotional problems at ages 7 as well as 11 years, relative to either heterozygous or homozygous carriers of the Val158Met polymorphism, only when they were exposed to maternal stress in utero. Met/Met homozygotes also had, on average, IQ scores four points higher than Val/Val homozygotes. These findings emphasize the potential long-term consequences of prenatal maternal stress for genetically susceptible individuals during neurodevelopment in utero. Our findings also add to our general understanding of the aetiology and developmental nature of childhood emotional and behavioural problems.