Saturday 23 August

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

1. Neural Excitability, Synapses, and Glia: Cellular Mechanisms I

Chair: Johanna Montgomery

7.15 pm	1.1	**PLENARY LECTURE:** **Richard Kramer,** ***University of California Berkeley, United States of America*** Optogenetic control of endogenous ion channels and receptors in the nervous system
8.00 pm	1.2	**Peter Freestone,** ***University of Auckland, New Zealand*** The hyperdirect pathway drives endocannabinoid modulation of GABAergic transmission in the Substantia Nigra pars compacta
8.15 pm	1.3	**Cliff Abraham,** ***University of Otago, New Zealand*** An STDP rule combined with BCM-like fast homeostasis accounts for LTP and concurrent LTD in the dentate gyrus
8.30 pm	1.4	**Karl Iremonger,** ***University of Otago, New Zealand*** Regulation of GnRH neuron nerve terminal excitability
8.45 pm	1.5	**Chantelle Fourie,** ***University of Auckland, New Zealand*** Zinc-dependent regulation of synapse function in Autism Spectrum Disorders
9.00 pm	1.6	**Nicole Neverman,** ***University of Otago, New Zealand*** Synaptic pathology in CLN6 ovine neuronal ceroid lipofuscinosis
9.30 pm		Rugby: All Blacks vs Australia in bar Refreshments served

Sunday 24 August
Morning Session

6.00-9.00 am Light Breakfast Available

2. Neural Excitability, Synapses, and Glia: Cellular Mechanisms II

Chair: Karl Iremonger

8.00 am	2.1	**PLENARY LECTURE:** **John Bekkers, *Australian National University, Australia*** Synapses and circuits for the cortical processing of odours
8.45 am	2.2	**Emmet Power, *University of Otago, New Zealand*** Prolonged metabotropic glutamate receptor activity in the early stages of a mouse model of human spino-cerebellar ataxia type 1, SCA1
9.00 am	2.3	**Lucy Goodman, *University of Auckland, New Zealand*** Super resolution imaging of SAP97-expressing synapses
9.15 am	2.4	**Steve Seo, *University of Otago, New Zealand*** Region-specific changes in $GABA_AR$ subunits in the thalamus of an animal model of absence epilepsy
9.30 am	2.5	**Katharina Dormanns, *University of Canterbury, New Zealand*** From experiments to differential equations - Possibilities and limitations of mathematical modelling and simulation of neurovascular coupling
9.45 am	2.6	**Marcus Wilson, *University of Waikato, New Zealand*** A comparison of spike-timing dependent plasticity and calcium dependent plasticity approaches in modelling of Transcranial Magnetic Stimulation (TMS)

10.00 am Tea/Coffee break

10.30-11.30 am CoRE Discussion

Sunday 24 August
Afternoon Session

3.45 pm Afternoon Tea Available

3. Disorders of the Nervous System I

Chair: Stephanie Hughes

4.00 pm	3.1	**PLENARY LECTURE:** **Josef Gecz, *University of Adelaide, Australia*** Defining the role of mRNA export and mRNA decay in eurodevelopmental disorders, intellectual disability and autism
4.45 pm	3.2	**Shabah Shadli, *University of Otago, New Zealand*** An improved human anxiety-specific biomarker: Personality, pharmacology, frequency band, and source characterisation
5.00 pm	3.3	**Sonja Seeger-Armbruster, *University of Otago, New Zealand*** Does optogenetic stimulation of motor thalamus improve reaching in Parkinsonian rats?
5.15 pm	3.4	**Amy Ewald, *Victoria University of Wellington, New Zealand*** Investigation of AL-1-99 as a potential anti-addiction pharmacotherapy: side effects and cellular mechanisms
5.30 pm	3.5	**Tracy Melzer, *New Zealand Brain Research Institute, New Zealand*** White matter lesions - a factor in developing dementia in patients with Parkinson's disease
5.45 pm	3.6	**Andrea Kwakowsky, *University of Otago, New Zealand*** Effects and mechanism of action of estren on beta amyloid-induced cholinergic and behavioural deficits

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 25 August
Morning Session

6.00-9.00 am Light Breakfast Available

4. Sensory and Motor Systems

Chair: Peter Thorne

9.00 am	4.1	**Peter Mombaerts,** ***Max Planck Research Unit for Neurogenetics, Germany*** An inconvenient truth: Trpc2-expressing sensory neurons in the mouse main olfactory epithelium
9.15 am	4.2	**Nitin Kumar,** ***Victoria University of Wellington, New Zealand*** Kappa opioids: New targets for the treatment of pain
9.30 am	4.3	**Timothy Carroll,** ***University of Queensland, Australia*** Inter-limb transfer of force-field adaptation is enhanced when the perturbation is aligned in extrinsic and joint-based coordinates
9.45 am	4.4	**Malinda Tantirigama,** ***Australian National University, Australia*** Laminar representation of odour in the mouse piriform cortex in vivo
10.00 am	4.5	**Catherine Theys,** ***University of Canterbury, New Zealand*** Auditory processing of dysarthric speech: An EEG study
10.15 am		Tea/Coffee break

Monday 25 August
Morning Session

5. Cognition and Behaviour I

Chair: Donna Rose Addis

10.30 am	5.1	**David Harper,** ***Victoria University of Wellington, New Zealand*** The effects of 3,4-methylenedioxymethamphetamine (MDMA) on reinforced responding in rats: Perseveration, variation or loss of stimulus control?
10.45 am	5.2	**Karen Waldie,** ***University of Auckland, New Zealand*** Correlations between reading performance and BOLD activation during word rhyming: The Auckland Comorbidity study
11.00 am	5.3	**Yaqub Jonmohamadi,** ***University of Otago, New Zealand*** Identification and localization of electrical activity in the brain associated with behavioural microsleeps
11.15 am	5.4	**Helen Fitzsimons,** *Massey U**niversity, New Zealand*** Genetic analysis of the role of HDAC4 in long-term memory: Interaction with the SUMO-conjugating enzyme Ubc9
11.30 am		Student travel grants distributed

6. Poster Session

- combined with medsci

NB: ben lomond room, rydges hotel

1.30-4.00 pm	Presenters will be in attendance during this time Presenters for Posters A will be in attendance from 1.30 to 2.45 pm Presenters for Posters B will be in attendance from 2.45 to 4.00 pm The poster session will be followed by a postgraduate dinner to be held at Winnies at 8.00 pm
6.1 - A	**Lisa Zhou,** ***University of Otago, New Zealand***
	Prefrontal cortex stroke results in delayed onset impairment
6.2 - B	**Dane Aronsen,** ***Victoria University of Wellington, New Zealand***
	Repeated exposure to a serotonin$_{1B}$ agonist facilitates acquisition of MDMA self-administration
6.3 - A	**Brook Perry,** ***University of Canterbury, New Zealand***
	Mammillothalamic tract lesions and spatial memory in rats
6.4 - B	**Kyla-Louise Wood,** ***University of Canterbury, New Zealand***
	Comparing mild cognitive impairment criteria in Parkinson's disease: Influence on dementia onset
6.5 - A	**Dion Henare,** ***University of Auckland, New Zealand***
	The effect of working memory load on target and distractor processing as indexed by lateralised event-related potentials
6.6 - B	**Takanobu Yamamoto,** ***Tezukayama University, Japan***
	Psychophysiological role of tryptophan and kynurenic acid in central fatigue induced by chronic sleep disorder
6.7 - A	**Gagandeep Singh Mallah,** ***University of Auckland, New Zealand***
	The influence of maternal cyclic-glycine-proline treatment during lactation on the growth and behaviour of offspring in rats

6.8 - B	**Silvia Schwartz, Massey *University, New Zealand***
	A genetic screen to identify genes that interact with Histone Deacetylase 4 (HDAC4): Investigating the interplay with ankyrin2 in the brain
6.9 - A	**Stephanie Mercer, *University of Canterbury, New Zealand***
	Enriched environments and recovery of spatial memory in the radial arm maze after anterior thalamic lesions
6.10 - B	**Carolyn Wu, *University of Auckland, New Zealand***
	Short-term musical training modulates functional connectivity of the sensorimotor system
6.11 - A	**Chris Murray, *University of Auckland, New Zealand***
	Remembering the past and imagining the future in depression
6.12 - B	**Sreekari Vogeti, *University of Auckland, New Zealand***
	Do the eyes have it? The role eye regions in the face specificity of the occipitotemporal component of the event-related potential, N170
6.13 - A	**Carla Bautista, *University of Auckland, New Zealand***
	Far, far away: Evidence of a greater effect of increased physical effort on low-level perception in depression
6.14 - B	**Sahina Haq, *University of Canterbury, New Zealand***
	Lesions of the hippocampal dentate gyrus induce drug supersensitivity and increased resistance to extinction of drug seeking responses
6.15 - A	**Kristina Wiebels, *University of Auckland, New Zealand***
	A novel approach to investigating structural differences in schizotypy: A structural PLS study
6.16 - B	**Eleanor Moloney, *University of Auckland, New Zealand***
	Characterizing cerebellar activity during autobiographical memory: ALE and functional connectivity investigations
6.17 - A	**Monica Xiong, *University of Otago, New Zealand***
	The effects of exogenous sAPPα on spatial memory and LTP in aging
6.18 - B	**Rachael Sumner, *University of Auckland, New Zealand***
	The effect of relational load on the neural correlates of future simulation
6.19 - A	**Laura Bell, *University of Waikato, New Zealand***
	General anaesthetic modulation of memory-related gene expression in the cerebral cortex
6.20 - B	**Haeme Park, *University of Auckland, New Zealand***
	Neural correlates of creativity in schizotypy: An fMRI study

Poster Session

6.21 - A **David Loxton, *University of Canterbury, New Zealand***

Exposure to alcohol and methamphetamine produces long-term emotional and cognitive deficits in adolescent rats

6.22 - B **Nicole McKay, *University of Auckland, New Zealand***

Using probabilistic tractography to investigate genetic influences on recognition memory circuit connectivity

6.23 - A **Sonya Ranchhod, *University of Auckland, New Zealand***

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

6.24 - B **Mark Burrell, *University of Auckland, New Zealand***

A novel fast-scan cyclic voltammetry (FSCV)-based technique for prolonged measurement of absolute levels of extracellular dopamine in brain slices

6.25 - A **Raquel Hulst, *Victoria University of Wellington, New Zealand***

Amphetamine-induced locomotor activity is enhanced in the adult serotonin transporter knock-out rat

6.26 - B **Curie Suk, *University of Auckland, New Zealand***

Inter-hemispheric transfer time in Autism Spectrum Disorder (ASD)

6.27 - A **Sophie Müller, *Victoria University of Wellington, New Zealand***

Effects of 5-HT_{1A} and 5-HT_{1B} manipulations on ±3, 4-methylenedioxy-methamphetamine (MDMA) primed reinstatement in rats

6.28 - B **Shane Little, *University of Otago, New Zealand***

Changes in reticular thalamic nucleus neuronal activity in anaesthetized parkinsonian rats

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

Determining the mechanisms of brain injury after perinatal inflammation: The role of the connexin hemichannel Cx43 in a rat model of infection

6.30 - B **Tania Fowke, *University of Auckland, New Zealand***

Enzymatic production of hyaluronan and its role in early neuronal development

6.31 - A **Lachlan Thompson, *University of Melbourne, Australia***

In vivo properties of neural grafts generated from human pluripotent stem cells

6.32 - B **Clare Parish, *University of Melbourne, Australia***

Manipulation of axon guidance cue, EphrinA5, affects the integration of dopaminergic neural grafts in an animal model of Parkinson's disease

6.33 - A **Ji-Zhong Bai, *University of Auckland, New Zealand***

Cellular expression of LRRFIP1 and its potential role in CNS immune response

6.34 - B **Mustafa Almuqbel, *University of Otago, New Zealand***

Cognitive status in Parkinson's disease characterised by magnetic resonance spectroscopy

6.35 - A **Jennifer Hamilton, *University of Canterbury, New Zealand***

Stimulation of the nucleus accumbens at high or low frequencies reduces cocaine seeking

6.36 - B **Mohammed Kashem, *University of Sydney, Australia***

Differential neurotransmitter expression in the sub-regions of striatum in human alcoholics: A neurometabolomics study

6.37 - A **Nilufa Sultana, *University of Sydney, Australia***

Does Gamma-Aminbutyrate Receptor-B (GABA-R_B) play an antagonist role on alcohol induced disorder of Glutamate Transporter (GLAST)?

6.38 - B **Pei-Yu Huang, *National Cheng Kung University, Taiwan***

Assessments of cortical activity during electrical stimulation assisted cycling in stroke patients by near infrared spectroscopy

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

String vessels in vascular degeneration of Parkinson disease

6.40 - B **Stella Cameron, *University of Otago, New Zealand***

Cerebellar neural activity in a chronic rat model of Parkinson's disease

6.41 - A **James Miller, *University of Otago, New Zealand***

Establishing a rodent model of complex regional pain syndrome

6.42 - B **Wojciech Ambroziak, *University of Warsaw, Poland***

Genomic instability and Parkinson's disease

6.43 - A **Jeremy Webster, *Victoria University of Wellington, New Zealand***

The differential role of DA and 5-HT in the discriminative stimulus properties of high vs. low doses of ±3,4-Methylenedioxymethamphetamine (MDMA)

6.44 - B **Yue Pei, *University of Canterbury, New Zealand***

Trace amine-associated receptor 1 activation decreases cocaine's reinforcing efficacy and prevents cocaine-induced changes in brain reward thresholds

Poster Session

6.45 - A	**Megan Elder,** ***University of Otago, New Zealand***
	Secreted amyloid precursor protein-α attenuates apoptosis following amyloid-ß insult and ischemic injury
6.46 - B	**James Perry,** ***University of Canterbury, New Zealand***
	Progesterone reduces motor impairments in the unilateral striatal 6-hydroxydopamine lesion model of Parkinson's disease
6.47 - A	**Timothy Wright,** ***University of Otago, New Zealand***
	Environmental enrichment and stroke: Good or bad?
6.48 - B	**Sheena Sharma,** *Northwestern* ***University, United States of America***
	Propulsive and mediolateral ground reaction force changes in the trailing leg after stroke
6.49 - A	**Donghyo Kim,** ***University of Auckland, New Zealand***
	Finding new therapeutic strategies for acute stroke: Asking the brain for direction
6.50 - B	**Elshin Joel,** ***University of Canterbury, New Zealand***
	Computational modelling of neurovascular coupling pathways with the effects of oxygen dependency of the neuronal membrane
6.51 - A	**Shane Ohline,** ***University of Otago, New Zealand***
	Awakening adult-born neurons in rats by exposure to an enriched environment
6.52 - B	**Liam Farley,** ***University of Otago, New Zealand***
	Nitric oxide regulates spontaneous, electrically stimulated, and seizure-like activities in the mouse olfactory bulb in vitro
6.53 - A	**Yukti Vyas,** ***University of Auckland, New Zealand***
	Synaptic alterations in Autism Spectrum Disorder-associated Shank2 mutations
6.54 - B	**Natalie Matheson,** ***University of Otago, New Zealand***
	The effects of transcranial magnetic stimulation on synaptic function and excitability of single neurons
6.55 - A	**Nadia Adotevi,** ***University of Otago, New Zealand***
	Cortical changes in AMPA receptor expression in the stargazer mouse model of absence epilepsy
6.56 - B	**Madeleine Kyrke-Smith,** ***University of Otago, New Zealand***
	Temporal analysis of HDAC1 and HDAC2 activity during Long-Term Potentiation

Poster Session

6.57 - A	**Zsuzsanna Barad, *University of Otago, New Zealand***
	Altered NMDAR subunit composition in the thalamus of a mouse model of absence epilepsy
6.58 - B	**Wan-Shan Chang Chien, *National Cheng-Kung University, Taiwan***
	Development of cortical electrical stimulation for modulating brain plasticity in Parkinson's disease rats
6.59 - A	**Nien Yu Lu, *National Cheng-Kung University, Taiwan***
	Investigation of tissue oxygenation in diabetics using near infrared spectroscopy
6.60 - B	**Valerie Tan, *University of Otago, New Zealand***
	Addressing Alzheimer's disease symptoms using lentiviral-mediated sAPPα overexpression in the hippocampus of a transgenic mouse model
6.61 - A	**Lakshini Mendis, *University of Auckland, New Zealand***
	Imaging lipid and protein changes in the human hippocampus in Alzheimer's disease using MALDI-mass-spectrometry imaging
6.62 - B	**Alexander Srzich, *University of Auckland, New Zealand***
	Level of hypnotic susceptibility does not affect simple or choice reaction times
6.63 - A	**Nehan Munasinghe, *University of Sydney, Australia***
	Effect of Voltage gated sodium channel toxins as therapeutic agents for chronic pain
6.64 - B	**Jennifer Chi Yi Chin, *University of Auckland, New Zealand***
	Ipsilateral corticospinal pathways to the lower limb: Detection and function
6.65 - A	**Kevin Lee, *University of Auckland, New Zealand***
	SHANK3 mutations identified in Autism Spectrum Disorder impair neuronal physiology
6.66 - B	**Keith Runnalls, *University of Auckland, New Zealand***
	Partial weight support differentially affects corticomotor excitability across muscles of the upper limb
4.00 pm	Posters to be removed at this time
8.00 pm	AWCBR Student Dinner Venue: Winnies Gourmet Pizza and Bar, 7-9 The Mall, Queenstown

Monday 25 August
Evening Session

7. Opening of Queenstown Research Week

Venue: Rydges Hotel, Ben Lomond

6.00 pm	Opening Remarks **Dr Justin Sullivan and Professor Peter Shephard**
6.05 pm	Opening Address **Dr Megan Woods** Labour spokesperson for Innovation, Research and Development
6.30-7.00 pm	A Showcase of New Zealand's CoRES and National Science Challenge **Professor David Cameron Smith,** High-value nutrition **Professor Rod Dunbar,** MWC **Professor Richard Faull,** Brain Research New Zealand **Professor Shaun Hendy,** Te Pūnaha Matatini: The Centre for Complex Systems and Networks **Professor Peter Hunter,** Medical Technologies
7.00-8.00 pm	QMB Debate: Investigator Lead Research will Flourish within the National Science and CoRE Funding Structure **Professor Richard Blaikie,** University of Otago **Professor David Cameron Smith,** University of Auckland **Professor Shaun Hendy,** University of Auckland **Professor Brigid Heywood,** Massey University **Professor Di McCarthy,** formerly RSNZ **Professor Jim Metson,** MBIE

Tuesday 26 August
Morning Session

6.00-9.00 am Light Breakfast Available

8. Disorders of the Nervous System II

Chair: Maurice Curtis

8.00 am	8.1	**Daniel Myall,** ***New Zealand Brain Research Institute, New Zealand*** Individualised medicine: Predicting dementia in Parkinson's disease
8.15 am	8.2	**Lynette Tippett,** ***University of Auckland, New Zealand*** Longitudinal investigation of presymptomatic Huntington's Disease: In pursuit of neuroimaging and neuropsychological biomarkers
8.30 am	8.3	**Alice Lagas,** ***University of Auckland, New Zealand*** Can SSRIs enhance human visual cortex plasticity?
8.45 am	8.4	**Ailsa McGregor,** ***University of Auckland, New Zealand*** Varenicline improves motor, cognitive and psychiatric symptoms in the YAC128 transgenic mouse model of Huntington's Disease
9.00 am	8.5	**Hannah Squire,** ***Victoria University of Wellington, New Zealand*** D1 Receptor Involvement in MDMA's acute memory impairments: An investigation using the DAD1-/- mutant rat
9.15 am		Tea/Coffee break

Tuesday 26 August
Morning Session

9. Stroke Symposium

Chair: Andrew Clarkson

9.30 am	9.1	**Cathy Stinear, *University of Auckland, New Zealand*** Is hemispheric balancing necessary for motor recovery after stroke?
9.45 am	9.2	**Penelope McNulty, *University of New South Wales, Australia*** Improving post-stroke rehabilitation with Wii-based Movement Therapy
10.00 am	9.3	**Laura Boddington, *University of Otago, New Zealand*** Improvement of stroke recovery following electrical theta-burst stimulation applied via implanted electrodes
10.15 am	9.4	**Siyi Chen, *University of Auckland, New Zealand*** Delayed administration of citalopram is associated with long-lasting improvements in skilled motor function after stroke
10.30 am		**ANNUAL GENERAL MEETING** All conference participants are invited to attend Tea/Coffee will be available for AGM attendees

Tuesday 26 August
Afternoon Session

12.50-1.30 pm The Honourable Mr Bill English, MP

Venue: Rydges

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10. Development and Novel Methods

Chair: Ruth Empson

4.00 pm	10.1	**Deborah Young,** ***University of Auckland, New Zealand*** Viral vector-mediated transgene-specific effects on astrocyte function
4.15 pm	10.2	**Christine French,** ***University of Canterbury, New Zealand*** Changing resistance affects flow within the circle of Willi
4.30 pm	10.3	**Yiwen Zheng,** ***University of Otago, New Zealand*** Neurogenesis in the rat cochlear nucleus and the effects of acoustic trauma
4.45 pm	10.4	**Lucia Schoderböck,** ***University of Otago, New Zealand*** The role of recently born neurons in the adult mouse hippocampus in memory storage
5.00 pm		Tea/Coffee break

Tuesday 26 August
Evening Session

11. Cognition and Behaviour II

Chair: Karen Waldie

5.15 pm	11.1	**Ryan Ward,** ***University of Otago, New Zealand*** Transient inhibition of orbitofrontal cortex impairs motivational modulation of attention
5.30 pm	11.2	**Jian Guan,** ***University of Auckland, New Zealand*** Behavioural and biological changes with age: The effect of obesity on brain aging
5.45 pm	11.3	**Reece Roberts,** ***University of Auckland, New Zealand*** The relationship between BOLD variability and mean BOLD signal during episodic and semantic memory tasks
6.00 pm	11.4	**Donna Rose Addis,** ***University of Auckland, New Zealand*** Neural changes associated with the generation of specific past and future events in depression

6.00-7.00 pm Fashionomics
Venue: Rydges

Wednesday 27 August
Combined Day with MedSci

6.00-9.00 am Light Breakfast Available

12. Combined MedSci and AWCBR Plenary Lecture

Venue: Rydges

9.00 am	**PLENARY LECTURE:** **Professor Patric Mollard, CNRS, France** Hormone and neuropeptide interactions in the hypothalamus
10.00 am	Tea/Coffee break

Wednesday 27 August
Combined Day with MedSci

13. Session with QMB

Venue: Rydges

Chair: Cliff Abraham

10.30 am	13.1	**Jason Kerr, *Max-Planck Institute, Germany*** What are they looking at? Imaging brain and behavior in the freely moving animal
11.15 am	13.2	**Mike Draganow, *University of Auckland, New Zealand*** Human brain pericytes, blood-brain barrier dysfunction and neurodegenerative disorders
11.45 am	13.3	**Stephanie Hughes, *University of Otago, New Zealand*** Batten disease in sheep – understanding lysosomal biology en route to therapies
12.00 pm	13.3	**Louise Parr-Brownlie, *University of Otago, New Zealand*** Virus infects electron microscopy; combining techniques for enhanced imaging of brain circuitry
12.15 pm	13.4	**Ruth Empson, *University of Otago, New Zealand*** Dynamic voltage imaging using a genetically encoded voltage indicator (Vsfp-Butterfly) in mouse brain

12.30 pm Closing Remarks

Light lunch and Student Prize Presentation - rydges

Acknowledgements
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ABSTRACTS

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ABSTRACTS

1.1

Optogenetic control of endogenous ion channels and receptors in the nervous system

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We employ synthetic photoswitch compounds to confer light sensitivity on endogenous ion channels and receptors of the nervous system. We do this for two reasons: 1) we want to better understand the functions of particular channels and receptors in the brain and 2) we want to use this technology to artificially input information into the nervous system, downstream from sites of damage or degeneration. For goal 1, we are focusing on K^+ channels, receptors for acetylcholine, and receptors for GABA. Each of these proteins come in multiple isoforms, but understanding what each type "does for a living" is a mystery. We can answer this question through *optogenetic pharmacology*, which allows light to control genetically-specified isoforms with high spatial, temporal and biochemical precision. For goal 2 we are developing photoswitches as a potential treatment for degenerative blinding diseases of the retina. In Retinitis Pigmentosa (RP) and Age-related Macular Degeneration (AMD) rods and cones die, leaving the remainder of the retina intact but unable to respond to light. Intra-ocular injection of photoswitches can restore electrophysiological and behavioral light responses to blind mice afflicted with RP. Ongoing studies are aimed at optimizing photoswitches to enable safe, effective, and long-lasting restoration of visual function, first in mice, and eventually in humans.

1.2

The hyperdirect pathway drives endocannabinoid modulation of GABAergic transmission in the Substantia Nigra pars compacta

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The hyperdirect pathway of the basal ganglia circuitry includes a glutamatergic projection from the Subthalamic Nucleus (STN) to the Substantia Nigra pars compacta (SNc). We recently showed that glutamate release drives endocannabinoid production in SNc dopaminergic neurons, which in turn inhibits GABAergic transmission in that region. The present study investigated the potential role of STN glutamatergic projections of the hyperdirect pathway in driving this novel endocannabinoid modulatory mechanism. Electrical (bipolar electrode), local pharmacological ('U-tube' application of carbachol) and optogenetic approaches were utilized to selectively stimulate STN neurons. GABAergic transmission to SNc dopaminergic neurons, evoked by electrical stimulation of the Substantia Nigra pars reticulata, was transiently inhibited by a single electrical stimulation of the STN (to 73% of control). This inhibition was dependent on activation of metabotropic glutamate receptor 1, and cannabinoid receptor 1; findings consistent with our previous work. Pharmacological stimulation of the STN also caused transient inhibition of GABAergic transmission. Application of optogenetic techniques, recently established in our lab, to discretely activate the STN will also be presented. These findings show that glutamate release from STN terminals modulates GABAergic transmission from the SNr through endocannabinoid signalling – a previously undescribed function of the hyperdirect pathway.

1.3

An STDP rule combined with BCM-like fast homeostasis accounts for LTP and concurrent LTD in the dentate gyrus

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Long-term potentiation (LTP) and long-term depression (LTD) are widely accepted as mechanisms of learning and memory. It remains uncertain, however, which activity rules and mechanisms driving such synaptic plasticity are actually utilized by hippocampal neurons to generate LTP and LTD in behaving animals. Recent experiments in the dentate gyrus of freely moving rats revealed that 400 Hz theta-burst stimulation (400-TBS) and 400 Hz delta-burst stimulation (400-DBS) elicited substantial LTP of the tetanized medial perforant path input and concurrent LTD of the non-tetanized lateral perforant path input. In contrast, 100 Hz theta-burst stimulation (100-TBS) was not able to produce significant LTP or concurrent LTD. Here we show in a computational dentate granule cell model (NEURON platform) that these data can be accounted for by a spike-timing-dependent plasticity (STDP) rule combined with a relatively fast Bienenstock-Cooper-Munro (BCM)-like homeostasis / metaplasticity rule, all on a background of ongoing spontaneous activity in the input fibres. Our results suggest that the interplay of STDP-BCM plasticity rules and ongoing pre- and postsynaptic background activity is sufficient to replicate qualitatively the experimentally observed patterns of input-specific LTP and concurrent LTD of granule cell synapses across the three different tetanisation protocols. These findings should inspire experimental testing of whether granule cells actually utilise these rules to induce synaptic plasticity.

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1.4

Regulation of GnRH neuron nerve terminal excitability

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Gonadotropin-releasing hormone (GnRH) neurons release GnRH peptide from their nerve terminals in the median eminence to control reproductive function. The GnRH neuron projection to the median eminence is unique in that it can both propagate action potentials while simultaneously receiving synaptic inputs along its entire length. Synaptic inputs that impinge close to the soma are effective at regulating spiking, while the effects of distal synaptic inputs on excitability are unclear. The aim of this study was to investigate how distal synaptic inputs regulate the excitability of GnRH neuron nerve terminals. To study GnRH nerve terminals, we have expressed the genetically-encoded calcium indicators GCaMP3 and GCaMP6s specifically in GnRH neurons with a Cre-loxP transgenic approach. Acute, horizontal brain sections were prepared from GnRH-GCaMP adult mice. Live confocal imaging was then performed on GnRH neuron projections and nerve terminal boutons in the median eminence. Electrical stimulation of GnRH neuron projections evoked large calcium transients in nerve terminal boutons, with response magnitude being frequency dependent. Stimulation evoked calcium transients could be blocked with local puff application of tetrodotoxin and blockers of voltage-gated calcium channels. To determine if local neuropeptides can directly regulate nerve terminal excitability, we locally puff-applied kisspeptin. Kisspeptin evoked calcium elevations in both boutons and projection fibres, however, only when imaged with the high sensitivity calcium indicator GCaMP6. Together, these data demonstrate that genetically encoded calcium indicators can be used to study GnRH neuron nerve terminal excitability in vitro. The level of nerve terminal calcium is dependent both on the action potential firing frequency as well as activation of local neurotransmitter receptors.

1.5

Zinc-dependent regulation of synapse function in Autism Spectrum Disorders

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Autism Spectrum Disorders (ASD) are a set of neurodevelopmental disorders characterised by impaired communication, social behaviour, learning deficits and repetitive behaviour. The behavioural dysfunctions that occur with ASD are thought to be causally linked to changes that converge at synapses. ASD has a strong genetic component where many of the mutated genes, such as the Shank family of proteins, encode proteins localised to excitatory glutamatergic synapses. We have previously characterised the synaptic dysfunction that occurs in Shank3 mutant primary hippocampal neurons. As zinc plays a modulatory role in synaptic transmission and plasticity at glutamatergic synapses and also binds to Shank3, we hypothesised that zinc regulates the activation of Shank3. We utilised our established protocols to induce various Shank3 mutations in primary hippocampal neurons and subsequently measure changes in glutamatergic synapse structure and function using imaging and electrophysiology techniques. We measured glutamatergic excitatory postsynaptic currents between pairs of synaptically connected hippocampal neurons where the postsynaptic neuron expresses one of the Shank3 mutations. Our results show that ASD-associated mutations in Shank3 impaired synaptic transmission but that zinc treatment could rescue AMPA receptor-mediated synaptic transmission in neurons expressing certain Shank3 mutations. This zinc effect was dependent on the expression of Shank3. Interestingly, the zinc effect was also dependent on the type of Shank3 ASD-associated mutation. Zinc treatment also resulted in an increase in transsynaptic signalling, measured as increases in pre- and postsynaptic protein expression, VGLUT1 and Homer1 respectively. Our data show that zinc can rescue transsynaptic signalling and functional excitatory synaptic transmission, but only in specific Shank3 ASD mutants.

1.6

Synaptic pathology in CLN6 ovine neuronal ceroid lipofuscinosis

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Naturally occurring forms of Batten disease (neuronal ceroid lipofuscinosis, NCL) in three breeds of sheep have been extensively studied: CLN6 in New Zealand South Hampshires and Australian Merinos, and CLN5 in New Zealand Borderdales. Established flocks provide excellent large animal models to study the pathology and potential treatment strategies in both forms of NCL. Primary neural cell cultures from fetal South Hampshire sheep ($CLN6^{-/-}$ and $CLN6^{+/-}$ control) were studied to identify pathological features at the neuronal synapse. We have previously shown defects in lysosomal acidity in $CLN6^{-/-}$ neural cultures which led us to investigate the functionality and integrity of $CLN6^{-/-}$ synapses. Excitation-induced synaptic endocytosis of both 10,000 and 40,000 molecular weight dextrans was significantly impaired (10,000 $p = 0.001$, 40,000 $p = 0.0024$, unpaired t-test). Expression of the key pre-synaptic vesicle protein, synaptophysin, was also significantly reduced in $CLN6^{-/-}$ neurons ($p = 0.0069$, unpaired t-test) and not trafficked to the synapse. Together, these pathologies suggest major consequences for neuronal function in affected sheep, and indicate possible target sites for therapeutic correction.

2.1

Synapses and circuits for the cortical processing of odours

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When you sniff your morning cuppa, the numerous volatile chemicals detected by your nose are somehow assembled into a unified mental representation of 'coffee'. This remarkable synthesis is achieved in the primary olfactory cortex (also called the piriform cortex), which is an anatomically simple paleocortex located in the ventral forebrain. I will be presenting our recent work that seeks to understand the processing power of the piriform cortex in terms of its synapses and circuits. Over the past few years we have used patch clamping in brain slices to work out a basic circuit diagram for the piriform cortex of mice. For example, by using optogenetics in slices from transgenic mice we have identified neuronal classes and traced some of the sources of intracortical circuits. More recently, we have turned to *in vivo* experiments to study how piriform circuits respond to real odours. Using a combination of 2-photon targeted patch clamping and functional calcium imaging *in vivo*, we have begun to work out how identified classes of neurons respond to odour application, and how odour identity might be encoded in these responses. Inevitably, perhaps, the results are complicated, demonstrating that even a 'simple' cortex is not so simple. Nevertheless, we are confident that study of this evolutionarily ancient cortical structure will unmask some of the principles of cortical processing that enable our brains to make sense of the outside world.

2.2

Prolonged metabotropic glutamate receptor activity in the early stages of a mouse model of human spino-cerebellar ataxia type 1, SCA1

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Spino-cerebellar ataxia type 1(SCA1) is an incurable, autosomal dominant and progressive neurodegenerative motor disorder resulting from a CAG trinucleotide expansion within ataxin-1. In this study, we use a transgenic mouse model of SCA1, where the CAG expansion is restricted to cerebellar Purkinje neurons (PNs) and under doxycycline repressible transcriptional control. Our aim is to use this model to identify mechanisms that contribute to the early stages of SCA1 progression. Behavioural testing using the rotarod showed that 6 week old SCA1 transgenic mice exhibited very mild motor symptoms ($P=0.052$) but progressed to full ataxia by 12 weeks of age ($P<0.002$) unless they received doxycycline from 0-6 weeks of age. Whole cell patch clamp recordings from PNs from SCA1 transgenic mice revealed an increase in input resistance at both 6 ($P<0.001$) and 12 weeks of age ($P<0.0001$), consistent with shrinkage of the PN dendrite. Parallel fibre evoked metabotropic glutamate receptor (mGluR) currents were also prolonged in PNs at 6 weeks of age ($P<0.05$) and further prolonged at 12 weeks of age ($P<0.001$). Doxycycline treatment prevented the reduced input resistance of 12 week old PNs, but did not prevent the prolonged mGluR current ($P<0.001$). The prolonged mGluR function suggests disordered PN calcium homeostasis in the early stages of SCA1 and contrasts with the molecular down-regulation of mGluR expression seen in older SCA1 mice. Since doxycycline rescued the decrease in PN input resistance but not the prolonged mGluR current suggests that mGluR receptors are a primary target for early therapeutic treatment of SCA1 onset and progression.

2.3

Super resolution imaging of SAP97-expressing 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 scaffolding proteins may reveal whether structural changes in architecture are correlated with synaptic plasticity. Of particular interest are two N-terminal isoforms of SAP97 ($\alpha-$ and β-SAP97) that are known to differentially regulate synaptic plasticity, potentially by localising surface glutamate receptors to different synaptic compartments (Li et al., 2011; Waites et al., 2009)mechanisms responsible for GluR1 insertion and retention at the synapse are unclear. The synapse-associated protein SAP97 directly binds GluR1 and participates in its forward trafficking from the Golgi network to the plasma membrane. Whether SAP97 also plays a role in scaffolding GluR1 at the postsynaptic membrane is controversial, attributable to its expression as a collection of alternatively spliced isoforms with ill-defined spatial and temporal distributions. In the present study, we have used live imaging and electrophysiology to demonstrate that two postsynaptic, N-terminal isoforms of SAP97 directly modulate the levels, dynamics, and function of synaptic GluR1-containing AMPARs. Specifically, the unique N-terminal domains confer distinct subsynaptic localizations onto SAP97, targeting the palmitoylated alpha-isoform to the postsynaptic density (PSD. However, the ~200 nm resolution limit of traditional optical microscopy has greatly complicated detailed study of protein arrangements within the densely packed PSD. We have applied a single molecule localisation method of super resolution imaging known as dSTORM (Baddeley et al., 2011) to image the distribution of surface AMPA receptors in cultured rat hippocampal neurons. A comparison between neurons transiently overexpressing $\alpha-$ or β-SAP97 isoforms shows differences in synapse size, with α-SAP97 expressing PSDs larger than those expressing β-SAP97 (median: α = 0.18um^2; β = 0.10um^2) with no differences in synapse density. We also observe differences in the distribution of surface AMPA receptors between the two populations. Our data reveal that different isoforms of the same PSD protein can differentially affect synaptic architecture, which may dictate diverse functional roles in synaptic plasticity.

2.4

Region-specific changes in $GABA_AR$ subunits in the thalamus of an animal model of absence epilepsy

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Absence epilepsy is a type of generalized non-convulsive epilepsy, featuring 2.5-4Hz spike-wave discharges (SWDs) on the electroencephalogram. It is characterized by abrupt, brief disruption of consciousness and has an adverse impact on childhood learning. Experimental evidence from rodent absence models suggests region-specific changes in $GABA_A$ receptor ($GABA_AR$) inhibition in the thalamus may contribute to hypersynchronous oscillations in absence epilepsy. The aim of this study was to investigate changes in $GABA_AR$ expression in the reticular thalamic nucleus (RTN) and ventral posterior (VP) region of the stargazer mouse model of absence epilepsy. Immunofluorescence confocal microscopy showed that $GABA_AR$ α1 and β2 subunits were mainly localized to the VP, whereas $GABA_AR$ α3 and β3 subunits were predominantly expressed in the RTN. Western blotting analysis of RTN and VP samples showed that tissue levels of $GABA_AR$ subunits in the VP were increased in epileptic mice (α1: 33% increase, n=8, $p<0.05$; β2: 96% increase, n=8, $p<0.01$), whereas expression of α3 and β3 in the RTN remained unchanged (both n=8, $p>0.05$). Electron-microscopy immunogold cytochemistry was used to analyse synaptic expression of $GABA_AR$ subunits in the VP of epileptic mice compared to matched non-epileptic controls (n=3 pairs, 200 synapses/subunit). In the epileptic mice, synaptic levels of both $GABA_AR$ α1 and β2 subunits were significantly increased by 54%($p<0.01$) and 49%($p<0.01$), respectively. These findings suggest upregulation of phasic $GABA_AR$ mediated inhibition at thalamocortical synapses in the VP may be one of many factors contributing to hypersynchronous thalamocortical activity in absence seizures. Currently available anti-epileptics are associated with adverse side effects and inefficacy, and understanding region-specific mechanisms underlying SWDs in absence epilepsy could be crucial for identifying novel drug targets for absence epilepsy treatment.

2.5

From experiments to differential equations - Possibilities and limitations of mathematical modelling and simulation of neurovascular coupling

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The importance of neurovascular coupling, i.e. the ability of the vasculature to regulate cerebral perfusion, has become better understood within the last decade. Recent research suggests that impaired neurovascular coupling is associated with several pathologies such as hypertension, Alzheimer's Disease and stroke. However, little is known of the complete pathway for this phenomenon and only limited experimental data is available. Our research group has developed a numerical model able to describe the process of neurovascular coupling from neuronal activation to vascular response and hence bloodflow regulation. Abstractions of different cell types are made to develop a virtual neurovascular unit, consisting of neurons, astrocytes, smooth muscle cells and endothelial cells lining arterioles. Communication between cells is simulated by a coupled set of differential equations describing ion fluxes, chemical reactions and change of membrane potentials, based on and validated with experimental results. We show that the model is able to regulate widening or narrowing of the arteries in response to a neuronal input signal. Results indicate that local temporary neuronal activity leading to potassium release into the synaptic cleft induces a membrane potential drop in the smooth muscle cells. Thence, voltage-operated ion channels close and the calcium concentration in the cytosol decreases resulting in a dilating regulation of the blood vessel diameter. A spatial model is able to globally couple multiple neurovascular units by a simulated vascular tree that bifurcates into a fine capillary bed. Limited available experimental data under specific and non-congruent conditions along with necessary mathematical assumptions necessitate caution of our model while still allowing us to study a number of important pathological scenarios.

2.6

A comparison of spike-timing dependent plasticity and calcium dependent plasticity approaches in modelling of Transcranial Magnetic Stimulation (TMS)

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In TMS, magnetic pulses are applied to the brain in order to induce long-term potentiation (LTP) or depression (LTD). Although TMS has been used to treat stroke, Parkinson's disease and depression, results are plagued by contradictions. Particular protocols may work in some subsets of people, but have opposite effects in others. We are motivated to develop robust biophysical models that can aid the development of the method. We compare and contrast two approaches to modelling plasticity: spike-timing dependent plasticity (STDP) and calcium dependent plasticity (CaDP). The former is straightforward to implement; the latter is more biophysical but is non-linear and numerically intensive. Both are incorporated into neural-field models of brain dynamics. We model different TMS protocols, particularly continuous and intermittent theta-burst stimulation (cTBS and iTBS). STDP and CaDP give similar predictions under moderate stimulation amplitudes, despite having different underlying assumptions. Results compare well with experiment, for example intermittent protocols can produce LTP at high (> 5 Hz) burst frequencies while continuous protocols are more likely to produce LTD. CaDP predicts that there can be oscillations in potentiation with time (timescale of order a minute), meaning that a protocol that initially produces LTP may also produce LTD if it is run for longer. This may contribute to the ambiguity in experimental results of TMS. Both methods show potential for contributing to systematic modelling studies of TMS effects.

3.1

Defining the role of mRNA export and mRNA decay in neurodevelopmental disorders, intellectual disability and autism

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The flow of genetic information from DNA to RNA to proteins is of fundamental biological significance and have been formulated in 1956 by Francis Crick into the central dogma of molecular biology. The importance and enormous complexity of the 'middle', RNA step, also for the development and cognition has not been appreciated until more recently. In this presentation we will focus on messenger RNA, mRNA. Efficient mRNA export from nucleus to cytoplasm and its quality control is essential for every cell. We have identified genetic mutations affecting either of these processes, Nonsense-Mediated mRNA Decay (NMD) and mRNA export. NMD is physiologically relevant regulatory pathway that was discovered by means of degradation of transcripts containing premature termination codons (PTCs). NMD maintains transcriptome homeostasis and is crucial for neuronal progenitor cell proliferation as well as differentiation, among its other functions. Consequently it may not come as a surprise that we (and others) found mutations of UPF3B, as well as several other NMD factors, in a range of neurodevelopmental disorders, including intellectual disability, autism, schizophrenia and ADHD. We also gather evidence that the magnitude of NMD may vary between individuals, which could explain broad clinical expressivity of NMD factor mutations. Variable NMD efficiency has not only been shown to correlate with clinical presentations but also the patients' responses to drugs that promote read-through of PTCs. Nonsense and frameshift mutations that generate PTCs have been identified in about one-third of human genetic diseases suggesting NMD role in many of these. Before mRNA is quality checked, it ought to be efficiently exported from nucleus to cytoplasm, process closely linked to NMD. Using X-exome sequencing we identified mutations in THOC2, one of the essential mRNA export components of the TREX (TRanscription-EXport) complex. THOC2 deficiency interferes with mRNA export and in neurons with neurite outgrowth. It is crucial also for chromosome alignment, mitotic progression and genomic stability, suggesting that it plays critical functions in different cellular pathways. We show that THOC2 missense mutations affect THOC2 and consequently also TREX multiprotein complex stability, which leads to defects in mRNA export (as tested by RNA-sequencing using patient cell nuclear and total RNA). While currently known THOC2 mutations lead primarily to non-syndromic intellectual disability, we expect the clinical spectrum of THOC2 patients, as they get identified from e.g. large exome/genome sequencing studies of various patient cohorts, to broaden. Both mRNA export and NMD operate in almost every cell, yet the phenotype of our patients is predominantly neurological. While functional redundancy (i.e. multiple NMDs operating in neurons) provides a possible explanation, why certain cell types and neurons in particular are so sensitive, remains to be determined.

3.2

An improved human anxiety-specific biomarker: Personality, pharmacology, frequency band, and source characterisation

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Anxiety disorders are among the most common mental illness in the western world with a major impact on disability. Until now their diagnosis has not been based on objective biomarkers. To solve this problem, we developed a human EEG biomarker, conflict specific rhythmicity (CSR) in the stop signal task (SST) that could identify one specific type of anxiety disorder. Here we report the characteristics of an improved version of the SST. This uses non-overlapping short and long stop signal delays (SSDs), which are set as a proportion of the average Go reaction time coupled with intermediate SSDs set, as usual, to track 50% correct stopping. This SST provided almost equal number of trials for each of three delay lengths. This SST produced CSR at F8 as expected, and with a broader frequency range (4-12Hz) than previously reported. CSR correlated with neuroticism and trait anxiety but to different extents in different trial blocks. It was reduced by three chemically distinct drugs (administered double-blind): buspirone (10mg), triazolam (0.25mg), and pregabalin (25mg). These drugs each share anxiolytic, but no other, action. sLORETA located the CSR source in the right inferior frontal gyrus (rIFG) and middle frontal gyrus, locations previously linked to SST control. This new form of the SST should be particularly suitable for generating CSR as a biomarker for one specific type of anxiety disorder.

3.3

Does optogenetic stimulation of motor thalamus improve reaching in Parkinsonian rats?

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High frequency deep brain stimulation (DBS) in motor thalamus (Mthal) ameliorates tremor in advanced Parkinson's disease but not akinesia. The primary aim of this study was to investigate if there are methods of Mthal stimulation effective for akinesia. Glutamatergic Mthal neurons, transduced with channelrhodopsin-2 by injection of lentiviral vector (pLenti.CamKIIα.hChR2(H134R).mCherry), were selectively stimulated with blue light (473 nm) via a chronically implanted fibreoptic probe. Rats performed a reach-to-grasp task in either acute parkinsonian (0.03-0.07 mg/kg haloperidol, s.c.) or control (vehicle injection) conditions and the number of reaches was recorded for 5 minutes before, during and after optogenetic stimulation. We compared the effect of DBS using a complex physiological pattern previously recorded in the Mthal of a control rat during reaching, with tonic DBS delivering the same average stimuli per second (rate-control 6.2 Hz) and with stimulation patterns commonly used in other brain regions (tonic 130 Hz, continuous theta burst (cTBS), and tonic 15 Hz rate-control for cTBS) to treat neurological conditions. Control rats typically executed >150 reaches per 5 minute period, which was unaffected by any of the stimulation patterns. Parkinsonian rats executed <20 reaches, displaying marked akinesia, which was significantly improved by stimulating with the physiological reaching pattern or cTBS (both $p<0.05$), whereas all tonic patterns failed to improve reaching. These data indicate that the pattern of Mthal stimulation is critical for improving reaching in parkinsonian rats and that the Mthal may be an effective site to treat akinesia.

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3.4

Investigation of AL-1-99 as a potential anti-addiction pharmacotherapy: side effects and cellular mechanisms

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Psychostimulant abuse is a major health, social and economic burden worldwide as there are currently no FDA approved therapeutics available to treat psychostimulant abuse. It is well established that kappa opioid receptor (KOPr) activation reduces drug-seeking behaviour. However, classic agonists present side effects such as sedation and depression that prevent clinical use. Recently, a structurally novel KOPr agonist called Salvinorin A was shown to have anti-addictive effects with less side effects than traditional KOPr agonists but its short duration of action still limits its therapeutic development. We have identified a longer acting structural analogue of salvinorin A called AL-1-99, which we have shown to have anti-addiction effects. It attenuates cocaine-primed induced reinstatement in cocaine self-administering rats and significantly decreased cocaine-induced hyperactivity ($p<0.05$). We also tested AL-1-99 for possible side effects. We have shown that 1.0 mg/kg of AL-1-99 (the dose that attenuates drug seeking) does not produce sedation in the open field activity test. AL-1-99 had no effect on immobility times in the forced swim test, a behavioural model of depression and does not modulate natural reward seeking in rats. These results combined indicate an improved pharmacokinetic and side-effect profile of this compound. Using Western blotting, we studied the possible pathways via which AL-1-99 signal. AL-1-99 significantly activated the early but not late phase mitogen activated protein kinases/extracellular regulated kinases (MAPK/ERK) pathway ($p<0.05$). Differences in the behavioural and molecular actions of AL-1-99 compared to classic agonists will provide more information for the development of effective anti-addiction pharmacotherapies with fewer side effects.

3.5

White matter lesions - a factor in developing dementia in patients with Parkinson's disease

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Small vessel cerebrovascular disease is commonly visualized as hyperintense signal on T2-weighted magnetic resonance imaging (MRI) scans. These areas of abnormality are referred to as white matter lesions (WMLs). In healthy individuals, age-related WMLs are associated with both motor and cognitive impairments. Hence, comorbid WMLs are likely to exacerbate clinical symptoms of Parkinson's disease (PD), but there is no clear evidence associating WMLs with cognitive decline and dementia in PD. We examined WMLs in 130 participants with PD and 50 matched healthy individuals. Of these participants 69 PD and 41 controls had multiple assessments over 1-6 years, including detailed neuropsychological and clinical assessment and a T2-weighted MRI scan. A linear mixed effects model assessed the relationship between total WML volume and whether an individual developed dementia, accounting for subject group, cognition, baseline age, time from first scan, sex, and intracranial volume. WML volume increased significantly with age and higher WML volume was associated with greater levels of cognitive impairment. PD patients who developed dementia over the follow-up period had significantly higher WML volume relative to PD participants who did not develop dementia. These findings suggest that WMLs are associated with the development of dementia in PD and may provide an easily accessible, non-invasive MRI-based early marker of future cognitive decline in PD.

3.6

Effects and mechanism of action of estren on beta amyloid-induced cholinergic and behavioural deficits

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Estren (4-estren-3alpha, 17beta-diol) is a selective non-classical estrogen like signaling activator with neuroprotective effects *in vitro*. Alzheimer`s disease (AD) is characterized by accumulation of neurotoxic beta-amyloid (Aβ) and impaired cognitive function linked to early loss of cholinergic neurons. In this study, we have examined the effects and mechanism of action of estren treatment on Ab_{1-42}-induced cholinergic neurotoxicity and behavioural deficit *in vivo*. Evaluation of adult female wild-type mice that received unilateral Ab_{1-42} injection into the nucleus basalis magnocellularis complex (NBM) of the basal forebrain showed 30 % decrease in cholin-acetyltransferase (ChAT)-immunoreactive cell bodies in the NBM and acetylcholinesyterase (AChE)-stained fibers in the somatosensory cortex of the lesioned hemisphere. A single injection of 0.33 ng/g estren 1 h after Ab_{1-42} administration did not have an effect on cholinergic cell loss in the NBM, but it restored the ipsilateral cholinergic fiber density in the somatosensory cortex. Mice that received bilateral injection of Ab_{1-42} into the NBM demonstrated impaired learning skills compared to control groups. However, a single 33 ng/g estren treatment was able to restore the deficits of learning behaviours. We have previously reported that estradiol rapidly induces extracellular-signal-regulated kinase 1 and 2 (ERK1/2) and cAMP response element binding protein (CREB) phosphorylation in cholinergic neurons. In the present study, we found that administration of estren to adult female mice resulted in significantly increased phosphorylation of ERK1/2 and CREB in cholinergic neurons of the NBM within 30 min. In summary, these findings indicate that estren might hold potential as a molecular target for AD prevention and treatment.

4.1

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

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The mouse olfactory system contains two distinct chemosensory epithelia, the main olfactory epithelium and the vomeronasal epithelium. Their sensory neurons express, respectively, odorant receptor genes and vomeronasal receptor genes, and differ fundamentally in signal transduction pathways. Genes required for chemosensory transduction are, respectively, the cyclic nucleotide-gated channel subunit *Cnga2* and the transient receptor potential cation channel *Trpc2*. Here we document two previously unrecognized types of Trpc2+ neurons in the mouse main olfactory epithelium at various ages including adults. These cell types express *Cnga2* and can be distinguished by expression of adenylate cyclase *Adcy3* (positive, type A; negative, type B). A third of main olfactory epithelium neurons that express the odorant receptor genes *Olfr68/Olfr69* coexpress *Trpc2* and are type A cells. In Trpc2-IRES-taulacZ gene-targeted mice, some labeled axons coalesce into glomeruli in the main olfactory bulb, and this pattern is perturbed in Cnga2 knockout mice. Our findings have implications for the conventional interpretation of the striking behavioral phenotypes of Trpc2 knockout mice, which has been based on the unproven assumption that Trpc2 is expressed only in vomeronasal sensory neurons.

4.2

Kappa opioids: New targets for the treatment of pain

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Pain, although necessary for survival, can become pathological affecting an estimated 1 in 5 adults globally. It is also the most common reason people seek medical attention. Mu opioid receptor activating drugs such as morphine are the gold standard treatment for pain. Although these drugs have excellent analgesic properties, side effects such as addiction, tolerance, respiratory depression and constipation make their use problematic. An estimated 10,000 New Zealanders are addicted to prescription opiates, highlighting the need for better drugs to treat pain. Kappa opioid receptor agonists have analgesic properties but, unlike mu opioid agonists, are also anti-addictive. Unfortunately, centrally mediated side-effects such as dysphoria, have limited their therapeutic use. However, if kappa opoid agonists are restricted to act only in the periphery, they have limited side-effects and possess effective anti-pain and anti-inflammatory actions. This study uses animal behavioural models to characterise the anti-pain effects of a structurally new class of kappa opioid agonists including Salvinorin A, Mesyl Salvinorin B, KMS and the known peripherally restricted compound ICI 204,448. All compounds tested showed a dose-dependent analgesic effect as assessed by the formalin test ($P<0.01$ for Salvinorin A, ICI 204,448, KMS at 2 mg/kg). Unfortunately doses that produced analgesia also produced sedation. However, ICI 204,448 was the only compound to reduce inflammatory pain ($P<0.05$ at 1 mg/kg) without producing any centrally mediated effects, shown by the tail flick and rotarod behavioural assays. This peripherally restricted mechanism of producing analgesia may prove to be a more therapeutically efficient method in the treatment of pain.

4.3

Inter-limb transfer of force-field adaptation is enhanced when the perturbation is aligned in extrinsic and joint-based coordinates

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Humans are able to adapt their motor commands in order to make accurate movements in novel sensorimotor environments, such as when wielding tools that alter limb dynamics. However, it is unclear whether sensorimotor representations obtained through experience with one limb are available to the opposite (untrained) limb and, if so, in which form they are available. Here we compared cross-limb transfer of force-field compensation after participants adapted to a velocity-dependent curl field (0.13 $N.m^{-1}.s$) oriented either in the horizontal or transverse plane. Due to the mirror symmetry of the limbs, the force field had identical effects in joint and extrinsic coordinates in the sagittal plane, but opposite joint-based effects in the transverse plane. Subjects reached to visual targets in a virtual reality environment that provided three-dimensional feedback of hand and target position. Three different groups (each, n=8) adapted to the transverse force field with the right arm when the field was introduced either (1) abruptly or (2) gradually, and with the left arm when the field was introduced (3) abruptly. Another three groups (4-6) did the same task but with movement in the sagittal plane. Performance with the opposite arm was subsequently tested for the same plane of movement and the same field. The degree of force-field compensation exhibited by the opposite arm in probe trials immediately after adaptation was significantly greater for sagittal (27 ± 15 %) than horizontal plane groups (7 ± 12; $p < 0.001$), which indicates that transfer was impaired when the orientation of imposed dynamics conflicted in intrinsic coordinates for the two limbs. The data imply that neural representations of novel dynamics are partially available to the opposite limb, but that bilateral performance benefits depend on the degree to which the perturbation is spatially compatible for the two limbs according to multiple frames of reference.

4.4

Laminar representation of odour in the mouse piriform cortex *in vivo*

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The anterior piriform cortex (aPC) is a relatively simple paleocortical structure dedicated to processing odour information. The aPC is highly laminar, with its main input layer (layer 2) containing two distinct populations of glutamatergic neurons: semilunar (SL) cells in layer 2a and superficial pyramidal (SP) cells in layer 2b. However, little is known about how odour information is represented in neuronal populations in different layers. Here, we simultaneously measured the activity of up to 158 neurons in each layer of the aPC in anesthetised mice *in vivo* using 2-photon microscopy and functional calcium imaging, employing the calcium indicator dyes Oregon Green BAPTA-1 AM and Cal-520, or the genetically encoded calcium sensor GCaMP6s. With the higher signal-to-noise ratio of Cal-520 and GCaMP6s, we detected spontaneous activity in the somata of SL and SP cells, as well as in their dendrites in layer 1. Presentation of a palette of seven structurally-distinct odorants excited up to 15 % of neurons in an ensemble pattern that was unique for each odorant. On average, a given SL or SP cell responded to 0.5 of seven odorants. However, the distribution of the number of odours that each cell responded to was 6.6 times more positively skewed in SP cells than in SL cells, indicating that responsive SP cells are excited by a larger number of odorants. These results suggest that SL and SP cells are spontaneously active in the mouse aPC and may employ distinctive codes for representing odours *in vivo*.

4.5

Auditory processing of dysarthric speech: An EEG study

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Reduced speech intelligibility associated with dysarthria impacts both speaker and listener. When attempting to decipher the distorted speech signal, listeners employ a combination of bottom-up and top-down processing. The aim of the present study was to investigate the relative contribution of early, sensory-driven processing and later, cognitive-linguistic processing when listeners are presented with dysarthric speech. In addition, we aimed to assess any learning effects due to repeated exposure to dysarthric speech. Twenty healthy, native English speakers (7 males, 18-45 years) participated. Stimuli consisted of 110 sentences, half of which were uttered by speakers with moderate hypokinetic dysarthria and the other half by controls speakers, matched for age and gender. During the EEG experiment, participants were instructed to listen to each sentence and then judge its level of intelligibility. The same experiment was repeated one week later. Data analysis included referencing to the bilateral ears, 1-20 Hz filtering, and artifact rejection. The EEG signal was segmented into 1300msec epochs, and baseline corrected. One-tailed t-tests were used to compare the mean amplitude of the auditory N100 (50-150msec interval) and N400 (400-600msec interval) over electrode Cz. At session one, listeners exhibited significant increases in the mean amplitudes of the N100 (T_{19}=1.8, p=.04), measuring early sensory processing, and N400 (T_{19}=2.5, p=.01), measuring later cognitive-linguistic processing when listening to dysarthric compared to control speech. Comparison with data from session two indicated no apparent learning effect due to repeated exposure to the experimental stimuli. In sum, the results show that listening to dysarthric speech leads to increased neural rocessing in both early, sensory-driven, bottom-up processes, as well as in later, linguistic-cognitive, top-down processes.

5.1

The effects of 3,4-methylenedioxymethamphetamine (MDMA) on reinforced responding in rats: Perseveration, variation or loss of stimulus control?

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Over the last 10 years evidence has accumulated that the effects of acute MDMA on memory function in rats can frequently be attributed to an increase in 'response perseveration' (i.e. immediately preceding responses or sequences are likely to be repeated on a subsequent trial). However, not all procedures have yielded results consistent with this interpretation and typically the analyses conducted have been post hoc, rather than a direct test. The current study reports the results from a 'reinforced variability' procedure that signalled to rats they would be either reinforced for repeating a sequence of lever responses versus reinforced for conducting a novel sequence of lever presses (defined as any sequence different from the preceding 10 trials). Although we expected MDMA to increase perseveration (i.e. enhance performance on the 'repeat' trials and impair performance on the 'vary' trials) the pattern of effect was much more consistent with an overall increase in variability (i.e. impaired performance on the 'repeat' trials and improved performance on the 'vary' trials). This effect is not consistent with the perseveration-based account of impaired memory function following acute exposure to MDMA.

5.2

Correlations between reading performance and BOLD activation during word rhyming: The Auckland Comorbidity study

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Reading is a complex process, drawing on a variety of brain functions in order to link symbols to words and concepts. Our earlier functional Magnetic Resonance Imaging (fMRI) findings with individuals with dyslexia have confirmed the expected hypo-activation in the left posterior areas, but also showed areas of overactivation in the right hemisphere during pseudoword decisions. It remains unclear, however, as to the role of right hemisphere reading. Does it help or hinder reading performance? The current study investigated differences activation between individuals with dyslexia and with comorbid dyscalculia in a rhyming task during fMRI. We compared n=48 adults with either reading disabilities (RD), mathematical disabilities (MD), both (MDRD) or no learning disability (Control). Prior to scanning, participants were tested on a computerized cognitive profiling battery including tasks targeting core cognitive networks involved in reading and phonological awareness (word attack, phoneme reversal). Here we focus on BOLD activation during the rhyming task (vs. line judgment control) intended to target the phonological network in reading in our blocked fMRI design and (out of scanner) phonological task performance. BOLD results were compared between groups and behavioural data was correlated with significant activation (controls>experimental groups; experimental groups>controls). We found that reading and phonological task performance was positively and significantly correlated with left hemisphere reading network activation in typical readers only. In contrast, the RD and MDRD groups showed a negative correlation between performance and activation. We found that insular activity is associated with reading performance in both the RD and MDRD groups but not in the Controls or MD groups. Our finding that insula activation was associated with better reading performance only in the dyslexia groups was unexpected. Meta-analyses are consistent with this, however, showing that the anterior insula is a region reliably activated to a greater degree in people with dyslexia. The anterior insula, which receives input from the autonomic nervous system, has been shown to increase activity in response to aversive visual stimuli. As such, one interpretation for our finding is the aversive nature of reading for individuals who have suffered reading failure since childhood. Overactivation may also reflect compensation.

5.3

Identification and localization of electrical activity in the brain associated with behavioural microsleeps

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Behavioural microsleeps involve complete disruption of performance of 0.5–15 s and can result in injury or death, especially in the transport sector (e.g., pilots, air-traffic controllers, car/truck drivers). The high temporal resolution of EEG provides an opportunity to study the highly transient brain activities happening during microsleeps, which may help in real-time EEG-based detections of microsleeps. EEGs from 5 healthy non-sleep-deprived subjects were recorded, together with eye-video, while they were performing a 1-h long visuomotor tracking task. Behavioural rating found the occurrence of a total of 103 microsleeps. Identification and localization of neuroelectric activity during microsleeps was carried out via source-space independent componenet analysis – a novel combination of EEG spatial filtering and blind source separation. Theta- and alpha-band bursts were seen in some, but not all, microsleeps. The time-courses of these activities were reconstructed and tomographic maps obtained. The frontal orbital lobe was found to be the origin of the theta burst oscillations and the hippocampus to be the origin of the alpha bursts. While strong theta activity indicates the state of drowsiness, the alpha bursts had the same appearance as sleep spindles seen in the EEG during stage II sleep. This indicates that behavioural microsleeps are brief transitions from stage I sleep (drowsy but responsive) into stage II sleep (non-responsive).

5.4

Genetic analysis of the role of HDAC4 in long-term memory: Interaction with the SUMO-conjugating enzyme Ubc9

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The Class IIa histone deacetylase HDAC4 is highly expressed in the brain and is regulated via shuttling between the nucleus and cytoplasm in response to physiological stimuli. Overexpression of HDAC4 in neurons results in a specific impairment in long-term memory (LTM) in Drosophila, and interestingly, this effect is independent of its deacetylase activity. RNAi-mediated knockdown of HDAC4 also impairs LTM, suggesting that wild-type levels of HDAC4 are required for normal LTM, however the specific mechanisms through which HDAC4 regulates memory are not known. In order to identify genes that interact genetically with HDAC4, an enhancer screen was performed by screening RNAi lines for enhancement of a “rough eye” phenotype caused by overexpression of HDAC4 in the Drosophila eye. 26 genes were identified, one of which was *Ubc9*, a SUMO E2-conjugating enzyme. Immunohistochemical analysis of Ubc9 expression in the Drosophila brain revealed that it is predominantly localised to the synaptic neuropil, as well as the nuclei of Kenyon cells. These are the intrinsic neurons of the mushroom body, a region of the brain critical for learning and memory in Drosophila. Within Kenyon cell nuclei, Ubc9 colocalised with FLAG-HDAC4 in punctate nuclear bodies. The effect of RNAi-mediated knock-down of Ubc9 on LTM was assessed using the Drosophila courtship suppression assay and a significant impairment of long-term memory was observed ($p<0.01$, ANOVA). The ongoing analysis of these interactions in the brain will assist in understanding the mechanisms by which HDAC4 regulates LTM.

Poster 6.1

Prefrontal cortex stroke results in delayed onset impairment

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Stroke is a leading cause of disability worldwide. Post-stroke, cognition can be impaired leading to stress, depression and frustration in patients. Studies focusing on post-stroke cognition are limited and often confounded by motor impairments. Therefore we aimed to establish a model of stroke that would allow us to assess components of learning and memory. We chose to target the medial prefrontal cortex (mPFC), as epidemiological evidence suggests small infarctions to the mPFC often result in cognitive impairments. Bilateral infarcts were induced in the mPFC using the photothrombotic (PT) stroke model (22-minute light exposure) in 3-month old C57Bl/6J male mice. Using this model of stroke, mice received either sham (n=14) or stroke (n = 15) surgeries and assessed on novel object (NO) and object-location recognition (OLR) tasks. Open field and elevated plus maze (EPM) tests were also used to assess for motor impairments or increased anxiety. Infarct volume analysis was carried out 3-days post-stroke using cresyl-violet staining and ImageJ software to quantify infarcts in both left and right hemispheres. No differences between sham and stroked groups were observed at either 1 or 4-weeks after stroke in the open field test, on the EPM test or in the NO task ($P \geq 0.05$). Assessment on the OLR task showed no differences between treatment groups at 1-week post-stroke, however, assessment carried out at 4-weeks revealed a significant impairment in the ability to recognize that one of the objects had been moved in the stroke group compared to sham controls ($P \leq 0.05$). This is the first experimental evidence that strokes to the mPFC result in delayed onset memory impairments, similar to human studies. We suggest that this model may therefore be a useful tool in assessing potential rehabilitative/cognitive therapies after stroke.

Poster 6.2

Repeated exposure to a serotonin$_{1B}$ agonist facilitates acquisition of MDMA self-administration

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The latency to acquisition of (±)3,4-methylenedioxymethamphetamine (MDMA) self-administration is dependent on the magnitude of MDMA-produced increases in both synaptic serotonin (5-HT) and dopamine (DA). We have shown that neurotoxic lesions, or a mutation that prevents 5-HT transporter function, reduced the latency to acquisition of MDMA self-administration. Thus, our data are consistent with the idea that MDMA-produced increased 5-HT is initially inhibitory to self-administration. We have suggested that the progression to high rates of self-administration is dependent on the well documented neurotoxic effects of repeated exposure to MDMA. As a result of these MDMA-produced decreases in 5-HT neurotransmission, we propose that MDMA-produced DA release is enhanced and this sensitised DA response underlies the development of high rates of self-administration. An additional mechanism for the enhanced reinforcing efficacy of MDMA following repeated exposure is MDMA-produced alterations in 5-HT receptor mechanisms. Of particular interest is the 5-HT$_{1B}$ receptor subtype because activation modulates DA neurotransmission. Repeated activation of this receptor subtype by MDMA-produced synaptic 5-HT would be expected to down-regulate the receptor, thereby altering the MDMA-produced DA response. In the present study we evaluated the consequences of repeated exposure to the 5-HT$_{1B}$ agonist, RU 24969, on a behavioural response to RU24969 and on the latency to acquisition of MDMA self-administration. Repeated 5-HT$_{1B}$ activation produced tolerance to the behavioural effects of RU24969, decreased the latency to acquisition of MDMA self-administration, and increased the percentage of rats that acquired MDMA self-administration. These findings suggest 5-HT$_{1B}$ receptor activation inhibits the reinforcing efficacy of MDMA.

Poster 6.3

Mammillothalamic tract lesions and spatial memory in rats

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In humans, damage to the mammillothalamic tract (MTT) is believed to be a critical site that causes stroke-induced diencephalic amnesia. The amnesia is likely to be a result of the MTT's influence on an extended hippocampal circuit for episodic memory. Unlike ATN lesions, however, MTT lesions produce mixed results or only mild deficits in animal lesion models. The current study used total or near total bilateral radiofrequency lesions of the MTT and examined performance across several spatial memory tasks. MTT (n = 9; shams n = 13) lesions resulted in no deficit in the standard reference memory water maze task. However, a deficit was evident for working memory in both the water maze (d = 1.3, CI 0.41- 2.19) and the radial arm maze (d = 1.24, CI 0.36 – 2.11). The deficit in the radial arm maze was exacerbated when a delay (d = 1.52, CI 0.64 – 2.39) and especially maze rotation (d = 2.25, CI 1.37 - 3.12) was introduced. MTT lesions also impaired acquisition of an object place association task (d = 1.83, CI 0.95 – 2.70). Preliminary results suggest, however, that rats with ATN lesions (awaiting lesion verification) showed greater spatial memory impairments. The possible association between memory deficits and zif-268 and BDNF expression is also being examined. The behavioural results suggest that substantial injury to the MTT contributes to diencephalic amnesia. It is possible that the severity of deficits in human cases is often worsened by additional damage to adjacent structures.

Poster 6.4

Comparing mild cognitive impairment criteria in Parkinson's disease: influence on dementia onset

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Many patients with Parkinson's disease (PD) are likely to progress to dementia (PDD). The influence on conversion to dementia of different mild cognitive impairment (PDMCI) criteria meeting current PDMCI guidelines is unclear. Repeat assessments of 24 neuropsychological measures across five cognitive domains were made in 142 PD patients over a two to four year period, with onset of PDD as the outcome variable. Six criteria were defined as impairments in two (or more) tests in one cognitive domain at 1, 1.5 or 2SD below normative data (e.g. "2@1SD in 1 domain"), or impairments in at least one test in two (or more) cognitive domains at 1, 1.5 or 2SD below normative data (e.g. "1@1SD in 2 domains"). Progression to dementia was significantly increased for all of the PDMCI criteria compared to the patients not meeting any given criterion (latter specified as showing "normal" cognition). The 1SD criteria captured too many patients who did not develop PDD while the 2SD criteria failed to capture sufficient PDD converters or had a high rate of reversion from PDMCI to normal cognition. When patients who met the (a) "1@1.5SD in 2 domains" criterion were separated from those who exclusively met the (b) "2@1.5SD in 1 domain" criterion there was progression in cognitive impairment from the (a) criterion to the (b) criterion rather than conversion to PDD. The balance of evidence suggests that two impairments at 1.5SD in one domain is an optimal PDMCI criterion for identifying patients at imminent risk of PDD.

Poster 6.5

The effect of working memory load on target and distractor processing as indexed by lateralised event-related potentials

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Visual selective attention is often considered to be a gating mechanism for high level, limited capacity processes like working memory. Recent evidence has also shown however that working memory may play an essential role in the successful deployment of attention. A low working memory capacity, as well as an increased working memory load has been associated with decreased performance on attention based tasks. Research so far has failed to isolate the specific mechanism being affected by the availability of working memory. In this experiment we recorded scalp EEG while participants perform a modified version of the localised attentional interference (LAI) paradigm under different levels of working memory load. The behavioural data replicate previous effects in which increased memory load is associated with decreased performance on the visual search task. The LAI paradigm also allows us to show working-memory load effects on the amplitude of the attention-related lateralised components of the event-related brain potential (N2pc, Ptc, and SPCN), which have been related to target selection, distractor suppression, and working memory processes respectively. Under low load, these components display a typical pattern of results. While targets elicit an N2pc (attentional selection) and SPCN (short-term feature maintenance), distractors elicit an N2pc (attentional selection) and Ptc (distractor disengagement). Under high load, target processing is the same as in the low load condition, eliciting an N2pc and SPCN. Distractors however no longer elicit the suppression related Ptc, and instead produce an SPCN. Our findings suggest that increased working memory load leads to increased processing of distractor representations due to impaired mechanisms of distractor suppression.

Poster 6.6

Psychophysiological role of tryptophan and kynurenic acid in central fatigue induced by chronic sleep disorder

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Central fatigue is implicated in clinical conditions such as chronic fatigue syndrome, and leads to reduced cognitive function, disrupted social life, and impaired brain functions. For instance, the prevalence of central fatigue that is induced by chronic sleep disorders in schoolchildren has been reported at 40-80%, and children are occasionally excused from school. Tryptophan (TRP) and its neuroactive metabolite, kynurenic acid (KYNA), are thought to play key roles in central fatigue, but the specifics are still unknown. To clarify their roles in the brain, we developed a rat model of central fatigue induced by chronic sleep disorder (CFSD) by disturbing the sleep-wake cycle. TRP, KYNA, and 5-hydroxytryptamine (5-HT) concentrations were measured in brain regions of CFSD and control rats. Results showed that while 5-HT concentration did not differ between control and CFSD groups, levels of TRP and KYNA in the CFSD group were about 2 and 5 times higher in the hypothalamus, and 2 and 3.5 times higher in the hippocampus, respectively. Moreover, fatigue and social behavior were measured by using treadmill and social-interaction tests, respectively. CFSD-induced fatigue led to decreased running performance and social interaction. These results support a TRP-KYNA hypothesis in central fatigue in which increased TRP concentration in the brain and subsequently synthesized KYNA may produce an amplified effect on central fatigue, with enhanced concentrations being a possible mechanism by which social-interaction deficits are generated.

Poster 6.7

The influence of maternal cyclic-glycine-proline treatment during lactation on the growth and behaviour of offspring in rats

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The decline in milk production following peak lactation in cows and humans is associated with the loss of milk producing mammary epithelial cells (MECs) by apoptosis. Treatment of rats with cyclic-glycine-proline (cGP), a diketopiperazine derived from IGF-I, during peak lactation (d13-15) increases the number of MECs. We hypothesised that treatment of rats with cGP throughout lactation may maintain the production of milk. We also sought to determine if cGP influenced the behaviour of the offspring. Either cGP or saline was given to Sprague-Dawley rats by gavage from d8-d22 of lactation. Growth rate of pups was evaluated, and changes in milk protein and lipid content were determined before, during and after treatment with cGP. Four behavioural tests were carried out (d35-70) to test the learning/memory ability (Novel Object Recognition test (NORT) and Morris Water Maze test (MWM)), anxiety-like behaviour (Light/Dark Box test) and general locomotory function (Open Field test) of pups. Treatment with cGP showed a trend for an increase in the growth rate of pups during early lactation (d7-d14) compared to the control group ($P=0.1$). cGP did not change the protein or lipid content of milk at any stage of lactation. cGP improved the learning/memory abilities of the pups ($P<0.05$ both NORT and MWM), without affecting their anxiety-like behaviour ($P>0.1$) or general locomotory function ($P>0.1$). Our data suggests that treatment of lactating dams with cGP increases milk production in early lactation, which tends to increase the growth rate of pups. Furthermore, cGP improves the learning/memory abilities of the offspring without affecting their general well-being.

Poster 6.8

A genetic screen to identify genes that interact with Histone Deacetylase 4 (HDAC4): Investigating the interplay with ankyrin2 in the brain

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HDAC4 has been proposed to be key regulator of memory formation, however its specific functions during memory formation have not yet been elucidated. In order to identify genes in the HDAC4 memory pathway, a genetic screen was performed in Drosophila. Overexpression of HDAC4 in the Drosophila eye results in a mild “rough eye” phenotype, with disorganisation of bristles and ommatidia. This phenotype is ideal for screening for enhancers of HDAC4 activity, as it is an *in vivo* phenotype that is easily scored and does not affect viability. A panel of 114 RNAi lines were selected for screening and 26 were found to significantly enhance the HDAC4-induced rough eye phenotype. As each individual gene did not itself induce a significant rough eye phenotype, the enhancement of the HDAC4 phenotype would suggest that that the gene interacts in the same molecular pathway as HDAC4. The genes identified coded for both nuclear (e.g CREB, MEF2) and synaptically localised (e.g. prosap) proteins. The screen confirmed several genes known to interact with HDAC4 in other organisms or tissues, e.g. Mef2, PCAF, SMRT and 14-3-3ζ. Ten novel HDAC4 interacting factors were identified including, prosap, RFXANK and ankyrin2. Ankyrin2 was chosen as a candidate for further investigation and immunohistochemical analyses showed that ankyrin2 is strongly expressed in the adult brain and co-localises with HDAC4 in the mushroom body, a key structure for memory formation in flies. Behavioural studies will determine if the association between ankyrin2 and HDAC4 leads to changes in long-term memory formation in flies. The results obtained will contribute to elucidating the mechanisms by which HDAC4 regulates brain plasticity.

Poster 6.9

Enriched environments and recovery of spatial memory in the radial arm maze after anterior thalamic lesions

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Lesions of the anterior thalamic nuclei (ATN), a brain region implicated in diencephalic amnesia, produce memory impairments in animal models. Previously, recovery of function following environmental enrichment has been found in rats with ATN lesions, although mixed findings have been reported for spatial memory in the radial arm maze (RAM). Here, functional recovery using enrichment was re-examined in (1) a standard RAM task, (2) a mid-trial delay, and (3) a mid-trial rotation. The rotation procedure has previously been shown to be particularly sensitive to retrosplenial cortex (RSC) lesions, and thus may be a barometer of extended hippocampal system dysfunction. In all three RAM tasks, lesions to the ATN in standard-housed rats produced severe spatial memory impairments compared to sham-lesion controls, but enriched rats with ATN lesions showed recovery of function with an intermediate level of performance. The influence of ATN lesions and enrichment on immediate early gene activity in the RSC associated with performance after a mid-trial rotation is currently under examination. This pending neurobiological analysis, together with this new behavioural evidence, may improve our understanding of the role of the ATN and the RSC for spatial memory in the extended hippocampal system.

Poster 6.10

Short-term musical training modulates functional connectivity of the sensorimotor system

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Musical training requires integration between auditory and motor processes. During passive listening, previous studies have demonstrated action representation effects for sounds to which the appropriate action is known, in highly-skilled musicians and non-musicians after a short period of training. However, another view is that specific actions required to produce the sound need not be known as humans inherently move to music. According to this view, the presence of a rhythm may be sufficient for action representation to occur when listening to music. We aimed to determine if audiomotor training leads to changes in functional connectivity that can be measured by EEG coherence during passive listening, and sought to examine this alternative view. Non-musicians underwent short-term piano training, where they aimed to learn a limited range of sound-action mappings. EEG was recorded pre- and post-training, while participants listened to three types of stimuli: piano tones included in training; piano tones not included in training; and a woodblock rhythm. This enabled us to investigate specificity in the audiomotor networks for certain sounds. An increase in coherence of the beta band between specific sensorimotor electrode pairs was found post-training. This was only revealed in piano tone tasks, however, and not when a rhythmic sequence was heard. This suggests that the coherence effect is not specific to the learned sound-action mappings. However, there is some degree of specificity as listening to similar rhythm sequences did not result in any coherence increase. Our study shows that further insight into oscillatory coupling changes that occur due to musical training can be gained using EEG, contributing to evidence that action representation occurs through musical training.

Poster 6.11

Remembering the past and imagining the future in depression

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Autobiographical Memory (AM) refers to the recollection of personally experienced events. This aspect of memory not only allows us to maintain a consistent sense of self, but also plays a significant role in how we imagine the future. Previous research suggests that individuals who suffer from depression tend to recall AMs in an overgeneralised, non-specific manner. This phenomenon, referred to as overgeneral memory (OGM), is a robust finding and is seen as a core cognitive deficit in depression that is also evident during remission and in dysphoria. Additionally, OGM has been associated with reduced specificity of future thinking. Until now, previous research has not directly compared specificity of remembered and imagined events. Furthermore, OGM research has generally employed one standard measure to assess specificity; namely the Autobiographical Memory Test (AMT) which uses cue-words of emotion valence (e.g., happy, sorry). In the current study, 17 depressed participants and 16 matched controls were instructed to generate past and future events in response to neutral event-cues (e.g., Winter's Day, New Year's Eve). These responses were scored for specificity using two different methods of scoring: the traditional AMT method and also a newer method; the Autobiographical Interview (AI). Both scoring methods demonstrated that, as predicted, depressed participants were significantly less specific in both their past and future responses to event-cues in comparison to controls. This group difference in specificity was particularly marked when imagining future events in comparison to recalling past events. Additionally, a comparison of the AMT and the AI scoring methods suggests that the AI is a more fine-tuned and nuanced approach to examine the specificity of autobiographical events.

Poster 6.12

Do the eyes have it? The role eye regions in the face specificity of the occipitotemporal component of the event-related potential, N170

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The N170, an occipitotemporal component of the event-related potential (ERP) occurs earlier and has a greater amplitude when evoked for faces than other objects. This is considered, by some, to reflect early processing specificity for faces. Some authors suggest that the eye regions have a dominant contribution in the face specificity of the N170 (Itier, Alain, Sedore & McIntosh, 2007); however a majority of studies have failed to report modulations of the N170 that support this idea. In the present study we employed the competitive modulation of N170 amplitude as a paradigm to explore the role that the internal features of the face (in particular, the eye regions) play in competition for representation. We presented face stimuli drawn from three categories of internal face stimuli: features intact (FI), no eye region (NER), or no internal features (NIF). The N170 showed greater attenuation when intact internal faces were presented in the context of faces that appear more face-like (i.e. with FI and NER flankers) than with faces without any face-like features (NIF flankers). This data are suggestive that the eye regions do not dominate the face-sensitivity of the N170.

Poster 6.13

Far, far away: Evidence of a greater effect of increased physical effort on low-level perception in depression

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While perception was traditionally considered stable or unchanging across individuals and an individual's lifetime, it is now known that perception is a constructive process. That is, our reality, or the perception of physical properties of our environment, is created in a moment-to-moment fashion and influenced by many extraneous factors. For example, our metabolic state (or energy levels), and our current mood can influence height or distance estimates. Carrying a heavy backpack can increase the perceived distance between two points, and a fear of heights can increase estimates of a vertical distance. However, little is known about how extraneous factors such as mood and energy levels may *interact* to produce a perceptual experience. The present study aimed to examine this interaction by investigating spatial perception in depressed participants under conditions of increased physical effort. Specifically, a group of depressed and matched non-depressed participants completed a spatial task under two conditions - with and without weights. The directional bias evident in participants' performance served as an indicator of the perceived distance to the stimulus. Our results suggest that when not carrying weights, depressed participants perceive stimuli as equidistant compared to non-depressed participants. However, when wearing weights the perceived stimulus distance was significantly greater for depressed participants. That is, increased physical effort affected depressed participants to a greater extent than controls. These results are consistent with evidence of other perceptual and cognitive biases present in depressed individuals, such as taking a distanced perspective on memories for life events.

Poster 6.14

Lesions of the hippocampal dentate gyrus induce drug supersensitivity and increased resistance to extinction of drug seeking responses

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The hippocampal dorsal dentate gyrus (DDG) plays a role in the expression of different forms of flexible behaviour mainly due to its ability to sustain neurogenesis throughout life. Here, we examined the role that the DDG plays in flexible behaviour and cognitive processing. We used the neurotoxin, colchicine, to induce DDG lesions and a range of behavioural and cognitive tasks. In experiment one, rats were tested for (1) perseverative behaviour before and after receiving chronic methamphetamine treatment, (2) methamphetamine-induced locomotor activity and stereotypy in an open field, and (3) working memory in a T-maze. In experiment two, we assessed (1) the acquisition and reversal of a T-maze stimulus-response (S-R) learning task, and(2) drug sensitivity, extinction and reinstatement of drug seeking responses in a cocaine self-administration (S-A) task (0, 0.02, 0.15, 0.5 and 1 mg/kg/infusion). The results showed that lesioned rats exhibited supersensitivity to locomotor- and stereotypy-inducing effects of methamphetamine (0, 0.1, 0.3, 1 mg/kg i.p.) as well as increased long-term methamphetamine sensitization. Lesioned rats also showed working memory deficits. On the other hand, the performance of sham and lesioned rats in the S-R task was comparable, as was in the task reversal. In the cocaine S-A paradigm, both groups showed similar sensitivity to the reinforcing efficacy of cocaine. An extinction-reinstatement phase followed the cocaine S-A phase. There was evidence of delayed extinction of cocaine S-A in the lesioned group, suggesting increased perseveration of drug seeking responses. Taken together, these results reveal specific forms of behavioural inflexibility in DDG lesioned rats that are mainly associated with drug-related behaviours, including stimulant motor supersensitivity, drug sensitization, and perseverative drug seeking behaviour.

Poster 6.15

A novel approach to investigating structural differences in schizotypy: A structural PLS study

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Schizotypy refers to a set of sub-clinical personality traits which resemble those associated with the schizophrenia spectrum. In addition to an overlap of schizotypy and schizophrenia across several cognitive and behavioural domains, there might also be similar structural differences in the brain. Numerous CT and MRI studies have established that individuals with schizophrenia, when compared with healthy controls, show gray matter volume reductions in several brain areas, including frontal and temporal cortices, hippocampus, amygdala, and cerebellum. To date, few researchers have looked at structural differences in schizotypy and those that have investigated this have reported heterogeneous results. The aim of the present study was to investigate whether gray matter abnormalities can be observed in individuals with high schizotypal traits when compared to those with low schizotypal traits. We obtained MRI scans of 49 individuals and divided them into two groups, based on their score on the O-LIFE schizotypy scale. Using structural partial least squares (PLS) analysis we found a correlation between high positive schizotypy and gray matter alterations in several brain areas (superior frontal and precentral gyri amongst others), several of which correspond to those previously identified in schizophrenia. Our results suggest that gray matter differences do not exclusively occur at a clinical level, but instead can be observed in the general population. These alterations might represent a biomarker of a subset of symptoms associated with the schizophrenia spectrum. Further research holds the promise of providing insights into the aetiology of schizophrenia and might enable us to identify individuals at risk of developing the disorder.

Poster 6.16

Characterizing cerebellar activity during autobiographical memory: ALE and functional connectivity investigations

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Previous neuroimaging research has shown that the cerebellum is often activated during autobiographical memory (AM) retrieval. However, the reliability of that activation, its localization within the cerebellum, and its relationship to other areas of the AM network remains unknown. The current study used Activation Likelihood Estimation meta-analysis (ALE), task-related functional connectivity (PLS) analysis, and resting state functional connectivity analysis to better characterize cerebellar activation in relation to AM. The ALE meta-analysis was run on 32 neuroimaging studies of AM retrieval. The results revealed two clusters of reliable AM-related activity within the Crus I lobule of the right posterior cerebellum. Using the peak ALE coordinate within Crus I as a seed region, both task-related and resting state functional connectivity analyses were run on fMRI data from 16 healthy participants. To determine the specificity of connectivity patterns to Crus I, we also included a cerebellar seed region in right Lobule IV identified by an ALE meta-analysis as associated with working memory. The Crus I seed region exhibited significant resting state connectivity with regions comprising the default network previously associated with AM retrieval. Importantly, the Lobule IV seed region exhibited a different pattern of connectivity with areas of the working memory network. The task-related connectivity analyses revealed a similar pattern, where the Crus I seed exhibited significant connectivity with the default network while the Lobule IV seed did not. The results of the current analyses indicate that the right posterior cerebellum, specifically Crus I, is reliably activated during AM and is functionally connected with the default network both during AM retrieval and at rest. These results suggest the cerebellum may play a critical role in AM.

Poster 6.17

The effects of exogenous sAPPα on spatial memory and LTP in aging

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Impairments in cognition, especially in spatial memory, have long been associated with senescence. Previous research has identified alterations in long-term potentiation (LTP) in the hippocampus as one of the contributors to memory decline. Secreted amyloid precursor protein-α (sAPPα) is cleaved via the non-amyloidogenic pathway from amyloid precursor protein, and has been shown to enhance memory and LTP in young rodent models. Because endogenous levels of sAPPα may be depleted during aging and thus contribute to memory and LTP deficits, we administered sAPPα in an attempt to ameliorate these deficits in aged, male Long-Evans**.** We applied sAPPα (30 or 300 nM) or a vehicle solution into the hippocampus of aged (24 mo, n=12) and young (5.5 mo, n=9) rats prior to a novel object location task and the Morris watermaze task. Preliminary results suggest that aged rats administered with 300 nM sAPPα showed facilitated preference for a familiar object placed in a novel location ($p<0.05$). In the watermaze task, there was impaired learning in the older rats ($p<0.05$), but only a trend for an effect of sAPPα. In *in vitro* CA1 field recordings, aged hippocampal slices treated with 10 nM sAPPα showed greater LTP maintenance following theta-burst stimulation while there was no effect on LTP in slices from young animals, implying a potential difference in drug threshold during aging. If sAPPα can be shown to rescue memory and plasticity in aged rats, this will give further support for its targeting as a therapeutic agent in both normal and pathological aging.

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Poster 6.18

The effect of relational load on the neural correlates of future simulation

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Constructing episodic future simulations, like retrieving episodic memories, engages many regions of the default mode network. Some areas have even been shown to produce a greater BOLD response during future simulation relative to past event retrieval. One hypothesis for this difference suggests future simulations hold a higher relational load (HRL) than remembered past events, resulting in greater activation. In this study, imagined future events were experimentally manipulated to hold either HRL or low relational load (LRL), by giving participants either more or less disparate details to include in the simulation. Behavioural data revealed that trials in the LRL condition were constructed faster and rated as more detailed than in the HRL condition. The fMRI data were first analysed using mean-centred partial least squares (PLS). This analysis showed HRL and LRL conditions both recruited regions of the default mode network significantly more than a control task. However, contrary to the relational load hypothesis, events with LRL showed greater activation of the network than events with HRL. Following this result, we did a non-rotated PLS analysis directly comparing HRL and LRL conditions. Again, a number of regions in the network were recruited more strongly by the LRL condition. In addition, frontal regions which have been implicated in externally based attention and are usually deactivated during future simulation, showed less deactivation for the HRL relative to the LRL condition. These results, along with the behavioural findings, indicate a possible failure to engage in fully episodic simulation for the HRL tasks.

Poster 6.19

General anaesthetic modulation of memory-related gene expression in the cerebral cortex

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General anaesthetics have been in clinical use since the mid 19th century, having remained one of the most important drugs in medicine by enabling major surgical procedures to be carried out. One of the fundamental outcomes of anaesthesia is amnesia, as this prevents recall of events surrounding surgery. Currently, very little is known about how anaesthetics produce amnesia. The hippocampal region of the brain has been widely investigated for its role in memory formation however, the cerebral cortex has newly recognised importance in memory consolidation and storage processes. Although general anaesthetics cause widespread neurochemical changes in the brain, disruption to memory consolidation processes is likely to involve alteration to the expression of memory-related genes. The aim of this research was to investigate the gene expression patterns of *Arc, Bdnf, CamKII*α*, Grin1* and *Gjd2* during periods of anaesthesia (*t*=4 hrs) induced by sevoflurane, isoflurane and propofol. These genes all encode proteins with documented roles in memory consolidation. Real-time quantitative PCR (qPCR) was used to analyse expression of mRNA extracted from the cerebral cortex of the mouse brain. As brain activity is reduced during periods of anaesthesia, we expected to see potential down-regulation of the activity-dependent genes selected for this study. Different age groups of mice will also used for a comparative age-related analysis of anaesthetic effects in the brain.

Poster 6.20

Neural correlates of creativity in schizotypy: An fMRI study

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Creativity is considered to be one of the attributes that define humanity, and is tied to the concepts of originality, flexibility, and variety. Evidence suggests a link between creativity and psychopathology, where a positive association is seen between aberrant/psychotic behaviours and high achievers. Research has also found a positive correlation between tests of creativity and measures which assess psychosis liability, specifically schizotypy. Schizotypy is defined as a cluster of subclinical symptoms and personality traits within a healthy population, which may lead to a predisposition to schizophrenia. The aim of this study was to use fMRI to determine the neural correlates of highly schizotypic individuals during creative performance. Functional images were acquired for 35 healthy adults, who were given verbal and performance creativity tasks. The results indicate an overall greater cortical activation for those with high schizotypy levels compared to the control group, where increased activations were observed in the left middle temporal gyrus for the verbal task, and in the right inferior frontal gyrus for the performance task. These results suggest that individuals who display schizotypal traits are able to utilise additional cortical regions when completing tasks which require creative thought, and are in line with research which indicate that a greater spread of cortical activation is an important factor in creative thinking. Furthermore, there is evidence of task specificity, where different types of task (verbal vs. performance) contribute to the activation of distinctive cortical areas (left vs. right hemisphere), adding to the idea that there may be specialised regions for different domains of creative behaviour.

Poster 6.21

Exposure to alcohol and methamphetamine produces long-term emotional and cognitive deficits in adolescent rats

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Polydrug exposure can lead to increased neurotoxicity and neuropsychological dysfunction. Methamphetamine (MA) use has increased significantly in the last decade in New Zealand and worldwide where it is often used in combination with other substances, including alcohol. Our previous data showed that combined exposure to alcohol and MDMA ("ecstasy") during embryonic development or during adolescence produces long-lasting effects on memory function. Here, we assessed in adolescent rats the effects of repeated exposure (5-day treatment, q.d., by gavage) to alcohol (1.5 g/kg, 20%) and MA (2 mg/kg), given alone or in combination, on anxiety-like behaviour and memory function. Behavioural tests began 15 days after cessation of drug treatments. In the open field test the results showed that drug treatments produced anxiogenic effects, increasing immobility and reducing the number of transitions and the time spent in the centre of the arena. The effects of the combined treatment tended to be more severe than those of single exposure. In the elevated plus maze, all three drug treatments decreased the time spent, and the number of entries into, the open arms. Similarly, in the radial arm maze the drug treatments induced mild but significant impairments in spatial orientation (reference memory). Interestingly, the co-administration of alcohol and MA produced a unique pattern of working memory deficits which was not observed after single exposure. Taken together, these findings demonstrate deleterious long-term effects of drug exposure during adolescence on emotional behaviour and cognitive function and highlight the incremented risks associated with the concurrent recreational use of alcohol and MA.

Poster 6.22

Using probabilistic tractography to investigate genetic influences on recognition memory circuit connectivity

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Both brain structure and memory performance can be influenced by a common single nucleotide polymorphism (SNP) within the gene for brain derived neurotrophic factor (BDNF). However, the influence of the BDNF genotype on recognition memory performance and related brain structures has not been extensively investigated. Recognition memory is comprised of two subcomponents – familiarity and recollection – that are dependent upon related but distinct neural circuits. The medial dorsal thalamic nucleus network underlies processing of familiarity-based recognition judgments, while the anterior thalamic nucleus has been linked to recollection-based processing. In the current study, carriers of at least one copy of the BDNF SNP were compared with non-carriers on two recognition memory tasks. Connectivity analyses were conducted to determine whether differences exist in white matter connectivity across familiarity- or recollection-associated tracts seeded from the relevant thalamic nuclei. In order to do this, probabilistic tractography was conducted. No performance differences were observed between SNP carriers and non-carriers on either recognition memory task. However, connectivity differences were found across both familiarity- and recollection-associated tracts: carriers of the BDNF SNP displayed lower connectivity compared to non-carriers. This finding is consistent with those of previous studies that have found reduced memory performance in carriers of the BDNF SNP, as well as abnormal grey matter structure. White matter microstructure differences in the recognition and familiarity tracts may provide the mechanism behind these behavioural differences between these two genetic groups.

Poster 6.23

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

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Background: low level systemic (subclinical) infection during or after preterm birth is associated with white matter and cortical injury. However, underlying mechanisms of infection-mediated injury remain unclear. Numerous rodent models suggest an effect of systemic inflammation on oligodendrocyte and neuronal survival. However, the majority of these studies use models that do not accurately represent the maturation state of preterm infants and involve severe inflammatory insults representative of sepsis. Thus, the overall aim of this study was to develop a neonatal rat model of mild systemic inflammation that models subclinical infection observed in preterm infants born 22-28 weeks gestation. Methods: postnatal day 1–3 rats received daily injections of lipopolysaccharide (0.3mg/kg i.p.). At this age, white matter oligodendrocyte and cortical neuronal maturation are equivalent to preterm infants. Animals were recovered until pnd2, 4, 7, 14, or 21. Brains were processed for immunohistochemistry or golgi-impregnation for analysis of oligodendrocyte/neuronal survival/maturation, and white matter/cortical growth. Results: lps was associated with a significant decrease in body weight and a trend for decreased brain weight. Lps resulted in acute selective oligodendrocyte progenitor cell (opc) death at pnd2-4, followed by opc regeneration at pnd14-21, but impaired opc maturation into mature cells. In the cortex, there was no evidence of neuronal cell death with lps. Cortical growth and neuronal maturation are being examined. Discussion: mild systemic inflammation in neonatal rats results in white matter injury similar to that observed in preterm infants. Further studies examining the cellular mechanisms of opc arrest and treatments to promote normal maturation following preterm infection are undergoing.

Poster 6.24

A novel fast-scan cyclic voltammetry (FSCV)-based technique for prolonged measurement of absolute levels of extracellular dopamine in brain slices

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Carbon fibre microelectrodes and FSCV have been used extensively to quantify stimulus-induced release and uptake of dopamine and other electrochemically active substances, both *in vivo* and in brain slices. However, this technique requires background subtraction, thus does not provide information about absolute (baseline) extracellular concentrations and is generally unsuitable for recordings >90 sec. Altered in several brain disorders, baseline dopamine levels influence both the activity of dopaminergic neurons and the dynamics of dopaminergic transmission; hence it is important to measure these levels and experimentally-evoked changes over prolonged periods. Following a recent report that a modified FSCV approach called 'fast-scan controlled-adsorption voltammetry' (FSCAV) can be used to measure absolute dopamine levels in solutions (Atcherley et al. 2013, Langmuir 29:14885), we have adopted this technique to measure dopamine concentration in submerged forebrain slices (300 µm, 32°C) obtained from rats. As proof-of-concept, increased dopamine levels were detectable within the slice, in a depth-dependent manner, following application of exogenous dopamine (500 nM, 10 min). After blocking MAO with pargyline (10 µM), L-DOPA (50 µM, 10 min) evoked a prolonged (>20min after washout) increase in baseline dopamine concentration in the dorsal striatum, but not in a cortical region with minimal dopaminergic input. Concurrent FSCV-measurements demonstrated L-DOPA increases stimulus-evoked dopamine release. Thus, performed on the one electrode, combined FSCAV-FSCV allows simultaneous study of releasable intracellular stores and absolute extracellular concentrations. These data show for the first time that FSCAV can measure extracellular levels of endogenous dopamine in brain slices, which cannot be accomplished with other techniques (e.g. microdialysis).

Poster 6.25

Amphetamine-induced locomotor activity is enhanced in the adult serotonin transporter knock-out rat

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Although dopamine (DA) is still considered the most important neurotransmitter in addiction, there is growing interest in how the dopaminergic activity is modulated by other neurotransmitters, most notably serotonin. Recently, it has been shown that rats with a genetic deletion of the serotonin transporter (SERT) exhibit increased sensitivity to the rewarding properties of MDMA (3,4-methylenedioxyamphetamine) and cocaine. The rewarding properties of drugs of abuse are, to a large degree, mediated by DA, and drugs of abuse share the common feature of increasing synaptic DA levels. Therefore, the present study investigated the hypothesis that a genetic deletion of the SERT leads to long-term changes in the sensitivity of the dopaminergic system. Young (postnatal day 27-29) and adult (postnatal day 60-63) male SERT knock-out ($SERT^{-/-}$) rats were tested for amphetamine (0.5 mg/kg, intraperitoneal)-induced locomotor activity and compared to age-matched wild-type control ($SERT^{+/+}$) rats. In addition, rats were perfusion-fixed 2 hours after the amphetamine challenge and c-Fos expression in the brain was examined immunohistochemically. Preliminary data show that amphetamine-induced locomotor activity is enhanced in adult $SERT^{-/-}$ rats, but not in young $SERT^{-/-}$ rats. c-Fos expression in several regions of the brain is currently being investigated. Our preliminary data suggest that rats with a genetic deletion of the SERT have a hypersensitive dopaminergic system that manifests during adulthood.

Poster 6.26

Inter-hemispheric transfer time in Autism Spectrum Disorder (ASD)

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The two independent hemispheres of the brain communicate with one another via the corpus callosum. In neurologically healthy individuals, the time taken for such inter-hemispheric transfer is asymmetric, in that it takes significantly less time for information to be transferred from the right hemisphere to the left, relative to transmission in the opposite direction. However, several studies have suggested that this may not be the case for those who present with neurological disorders. While there is much evidence to suggest brain abnormalities in ASD, including aberrant brain connectivity and callosal deficit, it is unclear whether inter-hemispheric transfer time (IHTT) is affected. This study utilised 128-channel EEG to examine whether there was a group difference in IHTT between individuals diagnosed on the autism spectrum and a neurotypical control population. Directional IHTT was estimated by comparing latencies of N170 and P100 ERP components in the hemispheres contralateral and ipsilateral to the side of visual stimulation. Both groups exhibited speeded right-to-left information transfer relative to left-to-right, and this was consistent across the two ERP components. However, the ASD group demonstrated significantly faster IHTT than controls in both right-to-left and left-to-right transfer. Our findings may be interpreted in terms of the local-network over-connectivity theory of ASD.

Poster 6.27

Effects of 5-HT$_{1A}$ and 5-HT$_{1B}$ manipulations on ±3, 4-methylenedioxymethamphetamine (MDMA) primed reinstatement in rats

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Drug dependence is a chronically relapsing disorder. Even after years of abstinence, exposure to small amounts of the abused drug can trigger craving and relapse. The use of animal models has contributed a great deal to our understanding of factors that might underlie relapse to drug-seeking. MDMA preferentially increases synaptic serotonin (5-HT) but following repeated exposure many indices of 5-HT neurotransmission are decreased. Our lab has shown that dopaminergic mechanisms are important for the reinstatement of drug-seeking following extinction of ±3, 4-methylenedioxymethamphetamine (MDMA) self-administration. The role of 5-HT in drug-seeking is, however, unknown. The present study was designed to determine the role of 5-HT receptors in MDMA-seeking behaviour. Following acquisition and extinction of MDMA self-administration, drug seeking was produced by an experimenter-administered injection of MDMA (10.0 mg/kg, IP). The effect of serotonergic ligands on MDMA produced drug seeking was examined. Drug seeking was dose- dependently attenuated by the 5-HT1B/1A agonist, RU 24 969 (0.3, 1.0 mg/kg, SC) and the 5-HT1A agonist, 8-OH-DPAT (0.01, 0.1mg/kg, SC). These data suggest a role of 5-HT1A and 5HT1B receptors in drug seeking and support the idea that manipulations of these 5-HT receptor mechanisms might be effective in relapse prevention.

Poster 6.28

Changes in reticular thalamic nucleus neuronal activity in anaesthetized parkinsonian rats

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The reticular thalamic nucleus (RTN) is located between cerebral cortex, motor thalamus and the basal ganglia and thought to be implicated in the inhibitory-mediated regulation of motor control. Parkinson's disease is a neurodegenerative motor disorder caused by midbrain dopamine neuron degeneration followed by abnormal electrophysiological activity throughout the basal ganglia-thalamo-cortical network. Interestingly, the role of the RTN in modulating basal ganglia-thalamo-cortical network activity is poorly understood in control conditions and has not been explored at all in parkinsonism. To address this, the present study characterized neuronal activity of rostral RTN (rRTN) neurons in urethane-anesthetized rats. Furthermore, this study investigated the effect that 6-hydroxydopamine (6-OHDA) induced chronic dopamine neurodegeneration of the substantia nigra pars compacta had on rRTN neural activity. Extracellular spike train data were recorded for at least five minutes using glass electrodes. Consistent with existing literature, electrophysiological and immunohistochemical data indicate that the rRTN contains primarily putative GABAergic neurons (AP spike width ≤0.47 ms). Approximately 60% of GABAergic neurons demonstrated low threshold calcium spike (LTS) bursts (~200 Hz), which are characteristic of thalamic activity. LTS bursting in the RTN was dominated by doublets. Dopaminergic lesion significantly increased the incidence (~80%) of LTS bursting in GABAergic RTN neurons ($X^2 = 38.37$, $p<0.0001$) and non-doublet LTS bursts were dominant. These data indicate that parkinsonism significantly affects LTS bursting characteristics in rRTN. Considering the reciprocal connections between RTN, basal ganglia nuclei and motor thalamus, the RTN might be involved in producing some of the changes in the basal ganglia-thalamo-cortical network activity that underlies parkinsonian symptoms.

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Poster 6.29

Determining the mechanisms of brain injury after perinatal inflammation: The role of the connexin hemichannel Cx43 in a rat model of infection

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Diffuse white matter injury (WMI) is a common and costly problem of premature birth, resulting in a spectrum of neurodevelopmental and motor disorders. Its etiology is not well understood, but there is strong evidence for the involvement of perinatal systemic inflammation as a cause of injury. The exact mechanisms by which inflammation produces WMI are unknown, though pathological blood brain barrier (BBB) opening has been implicated in a number of tissues and models. Recent evidence suggests that opening of connexin43 (Cx43) hemichannels may be involved, though its role has yet to be quantified. Preterm-equivalent neonatal rat pups (P1-4) received intraperitoneal saline or 0.3mg/kg lipopolysaccharide (LPS), or a combination of LPS and a Cx43 channel inhibitor (peptide 5). After 1 or 3 day treatments, tissue was collected for immunohistochemistry, western blotting and qPCR to evaluate the role of Cx43 in WMI and to assess the extent of albumin extravasation (a marker of BBB permeability), cell death and gliosis in the CNS after LPS. LPS administration induced oligodendrocyte cell death in the white matter at 1 and 3 days recovery. Cell death was associated with evidence of BBB breakdown and activation of microglia, but no evidence of astrocytosis or regulation of mRNA levels of Cx43, TLR2, or TLR4. Cx43 protein levels were not changed with western blotting or immunohistochemistry. Analysis of the effect of peptide 5 on BBB integrity and oligodendrocyte cell death, as well as the activation of the CNS cytokine pathways, are currently being examined. Preliminary results suggest a role for mild systemic inflammation in regulation of BBB breakdown and oligodendrocyte cell death in the absence of astrogliosis and regulation of Cx43 channel expression. The role of Cx43 opening is still being assessed.

Poster 6.30

Enzymatic production of hyaluronan and its role in early neuronal development

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In peripheral tissues there is strong evidence for a role of the extracellular matrix molecule hyaluronan (HA) in controlling cellular differentiation and process extension. In neurons, hyaluronan is known to be expressed in a pericellular pattern, where it is thought to play a role in neuronal signalling. However, a specific role for hyaluronan in neurite initiation and process growth is unknown. Thus, the aim of this project was to investigate the general role of HAS enzymes and the specific role of HAS2 in early developing neurons, with the hypothesis that HAS inhibition will impair neuronal process development. Primary cortical neuronal cultures were established from E16 rats. Neurons were collected at days *in vitro* 1 (DIV1; 4h), DIV3, and DIV5 for assessment of neuronal hyaluronan synthase mRNA (HAS1-3), and for immunocytochemical hyaluronan expression (biotinylated hyaluronic acid binding protein (bHABP)) on neuronal processes (MAP2) and filopodia/lamellipodia (actin). To inhibit hyaluronan production, neurons were treated with the broad hyaluronan synthase inhibitor 4-methylumbelliferone (4-MU). Morphological analysis of neurite development was examined using the ImageXpress/MetaXpress system. To specifically determine the role of HAS2, neurons were also transfected with a HAS2 shRNA. By qPCR, neurons expressed mRNA for the entire HAS family (HAS1-3), with particularly high levels of HAS2. By immunocytochemistry, hyaluronan expression was observed in neuronal progenitor cells and in developing processes. Treatment of neurons with 4-MU markedly reduced the expression of neuronal hyaluronan. MetaXpress analysis of process development and the effects of shRNA targeting are currently in progress. These preliminary data suggest a potential role of HAS2 in neuronal hyaluronan production and process development.

Poster 6.31

In vivo properties of neural grafts generated from human pluripotent stem cells

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Significant progress has been made in the stem cell field over the last decade such that a diverse range of potentially therapeutic cell types can be generated from human pluripotent starting material. Unfortunately, this success at the *in vitro* level has not translated well to *in vivo*, neural grafting procedures. Results from transplantation in animal models of human neurological conditions have been highly variable and overall disappointing. Progress in this area needs to be built on a better understanding of the capacity of stem cell derived neurons to structurally and functionally integrate into existing circuitry in a host brain. Here we have used the human embryonic stem cell line 'Envy', which ubiquitously expresses GFP, to provide a detailed description of the anatomical and functional properties of neural grafts after transplantation into the neonatal rat brain. Significantly, we find that transplanted neurons are intrinsically functional and appear to receive afferent input at the electrophysiological level and are also capable of extensive axonal growth within the host brain. The most conspicuous pattern of growth matches with the normal trajectory of cortical projection neurons. This is consistent with the regional 'dorsal forebrain' identity of the neural progenitors at the time of transplantation. These results motivate further studies into the therapeutic potential of cortical neuron placement in models of pathology where cortical cell loss is a significant contributing factor, i.e. focal cortical ischemia.

Poster 6.32

Manipulation of axon guidance cue, EphrinA5, affects the integration of dopaminergic neural grafts in an animal model of Parkinson's disease

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Both attractive and repellent cues are required to assist axons to grow to their correct target within the brain. These cues are not only required for development, but are likely to be required for regeneration. Following the completion of development, the expression of many guidance cues is significantly decreased. Interestingly it has been observed that many CNS neurons will continue to express the receptors for guidance cues into adulthood, implying that these same neurons may remain responsive to these cues throughout life and that there are additional roles for guidance cues beyond that of initial development. EphrinA5 is a ligand known to play a role in regulating DA axon growth and guidance during development. Our work aimed to determine whether manipulation of EphrinA5 could influence the outgrowth of a fetal dopaminergic graft in a mouse model of Parkinson's disease, as insufficient reinnervation of the host brain has been a major limitation in cell based therapy for PD. In loss- and gain-of-function studies, we have found that EphrinA5 plays a significant role in graft integration. We demonstrate that loss of EphrinA5 significantly decreases the area of the striatum innervated by the graft and the density of the dopaminergic fibers whilst having no effect on cell survival. We are currently developing methodologies to assess the consequence of EphrinA5 over-expression in the host tissue to determine whether we can boost reinnervation and function of dopamine cells transplanted in PD models. These findings hold significant implications for enhancing reinnervation following neural injury.

Poster 6.33

Cellular expression of LRRFIP1 and its potential role in CNS immune response

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In peripheral immune cells, LRRFIP1 [leucine-rich repeat (in FLII) interacting protein 1] is an intracellular nucleic acid sensor that detects microbial RNA and DNA, resulting in release of proinflammatory cytokines. LRRFIP1 is also recruited as part of the toll-like receptor (TLR) signaling pathway that plays a key role in innatre immunity. It is well established that TLR signalling is also important for controlling innate immunity and inflammation in the CNS. However, a role for LRRFIP1 in the CNS immune response remains unknown. Thus, we examined the cellular expression of LRRFIP1 in the developing brain, and its regualtion following CNS inflammation. Brains from Sprague Dawley (SD) rats were collected at postnatal days 1 (P1), P4, and P14, and fixed in 4% PFA. Colocalisation of LRRFIP1 with neurons/neuronal processes (NeuN, Map2), oligodendrocytes (olig2), and microglia (Iba1) was examined using immunohistochemistry and confocal microscopy. In a second set of experiments, P1 rats were exposed to the potent TLR4 agonist lipopolysaccharide (LPS), and the brains collected at P2, P7, and P14 for real-time PCR (qPCR) analysis of LRRFIP1 mRNA expression. By immunohistochemistry, LRRFIP1 showed colocalisation with (1) developing microglial cells, (2) mature oligodendrocytres, (3) and the apical dendrite of a subpopulation of mature cortical layer 5 pyramidal neurons. Following exposure to LPS, there was also a significant increase in the expression of LRRFIP1 mRNA in the brain (~2-fold). These preliminary results suggest that LRRFIP1 is differentially expressed in microglia, oligodendrocytes and pyramidal neurons of the rat brain, and also forms part of CNS inflammatory signalling response. Studies examining the specific cellular role of LRRFIP1 in the development brain and in response to inflammation are ongoing.

Poster 6.34

Cognitive status in Parkinson's disease characterised by magnetic resonance spectroscopy

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Parkinson's disease (PD) is a motor disorder, but patients also develop cognitive impairment, and most eventually dementia (PDD). Predictive neurobiomarkers may be useful in future studies to identify those patients at risk of PDD. As a result of the compromised neuronal integrity in PD, brain metabolites experience measurable alterations. Here, magnetic resonance spectroscopy (MRS) was used to identify brain metabolic changes associated with cognitive impairment and dementia in PD. Forty two healthy participants and 109 PD patients completed neuropsychological testing. Patients were classified as either having normal cognitive status (PDN, n=63), mild cognitive impairment (PD-MCI, n=29), or dementia (PDD, n=17). A 2×2×3cm MRS voxel was placed in the posterior cingulate cortex (PCC) to quantify N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and myo-inositol (mI). For each ratio (NAA/Cr, Cho/Cr, and mI/Cr), an ANCOVA model assessed group differences with age, sex, years of education, and medication as covariates. Reduced NAA/Cr, relative to both PDN and controls, was found in PDD, indicating neuronal loss in advanced disease. Elevated Cho/Cr and mI/Cr were also evident in PDD and likely indicate gliosis. The intermediate and non-significant metabolic alterations in PD-MCI reflect an intermediate level of degeneration, but also the potential for disease reversibility. MRS of the PCC may be a quantitative marker for cognitive impairment in PD, but will need confirmation in future longitudinal studies.

Poster 6.35

Stimulation of the nucleus accumbens at high or low frequencies reduces cocaine seeking

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Deep brain stimulation (DBS) is a neurosurgical manipulation that is used to modulate the activity of specific brain pathways affected by neurological dysfunction. DBS has proven effective in the treatment of movement disorders and is now being considered as an alternative form of therapy for severe cases of drug addiction. Recent research suggests that the nucleus accumbens (NAc) may be a promising target area, but much work is required to define optimal parameters of stimulation and long-term efficacy. In the present experiments, rats were implanted with a stimulating electrode in the right NAc and exposed to chronic cocaine self-administration (0.5 mg/kg/infusion). Following a period of abstinence, rats underwent drug seeking tests through exposure to the self-administration context paired with cocaine challenge (5 mg/kg i.p.) on days 1, 15 and 30. Cocaine was not available in the drug seeking tests. Either low-frequency (LF, 20 Hz) or high-frequency (HF, 160 Hz) DBS was applied for 30 min daily for 14 consecutive days starting one day after drug withdrawal. Rats showed robust drug seeking on days 1, 15 and 30 after withdrawal from cocaine self-administration, with responding being highest on day 15. On day 15 post-withdrawal both LF and HF attenuated cocaine seeking significantly by 36 and 48%, respectively. Both forms of stimulation were ineffective on the tests conducted on days 1 and 30. These results demonstrated that repeated unilateral DBS of the NAc effectively reduced cocaine seeking after 15 days of drug withdrawal, with therapeutic effects seemingly diminishing after DBS discontinuation. These data support the use of DBS of the NAc as a promising avenue for the treatment of intractable addictions.

Poster 6.36

Differential neurotransmitter expression in the sub-regions of striatum in human alcoholics: A neurometabolomics study

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The nucleus accumbens (NAc), the caudate nucleus and the putamen are the major components of the striatum. In terms of cytoarchitecture all these regions are similar but functional circuitry in relation to addiction is thought to be region-specific. This might be reflected in differences in biochemical make up, as we noted in our previous proteomics study in sub-regions of the corpus callosum (Kashem et al., 2009. Neurochem. Int. 55: 483-490). The present study investigates global metabolomics using these regions to help to identify neurochemical correlates of alcoholism in brain thought to be most involved in the development of drug addiction. Brain regions were obtained from Brain Bank. Extracted metabolites were analyzed by LC-MS/MS. Moreover, we have examined, using an immunological approach, the expression of metabolites regulatory proteins. There were no significant differences in the expression of dopamine (DA), 3,4-dihydgulatoryroxyphenylacetic acid, serotonin (5HT), homovanillic acid, 5-hydroxyindoleacetic acid, histamine, glutamate, gamma-aminobutyric acid (GABA), tyrosine and tryptophan between these regions of non-alcoholic control brains except for choline, acetylcholine and norepinephrine. Alcohol significantly decreased all above metabolites except for glutamate. Analysis by western blotting revealed that the regulatory proteins related to DA, 5HT, histamine and GABA are changed in line with the depletion of these metabolites. Moreover, signaling proteins DARPP-32 (dopamine and cAMP-regulated phosphoprotein) and CREB (cAMP-response element binding protein) expression were decreased by alcohol, too. In conclusion, the dopaminergic neurotransmission in the NAc is not the only neurotransmitter system altered in alcohol addiction. Other neurotransmitter systems might contribute to the accompanying metabolic changes. The nuclear protein CREB and DARPP-32 could be involved in signaling for the biosynthesis of DA, 5HT, histamine, GABA and glutamate.

Poster 6.37

Does Gamma-Aminbutyrate Receptor-B (GABA-R_B) play an antagonist role on alcohol induced disorder of Glutamate Transporter (GLAST)?

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Hyperglutamatergic neurotransmission (increased extracellular glutamate) may be involved in alcohol (EtOH) intoxication and addiction. One of the several glutamate transporters (EAAT1-5), EAAT1 (GLAST) mainly expressed in the astrocytes and could play part in limiting the hyperglutamatergic states linked to craving for alcohol. Baclofen, an agonist at GABA-R_B, has been suggested as an agent to relieve such craving; however, its molecular actions particularly in the expression of GLAST have never been studied. The present study looks at GLAST expression in alcoholic human brain and examines the mode of action of baclofen in EtOH treated rat primary astrocytes. The prefrontal cortex of human brain tissues are used for western analysis. Astrocytes originated from the rat cortex (embryonic day-19) and exposed to various concentrations of EtOH in presence or absence of baclofen, and performed GLAST-immunocytochemistry and flow cytometry analysis. Alcohol increased GLAST expression both in nuclear and microsomal fractions of alcoholic human brain relative to non-alcoholic controls. Acute EtOH induced an increase of GLAST in astrocyte's plasma membrane. Flow cytometry analysis confirmed the immunocytochemistry results. Baclofen inhibited EtOH induced GLAST expression in the astrocytes. In conclusion chronic alcoholism appears to increase the expression of GLAST in alcoholic brain tissue thus perhaps mitigating, through the antihyperglutamatergic effect of glutamate transport, the occasional cravings. In acute in vitro experiments EtOH also seems to activate GLAST, however, baclofen opposes this action suggesting that the baclofen-induced relief of alcohol craving may not be explained by a simple replacement of EtOH actions on glutamate transport.

Poster 6.38

Assessments of cortical activity during electrical stimulation assisted cycling in stroke patients by near infrared spectroscopy

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Hemiplegia especially lower extremity is one of the primary disabilities induced by stroke. Functional electrical stimulation assisted cycling (FES-cycling), application of electrical stimulation (ES) during cycling under certain angle corresponding to muscle contraction, can help patients to enhance muscle force output. However, the brain activity change during the effect of FES-cycling has seldom been investigated. The aim of this study was to investigate the effect of FES cycling on brain activities observed from hemodynamic changes using near-infrared spectroscopy (NIRS). Also, the cycling performance was observed from symmetry of pedaling force measured from load cells placed on the pedal of ergometer. Subjects were asked to pedal in six conditions: volitional and passive cycling without or with ES at 10mA or 30mA applied on quadriceps of affected side. The shape symmetry index (SSI) and area symmetry index (ASI) were used to quantify the level of symmetry obtained from load cells. Multichannel NIRS measurements were applied on brain regions of sensorimotor cortex (SMC), supplementary motor area (SMA), primary motor cortex (PMC), and secondary sensory cortex (S2). Our results showed that cycling under ES of 10 mA could lead to higher cortical activation compared to those without ES and stimulation at 30 mA during both passive and active cycling. Also, 10 mA ES during active cycling showed higher shape symmetry index. Our study concludes that cycling with low intensity stimulation in affected side of hemiplegic subject could provide better facilitation to brain activity and cycling performance, which could be adopted as a future neuro-rehabilitation protocol for stroke subject.

Poster 6.39

String vessels in vascular degeneration of Parkinson disease

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String vessels are collapsed capillaries containing no endothelium but consist of empty basement membrane tubes that do not carry blood. Increased string vessel formation has been observed in Alzheimer's disease (AD) where vascular degeneration plays an important role in the progression of the disease. However, information about vascular change in Parkinson' disease (PD) is very limited. Our previous study has indicated degeneration of endothelium in PD brains. This study aimed to investigate string vessel formation, their association with neuronal degeneration and changes of astrocytes and blood-brain-barrier (BBB) integrity in PD. The present study used substantia nigra, caudate nucleus and middle frontal gyrus from post-mortem human brain from PD and age-matched control cases. Immunohistochemical staining of collagen IV, NeuN, tyrosine hydroxylase, GFAP, fibrinogen and Factor VIII were observed and quantitatively analysed using image analysis programmes. Although the overall basement-membrane density was similar between the two groups, the density of string vessels increased in PD brains, particularly in the substantia nigra. However, neuronal degeneration was found in all brain regions. GFAP and fibrinogen were increased in the caudate nuclei of PD brains. These results suggest that the increased string vessel formation in PD could be a result of endothelial cell degeneration and basement membrane preservation. Hypoperfusion may play a role in the neuronal degeneration of PD. The elevated astrocytosis in the caudate nucleus may be associated with the BBB being compromised in this brain region in PD.

Poster 6.40

Cerebellar neural activity in a chronic rat model of Parkinson's disease

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The cerebellum is crucial for precise motor control and coordination. Despite this, very few studies have examined changes in cerebellar neural activity in Parkinson's disease (PD); a disorder characterised by motor disabilities. PD patients exhibit hyperactivation of the cerebellum. This may be a pathophysiological effect due to the disruption of basal ganglia inhibitory circuits and subsequent hyperactivation of the subthalamic nucleus, which projects to the cerebellum via pontine nuclei. This in turn may affect efferent cerebellar projections. Specifically, the deep cerebellar nuclei (DCN) have excitatory inputs to the motor thalamus (Mthal), which may have an important integrator role for motor control and learning. To better understand how DCN inputs to the Mthal are affected by PD we investigated changes in neural coding of the deep cerebellar nuclei (DCN) in a chronic rat model of PD. We induced parkinsonism by infusing 6-hydroxydopamine (6-OHDA) unilaterally into the medial forebrain bundle. A successful dopaminergic lesion was confirmed behaviorally (cylinder and step tests) and by immunohistochemical staining in the substantia nigra for tryosine hydroxylase, a specific marker for dopaminergic neurons. We recorded extracellular neuronal activity in the DCN of urethane-anesthetized 6-OHDA-lesioned (ipsilateral hemisphere) and control rats. Preliminary findings indicate that there are no significant differences in firing rate (Student *t*-test, $p = 0.5829$) or spike train regularity, measured by interspike interval coefficient of variation (Student *t*-test, $p = 0.2813$), between 6-OHDA-lesioned (n=29) and control (n=28) neuronal recordings. Additional electrophysiological investigation, such as burst pattern analysis, is required to further characterise changes in DCN neural coding in parkinsonian rats.

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Poster 6.41

Establishing a rodent model of complex regional pain syndrome

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Complex regional pain syndrome (CRPS) is a neurological chronic pain condition with approximately 1100 new cases in New Zealand each year. CRPS may develop following seemingly trivial injuries but is most common following fractures and occurs in women 5 times more often than men. The pathophysiology of CRPS is thought to be caused by a combination of neurogenic inflammation, sympathetic nervous system dysfunction and central sensitization. The aim of this project is to establish a rodent model of CRPS using chronic post-ischemia pain (CPIP) and to investigate histological changes in the brain and spinal cord. Rats received prolonged ischemia (3h) of their hindpaw by applying a tight fitting tourniquet just proximal to the ankle joint, followed by the removal of the tourniquet to allow rapid reperfusion. To determine if rats have CRPS, they undergo a series of behavioural tests such as sensitivity to innocuous mechanical stimulation (allodynia) with von Frey hairs and the rat grimace scale for pain state. Control rats do not react to von Frey stimulation and have a severity score of 0 on the rat grimace scale. We are currently collecting data from affected rats and we will investigate histological changes in somatosensory cortex, thalamus, anterior cingulate cortex and spinal cord. Once this model of CRPS has been established, we will explore changes in the histology and electrophysiology of the brain associated with chronic pain. Eventually, this model will lead to a better understanding of the pathology underlying CRPS and exploring novel treatments for this debilitating syndrome.

Poster 6.42

Genomic instability and Parkinson's disease

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Parkinson's disease (PD) is the second most common neurodegenerative brain disorder affecting mostly the elderly, although there is a group of patients developing so-called early-onset PD (EOPD). Mutations in the *PARK2* gene are a common cause of EOPD following autosomal-recessive pattern of inheritance. *PARK2* belongs to the family of human "extremely large genes" which are often localised in genomic common fragile sites (CFSs) and exhibit gross genomic instability. *PARK2* is located in the centre of FRA6E, third most mutation susceptible CFS, it contains 12 exons and encompasses a genomic region of 3.6Mbs. Among mutations of the *PARK2* gene Copy Number Variants (CNVs) of single or multiple exons account for around 50%. We analysed a group of 350 PD patients with EOPD and classical form of the disease. CNVs were found in 8 subjects (5 deletions and 3 duplications). Rearrangements were first identified using MLPA, their ranges characterized by aCGH. The exact breakpoints were mapped using direct sequencing. Rearrangements covered exons 2 to 7 and most mutations were non-recurrent. No repetitive sequences or extended homologies were identified in the sequences flanking breakpoint junctions. However, in most cases, 2-3bp microhomologies were present strongly suggesting that microhomology-mediated mechanisms, specifically NHEJ and FoSTeS/MMBIR, are predominantly involved in rearrangement processes in this genomic region.

Poster 6.43

The differential role of DA and 5-HT in the discriminative stimulus properties of high vs. low doses of ±3,4-Methylenedioxymethamphetamine (MDMA)

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The primary psychoactive ingredient of the recreational drug 'ecstasy' is ±3,4-methylenedioxymethamphetamine (MDMA). MDMA produces discriminative stimulus effects that can be measured in humans and animals using the drug discrimination paradigm. In this paradigm subjects are trained to make one response in the presence of the drug stimulus, and another response in the presence of a placebo. This discrimination is learned within 30-40 sessions. Once acquired, several aspects of this discrimination can be examined, including the neurochemical basis for the subjective drug effects. In this case, selective agonists or antagonists are administered to determine the role of specific neurotransmitter systems. The current experiment probes the roles of dopamine (DA) and serotonin (5-HT) in the stimulus effects of MDMA. Two groups of rats were trained to discriminate between MDMA (1.5mg/kg or 3.0mg/kg) and vehicle in a typical 2-lever drug discrimination paradigm. The ability of DA (d-amphetamine, apomorphine) and 5-HT (mCPP, DOI, Fluoxetine) agonists to produce MDMA-appropriate responding (substitution) was tested. Serotonin agonists substituted more readily in rats trained with a low dose of MDMA (1.5mg/kg) compared to those trained with a higher dose (3.0mg/kg). Conversely, DA agonists partially substituted in the high dose group but not in the low dose group. These results suggest that the discriminative stimulus effects produced by high vs. low doses of MDMA are qualitatively distinct. The relative contributions of 5-HT and DA at these doses may underlie this observed difference. These findings have implications for the characterisation of MDMA as a potential drug of abuse.

Poster 6.44

Trace amine-associated receptor 1 activation decreases cocaine's reinforcing efficacy and prevents cocaine-induced changes in brain reward thresholds

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Addiction to cocaine is a major burden to society worldwide, with current treatment options being largely ineffective. The newly discovered trace amine-associated receptor 1 (TAAR1) has emerged as a promising target for medication development in stimulant addiction due to its ability to regulate dopamine function. Recent findings indicate that activation of this receptor blocks cocaine self-administration (Revel et al., 2012) and relapse to cocaine seeking (Pei et al., 2014). However, a reduction in cocaine self-administration could result from an increase in the reinforcing efficacy of cocaine, which would not be a desirable effect TAAR1 activation to have. Here, in order to shed light into the influence of TAAR1 on cocaine's reinforcement and brain reward, we studied the effects of RO5203648 and RO5256390, selective partial and full TAAR1 agonists, respectively, on (1) the dose-response curve for cocaine self-administration and (2) cocaine-induced changes in intracranial self-stimulation (ICSS). In the first experiment, we examined the effects of the agonists on the self-administration of five unit-injection doses of cocaine (0.03, 0.1, 0.2, 0.45, and 1 mg/kg/infusion) under a fixed ratio 1 schedule of reinforcement. Both RO5203648 and RO5256390 induced dose-dependent downward shifts in the cocaine dose-response curve, indicating that both partial and full TAAR1 activation decrease cocaine's reinforcement efficacy at all the self-administered doses. In the second experiment, TAAR1 activation prevented cocaine-induced lowering of ICSS reward thresholds. Taken together, these data clearly demonstrate that the rewarding and reinforcing effects of cocaine are strongly modulated by TAAR1 activation, thus supporting the candidacy of TAAR1 as a drug discovery target for the treatment of cocaine addiction.

Poster 6.45

Secreted amyloid precursor protein-α attenuates apoptosis following amyloid-ß insult and ischemic injury

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Alzheimer's disease (AD) is a neurodegenerative condition characterized by deposition of neurotoxic amyloid-beta (Aβ) aggregates, and apoptotic cell death in brain areas such as the hippocampus. Curiously, secreted amyloid precursor protein-α (sAPPα) is cleaved from the same precursor protein as Aβ, yet is neuroprotective, while sAPPβ, which is identical to sAPPα save the *C*-terminal 16 amino acids, has significantly reduced neuroprotective properties. To further explore the neuroprotective properties of sAPPα we tested whether sAPPα could prevent apoptosis and cell death in organotypic hippocampal slices, following oxygen-glucose deprivation (OGD), or Aβ insult. Slices (400 µm) were prepared from hippocampi of p7-10 Sprague-Dawley rat pups and maintained on membranes (37°C, 10 days). They were then treated with 1 nM sAPPα, 1 nM sAPPβ or PBS prior to insult (20 min exposure to a glucose-free anoxic environment, or 2.5 µM $A\beta_{25-35}$, 48 h). The extent of apoptosis was measured by Western blot using antibodies recognising cleaved caspase-3. Total cell death was measured by fluorescence microscopy following incubation with propidium iodide (7.5 µM, 24 h). While OGD induced cell death relative to untreated slices ($p<0.0005$; Tukey's multiple comparisons), no reduction in cell death was measurable following sAPPα treatment. By contrast, sAPPα significantly reduced ODG-induced apoptosis compared to PBS-treated slices ($p<0.0005$). Furthermore, sAPPα significantly reduced overall Aβ-induced cell death in the dentate gyrus ($p<0.05$). This study supports the validity of both OGD and Aβ insult in organotypic hippocampal slices for modelling aspects of neurodegenerative disease, and confirms the neuroprotective potential of sAPPα.

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Poster 6.46

Progesterone reduces motor impairments in the unilateral striatal 6-hydroxydopamine lesion model of Parkinson's disease

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The neurosteroid progesterone (P4) has improved functional outcomes in animal models of traumatic brain injury and stroke. Here, we examined P4's influence following striatal 6-OHDA lesions, a model of motor impairments in Parkinson's disease (PD). Rats received either two or four unilateral striatal infusions of 6-OHDA, to model early and late stages respectively of dopamine degeneration in PD (n = 11-12 per group; sham = 14). On post-lesion day 7, the large lesions produced more substantial ipsilateral rotation impairment in response to d-amphetamine (3mg/kg i.p.) than did small lesions. This test established a PD-like impairment before rats were given P4 on days 8 to 14 (8mg/kg vs sesame oil vehicle, s.c.; tapered withdrawal). The adjusting steps test (akinesia), postural instability test, and corridor and whisker tests (sensorimotor deficits) were assessed on days 17-23, 27-29, 39-45, and 56-62. Large lesions caused substantial and enduring impairments on all four tests; small lesions produced no impairment on the corridor test but moderate impairments on the other three tests. After large lesions P4 reduced impairment in the adjusting steps test; it did not reduce postural instability of the impaired forelimb but normalised compensatory function of the "intact" forelimb; impairments in the corridor or whisker tests were not changed. Following small lesions P4 prevented impairment in the adjusting steps and whisker tests but not postural instability; performance in the corridor was not changed. P4 reduces motor impairments in the 6-OHDA model of the early and late stages of PD and is most effective at reducing akinesia.

Poster 6.47

Environmental enrichment and stroke: Good or bad?

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Depressive disorders have previously been reported to have a negative impact on stroke recovery. Experimental models of stroke appear to replicate clinical findings concerning the negative impact of stress on stroke recovery. Current models of stress, however, fail to emulate what happens to humans after stroke. Accordingly, we have established a more realistic model of distress that involves moving animals from an enriched to an impoverished environment after stroke. Following photothrombosis to the medial prefrontal cortex (mPFC), animals were split into three groups: standard enrichment (SE - group housing; toys changed once / week), enhanced enrichment (EE – group housing; toys changed 3-4 times / week) and impoverishment (IE – individual housing without toys). Assessment of sham animals (n=15 / group) on the elevated plus maze confirms that our model of de-enrichment induces anxiety in mice assessed at 1 & 4-weeks post-sham surgery ($P<0.05$). Interestingly however, assessment of stroke animals (n=15 / group) revealed the opposite effect: animals in IE were less anxious whereas animals in EE were more anxious and showed less activity in the open field. We have previously reported that stroke to the mPFC results in delayed-onset memory impairment. In our model of stroke we show that animals in IE perform better on the object location recognition task, whereas animals in EE showed no recovery. These data indicate that mPFC strokes maybe interfering with the hypothalamic stress axis and that enhancing EE maybe acting as an added stressor. We have reliably set up a model to induce stress and assess its impact on stroke recovery; however, our data indicates caution should be taken depending on stroke location so as to not impair recovery.

Poster 6.48

Propulsive and mediolateral ground reaction force changes in the trailing leg after stroke

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Little is known about how ground reaction forces (GRFs) change after a stroke during gait initiation (GI). In this study healthy, left paretic, and right paretic subjects initiated gait with the pre-instructed leg at the sound of auditory cue while standing with each leg on a force plate. Peak propulsive force was calculated for each leg as the trailing leg and an asymmetry index (PFA where PFA>1 indicated greater left trailing leg peak propulsive force than of the right trailing leg) was used to demonstrate whether one trailing leg generated more force than the other. Similar asymmetry indices were created to express differences in peak lateral and medial forces, respectively, between both trailing legs (LFA and MFA). During gait initiation, healthy participants had equal peak propulsive GRFs acting on the left and right legs (PFA=1.07±.23). Left paretic and right paretic subjects had more peak propulsive GRFs acting on their left trailing legs compared to healthy though only the left paretic group statistical differed from the healthy group. LFA values indicate that left paretic participants had equal GRFs acting on both trailing legs *(0.98 ± 0.37*) while right paretic participants had greater lateral GRFs acting on their left trailing leg compared to their right *(4.7 ± 5.07).* MFA values indicate LParetic and RParetic participants had symmetrical GRFs acting on both trailing legs. Since an effective trailing leg must generate adequate forward propulsion while also maintaining equilibrium these results may suggest that the left leg is better optimized to be a trailing leg in stroke patients.

Poster 6.49

Finding new therapeutic strategies for acute stroke: Asking the brain for direction

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Our understanding of the overall pathological process involved in stroke (cerebral ischaemia) has changed little in the last 30 years. Many classes of compounds targeting the very early events within the ischaemic cell death cascade protect brain tissue in experimental models but show no effect in stroke patients. In this study we performed large-scale differential proteomics in combination with bioinformatics to provide a fresh perspective on the pathological mechanisms occurring immediately after stroke. Male C57B16/J mice were subjected to 60 minute occlusion of the middle cerebral artery (n=11) or sham surgery (n=13). Ipsilateral cortical samples were harvested at 3 hour post occlusion and a large-scale Western array screen was used to investigate changes in protein expression. Raw intensity data was standardised using log-quantile normalisation and a linear model used to estimate fold changes for sham versus stroke for each protein. Differentially expressed proteins were categorised according to function and network analysis was performed. Thirty-eight proteins were altered by stroke, 22 showed increased and 16 showed decreased expression relative to sham. The majority of differentially expressed proteins play key roles in cell death and survival (nNOS, p38MAPK, Stat3, Tau) and were consistent with the established view of acute stroke pathology within the literature. Additionally, proteins involved in cell signalling and transcription were also identified (IRF5, NCK1, p36) which have not been previously associated with stroke pathophysiology. Proteomics combined with bioinformatics provides a comprehensive profile of the molecular changes occurring in the acute phase following stroke. Previously identified proteins serve to validate this approach. Novel proteins not previously associated with stroke pathophysiology require further investigation as potential therapeutic targets.

Poster 6.50

Computational modelling of neurovascular coupling pathways with the effects of oxygen dependency of the neuronal membrane

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A disordered neurovascular coupling has been associated with neurological disorders such as hypertension, stroke and Alzheimer's disease. Modelling this incompletely understood mechanism can be used to predict the system behaviour in various conditions which is either not feasible or difficult through physical experiments. There is evidence for both biochemically driven and electrically driven signalling pathways for neurovascular coupling. Based on this, Farr & David[1] developed a mathematical model of neurovascular coupling through potassium and EET (epoxyeicosatrienoic acids) signalling pathways. However the model does not take into consideration neuronal oxygen dependency for energy production (ATP) which is one of the primary purposes of neurovascular coupling mechanism. The physiologic brain tissue oxygen content would sustain unimpeded brain function for only one second if continuous oxygen supply would suddenly stop. Hence, we have further developed a mathematical model of neurovascular coupling through potassium and EET signalling with the effects of oxygen dependency of the sodium-potassium exchange pumps in the neuronal membrane. We have formulated an eight-compartment continuum mathematical model comprising of all the cells involved in the process with a set of ODEs (Ordinary differential equations). The numerical solutions of our mathematical model provide insights on the minimum amount of oxygen required to restore ionic homeostasis after an action potential and also on the respective arterial radius change required to provide that quantity of oxygen.

[1]Farr H, David T (2011) Models of neurovascular coupling via potassium and EET signalling. *Journal of Theoretical Biology 286:* 13-23.

Poster 6.51

Awakening adult-born neurons in rats by exposure to an enriched environment

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Neurogenesis occurs throughout adulthood in mammals. However, there is controversy about whether or not old neurons "retire" and newly born neurons take their place in the neural circuitry. In previous work, we found that in 10 month old animals, neurons 8 months old did not retire, but were as active as 4 week old cells, as indexed by immediate early gene (IEG) expression. Interestingly, there was less activity in cells that were 6-12 weeks old. In an attempt to "activate" these 12 week old cells, we exposed our rats to an enriched environment (EE), known to cause a greater neurogenesis, synaptogenesis, and cell excitability. In the present study, we examined the difference between the activity levels of adult born neurons by comparing 5 month old animals either held in their home cage (HC) or exposed to 10 days of overnight EE. We "birth-dated" the newly born neurons using two thymidine analogues, CldU and IdU, one given at 12 weeks and the other at 4 weeks prior to study. Preliminary results, using immunofluorescence, indicate that HC animals showed no significant difference in activity between 4 and 12 week old neurons at this younger age of animal, as measured by co-localization of either CldU or IdU with Zif/268 and NeuN. However, compared to HC controls, EE exposure caused a significantly higher rate of activity (7.7% vs. 3.5%, n=6 (EE),n = 3 (HC); $p<0.05$) in 4 week old neurons, but not in neurons 12 weeks old (6.2% vs. 4.0%, n=6 (EE), n = 3 (HC); n.s.). Therefore, the younger cells appear to be preferentially "woken up" by exposure to EE, and thus may contribute to the elevated granule cell excitability and information processing generated in the dentate gyrus under these conditions.

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Poster 6.52

Nitric oxide regulates spontaneous, electrically stimulated, and seizure-like activities in the mouse olfactory bulb *in vitro*

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The olfactory bulbs (OB) are the first brain structures to receive and process odour information, and are among the most prominent nitrergic areas in the rodent brain. The neural function of nitric oxide (NO) in the OB is unknown. We used electrophysiological recording from output neurons of the OB (mitral cells) in mouse brain slice preparations (18 to 35 days old) to study the effects of NO on their spontaneous action potential activity and responses to olfactory nerve (ON) stimulation. Stimulation was continuous at 0.2 Hz, or to evoke seizure-like events (SLEs), was delivered episodically at 0.1 Hz for 50 seconds, repeated at intervals of 100 seconds, for a total of 500 seconds. We tested the effects of bath application of the nitric oxide synthase (NOS) substrate L-arginine (100 µM – 2 mM), the NO donors S-Nitroso-N-Acetyl-D, L-Penicillamine (SNAP; 20 – 100 µM) and Sodium Nitroprusside (SNP; 50 µM), and the NOS inhibitor (L-Nitro-Arginine Methyl Ester (L-NAME; 1 – 2 mM). When NO was increased, using bath application of L-arginine or NO donors, mitral cell responses to ON stimulation were decreased (decreased action potential frequency and response duration). Mitral cell spontaneous activity was also decreased. Inhibiting NOS to decrease NO had the opposite effects. Increased NO also strongly suppressed SLEs, defined as events of persistent firing for > 10 seconds following stimulation, with obvious spike inactivation (n = 6). These findings suggest that NO potently modulates spontaneous and synaptically evoked mitral cell action potential generation, including the suppression of seizure-like activity. The results suggest a role for NO in processing odour information, and in regulating neural circuit excitability.

Poster 6.53

Synaptic alterations in Autism Spectrum Disorder-associated Shank2 mutations

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Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by deficits in social communication and interactions, and repetitive behaviours. ASDs are predominantly genetic disorders. Many ASD-associated mutations encode proteins localised at the postsynaptic density (PSD) of excitatory glutamatergic synapses. The Shank proteins (Shank1, Shank2, and Shank3) are major scaffolding proteins and act as "master regulators" of the PSD. Numerous point mutations at well-conserved amino acids sites have been found in Shank2 in patients with ASD. Here we investigate the synaptic dysregulation caused by ASD-associated Shank2 mutations, and how they alter synapse structure and protein expression. Dissociated rat hippocampal cultures were transfected with control (EGFP-C1), EGFP-Shank2-WT, and Shank2 point mutations (EGFP-Shank2-R818H, -G1170R, -D1535N, -L1722P and -A729T). Neuronal cultures were immunostained for VGluT (presynaptic) and Homer (postsynaptic) markers. Dendritic density analysis of colocalised VGluT-Homer showed an increase (p-value < 0.05) in synapse numbers when Shank2 was overexpressed. However, ASD-associated Shank2 mutations significantly impaired (p-value < 0.001) Shank2's ability to increase synapse density. Furthermore, Shank2 mutations caused significant decreases (p-value < 0.001) in the amount of postsynaptic Homer, and also compromised Shank2's ability to transsynaptically increase the percentage of presynaptic VGluT. This current study demonstrates that Shank2 mutations in ASD cause significant dysregulation of pre- and postsynaptic protein expression and synapse density. These structural deficits caused by ASD-associated Shank2 mutations may have adverse implications on synaptic function and overall cellular homeostasis.

Poster 6.54

The effects of transcranial magnetic stimulation on synaptic function and excitability of single neurons

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Transcranial magnetic stimulation (TMS) is used to non-invasively activate neural circuits within the brain. Repetitive TMS (rTMS) has been shown to alter the excitability of neural circuits for a period of time outlasting the duration of stimulation. While this indicates a possible effect of rTMS on synaptic plasticity, the mechanisms are not well understood at the single neuron level. *In vivo* intracellular sharp-electrode electrophysiological recordings were made from single neurons in rats during the application of TMS. Spontaneous neuron activity was recorded in response to single TMS pulses and, where possible, rTMS. In addition, post-synaptic potentials (PSPs) elicited using electrical or magnetic stimulation of the ipsilateral hemisphere were also investigated, both pre and post rTMS. In preliminary recordings, single pulse TMS was found to elicit a large PSP and a single action potential in a spontaneously active cortical pyramidal neuron, followed by a pause of approximately 200 ms and then a transition to the up-state. This effect was dependent on the strength of the TMS pulse, with stronger pulses more reliably driving an up-state transition. Following rTMS, the maximum slope of excitatory PSPs was reduced by ≈50% for the first three minutes, followed immediately by short term potentiation, of 31% on average, lasting for approximately 15 minutes. These results provide the first indication of the effects that both single pulse and repetitive TMS have on cortical neuron excitability and synaptic plasticity. With a better understanding of these effects it is hoped TMS protocols may be more effectively optimised, providing better clinical results in the treatment of neurological disorders.

Poster 6.55

Cortical changes in AMPA receptor expression in the stargazer mouse model of absence epilepsy

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Absence seizures in humans are characterized by a brief loss of consciousness associated with spike-wave discharges (SWDs) resulting from aberrant hypersynchronous activity within the thalamocortical circuitry. Recent studies using the stargazer mouse and GRIA4 knockout models of absence epilepsy have shown that neuron- and synapse-specific changes in AMPA receptors contribute to the generation of SWDs within the thalamus. There is however limited experimental evidence about cortical changes and their contribution to circuit hypersynchrony. The aim of this study was to investigate cell-specific changes in AMPA receptor subunit expression within the somatosensory cortex of the stargazer model, and determine their contribution to the epileptic phenotype. Western blot analysis showed a significant loss of GluA2 ($n=18$, $p<0.01$) and GluA4 ($n=24$, $p<0.01$) subunits in the somatosensory cortex of the stargazer mice (stg/stg) compared to non-epileptic control mice (+/+, +/stg), but no difference in expression of the GluA1 ($n=24$, $p>0.5$) and GluA3 ($n=18$, $p>0.1$) subunits. Preliminary results from immunofluorescence confocal microscopy show a significant loss of the GluA4 subunit ($n=16$, $p<0.05$) within parvalbumin positive inhibitory neurons in the cortex of the stargazer mice compared to non-epileptic mice. The observed differential patterns in subunit expression indicate cell-specific loss of AMPA receptor subunits may contribute to aberrant oscillations within the cortical network. These findings are of major interest as the specific subunit composition dictates the different biophysical properties and function of an AMPA receptor. Subsequent results may provide an explanation into variances seen in the response to antiepileptic drug treatments among human patients, and aid in the development of more effective drugs against the disease.

Poster 6.56

Temporal analysis of HDAC1 and HDAC2 activity during Long-Term Potentiation

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Long-term potentiation (LTP) is widely accepted as a molecular mechanism underlying learning and memory. Epigenetic regulation by histone deacetylase 2 (HDAC2), is believed to negatively regulate the induction of LTP. However, our group has shown that mRNA expression of HDAC1 and HDAC2 is upregulated 5 hours and 24 hours, respectively, after LTP induction. We hypothesise that this upregulation occurs at these late time points to enhance LTP persistence, perhaps by impairing subsequent interfering synaptic plasticity. We have investigated the time-course of HDAC activity at 20 minutes, 5 hours, 12 hours and 24 hours after LTP induction in the dentate gyrus (DG) of awake adult male Sprague-Dawley rats. Extracted protein from dorsal DG of the stimulated hemisphere, the unstimulated control hemisphere and control animals, not given any stimulation, was used to perform immunoprecipitation and fluorometric activity assays. Surprisingly, preliminary analysis of the results show no increase in HDAC2 activity at any time-point, rather it is decreased at 12 hours and 24 hours in the control hemisphere of the test animals. Moreover, HDAC1 activity was increased, but this occurred in both hemispheres of the test animals at 20 minutes and 5 hours ($p<0.05$). Changes in both hemispheres of the test animals suggest that the stimulation, thought to affect only one side, may be having bilateral effects and thus could be affecting future LTP in either hemisphere. Further studies using Western blot analysis to measure HDAC1 and HDAC2 protein levels, as well as the level of histone acetylation, will assist in creating a more robust profile of HDAC activity, and their contribution to LTP.

Poster 6.57

Altered NMDAR subunit composition in the thalamus of a mouse model of absence epilepsy

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Absence seizures, which are non-convulsive, generalized seizures typical in childhood absence epilepsy (CAE) arise from abnormal hyper-oscillatory activity in the cortico-thalamic circuit. Although CAE is a genetically heterogeneous disorder and a variety of susceptibility loci have been identified, the network hyper-synchronicity is generally the result of excitatory-inhibitory imbalance within the network, which is often associated with region-specific changes in the synaptic proteome. The mouse strain stargazer is one of several rodent absence models used to study the cellular mechanisms that underlie seizures. A recessive mutation to the transmembrane protein stargazin in this strain leads to a dramatic decrease in AMPAR-mediated excitatory neurotransmission in the inhibitory reticular thalamic nucleus (RTN), which is caused by a reduction in synaptic AMPAR expression in the RTN. The reduction in AMPARs, however, may be compensated by NMDA-type glutamate receptors, which could increase the net excitation in the RTN and result in abnormal network oscillations. In the present study, we investigated the expression of NMDAR subunits NR1 (n=4 pairs), NR2A (n=6 pairs) and NR2B (n=6 pairs) in the RTN of stargazers and control mice by Western blot and found elevated NR1 (40%, $p<0.05$) and NR2A (60%, $p<0.05$) levels in stargazer RTN. Our results indicate region-specific differences in NMDAR subunit composition in the stargazers, which may contribute to abnormal oscillations. Further research is required to specify the subcellular location of these changes. Elucidating the alterations in cellular and subcellular protein expression caused directly and indirectly by mutations will enhance our understanding of CAE pathophysiology, and help the development of treatment strategies.

Poster 6.58

Development of cortical electrical stimulation for modulating brain plasticity in Parkinson's disease rats

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The theta burst stimulation (TBS) of rTMS protocols has been proven to be capable of modulating motor cortical excitability through plasticity-like mechanisms and might have therapeutic potential for Parkinson's disease (PD). However, the TBS application in rodents has been limited due to relatively large coil and poor spatial resolution of rTMS. To better understand the neural mechanism underlying the TBS effects and to enable translational research in PD rat models, the cortical electrical stimulation (CES) was developed in anesthetized rats. Furthermore, we applied CES protocol to examine the therapeutic effects of four weeks CES-TBS intervention from behavioral and electrophysiological findings in advanced PD rats. From the changes of motor plasticity following CES-TBS in normal rats, the motor evoked potentials (MEPs) traces showed no obvious change in the sham control. An increase in the MEP amplitude was found when intermittent TBS was applied. A reduction in the MEP amplitude was found following continuous TBS. For long-term effects, long-term CES-TBS treatment reduced motor deficits in PD rats over a 4-week time-course of observation in comparison with sham-treatment PD group. Furthermore, the amount of motor plasticity were impaired in sham-treatment PD rats but relatively better motor plasticity was found in long-term CES-TBS treated PD group. In conclusion, we have developed an animal model for testing CES-induced motor plasticity, and then further examined in long-term treated PD rats. The motor dysfunction and impaired motor plasticity can be reduced after CES-TBS treatment.

Poster 6.59

Investigation of tissue oxygenation in diabetics using near infrared spectroscopy

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Endothelium dysfunction is one of the major factors leading to the impaired microcirculation in diabetics. The serious impairment of microvasculature would result in amputation or/and ulceration in the lower limb of diabetics. Near-infrared spectroscopy (NIRS) is a non-invasive method to monitor the real-time concentration change of hemoglobin species. Previous research has shown that changes in spectral components of NIRS signal might provide some insights into pathogenic mechanisms of diseases. The purpose of present study was to quantify the vascular regulatory mechanisms in subjects with different glycemic status. NIRS signals were obtained simultaneously from prefrontal cortex and gastrocnemius muscle of diabetes (n=60), pre-diabetes (n=47) and normal groups (n=60), respectively. Three dominant frequencies in low-frequency oscillations (LFOs) including myogenic response of vascular smooth muscle (0.06-0.15 Hz), sympathetic innervation in the vessel wall (0.02-0.06 Hz) and endothelium related activity (0.005-0.02 Hz) using Welch's method. All participants were lying in recumbent posture for the 20 min resting measurement. Our results showed that muscle oxygenation oscillations of diabetes in frequency band of 0.005-0.02 Hz was greater than pre-diabetes (P=0.003) and normal (P=0.003) groups. In the frequency band of 0.02-0.06 Hz, the muscle oxygenation oscillations in diabetes was higher than normal (P=0.045). However, there were no significant differences among three groups in cerebral oxygenation oscillations. Observation from cerebral and peripheral vascular regulation, the compensatory mechanism of endothelium and sympathetic nerve aimed to supply adequate oxygen to the relative tissue hypoxia in diabetes.

Poster 6.60

Addressing Alzheimer's disease symptoms using lentiviral-mediated sAPPα overexpression in the hippocampus of a transgenic mouse model

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Alzheimer's disease (AD) is a neurodegenerative disease that is associated with memory loss and poor cognition. Neuropathologically, the disease is characterised by amyloid plaques and neurofibrillary tangles. The accumulation of amyloid plaques in the brain is thought to be due to an imbalance in amyloid precursor protein cleavage, leading to increased amyloid-β and decreased soluble precursor protein-alpha (sAPPα). Acutely administered exogenous sAPPα has been shown to be neuroprotective, supporting neurogenesis and regulating learning and memory. In the current study, a lentiviral vector containing sAPPα cDNA, under the control of a synapsin promoter, was injected bilaterally into the hippocampus of 4-month old male $APP_{Swe}/PS1_{\Delta E9}$ transgenic mice. The two control groups consisted of B6/C3 wildtype littermates and transgenic littermates injected with an empty vector. At 12 months of age, animals underwent field potential testing of synaptic transmission and plasticity in area CA1 of the hippocampus. There was no significant difference in input-output curves, or paired-pulse population spike inhibition between groups. However, long-term potentiation (LTP) magnitude at two hours post-theta burst stimulation of transgenic mice treated with the empty vector (106 ± 7%, n = 11) was significantly less ($p<0.05$) than that of wild-type littermates treated with the empty vector (135 ± 8%, n = 16). Transgenic mice treated with sAPPα showed an intermediate level of LTP (122 ± 4%, n = 16) that did not differ from either wild-type or empty transgenic animals. These early results indicate that the overexpression of sAPPα may partially prevent the LTP deficit observed in AD transgenic mice.

Supported by a grant from the Health Research Council.

Poster 6.61

Imaging lipid and protein changes in the human hippocampus in Alzheimer's disease using MALDI-mass-spectrometry imaging

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Alzheimer's disease (AD) is the most common form of dementia, and affects an estimated 28,000 New Zealanders. The accumulation of β-amyloid plaques and tau tangles, and significant atrophy of the hippocampus (which plays a role in memory formation and spatial navigation), are the pathological markers of this disease. However, since the actual biochemical basis of neurodegeneration is poorly understood, the aim of this study was to comprehensively investigate changes in human hippocampus lipidomic and proteomic distributions, and relative abundance in AD. Matrix-assisted laser desorption/ionisation (MALDI) mass spectrometry imaging (MSI) was used to spatially map changes in lipids and proteins in the normal and AD human hippocampus. Following tissue preparation, and matrix deposition, MALDI images were acquired using an Applied Biosystems Voyager DE-Pro in positive and negative ion modes, at 150µm spatial resolution. MALDI images were generated using BioMap software. Lipid and protein identities were assigned using published studies. Preliminary results indicate abundant lipid and protein signals in human hippocampal tissue, with distinct anatomical distributions. While many lipids were unchanged in AD, signals for sulfatides (eg, sulfatide 24:1-H- and 24:0 (OH)-H- detected at m/z 888.6 and 906.4, respectively) were decreased in the AD hippocampus. For protein analysis, signals that were unchanged, decreased or increased in intensity were detected in AD hippocampus. Together these results suggest several markers for human AD that require further investigation. This is to our knowledge, the first instance of lipidomic and proteomic mapping in the human hippocampus in normal and AD brains using MALDI-MSI.

Poster 6.62

Level of hypnotic susceptibility does not affect simple or choice reaction times

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Greater hypnotic susceptibility has been shown to correlate with faster reaction time in tasks with low stimulus/response compatibility. We investigated the effect of hypnotic susceptibility on the speed of information processing in humans using a precued simple (SRT) and choice (CRT) reaction time experiment. Eighteen right-handed participants (7 male), 19-31 y, assessed for hypnotic susceptibility (Stanford Hypnotic Susceptibility Scale Form C - SHSSC) were tested under hypnotised and non-hypnotised conditions performing a key-press task using their right or left index finger in response to a visual stimulus. Key-press forces and electromyographic (EMG) data were captured, from which premotor time, reaction time, motor time and movement time were measured. SHSSC scores revealed 9 "low" and 9 "high" susceptible participants. Between-group analysis of "high" vs "low" showed no difference in any of the measures. Within-group analysis showed that motor time was slower in hypnotised conditions for both the SRT ($p=0.007$) and CRT ($p=0.036$) tasks, with no difference between the conditions in on other measures. The findings do not support either of two hypotheses previously proposed to explain between person variability in hypnotic susceptibility, namely differences in focused attention abilities and response set theory. The slower motor times observed in the hypnotised state may be due to the type of hypnotic induction used.

Poster 6.63

Effect of Voltage gated sodium channel toxins as therapeutic agents for chronic pain

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In humans, the loss function mutation in the SCN9A gene that codes for voltage gated sodium channel 1.7 ($Na_V1.7$) was linked to channelopathy-associated insensitivity to pain, while gain of function mutations resulted in paroxysmal extreme pain disorder and primary erythermalgia. Thus it is evident that $Na_V1.7$ plays an important role in multiple pain conditions. $Na_V1.7$ channels are abundant in primary sensory neurons of the dorsal root ganglion (DRG). These DRG neurons conduct information from a wide range of receptors including nociceptors which sense noxious stimuli. Therefore, nerve injury or inflammation have been shown to cause a multitude of changes in DRG neurons with increased excitability and firing. This increased firing may be a result of changes in $Na_V1.7$ activity of DRG neurons. This project aimed to identify the efficacy of multiple animal toxins that blocked Na_V channels within DRG neurons as potential therapeutic agents in the treatment of pain. In order to identify changes in the channel kinetics, whole cell patch clamp electrophysiology was conducted on acutely isolated DRG neurons. The DRG neurons were differentiated based on presence of neuropeptides and cell size. Results revealed that synthetic spider toxins selective for $Na_V1.7$ were most effective at inhibiting small peptidergic DRG Na_V neuronal current. Since small peptidergic neurons are primarily nociceptive, this data suggests that $Na_V1.7$ selective compounds may have therapeutic potential in treating pain by decreasing hyperexcitability of nociceptive neurons.

Poster 6.64

Ipsilateral corticospinal pathways to the lower limb: Detection and function

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To investigate ipsilateral neural connectivity from the lower limb motor cortex to spinal motoneurons, transcranial magnetic stimulation (TMS) was employed to produce a medial to lateral (M – L) current within the lower limb motor cortex. Amplitudes of TMS-induced motor evoked potentials (MEPs) were calculated in the EMG recorded from contralateral and ipsilateral lower limb muscles. Fourteen of these subjects completed two behavioural assessments; a footedness assessment, and a knee and ankle visuo-motor tracking task. The strength of footedness and subjects' ability to accurately perform the visuo-motor tracking tasks was assessed in subjects with and without evidence of ipsilateral connectivity. The results indicate approximately 40% of the muscles tested in the 22 subjects had evidence of ipsilateral connectivity. Of the three muscles examined, the vastus lateralus (VL) more frequently revealed evidence of ipsilateral connectivity, and this evidence was more often revealed in muscles on the left side of the body. Subjects with ipsilateral connectivity to muscles on the left side of the body were more strongly right footed. This was taken to mean that they were more likely to use the left leg as a stance limb whilst manipulating or avoiding objects with the right leg and foot. The visuo-motor tracking task revealed that subjects with evidence of ipsilateral connectivity performed antiphase tracking less accurately than subjects without evidence of ipsilateral connectivity. Subjects without evidence of ipsilateral connectivity tended to perform *both* inphase and antiphase tracking more accurately compared to subjects with evidence of ipsilateral connectivity to one or both legs.

Poster 6.65

SHANK3 mutations identified in Autism Spectrum Disorder impair neuronal physiology

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Shank3 is a postsynaptic scaffolding protein that is central to regulating both function and structure of central excitatory synapses. Mutations in the Shank3 gene are associated with cognitive impairment in Autism Spectrum Disorders (ASDs). Currently little is known about the effects of *SHANK3* ASD-associated mutations on neuronal physiology. To assess the physiological consequences of *SHANK3* mutations, we expressed *SHANK3* wildtype and ASD-associated mutations (EGFP-Shank3-WT, EGFP-Shank3-R87C and EGFP-Shank3-Q396R) in dissociated rat hippocampal cultures. Confocal microscopy and electrophysiology techniques were applied to characterize the impact of *SHANK3* mutations on synapse number, basal synaptic transmission and synaptic plasticity. Overexpression of GFP-Shank3-WT significantly increased the number of synapses (p-value < 0.005) as well as the frequency of AMPA receptor-mediated miniature excitatory postsynaptic currents (mEPSC; p-value < 0.005), indicating that Shank3 promotes the formation of functional synapses. However, Shank3 ASD-associated failed to induce this same enhancement of synaptic structure and function. Furthermore, neurons expressing Shank3 ASD-associated mutations, R87C or Q396R, failed to undergo long-term potentiation (LTP). Rather, these neurons expressed depression in response to LTP-inducing paradigms. Altogether, data reveal the importance of Shank3 in strengthening synaptic structure and function and add further support towards the idea that deficits in Shank3 contribute to the pathogenesis of ASD.

Poster 6.66

Partial weight support differentially affects corticomotor excitability across muscles of the upper limb

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Partial weight support may hold promise as a therapeutic adjuvant during rehabilitation after stroke by reducing the expression of abnormal muscle synergies that cause upper limb impairment. We explored the neurophysiological effects of upper limb weight support in thirteen healthy young adults by measuring motor evoked potentials (MEPs) from transcranial magnetic stimulation (TMS) of primary motor cortex and electromyography from *anterior deltoid* (AD), *biceps brachii* (BB), *extensor carpi radialis* (ECR), and *first dorsal interosseous* (FDI). Five levels of weight support, varying from none to full, were provided to the arm using a commercial device (Saebo MAS). For each level of support, stimulus-response (S-R) curves were derived from MEPs across a range of TMS intensities. Weight support affected background EMG activity in each of the four muscles examined ($p < 0.0001$ for each muscle). Tonic background activity was primarily reduced in the AD; however, muscles that had no mechanical role in the task (ECR and FDI) were also affected. Weight support had a differential effect on the size of MEPs across muscles. After curve fitting, the S-R plateau for ECR increased at the lowest support level ($p = 0.004$). For FDI, the SR plateau increased at the highest support level ($p = 0.0003$). This study shows that weight support of the proximal upper limb modulates corticomotor excitability across the forearm and hand. The findings support a model of integrated control of the upper limb and may inform the use of weight support in clinical settings.

Abstracts

8.1

Individualised medicine: Predicting dementia in Parkinson's disease

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Many people with Parkinson's disease (PD) eventually develop dementia, which then becomes the most burdensome aspect of this progressive condition. To improve clinical management and planning, and facilitate the selection of patients for intervention studies to delay progression and enhance quality of life, it is important to identify those at the greatest risk of severe functional decline. We followed 142 people with PD, initially all without dementia, over 2-4 years. At baseline and follow-up assessments each individual had a battery of tests evaluating cognition and clinical status. During this period 26 developed dementia. We established individualised probabilities of developing dementia within 4 years, using a Bayesian probabilistic Gaussian process model that was trained on baseline data of age, UPDRS, and a global cognitive score derived from 21 component neuropsychological tests. Performance of the model was evaluated using leave-one-out cross validation. Probabilities of conversion derived from the model were higher for individuals that developed dementia (mean of 56% versus a prior probability of 18%) and the model achieved an AUC = 0.90 (95% CI 0.83-0.96) for discriminating between converters and non-converters to dementia within 4 years. Given these individual probabilities an optimal cutoff for making clinical decisions can be determined by using an appropriate loss function. To further improve the ability of the model to assign higher probabilities to individuals that convert to dementia it can be extended to incorporate MRI data and thereby learn the changes in grey matter, white matter, and perfusion that are predictive of imminent development of dementia in patients with Parkinson's disease.

8.2

Longitudinal investigation of presymptomatic Huntington's Disease: In pursuit of neuroimaging and neuropsychological biomarkers

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Since the discovery of the gene causing Huntington's disease (HD), individuals have been able to find out their gene status prior to onset of clinical symptoms. Identifying sensitive and reliable clinical and neuroimaging biomarkers to assist therapeutic trials that attempt to track proximity to symptom onset in individuals presymptomatic for Huntington's Disease (preHD), has proved elusive. The conventional view of HD as a disease primarily of the basal ganglia and striatal-frontal circuits has been challenged by neuropathological and neuroimaging studies, with some findings indicating posterior cortical changes predate changes in anterior cortex. We report the findings of a longitudinal study of 18 individuals presymptomatic for HD and 17 closely-matched controls using neuroimaging methods and neuropsychological measures that targeted cognitive functions likely to be disrupted by dysfunction of posterior regions of cerebral. The results revealed grey-matter changes in posterior cortical regions (using VBM), as well as significant decline on a posterior task involving egocentric rotation (Roadmap test on turns requiring rotation), most pronounced for those close to clinical onset. In contrast, there were no structural changes in anterior cortical regions and neuropsychological performance was unremarkable on tasks sensitive to anterior regions. Expected volume reductions of the striatum were also found. Putamen volumes at both time-points were a significant predictor of performance on the egocentric rotation task, suggesting that together these may be good candidates for early biomarkers of change prior to clinical onset of HD.

8.3

Can SSRIs enhance human visual cortex plasticity?

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Selective serotonin reuptake inhibitors (SSRIs) have been shown to enhance visual cortex plasticity in adult animals, an effect that was blocked by the benzodiazepine triazolam. The aim of this study was to assess whether SSRIs increase visual cortex plasticity in humans. In experiment 1, male participants (n = 20) with normal vision were randomized to a 3-week course of fluoxetine (20mg per day) or placebo. During the final 5 days of drug administration, participants were trained extensively on a motion discrimination task at a fixed motion direction. The amount of learning was assessed for the trained motion direction and an untrained direction with and without a single dose of the benzodiazepine triazolam (0.0625 mg). Adult patients with amblyopia (n = 7) took part in experiment 2, which employed a cross-over design whereby placebo and citalopram (20mg per day) were each combined with two weeks of occlusion therapy (2 hours per day). Visual functions, including visual acuity, were measured fortnightly on five occasions. In experiment 1 there was no effect of fluoxetine on learning. However, triazolam significantly impaired performance for the untrained but not the trained motion direction ($F = 3.3$, $p = 0.04$). In experiment 2, 3 patients experienced VA improvements of over 0.1 LogMAR when treated with citalopram but not with placebo. SSRI administration did not affect visual cortex plasticity in normal observers. However, separate learning mechanisms were unveiled; as only the untrained task was susceptible to neuronal hyperpolarization, caused by allosteric modulation of the GABA binding site by triazolam. Citalopram may allow for visual acuity improvements in some patients with amblyopia, however longer treatment durations may be required to improve visual functions such as acuity and stereopsis in a larger number of patients.

8.4

Varenicline improves motor, cognitive and psychiatric symptoms in the YAC128 transgenic mouse model of Huntington's Disease

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Huntington's Disease (HD) is a fatal, inherited neurodegenerative disorder characterized by progressive movement, cognitive and psychiatric symptoms. Post mortem human studies and studies in genetic mouse models report a significant loss of acetylcholine and choline acetyl transferase activity in the HD brain, but no change in the number of nicotinic acetylcholine receptors. This suggests dysfunctional cholinergic neurotransmission may be a contributing factor in the pathogenesis of HD. Direct activation of nicotinic acetylcholine receptors may therefore be a potential therapeutic strategy. This study investigated whether chronic treatment with the nicotinic agonist varenicline could reduce motor, cognitive and affective symptoms in a transgenic mouse model of HD. The performance of YAC128 transgenic HD mice (15 month old, mixed-sex cohorts) in the rotarod, T maze, novel object recognition, novelty suppressed feeding and modified Porsolt tests was assessed before and after treatment with varenicline for 4 weeks (5mg/kg/day). Thymidine analogues were used to assess progenitor cell proliferation and survival. DARPP32 and EM48 immunohistochemistry was performed to visualise medium spiny neurons and huntingtin aggregates in the striatum, hippocampus and cortex. Chronic administration of varenicline produced significant improvements in motor coordination, delay-dependent memory and short-term recognition memory in late-stage YAC128 mice. Varenicline treatment also significantly decreased anxiety and depressive-like behaviour. Immunohistochemical analysis of brain tissue revealed increased neurogenesis and DARPP32 immunoreactivity in the striatum and cortex of varenicline treated animals. An increased number of huntingtin aggregates were observed within the hippocampus of varenicline treated animals. These data suggest restoration of cholinergic neurotransmission via chronic administration of a nicotinic acetylcholine receptor agonist may be an effective therapeutic strategy in the treatment of HD.

8.5

D1 Receptor Involvement in MDMA's acute memory impairments: An investigation using the DAD1-/- mutant rat

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3,4 methylenedioxymethamphetamine (MDMA or 'ecstasy') is a recreationally abused substituted amphetamine with both hallucinogenic- and stimulant-eliciting properties. Chronic and acute memory impairments following MDMA use have been widely documented. Research from our laboratory using rats suggests that MDMA's action at the dopamine D1 receptor may be involved in MDMA's acute memory deficits on a delayed matching-to-sample (DMTS) task. The current research investigates the hypothesis that MDMA interferes with memory via its agonist actions at the D1 receptor site. The dopamine D1 receptor mutant (DAD1-/-) rat show down-regulated D1 receptor function but intact D5 receptor function. Memory performance of the DAD1-/- rats were compared to wild type controls on a non-reinforced spontaneous alternation T-maze task after administration of 3 mg/kg MDMA, SKF 81297 (D1 agonist) and saline. Contrary to our predictions, no significant differences between groups were observed. This unexpected finding could be due to a variety of factors including task differences or potential locomotor or exploration differences between the DAD1-/- rats and control subjects. Furthermore, we have conducted an immunohistochemical analysis of c-fos expression, an immediate-early gene used as a marker of neuronal activity, in order to investigate the neural level differences in responsiveness to MDMA between the DAD1-/- and wild type rats.

9.1

Is hemispheric balancing necessary for motor recovery after stroke?

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The prevailing model of motor recovery after stroke is that better recovery is associated with 're-balancing' of asymmetric corticomotor excitability and interhemispheric inhibition between the hemispheres. This model has driven the development of neuromodulation techniques to reduce contralesional excitability and promote recovery. We tested this model by collecting neurophysiological data from patients during the first 6 months post-stroke. TMS was used to elicit MEPs in extensor carpi radialis bilaterally from 46 patients after first ever monohemispheric ischemic stroke. Stimulus response (SR) curves and ipsilateral silent periods (iSPs) were obtained 2, 6, 12 and 26 weeks after stroke. The slope of each SR curve was calculated as a measure of corticomotor excitability. The persistence and depth of iSPs were determined as measures of interhemispheric inhibition. An asymmetry index for RMT and corticomotor excitability was calculated for each time point. RMT became more symmetrical over time ($p < 0.001$), due to decreased ipsilesional RMT ($p < 0.001$), with no effect of time on contralesional RMT ($p > 0.5$). Corticomotor excitability became more symmetrical over time ($p = 0.001$), due to increased ipsilesional excitability ($p = 0.008$), with no effect of time on contralesional excitability ($p > 0.2$). There were no effects of time or hemisphere on ipsilateral silent period persistence (both $p > 0.3$) or depth (both $p > 0.1$). These findings call into question strategies aimed at suppressing contralesional corticomotor excitability to promote recovery of motor function, particularly in the first few months after stroke.

9.2

Improving post-stroke rehabilitation with Wii-based Movement Therapy

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Increased hand function after stroke is most strongly associated with greater independence in activities of daily living. However the predominant focus in stroke rehabilitation is locomotion, speech and swallowing. The aim of Wii-based Movement Therapy (WMT) is to increase motor function and movement quality of the more-affected upper-limb and to increase independence in activities of daily living. Patients complete 60 min of formal therapy on 10 consecutive weekdays augmented by progressively increasing home practice. They are assessed immediately before and after therapy, and at 6 months. We recently compared WMT to the current best practice for upper-limb rehabilitation, Constraint-induced Movement Therapy in a randomised controlled trial (n=42). There were no differences between groups for age, time post-stroke or functional ability at baseline assessments. After therapy there were no differences between treatment groups for any upper-limb measure as assessed with linear mixed models. Only two differences were found, WMT promoted a significant improvement in both peak heart rate ($p<0.001$) and heart rate recovery ($p=0.02$) but Constraint-induced Movement Therapy did not. Second, there was a clear patient preference for WMT. Kinematic analyses of recordings made during therapy (n=12) demonstrated improved joint excursion, velocity, acceleration and deceleration with greater motor control seen as the ability to voluntarily select movement speed and amplitude. Preliminary data from brain imaging and transcranial magnetic stimulation show complex patterns of plasticity with recovery. Most importantly, at 6 months we found continued use of the Wii and WMT-activities and increased participation in work and the community. The improvements immediately after therapy were sustained at 6 months. These studies demonstrate that WMT provides an effective upper-limb rehabilitation protocol that is engaging, cheap, can be implemented in the home, and has high patient compliance.

9.3

Improvement of stroke recovery following electrical theta-burst stimulation applied via implanted electrodes

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Stroke can lead to an increase in inter-hemispheric inhibition (IHI), which may negatively impact functional recovery. Low-intensity theta-burst stimulation (TBS), when applied acutely to healthy rats, can reduce IHI, suggesting it may be beneficial if applied therapeutically for stroke. To investigate this in rats, photothrombotic stroke lesions were induced in the forelimb motor cortex and a cortical electrode was implanted in the contralesional homologous motor cortex for later application of sham stimulation or TBS. Forelimb functional recovery was assessed over time using a grid walking test, conducted both before and after application of stimulation. Finally, these chronically stimulated rats were anaesthetised with urethane and intracellular recordings from peri-infarct neurons were taken to investigate chronic changes in IHI after stroke and TBS. Rats receiving intermittent theta-burst stimulation (iTBS) beginning three days after stroke exhibited significantly improved forelimb function compared to both sham stimulation and continuous theta-burst stimulation (cTBS) treated rats ($P<0.05$; Dunn's multiple comparison test, n=8 per group). Preliminary behavioural analysis of rats receiving iTBS commencing fourteen days after stroke (n=9) revealed improved recovery at the final day of functional assessment compared with cTBS-treated rats (n=7), but not sham-treated rats (n=8). Whether first applied three or fourteen days after stroke, cTBS-treatment appeared to induce a persistent deficit in functional recovery compared to shams. Preliminary measurements of IHI in peri-infarct neurons suggest that chronic iTBS-treatment decreased IHI compared with no stimulation (11.6% ± 0.2, n=2; 16.1% ± 3.9, n=4, respectively); whereas, chronic cTBS-treatment appeared to increase IHI (23.2% ± 0.9; n=2). Ongoing studies will inform whether beginning TBS 31 days after stroke induction will effectively modulate functional recovery and IHI after stroke.

9.4

Delayed administration of citalopram is associated with long-lasting improvements in skilled motor function after stroke

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There is growing clinical and preclinical evidence that functional recovery after stroke may be modulated by concomitant administration of central nervous system medication. Recent evidence suggests treatment with antidepressants may promote, while anti-psychotics may suppress functional recovery. However, the timeframe in which these pharmacological agents can influence stroke recovery is not well understood. This research investigated whether delayed administration of citalopram, used clinically in the management of post-stroke depression, could improve functional recovery in an experimental mouse model of stroke.CSF1-EGFP mice were subjected to 45 minutes occlusion of the middle cerebral artery under isoflurane anaesthesia. Animals were administered citalopram (1mg/kg/day, n=13) or saline (n=12) 3 days after stroke for 4 weeks. Neurological deficits and functional performance in the sticky label removal, staircase, and corridor tests were assessed at 1, 2, 4, 6, and 8 weeks post-stroke. Brain tissue was processed for thionin and Luxol Fast Blue histology. Ischaemic stroke produced a unilateral impairment in food retrieval in the staircase test. Citalopram-treated animals showed significantly improved impaired forepaw use 1, 2, and 6 weeks post-stroke compared to controls (p<0.05). Citalopram associated improvements were evident up to 2 weeks after drug withdrawal (p<0.05). Improved motor function was associated with increased connectivity of white matter tracts within the ipsilateral hemisphere. Administration of the antidepressant citalopram in the sub-acute phase following stroke produced long lasting improvements in functional performance and may influence endogenous brain remodelling. The extended therapeutic window of 3 days suggests that citalopram may be a useful therapeutic strategy for the large number of stroke patients who experience delayed hospital admission.

10.1

Viral vector-mediated transgene-specific effects on astrocyte function

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Astrocyte dysfunction plays a role in the pathogenesis of many neurodegenerative diseases and their prevalence in the face of a depleted neuronal population may make them a better cell target for gene therapy. In previous work we found that adeno-associated viral (AAV) vector-mediated expression of microRNA sequences against adenosine kinase (miR-ADK) in rat hippocampal astrocytes significantly reduces the duration of experimental seizures, whilst overexpression of glutamine synthetase (GS) or excitatory amino acid transporter-2 (EAAT2) does not. This study aimed to determine whether this could be attributed to the expression levels or activity of these putative therapeutic transgenes. Male Sprague-Dawley rats received unilateral hippocampal infusions of AAV vectors expressing GS, EAAT2, miR-ADK or control transgenes and the brains from subgroups of animals were taken for Western blot or immunohistochemical analysis at 4 weeks. ADK protein levels were reduced by more than 90% following expression of miR-ADK compared to controls. In contrast, transgenic GS and EAAT2 expression was low relative to the high endogenous levels of these proteins in the hippocampus. As a result, no significant difference in GS protein level was found between GS vector and control luciferase vector-injected brains. However, transgene expression across all vector treatment groups caused a reduction in GS activity relative to hippocampal lysates prepared from phosphate buffered saline-injected or AAV empty vector consisting of viral vector capsids only (One-way ANOVA, p=0.003). These results show that astrocytes could be a good cell target for gene therapy but transgene choice needs careful consideration, as the strength of the glial fibrillary acidic promoter used in these vectors may be insufficient to drive adequate levels of transgene expression necessary to produce a therapeutic effect.

10.2

Changing resistance affects flow within the circle of Willis

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The primary purpose of the circle of Willis (CW) is to distribute blood to brain tissue, especially in the event of high stenosis or occlusion of one of the main feeding arteries. Blood flow is influenced by the resistance and compliance of the distal vessels perfusing the cortical tissue. Resistance is inversely proportional to the 4th power of radius and varies depending on metabolic demands. Increased local metabolism releases vasodilating chemicals into the blood stream. It is not fully understood how sensitive the cerebral flow is to these changes. A one-dimensional computer simulation, Nektar, was used to compare the subsequent effects of decreasing the peripheral resistance on the blood flow of the vessels that feed into, comprise, and leave the CW. Resistance decreases between 1% and 10% were induced separately on the anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA; respectively); unilaterally, on the right, and bilaterally. A 2% decrease of the right ACA resistance induced a 1.6% flow increase in itself. Similarly, a 2% decrease in the right MCA induced an increase of 1.7% in itself. The same test for the right PCA yielded a 1.6% increase in itself coupled with a 1.2% increase in the first portion of the right PCA. Flow increased in a linear fashion with decreasing resistance. A decrease of 10% in resistance of any of the efferent arteries, unilaterally or bilaterally, induced less than 1% flow change in the others due to the collateral capability of the CW.

10.3

Neurogenesis in the rat cochlear nucleus and the effects of acoustic trauma

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Acoustic trauma is the most common cause of tinnitus and has been shown to result in neuronal hyperactivity in the cochlear nucleus (CN). This hyperactivity is suggested to be responsible for the generation of tinnitus. In neurodegenerative diseases where neurons either become damaged or are hyperactive, the brain produces new neurons ('neurogenesis') in response to the injury. In the present study, we investigated the effects of acoustic trauma that has been proven to cause tinnitus, on cell proliferation and neurogenesis in the CN of rats. Rats received either sham or unilateral acoustic trauma (16 kHz at 115 dB for 1 h) under anaesthesia. Animals were injected with the cellular proliferation marker, BrdU, at 72 hs following the acoustic trauma, and then 2 hs or 24 hs later, were sacrificed by transcardial perfusion with 4% paraformaldehyde and the brains were removed, sectioned and stained for BrdU using immunohistochemistry. Double immunofluorescence was performed for BrdU and Ki-67, a marker for proliferating cells, CD11b, a marker for microglial cells, and doublecortin (DCX), a marker for immature neurons. Acoustic trauma resulted in an increase in BrdU labeling in the CN, which significantly co-labeled with Ki-67, suggesting that it was due to cell proliferation. There was no significant co-labeling for CD11b, suggesting that the new cells were not microglial cells. However, there was significant co-labeling for DCX, suggesting that many of the new cells were immature neurons. However, the number of newborn cells that survived was not significantly different between sham and acoustic trauma groups, suggesting that acoustic trauma may not alter the level of neurogenesis compared to sham animals.

10.4

The role of recently born neurons in the adult mouse hippocampus in memory storage

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Considerable effort has been made to elucidate the role of newly born neurons in the adult hippocampus in learning and memory, but the results remain inconclusive. We are reversibly silencing these neurons to study their function. A double-floxed inhibitory chloride channel, that is sensitive to the drug ivermectin, is delivered to the hippocampi of nestin-Cre transgenic mice using lentiviral vectors. The expression of the channel is restricted to recently born neurons by combining a Cre-lox system with a cell type-specific promoter. We characterised the constructs *in vitro* using transduced primary neuronal cultures prepared from nestin-cre mouse pups, which were treated with ivermectin or PBS. The number of transduced cells expressing the immediate early gene Zif268, induced by treatment with the GABA-A receptor antagonist gabazine, was reduced by 80% as compared to the mock-treated control, indicating that the channels were indeed able to silence the transduced cells. When delivered *in vivo* by stereotaxic injection, expression of the construct as indicated by the fluorescent marker mCherry was seen in cells along the subgranular zone and innermost layer of the granule cell layer. Mice are now being tested on contextual fear conditioning and Morris water maze tasks. Ivermectin is being administered before probe trials to test for effects on memory retrieval, while probe trials after an ivermectin washout period test for performance recovery. These behavioural tests will address the hypothesis that young adult-born neurons play a critical role in memory storage, as revealed by impaired behavioural performance when the neurons are silenced during memory retrieval.

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11.1

Transient inhibition of orbitofrontal cortex impairs motivational modulation of attention

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Interactions between motivation and cognition are thought to underlie functional impairments in clinical populations. However, the functional neural circuitry underlying this interaction is not well understood. We previously developed a behavioural task which assays the interaction between motivation and attention. In this task, an explicit cue signals the probability of reward for attending during a visual discrimination task. Using this task, we are able to manipulate attention (and the resulting discrimination accuracy) on a trial-by-trial basis. A large body of research has shown that orbitofrontal cortex (OFC) is involved in behaviour based on the learned value of anticipated outcomes. Therefore, in the present research, we generated mice in which the OFC could be transiently and reversibly inhibited during performance of our signalled-probability task. We found that silencing OFC abolished the ability of reward-associated cues to modulate attention. These data indicate that OFC is critical in the ability of a reward related signal to recruit other cognitive processes (in this case attention) which are necessary for the translation of information about the value of specific outcomes to effective choice behaviour. These data also begin to delineate the neural circuitry involved in the interaction between motivation and attention.

11.2

Behavioural and biological changes with age: The effect of obesity on brain aging

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Clinical observations suggest the contributory role of obesity in late-life dementia. The presentation compares the difference in biological and behavioural changes in the brains of aged rats with and without obesity. Normal aging: Two groups of rats, young and aged were used. Morris Water Maze tests were carried in both age groups and brain tissues were used for biological analysis Aging with obesity: Young, middle aged and aged Wistar rats were used. The middle aged and aged male rats were become naturally obese with age. The biological and histological changes in neurons, vessels and glial cells were analysed. The memory and anxiety were evaluated using behavioural tests. Normal aging: The aged rats had significantly impaired memory compared to the young rats. The aged rats showed the degenerative changes and the loss of the capillaries in the hippocampus compared to the young controls. The memory decline was also related to the loss of glial cells and white matter density. There was no neuronal degeneration in the hippocampus of aged rats. In Study 2we observed memory decline in aged rats, but not in middle aged rats. However we found neuronal degeneration in both middle aged and aged male rats. The middle aged rats showed an enhanced neuronal plasticity and vascular remodelling and the aged rats have elevated glial cells in the hippocampus. Memory decline with normal age may be a vascular disorder with a consequence of neurodegeneration. In contrast, obesity contributes to neuronal degeneration from middle age. Neuronal loss in middle aged rats is not correlated to the memory decline, which could be due to the compensatory mechanisms of neuronal plasticity and vascular remodelling. Memory decline only emerged when the brain further aged with loss of capacity for neuronal plasticity and vascular remodelling, as well as with the onset of aging pathology, for example the elevation of glial cells.

11.3

The relationship between BOLD variability and mean BOLD signal during episodic and semantic memory tasks

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Intraindividual BOLD variability (BV) is a novel measure of BOLD signal that provides a better indicator of task performance than mean BOLD signal (MB). These two measures present in largely non-overlapping neural regions during a range of externally driven cognitive tasks. The current study examined whether BV and MB also present in non-overlapping regions for internal mentation tasks requiring episodic (EM) and semantic memory (SM). Participants (N=16) completed a slow event-related fMRI study. In the EM task, participants viewed event-type cues (e.g. getting a pet) and were required to recall specific events from autobiographical memory. In the SM task, participants were presented with a common noun; they produced two semantically related objects and defined the object words. Means and standard deviations (SD) of BOLD signal were calculated for each voxel in each condition. Each dataset (mean, SD) was then submitted to a multivariate partial least squares analysis. An EM > SM contrast showed increased MB within regions of the default mode network, including bilateral medial temporal, parietal and frontal regions, while increased BV was observed in bilateral lingual, right supramarginal and right inferior frontal gyri. Overlap for these two measures was found in bilateral retrosplenial and hippocampal cortex. The SM > EM contrast was associated with an increase in MB in parietal, frontal and temporal regions bilaterally. Many of these regions also exhibited increased BV, predominantly in the left-hemisphere. These findings show that the degree of overlap for MB and BV measures depends on the task.

11.4

Neural changes associated with the generation of specific past and future events in depression

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It is well established that individuals affected by depression experience difficulty in remembering the past and imagining the future. In particular, individuals with depression typically generate fewer specific past and future events compared to non-depressed individuals. The present fMRI study investigated whether neural changes during the construction of autobiographical events are evident in depression, even when key aspects of performance (event specificity, vividness) are matched. During fMRI scanning, participants in the depression group (N=17) and control group (N=16) generated past and future events in response to cues (e.g., next New Year's Eve). Events were scored for specificity during a post-scan interview. We employed a multivariate technique (spatiotemporal Partial Least Squares) to examine whether task-related whole brain patterns of activation and functional connectivity of the hippocampus differed between depressed participants and non-depressed controls. Results indicate that although the depression group retained the ability to recruit the default network during the autobiographical tasks, there was reduced activity in regions associated with episodic richness and imagery (e.g., hippocampus, precuneus, cuneus). Moreover, patterns of hippocampal connectivity in the depression group were comparable to those of the control group, but the strength of this connectivity was reduced in depression. These depression-related reductions were accompanied by increased recruitment of lateral and medial frontal regions in the depression group, as well as distinct patterns of right hippocampal connectivity with regions in the default and dorsal attention networks. The recruitment of these additional neural resources may reflect compensatory increases in post-retrieval processing, greater effort and/or greater self-related referential processing in depression that support the generation of specific autobiographical events.

13.1

What are they looking at? Imaging brain and behavior in the freely moving animal

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Motivation underlies the performance of self-determined behavior and is fundamental to decision making, especially with regard to seeking food, mates, and avoiding peril. As many decision making based behaviors in rodents involve a combination of head movements, eye movements, vestibular driven neuronal activity and active sensing of the environment to guide the behavior, studying the freely moving animal is paramount. To achieve this, what is necessary is the precise tracking of the animal's movement and interaction with the environment. Here I will outline work from our group that focuses on how freely moving rodents use their vision during decision making tasks and resulting cortical activity. I will introduce methods that allow accurate recording of neuronal activity from populations of cortical neurons, using multiphoton imaging techniques, while simultaneously tracking eye and head movements during decision making in the freely moving rodent. The second half of the presentation will focus on recent results from our lab showing how freely moving rodents have a distinct eye movement strategy that is of major evolutionary benefit.

13.2

Human brain pericytes, blood-brain barrier dysfunction and neurodegenerative disorders

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Disease-modifying treatments for neurodegenerative disorders are currently not available. Understanding and targeting the underlying causes of these disorders will provide opportunities for the development of disease-modifying medications. A number of brain disorders are characterized by inflammation and blood-brain barrier (BBB) dysfunction. Although most attention has focused on brain immune-type cells in inflammation (eg: microglia, astrocytes) recent studies by us and others suggest that pericytes lining capillaries in the brain are also involved in inflammation and BBB dysfunction. Using pericytes grown from donated adult human brain tissue as well as human brain tissue microarray methods, we have been undertaking mechanistic studies of the role of these cells in brain inflammation and BBB dysfunction. Furthermore, using high content assays we are testing compounds for activity on human brain pericytes. This work is aimed at understanding the causes of BBB dysfunction, inflammation and neurodegeneration in the human brain and developing pericyte-targeted treatments.

13.3

Batten disease in sheep – understanding lysosomal biology en route to therapies

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The lysosome is the major site of cellular recycling and deficiencies in this system have been implicated in a wide variety of diseases including cancer, diabetes, Alzheimer's and Parkinson's disease. Much of our understanding of the lysosome has come from inherited lysosomal storage diseases (LSDs), a group of monogenic diseases caused by mutations in lysosomal proteins or trafficking molecules. Our group focuses on Batten disease, a subgroup of LSDs of childhood resulting in incessant decline in motor function and cognition, seizures, blindness and premature death. Naturally occurring forms of Batten disease have been extensively studied in three breeds of sheep: *CLN6* mutations in New Zealand South Hampshires and Australian Merinos, and a *CLN5* mutation in New Zealand Borderdales. Established flocks provide excellent large animal models to study the pathology and potential treatment strategies in both forms of Batten disease. In addition, we are investigating the earliest pathological changes using primary neuronal cultures from fetal sheep (1). The functions of neither CLN5 (a soluble lysosomal enzyme) nor CLN6 (an endoplasmic reticulum membrane protein) have been determined, and research has been hindered by a lack of good antibodies against them. We have recently generated and validated antibodies against both proteins using a novel viral-based method. Using these antibodies we have shown that CLN5 and CLN6 interact. CLN5 expression is severely reduced in both CLN6 sheep breeds, and viral-mediated co-expression of the proteins in CLN5-affected neural cultures induces CLN6 degradation. The mechanisms behind these findings are now being investigated. We have also embarked on gene therapy trials using lentiviral (2) and adeno-associated virus (AAV) mediated expression of wildtype CLN5 or CLN6. Lentivirus limits expression to the parenchymal injection sites, or ependyma when injected into the ventricle. AAV serotype 9 spreads throughout the sheep central nervous system after intraventricular injection, however there are signs of viral mediated inflammation following injection into the parenchyma. Progress on these trials will be presented.

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2. Linterman, K. S., Palmer, D. N., Kay, G. W., Barry, L. A., Mitchell, N. L., McFarlane, R. G., Black, M. A., Sands, M. S., and Hughes, S. M. (2011) Lentiviral-mediated gene transfer to the sheep brain: implications for gene therapy in Batten disease. *Hum Gene Ther* 22, 1011-1020

13.4

Virus infects electron microscopy; combining techniques for enhanced imaging of brain circuitry

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Ultrastructural investigation of synapses requires visualisation at the electron microscope (EM) level. Traditionally, brain circuitry has been mapped using neuronal tracers and knowledge of neuronal phenotype or synaptic structures obtained by combining immunohistochemical labelling with EM. While rigorous, interpretation of the microcircuitry is limited because we have been unable to definitively identify a specific neuronal phenotype from only one pathway in the brain. To address this issue, we combined a lentiviral vector that targets GABAergic neurons (LV-GAD67copGFP) and immunohistochemical staining of tyrosine hydroxylase, an enzyme that labels dopamine neurons in the midbrain. We investigated the innervation pattern of GABAergic terminals from neurons with somata in the rostromedial tegmental nucleus (RMTg) that synapse onto dopamine neurons in the posterior ventral tegmental nucleus (pVTA). GFP-tagged GABAergic axon terminals, made electron dense by further immunolabelling, formed symmetrical synapses with pVTA dopaminergic dendrites. Importantly, there were complex synaptic triads at all examined synapses. Specifically, RMTg GABAergic presynaptic terminals were consistently innervated by one or two asymmetric, presumably glutamatergic, synapses. We hypothesise that these excitatory synapses onto GABAergic presynaptic terminals would intensify GABA release at synapses onto dopaminergic dendrites, thus, reinforcing signalling in this aversive pathway controlling behavior. Our findings have important implications for understanding drug addiction because the pVTA is a region where drugs of abuse exert strong rewarding effects. Finally, by combining viral vector technology and immunohistochemistry we can selectively visualise synapses at the EM level formed by one neuronal phenotype in one pathway in the brain.

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13.5

Dynamic voltage imaging using a genetically encoded voltage indicator (*Vsfp-Butterfly*) in mouse brain

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The ability to monitor the electrical behaviour of groups of uniquely identified, and connected, neurons is a major goal if we are to understand how the brain works. Towards this goal we have developed molecular technology that harnesses light to measure voltage[1] and coupled this with an advanced genetic targeting strategy. The voltage indicator called *VSFP Butterfly,* uses FRET-based technology and the targeting strategy delivers the indicator to layer 2/3 (L2/3) cortical pyramidal neurons and hippocampal dentate granule (DG) neurons using *ras-grf2*[2] and CaMkinaseII regulatory sequences. Immunohistochemistry and confocal microscopy confirmed *VSFP Butterfly* expression in the plasma membrane of DG neurons, and in CaMkinaseII-positive layer 2/3 cortical neurons 91 ± 5%, n = 5 mice. *VSFP Butterfly* expression also respected the L2/3 to L5 and L2/3 to L1 cortical boundaries identified by the layer-specific marker Vglut2. High speed (100Hz) live fluorescence imaging with synaptic stimulation and electrical recording revealed fast, robust changes in fluorescence from L2/3 neurons in motor cortex and DG neurons in hippocampal slices. Synaptic stimulation caused a decrease in the FRET donor (mCitrine) signal concomitant with an increase in the FRET acceptor (mKate) signal. These signals peaked within 10 ms, were 300-400 ms in duration and increased in amplitude with increasing voltage stimulation (n = 5 mice). These signals provide a real-time, ratiometric voltage signal from all L2/3 neurons within the field of view to generate a content-rich activity map. This exciting new transgenic mouse tool brings a modern and specific approach to voltage imaging in the brain that can help untangle the complexities of cortical microcircuits.

1. Akemann *et al* Nat Methods. 2010 Aug;7(8):643-9.

2. http://www.brain-map.org/

ABSTRACTS

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