ABSTRACTS

Proceedings of the 31st International Australasian Winter Conference on Brain Research, 2013

(ISSN 1176-3183)

Abstracts in Presentation Order

Editors

Dr Beulah Leitch

Dr Jonathan Shemmell

Proceedings of the International Australasian Winter Conference on Brain Research, 2013, 31, will be published on the AWCBR website.

www.otago.ac.nz/awcbr

ABSTRACTS

1.1

Epilepsy genetics: A successful marriage of next generation sequencing and next generation phenotyping

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It is almost inconceivable to see the rapid advances in our understanding of epilepsy genetics brought about by the advent of next generation sequencing. Suddenly there has been an exponential rise in the discovery of epilepsy genes particularly in the severe epilepsies of infancy and childhood called epileptic encephalopathies. Here children and adults with refractory seizures and cognitive impairment are receiving molecular diagnoses based on the discovery of de novo gene defects. Gene discoveries are providing insights into novel mechanisms which promise to open the door to targeted therapies. Genotype-phenotype correlations are being described that will help with diagnosis in the clinic. In the commonest group of epilepsies, the focal epilepsies where seizures result from a localized epileptic discharges, the first gene for common focal epilepsy has just been discovered. This gene causes different focal epilepsies in different family members, following autosomal dominant inheritance with low penetrance that often makes the genetic nature of the disorder difficult to distinguish. Affected individuals frequently experience temporal or frontal lobe epilepsies, although parietal, occipital and multifocal epilepsy are also observed. This gene, *DEPDC5*, is part of the GATOR complex, a group of proteins recently shown to be negative regulators of the mTOR pathway. Mutations in *DEPDC5* have been identified in cancer. Its relationship with the mTOR pathway raises the question of a tuberous sclerosis-like complex resulting in lesional and non-lesional epilepsies. Suddenly a whole new vista in our understanding of focal epilepsies is emerging raising the possibility of recognised therapies that target the mTOR pathway for focal epilepsy. Other important genetic mechanisms are being identified such as the key role of mosaicism and de novo mutations in both mild and severe epilepsies. Together with other genetic and epigenetic possibilities, the true complexity of the genetic underpinnings of human epilepsies is beginning to emerge.

1.2

Cellular mechanisms underlying modulation of interhemispheric inhibition by theta-burst stimulation

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Low-intensity stimulation of one cortical hemisphere inhibits the other hemisphere. This phenomenon, termed interhemispheric inhibition (IHI), is abnormal following a cortical stroke. Delivery of theta-burst stimulation (TBS) using transcranial magnetic stimulation (TMS) can potentially normalize interhemispheric balance in stroke patients. However, the results of clinical TMS studies aiming to improve motor function after stroke have been variable, and require a closer analysis of the effects of TBS on neuronal circuits. To study IHI and TBS together at the cellular level, we established an *in vivo* animal model of IHI. Our aim was to better understand the cellular mechanisms of IHI and TBS in order to inform clinical application of these protocols. We made intracellular recordings from individual pyramidal neurons in the motor cortex of urethane-anaesthetised rats, and applied TBS and IHI protocols using implanted electrodes for electrical stimulation in the contralateral hemisphere. We measured IHI of approximately 20% in our model and found that it could be suppressed by the application of contralateral TBS (trains of three stimulus pulses at 50 Hz, delivered at 5 Hz). This was effective only when delivered at low intensities, and was dependent on endocannabinoid-mediated plasticity. Further, we found evidence that low-threshold stimulation may be activating a crossed inhibitory circuit, rather than activating an interposed inhibitory interneuron. Our results suggest that TBS applied at low intensities may specifically regulate IHI, potentially by targeting a low-threshold-activated crossed pathway. These findings, if applicable to humans, may inform therapeutic strategies for TBS application to stroke.

Supported by Marsden grants from the Royal Society of NZ.

1.3

The multi-disciplinary brain recovery clinic for stroke: Results of a customer satisfaction survey

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Annually in New Zealand as many as 9000 people will suffer a stroke with up to 80% of these being triggered by an ischaemic event and 20% being due to a heamorraghic event. The chronic effects of stroke can be life changing where recovery varies significantly from person to person. In 2011 the Brain Recovery Clinic (BRC), a multi-disciplinary clinic for those who have had a stroke began. The team has a nurse coordinator, a Neurologist, Optometrist Speech and Language Therapist; Neurological Physiotherapist Rehabilitation Specialists. Referrals are mainly from Stroke Foundation Field Officer's, or General Practice. Patients are assessed clinically as well as for their potential for stroke related research programmes Attendees complete a satisfaction survey. Questions are grouped into three domains, 1. clinic facilities/reception; 2. referral process including pre clinic information 3. the BRC visit itself and summary report. Responses are rated using a 5 point scale; 1 = an unsatisfactory experience and 5 = the most satisfactory experience. The overall survey return rate is 57%. 43% sent as a retrospective mail out were returned. 82% returned their survey forms when given the survey at clinic visit. Key results are: 79% rated pre clinic information as helpful or very helpful; 72% thought their concerns were addressed satisfactorily or addressed thoroughly; and 85% said that overall their BRC visit was useful or very useful. Giving the survey to clients on the day of their clinic visit improves return rate. We conclude that the Brain Recovery Clinic is meeting a need, is well received and has been beneficial to those who have attended.

1.4

Enhancing tonic inhibition promotes post-stroke recovery

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Stroke is the common cause of death and long lasting disability in adults worldwide. Recent studies have shown that functional recovery in peri-infarct region, involves changes in brain excitability and boosting brain excitability can aid in improving motor functions after stroke. This in part involves reducing excessive GABA mediated tonic inhibition to promote functional recovery after stroke [1]. In this study, we investigated the role of zolpidem (benzodiazepine agonist with high selectivity for α1-subunit-containing $GABA_A$ receptors) in post-stroke recovery. Previous reports have shown in human stroke patients a temporary reversal in aphasia, whilst zolpidem was on board. The modulatory effects of zolpidem on both phasic and tonic GABA currents were investigated using young (2-4 months) and aged (20-24 months) mice in a photothrombotic model of focal ischemia. As reported previously, whole-cell patch-clamp recordings from brain slices prepared *ex vivo* at 3, 7, 14 and 28 days after stroke showed an increase in GABA mediated tonic inhibiton in layer 2/3 pyramidal neurons. We treated the brain slices with L-655,708 (a selective α5-$GABA_A$R inverse agonist) and saw a decrease in tonic inhibition. Treatment however with zolpidem resulted in an increase in tonic inhibition. Assessment of functional / behavioral recovery showed that zolpidem can enhance functional recovery in both the cylinder and gridwalking tasks in young and aged mice. The extent of functional recovery was most marked when treatment started 14-days post-stroke. These results extend on our previous findings and demonstrate that an enhancement in tonic inhibitory currents post-stroke rather than an inhibtion of tonic inhibitory currents can also afford an improvement in functional recovery.

[1] Clarkson, A.N., Huang, B.S., MacIsaac, S.E., Mody I, and Carmichael, S.T. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 2010 Nov 11;468(7321):305-9.

1.5

Modulating post-stroke tonic inhibition offers an extended therapeutic window for facilitating functional improvements

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Functional recovery is aided by extrinsic manipulation of neuronal excitability. Stroke results in prolonged elevation in tonic inhibition and dampening this increase in tonic GABA re-awakens silent connections and facilitates functional recovery [1]. The aim of the present set of experiments was to define the therapeutic window for treatment, using both $GABA_A$α5 or δ and $GABA_C$ receptor negative allosteric modulators. Photothrombotic stroke was induced in the mouse primary motor cortex of young (3-month) and aged (24-month) mice. Behavioral measures were assessed 1-week prior to stroking and then subsequently 1-, 2-, 4-, and 6-weeks post-stroke using both the cylinder and grid-walking task. Treatment with either L-655,708 (5mM), a selective $GABA_A$α5 negative allosteric modulator, or (S)- or (R)-ACPBPA, selective $GABA_C$ receptor (ρ-subunit) modulators (2.5-5mM) was via subcutaneously implanted osmotic minipumps. Significant forelimb deficits ($P<0.001$) were observed for at least 6-weeks post-insult on both behavioral measures. Treatment with L-655,708 resulted in improved functional recovery in both young and aged mice. Further treatment with L-655,708 starting 3-, 7- and 14-days post, but not 21-days post-stroke also affords significant gains in motor function. Assessment of motor functions following administration with either (S)- or (R)-ACPBPA results in marked functional improvements compared to vehicle-treated controls. These results extend on our previous findings and demonstrate that delayed suppression of tonic inhibitory currents out to 14-days post-stroke affords an early and sustained reversal of forelimb motor deficits after experimental stroke. In addition, functional improvements are seen following modulation of both $GABA_A$ and $GABA_C$ receptors.

[1] Clarkson, A.N., Huang, B.S., MacIsaac, S.E., Mody I, and Carmichael, S.T. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 2010 Nov 11;468(7321):305-9.

2.1

Effects of early treatment with L-Baclofen on the development of tinnitus induced by acoustic trauma in rats

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Chronic tinnitus is a debilitating condition affecting approximately 10% of the population and there are very limited drug treatment options, mainly due to a lack of understanding of the underlying mechanisms. Recently, we have demonstrated that L-baclofen, which activates inhibitory neurotransmission through $GABA_B$ receptors, dose-dependently reduced acoustic trauma-induced tinnitus in rats. In the present study, we further investigated the possibility of preventing the development of tinnitus by initiating a short period of L-baclofen treatment soon after noise trauma. Thirty-two male Wistar rats were divided into 4 groups (n = 8 per group): Sham-Vehicle, Sham-Baclofen, Acoustic trauma-Vehicle and Acoustic trauma-Baclofen. The acoustic trauma consisted of a 16 kHz, 115 dB pure tone delivered unilaterally for 1 h under anaesthesia. Vehicle or L-baclofen (5 mg/kg, s.c.) was administered at 30 min after the acoustic trauma and then once a day for 5 days. The behavioural signs of tinnitus in each rat were measured by a conditioned lick suppression paradigm at various time points after acoustic trauma. At 2 weeks after the acoustic trauma and the drug treatment, there was a significant group effect in response to 20 kHz testing stimuli ($F_{3, 26} = 3.448$, $p = 0.0311$). When tested again 10 weeks later, there was a significant group effect across all of the frequencies tested (Broad band noise, $F_{3, 26} = 3.467$, $p = 0.0305$; 20 kHz, $F_{3, 26} = 3.033$, $p = 0.0471$; 32 kHz, $F_{3, 25} = 3.168$, $p = 0.0419$). Post-hoc tests revealed that there was a significant difference between the Acoustic trauma-Vehicle group and both Sham-Vehicle and Sham-Baclofen groups. However, there was no significant difference between the Acoustic trauma-Baclofen group and the Sham groups. This suggests that early treatment with L-baclofen following acoustic trauma may provide partial prevention of the development of tinnitus in rats.

Supported by a grant from the New Zealand Neurological Foundation.

2.2

Connexin43 mimetic peptide, a new treatment for early age-related macular degeneration?

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Age-related macular degeneration (AMD) is the major cause of blindness in the elderly. There is currently no cure for AMD although several risk factors have been implicated in the pathogenesis and progression of the disease. These include oxidative stress, inflammation and vascular changes. Connexin43 (Cx43) is the most ubiquitous gap junction protein in mammals playing a role in intercellular communication. Increased Cx43 expression in the vasculature and astrocytes has been reported for many human central nervous system injuries. Light-damaged (LD) albino rats have been recognised as an animal model of AMD and were employed in the current study. Intravitreal injection of a Cx43 mimetic peptide was used to modulate the function of Cx43 hemichannels in the LD rats and the whole field retinal function was tested by electroretinogram (ERG) after treatments. A single dose Cx43 mimetic peptide treatment showed a trend toward improvement in functions of both rod and cone pathways when compared to sham-treated rats. Rats given a double dose treatment, one during LD and the second post-LD showed significant functional improvement to both rod and cone pathways compared to the sham-treated animals. Cellular analysis demonstrated that the glia-mediated inflammatory response was down-regulated in treated animals with decreased expression of glial fibrillary acidic protein (GFAP) and fewer activated microglia in the retina, and fewer macrophages in the choroid. These data indicate that modulation of Cx43 channels provides a potential target for stopping progression of AMD.

2.3

Current perspectives on Parkinson's disease: Cognition to the fore

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Our understanding of Parkinson's disease (PD) has advanced significantly from a motor disorder to one that reflects neuropathology and change to multiple neural systems, both before and especially after diagnosis. The field now recognises that cognitive change, well beyond that prescribed by dopaminergic brain systems, presents the key challenge for these patients. This change is reflected in new criteria for mild cognitive impairment and dementia, specifically in the context of PD. The ongoing PD study conducted at the New Zealand Brain Research Institute has collected data over a period of 5 years from over 184 patients, classified as either showing dementia (PD-D; now 46 patients), with mild cognitive impairment (PD-MCI; now 54 patients) or with cognition in the normal range (PD-N; now 84 patients). We summarise the value of identifying cognition in these patient groups, using longitudinal evidence on conversion to PD-D, and cross-sectional studies on brain imaging correlates from patients who have undertaken T1 MRI, diffusion MRI and perfusion MRI. We conclude that PD-MCI provides a valuable entity, but brain-cognition correlates may not conform to anticipated patterns of regional associations in PD. Beyond neuropsychological testing, suitable biomarkers are needed to discriminate those PD-MCI patients who are at imminent risk of dementia, to facilitate clinical management and improve prospects for future neuroprotective intervention.

2.4

The effects of galvanic vestibular stimulation on cell proliferation in the rat hippocampus and spatial memory

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Movement is known to increase hippocampal neurogenesis. However, since all movement activates the vestibular system, the contribution of vestibular stimulation alone to hippocampal cell proliferation and neurogenesis is unknown. In the present study this was investigated using galvanic vestibular stimulation (GVS) in anaesthetised rats. Animals were divided into three treatment groups: Sham; Cathode-left; and Cathode-right. GVS was delivered under anaesthesia via surgically-implanted electrodes in the tensor-tympanic muscles. Animals received 60 mins of GVS at 90% of their nystagmus threshold current. To study cell proliferation, animals (n = 5 per treatment) were injected with bromodeoxyuridine (BrdU; 150 mg/kg, i.p.) at 72 hs post-GVS, cardiac-perfused 2 hs later with 4% paraformaldehyde, and the brains removed. Forty µm sections were collected stereologically throughout the hippocampus, immunostained for BrdU, and the number of BrdU-positive nuclei in each hippocampus was estimated. To verify cell proliferation staining specificity, 3 sections from each animal were fluorescence-immunostained for both BrdU and Ki67 (a marker for cells in the S-phase); co-labelling for nestin (neural progenitor and stem cells) or doublecortin (DCX, immature neurons) was also investigated. The proportion of co-labelled cells was estimated for each animal. GVS significantly decreased hippocampal cell proliferation ($P \leq 0.001$); between 85-92% of BrdU-positive cells co-labelled for Ki67, with no differences between treatments, suggesting specific cell proliferation labelling. There were no significant differences in co-labelling for nestin; however, there was a significant decrease in co-labelling for DCX ($P \leq 0.05$) for the cathode-left group compared to sham controls, suggesting that the cell proliferation effects of GVS may reflect a decrease in neurogenesis. In further studies, at 72 hs, 4 weeks and 3 months post-GVS, animals (n = 8 per treatment) underwent a spatial memory task. Following 3 mins of exploration of 2 arms of a T-maze, the third arm was opened and the proportion of time spent in the novel arm during the subsequent 3 mins was calculated. There were no significant differences between treatments in the spatial memory task. These results suggest that GVS may decrease hippocampal cell proliferation and neurogenesis without affecting spatial memory.

Supported by a Marsden grant from the Royal Society of New Zealand.

3.1

Approach, avoid, or not? Trait anxiety, neuroticism and the frontal asymmetry of behavioural inhibition

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Discrete active approach and withdrawal systems have been associated with left and right frontal cortex respectively. There is also evidence for a third, right-frontal, anxiolytic-sensitive, stopping-related, Behavioural Inhibition System (BIS) with recurrent processing in the 4-12Hz range. We presented paid participants with a choice task in which net gain, gain:loss balance and net loss were visually cued. Payoff depended on the probability of delivery of fixed dollar amounts and no explicit instructions were given. Effects on the EEG of conflict were extracted as the quadratic contrast of payoff and effects of loss as the linear contrast. Consistent with links to the BIS, right frontal (F4) conflict theta power 4-7Hz) in females was positively related to reduced responding and, separately, to a factor shared by trait anxiety and neuroticism. Consistent with approach/withdrawal asymmetry, a factor unique to trait anxiety was related to loss theta power negatively at F7 in females but positively at F8 in males. We present a speculative model in which approach/advance is on the left, active avoidance/retreat is on the right and the BIS (approach-approach, avoidance-avoidance, and approach-avoidance conflict) is represented bilaterally. BIS output is postulated to decrease approach motivation on the left as well as increase active avoidance motivation on the right; while independently mediating stopping of both advance and retreat actions via right frontal medial and inferior cortex.

3.2

Memory following mammillothalamic tract lesions in rats

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Damage to the mammillothalamic tract (MTT), due to strokes, tumours or alcohol abuse, is implicated in diencephalic amnesia. This small neural pathway provides a unidirectional connection from the mammillary bodies to the anterior thalamic nuclei (ATN) and is seen as an important link that reveals a brainstem influence on the extended hippocampal system for episodic memory. Brain damage in clinical cases is, however, diffuse and the contribution of additional sites of pathology cannot excluded. Unfortunately, inconsistencies in lesion size and placement also exist in a surprisingly limited animal literature on MTT lesions. Here we made small MTT lesions in female rats (n = 6; shams, n = 14) with incomplete bilateral disconnection of the MTT, although some had substantial bilateral damage (81% to 50%). The severe working memory deficits expected for MTT rats in the water maze and cross-maze were not found and only a slight deficit in reference memory in the water maze was observed. Incomplete MTT lesions occur frequently in clinical cases, while previous research has shown that incomplete ATN lesions (50% or more) are sufficient to induce severe behavioural deficits in rats. If the MTT is as critical to memory, then incomplete but substantial bilateral disconnection would be expected to induce profound deficits in rats, at least on spatial working memory. Our results suggest that damage to the MTT alone may be insufficient to induce a memory deficit. Severe memory impairment may instead require pathology across a larger neural network including the MTT. Research is currently underway comparing larger MTT and ATN lesions to determine their relative contribution to learning and memory.

3.3

Supplementation of dairy complex lipid concentrate (DCLC) improved the memory of aged rats

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With increasing in aged population, the socio-economic impact from a decline of mental wellbeing of the elderly is escalating. Thus supplementation of functional foods for sustaining mental health in aged or even middle-aged population is desirable. The current project examined the effect of long-term supplementation of DCLC, a mixed dairy phospholipids concentrate, on memory and associated changes in vascular remodeling and neuroplasticity of aged rats. Fisher/Norway Brown rats were used. Two groups of aged rats (24 months) were fed with either gelatin-formulated DCLC or blank gelatin as the control, for 4 months. To determine age-related changes, a young group (5 months) was also fed with blank gelatin. Morris water maze test (MWM) was carried out after the supplementation and brain tissues were collected for biological analysis. During MWM tests, the aged control rats learnt to locate the platform slower than the young control rats during acquisition trials and made less entry to, more initial heading errors and more distance from the platform zone during the test trials. The aged rats were also more anxious. Without altering the learning during the acquisition trials, the DCLC supplementation improved memory by showing the reduced initial heading errors in a delayed probe trial (72 hours after acquisition). Better memory after DCLC supplementation was associated with the restoration of age-related loss of vascular density, dopamine depletion and neuroplasticity as determine by histology and analysis. The data suggested that the long-term supplementation of mixed dairy complex concentrate during the early stage of brain aging helps prevent memory decline through improving vascular-neuronal networking.

3.4

Functional relevance of gamma oscillations in schizophrenia

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An emerging literature implicates abnormalities in gamma frequency neural oscillations in the pathophysiology of schizophrenia. Prepulse inhibition (PPI) is a behavioural measure of sensorimotor gating which is disrupted in schizophrenia patients. Here we studied the relationships between both ongoing and sensory-evoked gamma frequency oscillations and PPI. The hypothesis was that elevating ongoing gamma power would lead to increased 'neural noise' in cortical circuits, mask evoked gamma responses and disrupt behaviour. Wistar rats were implanted with extradural recording electrodes. Rats received sc injection of ketamine (5mg/kg), MK801 (0.16mg/kg), amphetamine (0.5mg/kg), LY379268 (3mg/kg) or vehicle (saline) and underwent 90 minute PPI sessions and concurrent EEG measurement. The 3 psychotomimetic compounds (ketamine, MK801, amphetamine) increased the power of ongoing gamma oscillations and caused a time-matched disruption of PPI. In contrast, the mGluR 2/3 agonist LY379268 reduced ongoing gamma power, but had no significant effect on PPI. The gamma response which was evoked by the prepulse during the PPI behavioural task was reduced in animals treated with psychotomimetics, temporally matching the disruptions in PPI and the elevations in ongoing gamma power. This was most noticeable with ketamine and MK801, in which strong correlations were observed between these effects. Ketamine and MK801 increase ongoing gamma power and reduce sensory-evoked gamma power, both of which are temporally related to disruptions in sensorimotor gating. This appears to be due to antagonism of NMDA receptors, since amphetamine and LY379268 differentially impacted these outcomes and possess different receptor profiles. The abnormalities in gamma frequency oscillations in schizophrenia, if caused by NMDA receptor hypofunction, may mediate the sensor.

4.1

Perspectives on Huntington's disease: From original observations to current therapies

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Over the past 141 years since George Huntington published his paper "On Chorea", tremendous headway toward finding a cause and cure for the disease has been made. This is the 30th anniversary of finding the marker for the gene, the 20th anniversary of identifying the genetic defect and the 20th anniversary of founding the Huntington's Study Group to find new therapies. Much work remains to be done however to determine the proximal cause of cell dysfunction and death in the disease, explain the selective neuronal vulnerability in different clinical subtypes of the disease and develop effective neuroprotective therapies.

4.2

Region-specific cortical degeneration is a key component in understanding the neural basis of clinical heterogeneity in Huntington's disease

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Huntington's disease (HD) is characterised by variable symptoms and neuropathology in the basal ganglia and cerebral cortex. Our recent studies have shown that motor and mood symptoms of HD were related to pyramidal cell loss in the primary motor (BA 4) and anterior cingulate (BA 24) cortex in the HD human, respectively [1]. We have extended these studies in the same HD cases to the cortical interneurons to determine whether interneuron loss also correlates with symptom profile, and is linked to pyramidal cell loss. A double-blind study was conducted in 13 HD and 14 matched control cases using unbiased stereological cell counting methods to quantify three major types of interneurons immunoreactive for calbindin-D28k (CB), calretinin (CR), and parvalbumin (PV). Detailed data on symptomatology of HD cases was collected from family members and clinical records, and were categorised into dominant symptom groups ("motor" and "mood" symptoms) [2]. Overall, the pattern of interneuron loss showed a significant association between pyramidal cell loss and HD symptomatology. The HD cases which were dominated by "motor" dysfunction showed a significant loss of both CB+ interneurons (57% loss) and pyramidal cells (45% loss) in the motor cortex but no cell loss in the cingulate cortex. By contrast, cases with major "mood" dysfunction showed a significant major loss of all three interneuronal populations (71% loss CB+; 60% loss CR+; and 80% loss PV+ cells) and pyramidal cells (40% loss) in the cingulate cortex but no loss in the motor cortex. These findings suggest that region-specific degeneration of cortical interneurons and pyramidal neurons is a key component in understanding the neural basis of clinical heterogeneity in Huntington's disease.

Supported by Health Research Council of New Zealand; Neurological Foundation of New Zealand; Matthew Oswin Memorial Trust; Auckland Medical Research Foundation.

[1] Thu et al., Brain, 133; 2010.

[2] Tippett et al., Brain, 130; 2007.

4.3

Recovery of neurological functions in non-human primate model of Parkinson's disease (PD) by transplantation of encapsulated neonatal porcine choroid plexus cells

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Choroid plexus cells have been extensively studied as therapeutic tools in various animal models of neural damage and neurodegenerative diseases. The aim of this study was to determine the efficacy of alginate-polyornithine encapsulated neonatal porcine choroid plexus cells in ameliorating neurological deficits in MPTP-treated non-human primate model of PD. Rhesus monkeys were infused with MPTP via the right internal carotid artery to produce a lesion in the nigrostriatal pathway. After four weeks, all animals verified to have stable neurological deficits and apomorphine-induced circling (AIC) behaviour were selected for further study. Four to eight weeks after MPTP treatment, monkeys were implanted with 40 capsules containing neonatal porcine choroid plexus cells (T group, n =6) or with empty capsules (E group, n=6). In sham operated monkeys (S group, n= 3) catheters without capsules were introduced into the lesioned brains. The subjects were observed for abnormal turns and neurologic function for 6 months following the implants when the study was terminated and the basal ganglia examined by immunohistological analysis. All monkeys exhibited neurological deficits and apomorphine-stimulated asymmetrical turns prior to implantation. Following implantation, only the T group showed a significant improvement in neurological scores ($P<0.001$)and reduction in AIC scores ($P<0.001$). In the majority of the T-group monkeys, a continuous therapeutic effect was observed for at least six weeks. Histological examination indicated that striatal recovery of DA fibres correlated with behavioural improvements. Results suggest that therapeutic molecules released from neonatal porcine choroid plexus cells restore neural functions in the non-human primate model of Parkinson's disease.

4.4

Adenosine A_1 receptor signalling ameliorates noise-induced hearing loss

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Noise-induced hearing loss (NIHL) is recognized as a growing health and disability problem worldwide. We and others have shown that noise-induced cochlear injury can be reduced by administration of drugs acting on adenosine receptors in the inner ear. A selective A_1 adenosine receptor agonist, adenosine amine congener (ADAC), has emerged as a potentially effective treatment for NIHL after acute noise exposure. Here, we report a dose-dependent effect of ADAC on cochlear injury in rats and the time window for treatment after noise exposure. Increasing doses of ADAC (25–300µg/kg) were injected to Wistar rats (8-10 weeks old), 6 hours after traumatic noise exposure (8–16 kHz, 110dBSPL, 2 hours). ADAC injections were given intraperitoneally at 24-hour intervals for 5 consecutive days. Auditory thresholds were assessed before and 7 days after the last ADAC injection using auditory brainstem responses (ABR; frequency range 4-28 kHz). The optimal safe concentration of ADAC (200µg/kg) established in this study was then used for the efficacy study, in which ADAC was administered at different time intervals (12-72 hours) after noise exposure. The average ABR threshold shift in the control group was 34dB across the frequencies. ADAC diminished hearing loss at all doses. The most effective doses were 100 and 200µg/kg, which reduced average ABR threshold shifts by 19dB and 17dB respectively. ADAC (200µg/kg) reduced average ABR threshold shifts at 12 and 24 hours after noise exposure by 17dB and 16dB respectively, and by 8dB after 48 hours. The study demonstrates that ADAC provides partial protection from noise-induced cochlear injury and threshold shift up to 24 hours after noise exposure.

4.5

Sodium selenate reduces hyperphosphorylated tau and improves outcome in a rat model of repeated brain concussions

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Concussions account for the majority of traumatic brain injuries (TBI) and repetitive concussions can result in cumulative damage, long-term neurological abnormalities, and the neurodegenerative condition chronic traumatic encephalopathy (CTE). Hyperphosphorylated tau has been implicated in the pathogenesis of repeated concussion and CTE. Here we investigated whether treatment with sodium selenate, a drug that reduces the pathological hyperphosphorylation of tau by increasing the activity of the major tau phosphatase PP2A, would reduce neurodegeneration and functional impairments in a rat model of repeated concussion and CTE. After repeated mild fluid percussion injuries, or sham-injuries, young-adult male Long-Evans rats were given continuous sodium selenate treatment (1 mg/kg/day), administered via subcutaneous osmotic mini-pump, for a period of three months. Cognitive, motor, and emotional impairments were assessed at three months post-injury. Anatomical magnetic resonance imaging, diffusion weighted imaging and tractography neuroimaging methods were used to assess structural damage and axonal injury at three months post-injury. Immunohistochemical and western-blot analyses were used to assess levels of hyperphosphorylated tau and related pathologies. The results demonstrated that continuous sodium selenate treatment reduced neurodegeneration and behavioural impairments after repeated concussions in the rat. These data indicate that sodium selenate has neuroprotective effects in a rat model of repeated concussion, and may represent a novel approach to treat these injuries.

4.6

Repeated phencyclidine treatment alters arginine metabolism in rat hippocampus and prefrontal cortex

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Schizophrenia is a chronic mental disorder with prominent prefrontal and hippocampal dysfunction, and recent evidence suggests the involvement of arginine metabolism in the disease. Phencyclidine (PCP), a non-competitive N-methyl-D-aspartate glutamate receptor antagonist, induces schizophrenia-like symptoms and cognitive decline in health individuals. The present study aimed to investigate how repeated administration of a sub-chronic dose of PCP affected arginine metabolism in the hippocampus and prefrontal cortex in young adult rats. Animals were given subcutaneous injections of PCP (2 mg/kg, n=9) or saline (2 ml/kg, n=9) once daily for 12 consecutive days, and then sacrificed 2 weeks after the final treatment. The CA1, CA2/3 and dentate gyrus (DG) sub-regions of the hippocampus and prefrontal cortex (PFC) were freshly dissected out for quantification of L-arginine and its downstream metabolites using liquid chromatography/mass spectrometry and high performance liquid chromatography. We found significantly reduced L-ornithine, L-citrulline glutamine, glutamate and γ-aminobutyric acid levels in DG, and decreased agmatine and putrescine levels in CA1 and PFC respectively, in the PCP group when compared to the saline one. These results, for the first time, demonstrated that repeated PCP treatment at a sub-chronic dose altered the tissue concentrations of L-arginine and its metabolites in the hippocampus and PFC in a region-specific manner. The functional significance of these changes and the underlying mechanisms remain to be determined in the future.

5.1

Myelin deficits, with no change in the absolute number of mature oligodendrocytes, in male repeated hypoxic rats closely resembles human extreme prematurity

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Brain injury in the premature infant is associated with a high risk of neurodevelopmental disability. Previous small animal models of brain injury due to extreme prematurity typically fail to generate a spectrum of pathology and behaviour that closely resembles that observed in humans, even though they provide initial answers to numerous cellular, molecular and therapeutic questions. We tested the hypothesis that exposure of rats to repeated hypoxia from postnatal days (PN) 1-3 models the characteristic white matter neuropathological injury seen in children born extremely prematurely. Male Sprague-Dawley rats were exposed to repeated hypoxia or repeated normoxia from PN1-3. At PN13-15, the axon/myelin *g*-ratio, the shrinkage-corrected number of myelinated axons per 100μm^2 and the absolute number of glutathione S-transferase (GST)-π positive mature oligodendrocytes was quantified stereologically within the callosal periventricular white matter. Rats exposed to repeated hypoxia had a significant decrease in myelin per axon (i.e. an increased *g*-ratio) and a significant decrease in myelinated axon number, but no change in the absolute number of mature oligodendrocytes. These findings mimic abnormalities in myelin expression, without an overt loss of mature oligodendrocytes, seen clinically in extreme prematurity. When combined with our previous findings [1], this is a new small animal model of extreme prematurity that generates a spectrum of short- and long-term pathology and behaviour that closely resembles that observed in humans. This new rat model provides a clinically relevant tool to investigate numerous cellular, molecular and therapeutic questions on brain injury due to extreme prematurity.

[1] Oorschot, D. E. et al. (2013). Spectrum of Short- and Long-Term Brain Pathology and Long-Term Behavioral Deficits in Male Repeated Hypoxic Rats Closely Resembling Human Extreme Prematurity. *Journal of Neuroscience* 33: 11863-11877.

5.2

Microglia from neurogenic regions of the adult human brain are more proliferative than their cortical counterparts

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The adult human brain has two consistently neurogenic regions – the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus (Hp). These special areas contain extracellular and cellular components which are instructive for proliferation of neural progenitor cells and differentiation into neurons. Environmental cues present in different areas of the brain also regulate microglial activity. This study investigates whether environmental cues of adult neurogenic regions influence microglia phenotype. Biopsy tissue was obtained from epileptic patients (9 cases) undergoing surgery and consisted of both non-neurogenic cortical areas and neurogenic ventricular/Hp areas. Microglia were separately isolated from both regions and compared. A greater number of microglia resulted from isolation and culture of ventricular/Hp tissue than cortical tissue. This was found to be due to a greater proliferative capacity of microglia from neurogenic regions. Additionally, ventricular/Hp microglia had a greater proliferative response to the microglial mitogen Macrophage Colony-Stimulating Factor (M-CSF). This enhanced response was found to be associated with higher M-CSF receptor expression and intracellular proteins DAP12 and C/EBPβ. Microglia from the ventricular/Hp region also displayed higher expression of the receptor for Insulin-like Growth Factor-1, a molecule with some functional similarity to M-CSF. Compared to microglia isolated from the cortex, ventricular/Hp microglia had a more 'activated' phenotype of increased HLA-DP, DQ, DR protein expression, and rounded morphology. These findings show that microglia from adult human brain neurogenic regions are more proliferative than cortical microglia and have a unique protein expression profile. The data present a case for differential microglial phenotype and function in neurogenic vs non-neurogenic regions of the adult human brain.

5.3

Direct reprogramming of adult human dermal fibroblasts into neural precursor cells for in vitro disease modelling

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In an attempt to avoid ethical issues that arise from research on embryonic stem cells, the reprogramming field was born. The potential to generate induced pluripotent stem cells (iPSCs) from somatic cells was a stunning scientific breakthrough, however, low efficiency of iPS generation and complicated neural induction protocols reduce the ease of use of these cells. Using a novel direct reprogramming strategy, through plasmid transfection or lentivirus transduction of PAX6 and SOX2, our lab has directly generated induced neural precursor cells (iNPs) from adult human fibroblasts (aHDFs). Quantitative Taqman PCR of multiple iNP lines indicated upregulated expression of neuronal positional markers in iNP cells compared to aHDFs, including those of the dorsal forebrain (Gli3, Pax6, Ngn2, Emx2, Tbr2), ventral forebrain (Dlx2, Mash1, Olig2), midbrain (FoxA1, Lmx1A, Nurr1, Pitx3) and hindbrain (HoxB9), indicating a potential to generate neurons specific to different regions of the brain. Further, iNPs can be differentiated into GFAP+ astrocytes and electrophysiologically active neurons expressing TuJ1, NSE, and subtype specific markers GAD65/67, TH, calbindin and DARRP32. Our reprogramming method has direct application for 'disease modelling in a dish', as we have successfully derived TH+ disease-affected human neurons from aHDFs from a patient with Parkinson's disease. Our method can thus allow insights into disease progression, cellular mechanisms and toxicity studies not able to be examined using current models.

5.4

The functional development of the pyramidal cells in the dorsal cochlear nucleus of the mouse

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The dorsal cochlear nucleus (DCN) is a major subdivision of the cochlear nucleus (CN), which receives input from the cochlea and is thought to be involved in sound localization in the vertical plane and feature extraction of sound stimuli. The DCN has a layered structure and its main principal cell type (pyramidal cells) integrates auditory and multi-sensory inputs. Compared to the ventral CN, relatively little is known about the development of the DCN neuronal circuitry. This study was undertaken to describe the functional maturation of the DCN by measuring the electrophysiological properties of and synaptic inputs to the pyramidal cells in the neonatal mouse (P3-18). Spontaneous postsynaptic currents and evoked action potentials (APs) were recorded in these cells in acute brainstem slices. Age-dependent changes were observed including a decrease in input resistance, an increase in AP amplitude and a shortening in AP duration. These changes were significant ($p<0.05$) between P9 and P12, with only slight changes thereafter. In addition, spontaneous excitatory postsynaptic currents (sEPSC) were recorded as early as P3 while the first spontaneous inhibitory postsynaptic currents (sIPSC) were recorded at P6. However, the proportion of sIPSC recorded exceeded that of the sEPSC after P9 and reached peak frequency/amplitude by P12. The functional maturation correlated generally with the expression of excitatory (AMPA) and inhibitory ($GABA_A$ and Glycine) receptors in the developing DCN. Together, these results indicate that the basic DCN circuitry has been established before the hearing onset (P11/12), implying that they are influenced by cochlear spontaneous activity, although acoustic inputs could also play a role in refining the circuitry afterwards.

6.1

Estrous cycle plasticity in hyperpolarization-activated current is mediated by 17β-estradiol in preoptic kisspeptin neurons

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Kisspeptin is a critical regulator of the hypothalamo-pituitary-gonadal axis, via its action on gonadotropin releasing hormone (GnRH) neurons. In females, increased plasma levels of 17β-estradiol (E_2) at mid-cycle activate the GnRH neuronal network to trigger ovulation. Kisspeptin-synthesizing (Kiss) neurons located in the preoptic area (POA) of the hypothalamus are thought to integrate and convey this E_2 positive feedback to GnRH neurons in rodents. Whether E_2 positive feedback alters the electrophysiological properties of POA Kiss neurons remains thus far unexplored. Taking advantage of a mouse line expressing green fluorescent protein in Kiss neurons, we examined the electrophysiological properties of POA Kiss neurons in brain slices from ovariectomized (OVX; low E_2), diestrous (intermediate E_2) and proestrous (high E_2) female mice. Our results revealed that POA Kiss neurons express the hyperpolarization-activated current Ih. The magnitude of this current is low in OVX (low E2) mice, up-regulated in diestrous animals (mid-E2) and further elevated in proestrus (high E2). Experiments in OVX mice chronically treated with E_2 demonstrated that functional expression of Ih in kisspeptin neurons was, indeed, modulated by circulating levels of E_2. The role of Ih in POA Kiss neurons was assessed using the Ih blocker ZD7288. We found that whereas ZD7288 did not significantly alter the spontaneous firing of POA Kiss neurons in proestrus, blocking Ih had cycle stage-dependent effects on subthreshold membrane properties and on rebound firing in these neurons. Taken together, our results reveal that Ih in neurons can be modulated by circulating 17β-estradiol levels. The up-regulation of Ih in Kiss neurons on proestrus may be involved in the positive feedback mechanism triggering ovulation.

6.2

Using genetically encoded calcium indicators to study the excitability of neurosecretory nerve terminals

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Gonadotropin-releasing hormone (GnRH) neurons release GnRH peptide from their nerve terminals in the median eminence to control reproductive function. While a lot is known about the excitable properties of GnRH neuron soma and dendrites, nothing is known about the excitable properties of GnRH neuron nerve terminals. The aim of this current study was to determine the basal excitable properties of GnRH nerve terminals and investigate how synaptic inputs that impinge close to these nerve terminals regulate excitability and hence neurosecretion. To study GnRH nerve terminals, we have expressed the genetically encoded calcium indicator GCaMP3 specifically in GnRH neurons with a Cre-loxP transgenic approach. Acute, horizontal brain sections were prepared from GnRH-GCaMP3 adult mice. Live confocal imaging was then performed on GnRH nerve terminal boutons in the external zone of the median eminence. GCaMP3 imaging revealed two classes of GnRH nerve terminals boutons. One class exhibited high levels of spontaneous calcium transient activity, while the other class exhibited no spontaneous calcium transients. However electrical stimulation of the latter class evoked large calcium transients in many nerve terminal boutons. Stimulation evoked calcium transients could be blocked with local puff application of tetrodotoxin, however, spontaneous calcium transients were tetrodotoxin resistant. Low frequency electrical stimulation evoked small, but reliable calcium responses. In contrast, stimulation at 10 Hz or higher evoked large but transient calcium responses. Calcium responses could also be evoked by local puff application of glutamate. Together, these data demonstrate that GnRH neuron nerve terminals can be spontaneously active, show differential responses to electrical stimulation and possess functional glutamate receptors.

6.3

Say "NO" to Alzheimer's!
The importance of an uncommon messenger molecule shown in computational simulations

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Within the last few decades nitric oxide (NO) has been shown to play an important and unique role as an "exceptional" vaso-dilator for the neurovascular coupling (NVC) process in the human brain. NO is produced from the amino acid L-arginine and several co-factors from the enzyme family of nitric oxide sythases (NOS) that can be expressed by different cell types, importantly in endothelial cells and neurons [1] . The activation of NOS in endothelial cells (eNOS) and in neurons (nNOS) are regulated by calcium dynamics. More recent evidence suggests, however, that the expression of eNOS and nNOS can also be regulated under a number of conditions, such as neuronal activity and shear stress induced by blood flow [2]. Our research group have developed a complex mathematical model which includes all cells involved in the NVC. We believe that this is the first of its kind, leading the way to modelling the whole NVC process. The model links neuronal activation to the response in the vessel diameter via the glial cell calcium dynamics. Simulation of this process is obtained by the numerical solution of a set of differential equations describing the binding kinetics of chemicals and the rate of change of ion concentrations in and the membrane potential of the neuronal, glial and smooth muscle cells. With the implementation of the NO pathway in this model, we could show the important contribution of this uncommon biological messenger molecule within the NVC. Furthermore, we have simulated the role of NO in profoundly altered cerebrovascular function such as in Alzheimer's Disease (AD) patients. Our computational simulations provide an insight into these intricate mechanisms behind our proposal of a vicious cycle that enhances the Amyloid-*b* production within the AD pathogenesis based on impaired NO production.

[1] Calabrese, V., Mancuso, C., Calvani, M., Rizzarelli, E., Butterfield, D. A., & Stella, A. M. G. (2007). Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. Nature Reviews Neuroscience, 8(10), 766-775.

[2] Foerstermann, U., Boissel, J. P., & Kleinert, H. (1998). Expressional control of the 'constitutive' isoforms of nitric oxide synthase (NOS I and NOS III). The FASEB Journal, 12(10), 773-790.

6.4

Models of neurovascular coupling

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The brain is perfused at a variety of levels, from the whole body systemic pressure variation through the myogenic response down to that at the cortical scale commonly termed functional hyperaemia. Local neuronal activity above resting state requires an increase in tissue oxygen and glucose concentration in order to maintain the energy levels for synaptic and neuronal soma activity. Over the past decade a significant amount of experiment and theory has been presented in the neuroscience domain indicating the importance of neurovascular coupling [1]. Our research group has developed a fully coupled system starting from synaptic activitythrough astrocytic calcium and AA metabolite pathways to the smooth muscle/endothelial cell (SMC/EC) system whereby neuronal activity allows vessel dilation and contraction. The model shows a number of known and unknown aspects dependent on varying parameter states. In particular synaptic efflux of potassium and glucose elicit Ca^{2+} release from the astrocytic sarcoplasmic stores thereby mediating a BK channel at the end feet of the astrocyte. This channel supports a flow of K^+ into the perivascular space between astrocyte and SMC. The inwardly rectifying K_{IR} channel is then activated hyperpolarising the SMC and dilation occurs. Interestingly dependent on the concentration of agonist in the flowing blood the perfusing arteriolar vessel can oscillate at low frequencies (slower than the cardiac cycle). Our model provides an indication of the role of pH in hypo- and hypercapnic conditions thereby showing the effect of vaso-reactivity. Numerical simulation of this relatively complex model can now shed light on a number of pathological conditions, notably diabetes (lack of vasoreactivity), stroke (cortical spreading depression) and Alzheimer's disease.

[1] Iadecola, C., Nedergaard, M. (2007). Glial Regulation of the Cerebral Microvasculature. Nature Neuroscience, 10(11), 1369-1376.

6.5

Optogenetic stimulation of basal ganglia inputs to motor thalamus affects reaching in parkinsonian rats

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Parkinson's disease (PD) is a movement disorder characterised by dysfunctional neuronal activity throughout the basal ganglia (BG) network. The motor thalamus is strategically situated between the BG and motor cortex but how its activity is affected by pathological BG activity in PD remains unclear. However, this knowledge is critical for developing new therapies.Using optogenetic techniques, we selectively stimulated GABAergic terminals from one BG output nucleus (substantia nigra pars reticulata, SNpr) in the motor thalamus of control and parkinsonian rats by transducing SNpr neurons with the GAD67-ChR2-mCherry lentiviral vector developed in our lab. This construct causes expression of channelrhodopsin (ChR2) and mCherry fluorophore under the control of GAD67 promoter in GABAergic neurons. Rats executed a skilled forelimb-reaching task and the proportion of reaches by the dominant paw was impaired in parkinsonian rats ($p<0.0001$). Blue light stimulation of SNpr terminals in the motor thalamus with tonic patterns (9 -130 Hz) further reduced the proportion of reaches (45 ± 3% vs. 38 ± 3%, n=28 experiments, $p<0.05$) in 86% of experiments in parkinsonian rats. Conversely, preliminary data indicate that stimulating SNpr terminals with a spiking pattern previously recorded from healthy rats may increase the proportion of reaches (61 ± 1% vs. 67 ± 5%, 4/5 experiments). Our results indicate that the pattern of activity in SNpr neurons that innervate motor thalamus is critical for determining motor performance in rats, and restoring physiological patterns of activity may be sufficient to improve reaching in parkinsonian rats.

Funding from Neurological Foundation of New Zealand, Department of Anatomy Strategic Grant[1], and Department of Physiology Aim Grant[3].

Poster 7.1

A short course of fluoxetine does not enhance visual perceptual learning in healthy adults

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The selective serotonin reuptake inhibitor (SSRI) fluoxetine has been found to significantly enhance adult visual cortex plasticity in animal models. The aim of this study was to test the hypothesis that SSRIs would enhance visual perceptual learning, a well-established model of human visual cortex plasticity, in healthy adults. 20 male participants were randomized to a 3 week course of drug (20 mg fluoxetine per day) or placebo. On the first day of drug administration, a single dose of citalopram was administered rather than fluoxetine to test of acute effects of an SSRI. Psychometric functions of performance on a motion direction discrimination task were measured at baseline, 2 hours after citalopram/placebo administration and at weekly intervals for 4 weeks after the first drug dose. At each of the time points, transcranial magnetic stimulation was also used to measure phosphene thresholds, an index of visual cortex excitability. During the final 5 days of drug administration, participants were trained extensively on the motion discrimination task. Both groups showed significant learning; however there were no reliable differences between the two groups in the amount of perceptual learning, the rate of learning, the transfer of learning to an untrained stimuli, or phosphene thresholds. However, there was a tendency for the acute effects of citalopram to impair task performance relative to placebo ($p= .072$). These results from a small group of healthy adults suggest that a short course of fluoxetine does not enhance visual perceptual learning. It remains to be seen whether fluoxetine can enhance plasticity in observers with abnormal visual function.

Poster 7.2

Testing the activation–orientation account of spatial attentional asymmetries using transcranial direct current stimulation

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The general population shows an attentional bias to the left, known as pseudoneglect. This bias is thought to be driven by higher levels of activation in right parietal areas. Using transcranial direct current stimulation (tDCS) to manipulate activation, this study examined whether tDCS over the left and right posterior parietal cortices (PPC) affects pseudoneglect. Normal participants received tDCS over the left or right PPCs (15 in each group). Pseudoneglect was measured using the greyscales task, which requires a forced-choice discrimination of luminance between two opposing luminance gradients. The greyscales task was administered both before and after; (a) anodal (b) cathodal and (c) sham tDCS. Participants who received tDCS over the left PPC demonstrated pseudoneglect for the greyscales task, which was significantly reduced by anodal tDCS, but was unaffected by sham or cathodal tDCS. In contrast, for those participants who received right PPC tDCS, pseudoneglect for the greyscales task was unaffected by tDCS. Anodal tDCS, which is known to elevate neural excitation, may have overcome lower levels of activation in the left PPC, resulting in decreased pseudoneglect. These findings provide convincing evidence in support of an activation–orientation model of pseudoneglect and have implications for models of left neglect.

Poster 7.3

Attention to the front and then rotate: An ERP study of rotated object discriminations

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The process of mental rotation is thought to be required when making decisions about whether a rotated object would face to the left or to the right if imagined at the upright. Asymmetries in the response time functions for left and right facing objects indicate that successful discriminations are faster for objects that face the direction of the shortest angular rotation required. The current research investigated these asymmetries using event-related potentials. An early posterior contralateral negativity was observed, whereby amplitudes were more negative in the hemisphere contralateral to the location of the front of the object compared to amplitudes in the hemisphere ipsilateral to the front of the object ($p < 0.001$). This posterior contralateral negativity was found for both upright and inverted objects, suggesting that it reflects the directing of attention to the front of the object. Asymmetries, similar to those found in response times, were also evident in peak amplitudes and offset latencies of the late negative waveform thought to index mental rotation. It appears that the front of an object is located and this information may bias the direction in which rotation occurs so that the shortest direction is not always employed.

Poster 7.4

Repeated low-dose Δ^9-THC promotes long-term reductions in the acute neurobehavioral effects of the atypical antipsychotic risperidone

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Cannabis use is higher in schizophrenia patients than in the general population and is associated with poor treatment outcome. Few studies have examined whether cannabis reduces the effectiveness of antipsychotic drugs. The current study presents an animal model of cannabis-antipsychotic drug interactions by examining whether repeated pretreatment with the main psychoactive constituent of cannabis, Δ^9-tetrahydrocannabionl (THC), limits the acute effects of the widely prescribed atypical antipsychotic risperidone, long after withdrawal of THC. Male mice were repeatedly pre-treated with 14 daily injections (i.p.) of vehicle or a low dose of THC (0.5 mg/kg) typical of human consumption of the drug. After a 14 day washout period mice were challenged with vehicle or risperidone injection (0.3 or 1 mg/kg i.p.). Brain activation using c-Fos immunohistochemistry and behaviour in animal models of schizophrenia (prepulse inhibition of startle (PPI) and locomotor activity) was assessed. Risperidone-induced neuronal activation was attenuated by THC pre-treatment in a number of brain regions such as the ventral part of the lateral septum, the dorsomedial caudate putamen and the shell of the nucleus accumbens. Risperidone promoted PPI facilitation and locomotor suppression that was reversed by repeated pre-treatment with THC. These findings demonstrate that low, repeated doses of THC reduce the acute actions of risperidone on the brain long-after withdrawal of THC. This provides a novel mechanism for increased rates of cannabis-induced psychotic relapse and that risperidone might not be the treatment of choice for schizophrenia patients with comorbid cannabis dependence issues.

Poster 7.5

Transmembrane domain Nrg1 mutant mice show altered neurobehavioural responses to THC exposure in a conditioned place preference paradigm

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Our work in mice has shown that the schizophrenia candidate gene neuregulin 1 (*Nrg1)* modulates schizophrenia-relevant neurobehaviourals actions of cannabinoids. A recent human study showed single nucleotide polymorphisms in *NRG1* significantly increased the risk of developing cannabis dependence. To test whether the Nrg1 modulates the rewarding effects of cannabinoids, we tested male heterozygous *Nrg1* mutant (*Nrg1* HET) mice and wild type-like littermates (WT) in the conditioned place preference (CPP) paradigm for their neurobehavioural response to repeated Δ^9-tetrahydrocannabinol (THC, 5 mg/kg i.p. on alternate days, 10 days). Changes in chamber preference were assessed to elucidate the rewarding effect of THC. After which the brains were stained for ΔFosB, a marker of long-term neuroadaptive changes. A significant aversion to THC was found in the *Nrg1* HET mice that was not observed in THC-treated WT mice. Several reward and motivation related brain regions such as the dorsal lateral septum, the medial preoptic area and the medial amygdala postdorsal, showed significant differences in the number of ΔFos B positive cells. *Nrg1* mutation appears to increase the aversive nature of repeated THC exposure.

Poster 7.6

The dopamine uptake inhibitor JHW 007 blocks methamphetamine (MA)-induced locomotor activity, MA self-administration and reinstatement of MA seeking behaviour

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Illicit drug abuse and addiction is a major problem in New Zealand. Amphetamine-type drugs, more than any other class of drugs, have seen an increase in global usage since the early 1990's. The lack of approved medications for the treatment of stimulant addiction together with an increasing treatment demand drives the need for pharmaceutical intervention. With a primary focus on MA addiction, the present experiments were aimed at evaluating the therapeutic efficacy of JHW 007, a highly selective dopamine uptake inhibitor, using well-established rat models of locomotor activity, drug reinforcement, and relapse. JHW 007 was found to dose-dependently attenuate MA-induced locomotor activity and, when given as a pre-treatment, reduced MA self-administration (0.12mg/kg/infusion) without affecting responding for sucrose. However, results using a progressive-ratio schedule of reinforcement suggested that JHW 007 increased the reinforcing efficacy of both MA and sucrose. Importantly, JHW 007 was also found to significantly reduce MA seeking in an extinction-reinstatement model. Taken together, these data show that JHW 007 may have potential as an anti-abuse medication, with further investigation needed to better understand its mechanism of action.

Poster 7.7

Visual long term potentiation and directed forgetting

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Long term potentiation is a neural mechanism well associated with learning and memory. It has been identified as an increase in synaptic efficiency, following high frequency stimulation. Non-invasive induction of LTP in adult humans often involves an auditory or visual stimulus, and is measured via EEG recordings. Whilst a lot of research has been carried out regarding the role of LTP in learning and remembering, less has examined its role in forgetting. In order to investigate the role of LTP in forgetting, we chose a directed forgetting paradigm, which allows us to measure intentional as well as unintentional forgetting. Directed forgetting research often uses the item method task, where participants are presented with words one at a time, each followed by an instruction to remember or forget that word, during a 'study phase'. A recognition test follows, where participants must discriminate between 'old' words shown in the study phase, and 'new' words which were not. Test performance has shown a 'directed forgetting effect' where participants score worse for 'forget' instruction words than 'remember' instruction words. We measured EEG during the Item-method word task, intermixed with measuring visual LTP. We intend to examine if there is a correlation between the scores of the forget cued words and LTP. Preliminary results show a directed forgetting effect in the behavioural data of the majority of participants.

Poster 7.8

Effects of expertise: A functional magnetic resonance imaging study of visuospatial processing in expert musicians

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Expert musicians are regarded as an excellent model of neuroplasticity due to their early and intensive musical training. Cross-sectional research consistently identifies behavioural and neural differences between accomplished musicians and non-musicians, across a range of cognitive domains and brain regions. A smaller literature has demonstrated evidence of functional plasticity in participants learning to play a musical instrument. In this study, visuospatial processing and its neural correlates were assessed in 14 adult musicians and 13 non-musicians using functional magnetic resonance imaging (fMRI). Previous behavioural and electrophysiological research has indicated more balanced visual attention in musicians, however to date this has not been explored with fMRI. Two tests of visuospatial processing were employed: the Landmark task (a variant of a line bisection task) and a visual search task. The lateralization of activation was of particular interest, with musicians expected to have more bilateral, and non-musicians more right-sided activation. This was examined using laterality index scores and extraction of percent BOLD signal change in right-hemisphere parietal and occipital regions of interest (ROIs) taken from an independent data set, in addition to their left-hemisphere homologues. Preliminary data does not support our hypothesis, which indicates that musicians may not show functional plasticity in this cognitive domain, although more data is yet to be collected.

Poster 7.9

Effects of acute phencyclidine administration on behavioural function and brain arginine metabolism in rats

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Phencyclidine (PCP), a non-competitive N-methyl-D-aspartate glutamate receptor antagonist, induces psychotic and negative symptoms and cognitive impairment in healthy individuals that resemble clinical features of schizophrenia. The present study investigated the effects of acute PCP treatment on animals' behavioural function and arginine metabolism in the prefrontal cortex and hippocampus. Rats were given a single subcutaneous injection of PCP (2 mg/kg) or saline (2 ml/kg) and tested in the Y-maze, open field and water maze tasks 30 min post-treatment. After completion of the behavioural testing, the sub-regions of the hippocampus and prefrontal cortex were harvested to measure the enzyme activities of nitric oxide synthase and arginase, and the levels of L-arginine and its downstream metabolites (L-citrulline, L-ornithine, agmatine, putrescine, spermidine, spermine, glutamate, glutamine and γ-aminobutyric acid). PCP treated rats displayed reduced exploratory activity, increased locomotor activity, impaired spatial learning and memory, and decreased L-arginine, glutamate and glutamine levels primarily in the prefrontal cortex. Cluster analyses showed that L-arginine and its main metabolites formed distinct groups, which changed as a function of PCP. Multiple regression analysis revealed significant neurochemical - behavioural correlations. These results demonstrate, for the first time, that a single acute PCP treatment affects behavioural function and arginine metabolism primarily in the prefrontal cortex.

Poster 7.10

Behavioural relevance of retrosplenial c-Fos hypoactivation after anterior thalamic lesions

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Immediate-early gene markers of neuronal activation such as c-Fos have been previously linked to neural plasticity and learning. Previous evidence has shown that substantial c-Fos hypoactivation occurs in the retrosplenial cortex (RSC) in spite of otherwise normal neurohistology following lesions to the anterior thalamic nuclei (ATN), a brain injury associated with diencephalic amnesia. The idea that the ATN is part of an "extended hippocampal memory system" receives strong support from this observation in the RSC, but the functional relevance of this covert pathology for memory performance is unknown. In rats, spatial memory impairments after ATN lesions are ameliorated by postoperative environmental enrichment, so it is expected that c-Fos levels in the RSC might also be restored. However, previous research has failed to show a reversal of c-Fos hypoactivation in the RSC in enriched rats with ATN lesions. The previous tasks used in that context may, however, have been insensitive to the specific behavioural influences associated with RSC lesions. We will discuss the theoretical relevance of this observation and point to potential work with ATN lesions and enrichment, with behavioural tasks that are sensitive to RSC lesions, to address the current viewpoint concerning the functions of the "extended hippocampal system".

Poster 7.11

Identity-based competition in the human extrastriate visual cortex

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There is a debate concerning the manner in which the functional architecture of the ventral visual stream is organised in the recognition of objects. One longstanding view is that there are specific pools of neurons that are specialised, and even dedicated to the processing of certain object stimuli. An alternative argument is that these specialised pools of neurons are not specific to only one class of stimuli, rather a region that subserves many stimuli that share commonalities, such as visual expertise. To provide insights into this debate, our study used a competitive-based amplitude modulation technique to test the hypothesis of domain specificity versus expertise for face and word stimuli. Face and word stimuli were chosen to their dissimilarity in outward appearance and geometry, but similarity in sharing common characteristics that make them objects of human perceptual expertise. The ERP results showed evidence to suggest that faces and words were coded by disparate pools of neurons in the ventral visual stream. This was inferred through amplitude modulation and latency modulation of the N170 ERP component. The N170 for faces and words also differed in hemispheric lateralisation, with faces showing more activation in the right hemisphere, and words showing dominant activation in the left hemisphere. The study lastly discusses the use of the competition-based amplitude modulation as a technique to probe into the functional architecture of the ventral visual stream involved in object recognition.

Poster 7.12

Gene-environment interactions as a causative factor in an animal model for autism

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Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental disorder characterised by social, cognitive and behavioural deficits. Prior research suggests variants within the SLC6A4 gene, that encodes the serotonin transporter (SERT), are associated with ASD [1]. Additionally, a recent landmark article found a significant association between maternal infection in the first and second trimesters of pregnancy and ASD diagnoses in the resulting children [2]. The aim of the current research was to use a genetic rat model to investigate the interaction between these genetic and environmental risk factors for ASD. Male Wistar heterozygous SERT-knockouts and wild-type controls, treated prenatally at gestational day 10/11 with either LPS (lipopolysaccharide) or saline, were investigated using multiple social paradigms throughout their lifespan. We investigated whether social-reward-induced conditioned place preference in adolescent animals (PND 35), social approach behaviour in young-adult animals (PND 65), and preference for social odours in adult animals (PND 90+) demonstrated any gene x environment interactions. Preliminary results from both the conditioned place preference and social approach paradigms suggest no significant difference between treatment groups with regard to social behaviour and thus provide evidence against this particular genetic-environment interaction as a model of ASD. However, early results from the olfactory choice paradigm show a clear difference in time spent sniffing social odours between wild-type saline-treated animals and heterozygous LPS-treated animals. Data from this olfactory paradigm indicate that, at least in the later stages of the animals' lives, heterozygous SERT-knockouts, treated prenatally with LPS, may represent a promising model of ASD, at least with respect to a reduction in sociability.

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Poster 7.13

The Catechol-*O*-methyltransferase (COMT) gene and its implications for mental well-being

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The Catechol-*O*-methyltransferase (COMT) Val^{158}Met polymorphism (rs4680) affects the metabolism rate of prefrontal dopamine. Why both alleles (Valine [Val] and Methionine [Met]) are maintained within the human population remains a subject of debate. The 'Warrior-Worrier' hypothesis predicts that the Met allele (lower activity rates leading to higher dopamine) may lead to a cognitive advantage which is offset by affective instability, compared to the Val allele, which is related to a more stable emotional disposition (and lower dopamine availability due to higher activity rates). To test this hypothesis, 50 young adults completed a number of affective tasks, including facial emotional identification, emotional prosody and state emotional questionnaires. Viable genetic information was obtained from 48 of those, resulting in the following distribution of genotypes: 21 Val/Val, 22 Val/Met and 5 Met/Met participants. No differences between the genotype groups were found on the affective tasks, but there were differences on past use of mental health services, Kruskall-Wallis $H(2) = 11.371$, $p < .01$, and admission of past heavy drinking, Kruskall-Wallis $H(2) = 11.031$, $p < .01$. The Met homozygous group was associated with a significantly higher proportion of individuals who have accessed mental health services in the past and higher proportion of admission of heavy drinking in the past. These preliminary findings suggest that the Met allele of the COMT gene may have an effect on the mental health of an individual, which may manifest as either self-medicating behaviour (such as excess drinking) or duress severe enough to provoke seeking help from mental health professionals. This provides tentative support for the Warrior-Worrier hypothesis, otherwise not found on generic emotional identification tasks and affective questionnaires.

Poster 7.14

Optimising a biomarker for anxiety: Auditory and visual stop signals are different

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Anxiety disorders are the most common mental illness world-wide and their diagnosis is problematic. Go-stop (approach-avoidance) conflict in the Stop signal task (SST) generates rhythmic activity in the right frontal area as a result of activation of the behavioural inhibition system. Conflict rhythmicity was assessed as the difference between medium stop signal delay (SSD) power and the average of slow and fast SSD power. This right frontal conflict-specific EEG "theta" is reduced by anxiolytic drugs and so might be a biomarker for anxiety-specific processes. The SST used by [1] had an imbalance between short, medium and long trial numbers as these were sorted into 3 groups, with no clear division between them. We tested an SST with non-overlapping short and long SSDs set as a proportion of the average Go reaction time and intermediate SSDs set as before to track 50% correct stopping. Both visual and auditory stop signals have been used in the literature. So we recruited two groups of 14 participants through Student Job Search one for each stop signal. The participants first filled out BIS/BAS, EPQ-Revised, Trait and State anxiety questionnaires; and then performed the SST task while their EEG was recorded. The greater spread of SSDs produced larger conflict "theta" power as predicted, spread over wider frequency range. However, conflict theta only related to neuroticism and trait anxiety with the auditory stop signal and not with the visual one. The SST with an auditory stop signal may provide a biomarker for syndromal diagnosis of anxiety disorders.

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Poster 7.15

Reduced default mode network connectivity and autobiographical memory in mild cognitive impairment

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Individuals with mild cognitive impairment (MCI) show variable impairment in autobiographical memory function and reduced integrity in the brain's default mode network (DMN). There is overlap between the DMN, such as the medial posterior cortical hub, and brain regions that are active when participants recall autobiographical memories. To assess the association between autobiographical memory and the DMN, 14 MCI and eleven age and education-matched healthy control participants were assessed using the autobiographical memory interview (AMI) and underwent resting state *f*MRI scans. The MCI showed significantly reduced semantic as well episodic memory impairments using the AMI, evident across the lifespan for episodic memory but not for childhood semantic memory. Significantly poorer DMN connectivity, using a goodness of fit index (GOF) of the DMN template, was evident in the MCI group. A modest association between AMI semantic memory (r=0.4) scores, but not episodic memory scores (r=0.09), and DMN connectivity was found in these participants. Additional analyses will examine hubs of the DMN in this regard.

Poster 7.16

A genetic deletion in the serotonin transporter greatly enhances the reinforcing properties of MDMA in rats

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Many drugs of abuse preferentially increase synaptic dopamine (DA) but also exert effects on other brain systems that might either enhance or limit subsequent rewarding effects and abuse liability. For example, serotonin (5-HT) is generally considered to be inhibitory to DA. Therefore the ability of many drugs of abuse to also enhance 5-HT might limit reward-mediated self-administration. Accordingly, variations in drug-produced DA and/or 5-HT might explain between-subject variability in the propensity to self-administer drugs of abuse. MDMA (3,4-methylenedioxymethamphetamine or 'ecstasy') is an excellent candidate to test this idea because, unlike many other drugs of abuse, it preferentially increases 5-HT via blockade of the 5-HT transporter (SERT) and reverse transport. We show, for the first time, that rats with a genetic deletion of the SERT ($SERT^{-/-}$ rats) are much more sensitive to the reinforcing properties of MDMA. While only 55% of wild type rats met a standard criterion for acquisition of self-administration, all of the $SERT^{-/-}$ rats acquired self-administration, and acquisition proceeded with a shorter latency. Moreover, of those animals that acquired self-administration, $SERT^{-/-}$ rats produced a larger number of responses during maintenance of MDMA self-administration, and a higher breakpoint was achieved during responding under a progressive ratio schedule. Our results demonstrate that the genetic absence of a functional SERT greatly enhances the rewarding properties of MDMA and reduces the variability that characterizes self-administration of this drug. Because humans with genetically reduced SERT functioning are more vulnerable to some of the effects of MDMA, our current findings suggest that this genetic variable will enhance the sensitivity to the addictive properties of MDMA.

Poster 7.17

C-type Natriuretic Peptide in prefrontal cortex is associated with learning and memory in rodents

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C-type Natriuretic Peptide (CNP) is abundant throughout the CNS and exists in high concentration in limbic and temporal lobe structures involved in learning and memory. Previous study on CNP and memory used passive avoidance paradigms that include anxiety effects, also associated with CNP. Here, male 8-9 month old PVGc rats were trained on a continuous delayed non-matching to sample object-recognition task in Albasser's bow-tie maze, a task not associated with anxiety. One group (control/familiar) was exposed to the same set of objects throughout training, while a second group responded to a novel set of objects in each session (experimental/novel). Objects for both groups were the same on the day of sacrifice/tissue extraction, with group novel demonstrating a higher novelty discrimination index. An untrained control group was exposed to the testing environment to account for experience effects on CNP. Tissue concentrations of CNP in group novel were significantly increased in medial prefrontal cortex (mPFC; $t = 2.22$, $p = .033$) when compared to concentrations from pooled control groups (group familiar and untrained), which did not differ. No changes were found in other tissues (dorsal hippocampus; retrosplenial cortex; occipital cortex; hypothalamus). The results provide some evidence of changes in CNP during mnemonic processes, and to our knowledge this is the first study to measure CNP subsequent to a formal learning paradigm. CNP may have a role in the modulation of neuroplastic processes in limbic and temporal regions separate from anxiety based learning.

Poster 7.18

BDNF val66met polymorphism does not affect the FN400 evoked potential in human facial recognition memory

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Brain-derived neurotrophic factor (BDNF) has been shown to be an important modulator of synaptic plasticity and memory in humans. A common single nucleotide polymorphism (SNP) in the BDNF gene occurs in humans, which results in a valine-to-methionine substitution at codon 66 (val66met). This affects activity-dependent secretion of BDNF and is associated with lower performance in a variety of memory tasks. While there are various reports of behavioural differences between the genotypes (with the Val/Val variety often out performing individuals with a copy of a Met allele), it is unclear whether these differences are for all memory types, and whether or not these behavioural differences also reflect underlying neurological correlates of memory. Recognition memory is thought to involve two processes, familiarity and recollection. These processes have been shown to be functionally dissociable and show different neural activity. Recent evidence has shown that familiarity types of memory are associated with an early positive component centred on the frontal midline called the FN400. In the current study, we tested whether the val66met polymorphism was associated with electrophysiological changes in facial recognition memory. Surprisingly, results show that individuals with the met allele (Val/Met, Met/Met) did not perform any differently than Val/Val individuals. While both groups showed the characteristic FN400 results, there were no differences between the groups. This could be the result of varying levels of BDNF in distinct brain structures relating to different memory types. Future research aims to see whether these results will differ for recall types of recognition memory.

Poster 7.19

Application of source-space ICA in detection of brain connectivity

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Localizing different functional neural networks associated with a mental task is the principal aim of functional neuroimaging studies. Positron emission topography and functional magnetic resonance imaging are tools which have been applied extensively to this end. However, due to their poor temporal resolution, these methods cannot answer the question of when during the mental task the different parts of neural network become active and hence in which processing steps each part of the neural network is involved. Therefore, to investigate the temporal properties of brain networks, methods with higher temporal resolution are needed. Electroencephalography (EEG) and magnetoencephalography (MEG) measure brain electromagnetic activities with millisecond temporal resolution. Recently, we introduced source-space independent component analysis (ICA) for EEG source imaging which can detect multiple sources in a short time window (hundreds of milliseconds). In this study, we demonstrated the application of source-space ICA for detection of neural network sources associated with visually evoked potentials (ERPs). EEG from one subject with 48 visually ERPs were used. The visually ERPs was stimulated by presentation of face images to the subject. The result shows a brain network with 6 sources, with their orders, activated due to the presentation of face images. We conclude source-space ICA is a robust technique for identification, localization and time-course reconstruction of brain networks activated in a mental task for EEG and MEG signal processing.

Poster 7.20

Progress in molecular dissection of neuroinflammation in ovine Batten disease

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Batten disease is a group of devastating neurodegenerative diseases that affect children caused by mutations in a number of genes, but the underlying pathogenic mechanisms remain unclear. Immunohistochemical investigations on ovine Batten disease revealed neuroinflammation preceded neurodegeneration in a regionally specific manner. Chronic treatment with minocycline did not inhibit the neuroinflammation, indicating the need for molecular dissection of the inflammation cascade to allow targeted therapy. Selected neuroinflammatory modulators (TNF-α, TGF-β, IL-1β, IL-10, NF-ƙB, MnSOD and iNOS, TrkB and BDNF) were investigated by quantitative PCR on RNA extracted from different brain regions across the ages of disease development (2, 6, 9, 18 and 24 months). Longitudinal expression of MnSOD and iNOS was studied by immunohistochemistry on perfusion-fixed brain sections. Both pro- and anti-inflammatory cytokines (TNF-α, IL-1β, TGF-β, IL-10) were upregulated at the initiation of neurodegeneration, 4-6 months of age, prior to clinical disease and cortical atrophy evident at 10-14 months, whereas oxidative responsive genes MnSOD and iNOS were not. NF-ƙB activation followed elevation of cytokines. TrkB expression is increased at advanced disease while BDNF expression remained unchanged. PI3K signalling pathways are important for cell survival and vesicle transport, which may be defective in Batten disease. Western blots of protein from different brain regions at advanced disease revealed upregulation of phosphorylated Akt, suggesting an abnormal PI3K activity. The results show an uncontrolled neuroinflammatory pathway mediated by irregular cytokines signalling. Further investigation of the PI3K signalling cascade could lead to a better understanding of cell metabolism in pathogenesis of Batten disease.

Poster 7.21

Developing a kainic acid model of seizure-induced cardiomyopathy

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Temporal lobe epilepsy (TLE) is associated with a high incidence of arrhythmias including elevated heart rate and alterations in ventricle repolarisation. Systemic kainic acid (KA) administration is used as a model of TLE, as it induces seizures in the hippocampus before progressing to generalised seizure activity. We compared the effect of systemic (10mg/kg, sc) versus intrahippocampal (2nmol, 1 µl/min) KA on behavioural, electroencephalographic (EEG) and electrocardiographic (ECG) activity. Male Sprague-Dawley rats (320-350g) were implanted with EEG and ECG electrodes to allow simultaneous telemetric recordings during seizures. Behavioural activity was assessed based on a 0-5 point scale with EEG and ECG activity recorded for 180min following KA and periodically at 24 and 48 hours. Subcutaneous KA resulted in an immediate period of hypoactivity coinciding with elevated theta (4.75-6.75Hz) and alpha (7-12.5Hz) wave EEG activity and a reduction in heart rate of 2Poster 7.6±5.9%. As generalised seizure activity developed, heart rate increased by 33.1±7.4%. A cumulative behavioural score of 462.8±29.7 (16.2±1.7 in the control-saline group) was observed over the 180min recording period. Conversely, intrahippocampal KA produced an immediate increase in seizure behaviours (Level 3/4) with high amplitude EEG spiking and increased EEG power across all frequency bands (1.25-100Hz). This coincided with an increase in HR of 26.6±6.4% and prolonged cardiac repolarisation. Intrahippocampal KA resulted in a cumulative behavioural score of 569.8±19.2 over the 180min recording period. This study showed that systemic KA resulted in persistent seizure activity representative of status epilepticus over the 180min observation period with all values returning to baseline by the 24 hours. Intrahippocampal KA on the other hand resulted in intermittent seizure activity representative or generalised epilepsy with recurrent seizure episodes occurring up to 48 hours post-insult.

Poster 7.22

New perspectives in energy metabolism in human brain: Immunohistochemical localisation of creatine transporter and creatine kinases

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Creatine supports cellular energy metabolism in high-energy tissues such as muscle and brain. It is currently being tested in clinical trials as a neuroprotective agent in Huntington's disease (HD) and Parkinson's disease (PD). However, the distribution of the proteins that control creatine function in the brain are unclear. The objective was to characterise the distribution of the proteins which control creatine function in the human brain. Immunohistochemical staining was used for both light and confocal laser scanning microscopy to determine the distribution of the two creatine kinase isozymes (CKs) and the creatine transporter (CrT). In the normal brain, the cytosolic isoform of CK (BCK) was found predominantly expressed in astrocytes. The mitochondrial CK isoform (uMtCK) was selectively expressed in neurons – demonstrating that BCK and uMtCK are rarely expressed strongly together in the same cell. CrT was found to be variably expressed in neurons, but in the same cellular populations as uMtCK. In the human HD cortex we demonstrate that there are lower protein levels of BCK and also marked loss of both CrT-expressing and uMtCK-expressing neurons. These data indicate that cells express the creatine system proteins selectively in a manner which matches their energetic requirements. In HD brain the loss of BCK suggests that there may be a disruption in the creatine circuit within brain cells, and this may contribute to the energetic deficits seen in HD. Additionally, therapeutic supplementation of creatine in HD may be beneficial to cortical neurons which have the CrT.

Acknowledgements: HRC New Zealand; Neurological Foundation of NZ, The University of Auckland, AMRF, Freemasons NZ.

Poster 7.23

Behavioural evaluation of theta-burst stimulation after forelimb motor cortex lesion in rats

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Application of theta-burst stimulation (TBS) to the brain after stroke is a promising intervention to augment stroke rehabilitation. The aim of the present study was to evaluate the behavioural effects of electrical TBS in an animal model of stroke, and to define measures of recovery. Focal lesions were induced in the forelimb motor cortex of 18 rats by photothrombosis or aspiration (n=9 each) and an electrode implanted in the contralesional homologous motor cortex. Sham stimulation or TBS (bursts of 3 pulses at 50 Hz applied at 5 Hz) was applied intermittently (2 seconds separated by 8 seconds; total 450 pulses), or continuously (no pauses) to the electrode, to investigate the effects of TBS on recovery. The grid-walking task (measuring forelimb coordination) and the cylinder task (measuring forelimb asymmetry) were used to assess motor function. All groups exhibited coordination deficits of the affected forelimb in the grid-walking task ($P<0.001$; Repeated Measures ANOVA). This improved over 24 days, with iTBS inducing the most rapid recovery cf sham, while dysfunction persisted in the cTBS group ($P<0.05$; Repeated Measures ANOVA), suggesting the grid-walking task was sensitive to differential improvement in coordination deficits. High variability in performance prevented the detection of any differences between groups using the cylinder task. It is possible that this task is not sensitive to the deficits induced by the small focal lesions used in this study. Evaluation is ongoing of the staircase task as a measure of forelimb reaching and grasping. Preliminary results suggest that the task is able to detect objective deficits in fine motor control, however ongoing work will determine if differences between groups can be detected.

Poster 7.24

Neuregulin 1 and stress interact to trigger sensorimotor gating deficits, enhanced synaptic connectivity in the prefrontal cortex and neuroendocrine hypoactivity

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Stress has been linked to the pathogenesis of schizophrenia. Neuregulin 1 (*NRG1*), a schizophrenia susceptibility gene, modulates sensorimotor gating in schizophrenia patients, but it is unknown whether *NRG1* interacts with stress to alter sensorimotor gating and neurobiology. Here we examined whether *Nrg1* confers vulnerability to the effects of adolescent stress on prepulse inhibition of startle (PPI), blood corticosterone levels and dendritic morphology. Adolescent *Nrg1* heterozygous (HET) and wild type (WT) mice received 30 min restraint stress daily for 14 days or remained in their homecages. The mice underwent testing for PPI and anxiety-related behaviour on days 1 and 14 of stress exposure and blood corticosterone measurements were made. Golgi staining of brain tissue enabled examination of dendritic morphology. Repeated but not acute restraint stress triggered a profound PPI deficit in adolescent *Nrg1* HET mice that was not observed in non-stressed *Nrg1* HET mice or stressed WT mice. Conversely, *Nrg1* HET mice displayed greater anxiety to acute stress than WT mice, however both genotypes habituated to the effects of stress on anxiety following repeated exposure. Repeated stress selectively increased dendritic spine density in pyramidal neurons of the medial prefrontal cortex (mPFC) in *Nrg1* HET mice but not WT mice. *Nrg1* HET mice also showed a blunted stress-induced plasma corticosterone level compared to WT mice following repeated but not acute stress exposure. Partial genetic deletion of *Nrg1* confers vulnerability to stress-induced sensorimotor gating deficits, dendritic spine growth in the mPFC and a blunted neuroendocrine response in adolescence.

Poster 7.25

Microglial proliferation in alcoholics with hepatic encephalopathy

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Our group is interested in neurogenesis in alcohol-related brain damage but previously showed no differences in cell proliferation in the subventricular zone (SVZ) between chronic alcoholics and non-alcoholic controls. Interestingly one alcoholic with co-morbid hepatic encephalopathy (HE) had proliferating cells throughout the tissue adjacent to the SVZ. HE is a neuropsychiatric disorder secondary to liver failure and a common complication of chronic alcoholism. Patients suffer neurological symptoms ranging from mild cognitive dysfunction to coma and death. The HE brain is characterised by morphological glial changes but the exact pathogenesis is poorly understood. Although glial activation is common to many neuropathologies, proliferation has only rarely been definitively reported. Given the "cytokine storm" in HE we questioned whether microglial proliferation is a feature of this disease. We therefore examined fixed post-mortem human brain tissue from cirrhotic HE cases (n=9), alcoholics without HE (n=4) and controls (n=5) for proliferative and cell-specific markers using immunohistochemistry and immunofluorescence. 4/9 HE cases had proliferating cell nuclear antigen (PCNA)- and Ki-67-positive cells throughout their brain. We termed these cases 'atypical' HE (aHE). PCNA-positive cell counts were similar in grey matter (73.5 ± 49.8 cells/mm^2) and white matter (51.3 ± 27.8) and 10-fold higher than the other groups (mean =6.1 ± 6.1). These proliferating cells co-localised with the microglial marker, Iba1. As expected, Iba1-positive cell counts in aHEs (396.5 ± 111.6) was significantly higher than other cirrhotic HEs (170.7 ± 96.9;p=0.008) but not different to the non-HE alcoholics (234.0 ± 9.4;p=0.08) or controls (271.2 ± 98.5;p=0.1). As extensive microgliogenesis is rare in the human brain these findings have implications for both HE pathogenesis and our general understanding of these remarkable cells.

Poster 7.26

Construction and optimization of novel recombinant Adeno-Associated Virus rAAV2/5 for targeting microglia to regulate immune responses during neuroinflammation

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Activated microglia promotes central nervous system (CNS) inflammation through antigen presentation and secretion of pro-inflammatory cytokines and chemokines. Although this activation is necessary to protect the brain during infection, aberrant release of pro-inflammatory and/or cytotoxic factors may lead to neuronal damage and degeneration. Targeting microglia during neuroinflammation to regulate the expression of cytokines without affecting other cell types in the CNS is challenging since no specific microglial markers have yet been established that distinguish microglia from infiltrating, peripheral myeloid cells. Therefore, we propose that a viral-based gene delivery system might be a better strategy to regulate gene expression in microglia. Using the recombinant Adeno-associated virus (AAV) vector pseudotype 2/5, which preferentially infects microglia, we constructed a plasmid backbone which contains GFP under the control of the F4/80 promoter, a macrophage-specific marker. In order to demonstrate the specificity of this promoter for macrophages, we transfected human kidney cells HEK 293 cells, mouse leukemic macrophages RAW 264.7 cells and primary macrophages with the rAAV-F4/80-GFP construct or the control plasmid rAAV-CAG-GFP. Our results indicate that the rAAV-F4/80-GFP construct is selective for macrophages. To begin to assess the usefulness of this system to alter microglia function, we have cloned the Membrane Associated Ring-CH protein (MARCHI) into the rAAV-F4/80-GFP vector. MARCHI negatively regulates antigen presentation by inducing the intracellular sequestration of MHC class II. Currently, we are investigating MARCHI functionality in RAW 264.7 cells using rAAV-F4/80-GFP-MARCHI plasmid and evaluating its effect on MHC class II expression. Together this work will lead to the development of tools that will allow us to dissect the pathways by which microglia promote neuroinflammation.

Poster 7.27

A single amyloid beta$_{25-35}$ brain infusion induces long-term changes in L-arginine metabolism in the rat hippocampus and prefrontal cortex

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Amyloid beta (Ab) proteins have been proposed to play a central and causative role in the aetiology of Alzheimer's disease (AD), the most common cause of dementia among the elderly. Aβ_{25-35} is the neurotoxic domain of the full-length Aβ_{1-42}, and has been widely used to understand the toxicity of Aβ and its contributions to cognitive deficits in AD. A single intracerebroventricular (i.c.v) infusion induces AD-related pathologies and prolonged behavioural deficits. L-arginine is a metabolically versatile amino acid with a number of bioactive metabolites, and emerging evidence indicates an important role of altered L-arginine metabolism in AD pathogenesis. We have previously reported that a single i.c.v infusion of Aβ_{25-35} alters behavioural function and brain L-arginine metabolism at the time points of 6 and 42 days post-infusion in rats. The present study compared the L-arginine metabolic profiles in the sub-regions of the hippocampus and prefrontal cortex in male young adult Sprague-Dawley rats receiving a single bilateral i.c.v injection of Aβ_{25-35} (30 nmol, n = 8) or its reverse peptide Aβ_{35-25} (30 nmol, n = 8) at the time point of 97 days post-injection. There were significantly decreased levels of L-ornithine, putrescine and γ-aminobutyric acid in the prefrontal cortex, and increased spermine levels in the dentate gyrus of the hippocampus, in the Aβ_{25-35} group relative to control animals. These findings demonstrate that a single i.c.v infusion of Aβ_{25-35} can lead to long-term changes in brain L-arginine metabolism, which may contribute to the prolonged behavioural deficits induced by this toxic peptide.

Supported by the Health Research Council of New Zealand.

Poster 7.28

Within-category competition based modulation of the N170 – An ERP study

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When objects of the same perceptual category are presented at the same time, they 'compete' for attention. Evidence for this comes from studies that show that the ERP component N1 was attenuated when an object was flanked by other objects of the same perceptual category as opposed to objects from different categories, or phase scrambled control objects. An occipitotemporal event related potential (ERP) N170 has a greater amplitude when faces are viewed than other categories of stimuli tested. Some studies suggest that the eye region may drive the N170 'face effect'; however a majority of studies have failed to report modulations of the N170 that support this idea. Here, we use competition for representation – in particular, modulation of N170 amplitude, as a paradigm to explore what drives the N170 face effect. In the experiment, three categories of face stimuli (with features in-tact, eye regions removed, or all features removed) were presented on a monitor flanked by stimuli from the same category, a different category or phase scrambled control images. Although this study is still in progress, preliminary results suggest that intact faces compete less (N170 is less attenuated) with flanking faces without eye regions or features than with other intact faces. Further investigation will clarify the importance of the eye region and other features in driving the N170 'face effect' and add to our understanding of the functional organisation of human face processing in the brain.

Poster 7.29

The effect of Shh on sprouting after stroke: A neuronal tracer study in young and aged mice

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The mechanisms of neuronal reorganization and repair after stroke are not well characterized. Recent evidence has shown that a number of processes involved in neuronal development are reactivated after a stroke, including axonal sprouting. We aimed to assess the effects of sonic hedgehog (Shh), a morphogen that has been shown to play a critical role in neurogenesis and axon growth and guidance during development, on sprouting after stroke. Using an *in vivo* photothrombotic stroke model, Shh-impregnated biopolymer hydrogel was infused into the stroke cavity of young (3-month old) and aged (24-month old) C57BL/6J male mice, 5-days post-stroke. At 8-weeks post stroke the neuro-anatomical tracer BDA was injected anterior to the stroke. Brains were collected and processed 1-week after the tracer injection. Stroke induced a large sprouting response with widespread fibre staining in contralateral and ipsilateral cortex as well as in contralateral thalamic nuclei. Treatment with Shh resulted in a decreased sprouting response, as shown by reduced staining of both fibres and cells, and with staining being more localized to specific nuclei. This response was also apparent but not as clear in aged animals. These studies demonstrate that direct administration of Shh to the site of injury can alter mechanisms associated with repair i.e. axonal sprouting. However, they also suggest that post-stroke axonal sprouting may not always be positive and stroke researchers should be cautious about how to move forward in terms of stimulating a sprouting response after stroke.

The work is supported by an HRC project grant (A.N.C. and C.L.J.).

Poster 7.30

Grey matter hypoperfusion occurs in the presence of preserved grey matter structural integrity in early relapsing-remitting multiple sclerosis patients

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Grey matter (GM) abnormalities in multiple sclerosis (MS) are associated with disability and cognitive impairment. Their early detection in MS patients could prove valuable to understand long term outcomes. After segmentation using DARTEL and VBM8, we examined GM structural integrity across the entire brain (volume, using T1-weighted 3T-MRI; and fractional anisotropy (FA) and mean diffusivity (MD), using diffusion tensor imaging) and metabolic status (perfusion, using pseudo-continuous arterial spin labelling) in 25 early relapsing-remitting MS (RRMS) patients (≤ 5 years, symptom onset) and 25 age-matched healthy controls. Assessments, included neurological examination and neuropsychological tests, were performed as well. Statistical comparison of mean values for each participant was used to compare the patient versus control group using ANCOVA, covarying for age, gender and pre-morbid-IQ. There was a significant (p=0.04) decrease of GM perfusion in early RRMS patients (mean±SD: 50.6±5.8 mL/100g/min) relative to controls (54.4±7.6 mL/100g/min). There were no significant differences between control and MS patients in GM volume, FA and MD. We conclude that GM hypoperfusion, in the presence of preserved structural integrity, supports the existence of potentially reversible GM metabolic dysfunction in early RRMS. Future plans include expansion of the cohort size and a longitudinal follow-up study, to investigate the prognostic significance of the early GM perfusion deficits in MS.

Poster 7.31

Altered expression of group I metabotropic glutamate receptors in autism related ProSAP2 Shank3 mutants

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The enhanced activation of group I metabotropic glutamate receptor 5, mGluR5, have long been known as a major cause and also a target of treatment for the mental disorder, fragile X syndrome (FXS). One third of patients suffering FXS have autism and thereby, FXS is the most common known genetic cause of autism spectrum disorders (ASDs). At excitatory glutamatergic synapses, mGluRs interact with various proteins in the postsynaptic density, including the ProSAPs/Shanks. ProSAPs/Shanks are central to regulating both the function and structure of glutamatergic excitatory synapses and associate with mGluRs through Homer. Mutations in the ProSAP/Shank protein family have been identified in patients with ASDs. Here we have investigated whether the expression of Group I mGluRs is altered in neurons that express ASD associated mutations in, ProSAP2/Shank3. Rat hippocampal dissociated cultures were transfected with control (EGFP-C1), EGFP-ProSAP2-Wt, EGFP-ProSAP2-RNAi, and 4 rat ASD-related ProSPA2 mutant forms (point mutations: EGFP-ProSAP2-R87C, EGFP-ProSAP2-R375C and EGFP-ProSAP2-Q396R; frameshift mutation: EGFP-ProSAP2-InsG). Cultured neurons were then immunostained with primary antibodies against mGluR 5/1. Both density and intensity ratio of total mGluR 5/1 as well as synaptic mGluR 5/1 demonstrated significant increases (p-value < 0.005) and decreases (p-value < 0.005) when ProSAP2 was overexpressed or knock-downed. Interestingly, there were significant increases in density of mGluR 5/1 (p-value < 0.005) without any significant changes in intensity ratio when three ASD-related point mutant forms of Shank3 were expressed, while InsG mutation did not induce any significant change. The current study demonstrates the disparity between different ASD-related mutations in ProSAP2/Shank3, suggesting that altered mGluR-dependent signalling occurs in a subset of ASD-related mutations.

Poster 7.32

Neuronal activity in reticular thalamic nucleus in urethane-anaesthetized rats

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Reticular thalamic nucleus (RTn) receives information from the basal ganglia, most thalamic nuclei and the cortex. In contrast to most other thalamic nuclei, RTn contains GABAergic neurons and is thought to modulate activity relayed through the motor thalamus via reciprocal connections. To improve our understanding about how RTn neurons process information, this study characterized the neuronal activity of RTn neurons in urethane-anesthetized rats. Spike train data were recorded extracellularly using glass electrodes. Consistent with existing literature, preliminary electrophysiological data indicate that the RTn contains mainly putative GABAergic neurons (AP spike width = 0.35 ± 0.02 ms) with an overall mean firing rate of 4.4 ± 0.9 Hz (32 neurons in 6 rats). Two subpopulations of GABAergic neurons were identified based on a cluster analysis; a group with an irregular firing pattern (ISI CV 1.5 ± 0.2, n=15) displaying an average firing rate of 0.6 ± 0.2 Hz and a regular firing group (ISI CV 1.7 ± 0.3, n=17) with a mean firing rate of 7.7 ± 1.2 Hz. Furthermore, a number (n=9) of putative non-GABAergic neurons (AP spike width = 0.7 ± 0.1 ms, 8.8 ± 3.6 Hz) were identified and immunohistological staining has confirmed that a small number of neurons in the RTn are not GABAergic. These preliminary data indicate that the population of RTn neurons may be diverse, with 2 distinct populations of GABAergic neurons and a small proportion of non-GABAergic neurons. Fully characterizing the neuronal characteristics of RTn will be important for understanding its role in information processing, particularly in future studies examining its role in controlling movement.

Supported by a University of Otago Master's Scholarship.

Poster 7.33

Alterations in striatal spine morphological gene expression during L-DOPA induced dyskinesia

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L-DOPA induced dyskinesias (LIDs) affect more than half of all Parkinson's disease patients after chronic L-DOPA treatment. L-DOPA treatment appears to produce aberrant plasticity in cortical glutamatergic synapses onto the major output neurons of the striatum, the spiny projection neurons (SPN). Recent data indicates that rat SPN spine morphology changes with LIDs, altering the number and morphology of spines on striatal neurons. The Rac1 and RhoA GTPase pathways are associated with modulating spine morphology by regulating actin, and hence may be involved in LIDs. Our existing striatal dataset was interrogated for significantly differentially expressed genes related to GTPase pathways involved in spine morphology. This dataset was obtained from unilaterally 6-OHDA lesioned striatal rats treated with L-DOPA at a dose that produces dyskinesias in half the animals treated. An additional set of animals received vehicle only, thus there were three groups in the analysis: dyskinetic (D), non-dyskinetic (N), and untreated parkinsonian (P; n = 5 per group). Of the 88 differentially expressed genes in the dataset, several were related to striatal spine morphology. The Ca^{2+} protease calpain (CAPN1) was up-regulated in dyskinetic animals compared to non-dyskinetic (fold change 1.4, FDR p-value 0.00038). Calpain has been implicated in LTP formation, and could have a structural role during LIDs to produce aberrant plasticity. Myristoylated alanine-rich C kinase substrate (MARCKS), a PKC substrate that binds and cross-links f-actin, was significantly down-regulated in D v N animals (fold change 1.3, FDR p-value 0.00042). These results for Rho GTPase pathway-linked genes are being validated by qPCR. As well as these, additional genes in this pathway are currently being investigated.

Poster 7.34

PEGylated insulin-like growth factor I treatment efficacy in young and aged stroked mice

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Insulin-like growth factor-I (IGF-I) is critically involved in the maturation and maintenance of neurons, and defects in IGF-I signaling have been associated with various neurological disease conditions including stroke. The aim of the present set of studies was to investigate the efficacy of a newly developed and optimized IGF-I, whereby a 40 kDa polyethylene glycol (PEG) chain was added to lysine 68 of IGF-1 to form PEG-IGF-I. We have shown that dosing with PEG-IGF-I results in an improvement in vivo pharmacokinetics and allows for twice weekly dosing to maintain steady-state plasma levels. Using a photothrombotic stroke model in mice, we show that dosing from 3-hours post-stroke dose-dependently (0.3-1mg/kg) decreases the volume of infarction in young (3-month old) and corresponds to improved motor function on both the cylinder and grid-walking tasks. The degree of protection seen in aged (24-month old) mice was much less compared to young. To assess whether PEG-IGF-I can enhance the outgrowth of new connections, neurons (P7-9) were cultured on reactive astrocytes in the presence and absence of PEG-IGF-I. Neurons in the presence of PEG-IGF-I showed an increase in the length of the neurites, indicating that PEG-IGF-I can aid in sprouting of new connections. This data suggests a modulatory role of IGF-I in protective or regenerative processes in the nervous system, and indicates that therapeutic approaches have the best chance of success in disease conditions where PEG-IGF-1 can be given early and where the endogenous regenerative potential is still high.

Poster 7.35

Risk factors for poor outcome of a single Epley maneuver and residual positional vertigo in patients with benign paroxysmal positional vertigo

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Benign paroxysmal positional vertigo is a common vestibular disease and mainly affects the posterior semicircular canal (P-BPPV). The Epley maneuver is most commonly performed for the treatment. However, a high recurrence rate of positional vertigo after the maneuver in patients with secondary P-BPPV has been reported. We examined the efficacy of a single Epley maneuver and assessed the time course in remission of residual positional vertigo in patients with idiopathic P-BPPV and secondary P-BPPV. A total of 157 patients with idiopathic P-BPPV and 40 patients with secondary P-BPPV (secondary to head trauma in 8 patients, to prolonged bedrest in 14 patients and to inner ear disease in 18 patients) were treated with a single Epley maneuver. The negative rates of the Dix-Hallpike test on day 7 after a single Epley maneuver in both patients with P-BPPV secondary to head trauma (25%) and those with prolonged bedrest (36%) were significantly lower than that (73%) in patients with idiopathic P-BPPV. Additionally, the remission of residual positional vertigo in the former groups was significantly delayed in comparison with the latter group. However, there were no significant differences in the efficacy of a single Epley maneuver and persistent residual positional vertigo between idiopathic P-BPPV and P-BPPV secondary to inner ear disease. These findings suggest that in patients with P-BPPV, head trauma and prolonged bedrest, but not inner ear disease, are risk factors for poor outcome of a single Epley maneuver and persistent residual positional vertigo.

Poster 7.36

Criteria for parkinson's disease with mild cognitive impairment associated with increased progression to dementia

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Recently there has been an increased effort to identify patients with Parkinson's disease (PD) who are at risk of developing dementia (PD-D). PD-D has a cumulative prevalence of 75-90%, but the delay to onset varies from 2-20 years. An intermediate stage of cognitive decline has been suggested, PD with mild cognitive impairment (PD-MCI), to identify those at high risk of future dementia. A recent Movement Disorders Society Task Force (MDS-TF) to establish MCI criteria did not decide between a range of potential options and the effectiveness each criterion remains uncertain. The NZBRI PD-MCI criteria were consistent with one MDS-TF option, requiring 2 scores at -1.5SD below normative data within a single domain. Under these criteria, 40% of 40 patients who were PD-MCI at initial assessment progressed to dementia over a 2-4 years period, compared to only 6% of the remaining 87 patients who were unimpaired using these criteria (PD-U; absolute risk, 34%, RR = 6.96, $p<0.0001$). Alternate, "weaker" MDS-TF PD-MCI criteria, of one score at -1.5SD in each of two domains, were associated with 11% of the 20 PD-MCI patients progressing to dementia out of the remaining 87 patients (RR = 2.23, $p>0.3$). The higher conversion rate when using the NZBRI PD-MCI option suggests that these criteria provide a suitable representation of the intermediate stage of cognitive decline between relatively unimpaired cognition and dementia in PD patients.

Poster 7.37

Lentivirus-mediated sAPPα overexpression in an Alzheimer disease mouse model rescues the deficit in long-term potentiation

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An imbalance of amyloid precursor protein (APP) metabolism contributes to an increase in β-amyloid production and subsequently leads to Alzheimer disease (AD). A non-amyloidogenic metabolite of APP, secreted APP-α (sAPPα) that offers neurotrophic and neuroprotective effects, is also reduced in these patients. To investigate the effects of replenishing sAPPα, we developed a lentivirus to overexpress human sAPPα (from APP_{695}), and injected it bilaterally into the hippocampus of 10 month-old transgenic APPswe/PS1ΔE9 mice and B6/C3 littermate controls. Two months post-transduction, the mice were tested on a variety of behavioural tasks. They were then tested electrophysiologically for hippocampal synaptic transmission, paired-pulse facilitation (PPF), paired-pulse inhibition (PPI) and long-term potentiation (LTP). Our preliminary results showed no significant differences in the open field, elevated plus maze, Morris water maze, novel object recognition, or Barnes maze tasks. In CA1 extracellular field recordings *in vitro,* there was no significant difference in PPF, PPI or input-output curves between groups. The magnitude of LTP in the transgenic mice treated with empty vector (136.45 ± 10.0%, n=9) was significantly different ($p < 0.05$) from wild-type littermates treated with empty vector (171.5 ± 6.67%, n=11), but transgenic mice were rescued by sAPPα treatment (171.8 ± 6.9% of baseline, n=11, $p<0.05$) one hour post-theta burst stimulation. These results indicate that overexpression of sAPPα can rescue the deficit in LTP seen in this AD mouse model, even at an age when substantial amyloid plaques are observed.

Supported by a grant from the Health Research Council.

Poster 7.38

Effects of prefrontal cortex stroke on learning and memory

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Stroke is heterogeneous in its manifestation and site injury. Not only does stroke result in motor impairments, but it also results in impaired cognition and learning. One area of unexplored stroke research is the effect on learning and memory. Therefore we aimed to develop and validate a new model of stroke to assess stroke-induced learning impairments. We chose to target the prefrontal cortex of mice as it is thought to be involved in: motivation, episodic memory-like memory, decision-making and extinction associated with fear conditioning. We hypothesized that a stroke to the prefrontal cortex will result in impaired learning and memory on behavioural tasks such as novel object recognition. C57BL/6 mice were used to establish the photothrombotic stroke model with the light illumination period varying from 15, 18, 20 and 22 minutes, to optimize the size of the stroke. Mice were sacrificed at 3-days post-stroke; brains removed, processed through alcohols, embedded in wax and cut on a microtome. Eight-µm thick sections were taken every 200µm throughout the site of infarction, stained with cresyl violet, photographed and the area of infarction quantified using ImageJ. Behavioural testing was carried out at 1 and 4-weeks post stroke, using mice that had either had sham surgery or a 22-minute stroke (n=10 per group). Behavioural assessment on open field, novel object, object location and elevated plus maze are currently being analysed using the program Topscan. Data obtained to date suggests that the best model to use for photothrombotic stroke in the prefrontal cortex is 22 minutes of light illumination.

Poster 7.39

Functional relations between the vestibular system and hippocampus

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Clinical data demonstrate that people with a poor vestibular system, the sense organ of equilibrium located within the inner ear, exhibit disorders of spatial memory. Our group showed in a rodent model that the vestibular system also plays a major role in spatial memory. In addition, the spatial memory impairment in rodents with vestibular lesions appears to be correlated with structural changes in the hippocampus. This study aimed to explore the functional connections between the vestibular system and the hippocampus. Under fentanyl anaesthesia, the vestibular systems of adult Wistar rats were exposed carefully so that the sensory organs, i.e. the anterior ampulla, posterior ampulla, lateral ampulla, utricle and saccule, could be electrically stimulated selectively. Animals' eyes movements were monitored to confirm effective stimulation. The local field potential (LFP) in the hippocampus and electrocorticographic activity (ECoG) were recorded during stimulation. Thirty minutes after the last stimulation, the rats' brains were perfusion-fixed. Brain sections (60 µm) were immunolabelled for active cFos proteins. The results showed that only stimulation trains (>5 pulses, <400 µA, bipolar) can induce eye movement. However, single pulse and train stimulation induced similar LFP patterns in both the ipsilateral and contralateral hippocampus with a latency of 21.2 ± 1.1 ms (mean ± S.E.M., n=8). In addition, cFos expression was found in the posterior part of the hippocampus. Our study demonstrated electrophysiological evidence of connections between the vestibular system and the hippocampus. In the future, a 16-channel electrode array will be used to map the vestibular projections in the hippocampus.

This research was supported by the Royal Society of NZ Marsden fund, and a Marie Curie International Research Staff Exchange Scheme Fellowship within the 7th European Community Framework Programme.

Poster 7.40

The pharmacokinetics of Adenosine Amine Congener (ADAC) in plasma and inner ear

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Noise-induced hearing loss (NIHL) is a global health problem affecting up to 5% of the population. In many instances, NIHL results from acute exposure to traumatic noise. As the injury to the inner ear is mostly due to oxidative stress which continues after noise exposure, there is a brief window of opportunity to rescue cochlear tissues and prevent the hearing loss within the first 48 hours after exposure. We have shown that NIHL can be prevented by administration of drugs acting on adenosine receptors in the cochlea, and a selective A1 adenosine receptor agonist Adenosine Amine Congener (ADAC) has emerged as a potentially effective treatment for NIHL after acute noise trauma. This study investigated pharmacokinetic parameters of ADAC in rat plasma and cochlea after systemic (intravenous) and local (intratympanic) administration using reverse phase high pressure liquid chromatography (RP-HPLC). Our results show that ADAC remains stable at 37°C and no breakdown products were detected by HPLC. Both administration routes follow one-compartment bolus pharmacokinetic model with first-order output. In plasma, where the matrix effects are complex, majority of ADAC distributes in tissues and its half-life is estimated at 4.5 minutes. ADAC is capable of crossing the round window membrane of the cochlea after intratympanic injection, and the estimated diffusion rate is 2.7%. ADAC has a longer half-life of 37 minutes in cochlear fluids after intratympanic administration, and with the optimal dose, ADAC will remain in its therapeutic range for approximately 4 hours in perilymph. This study suggests that ADAC has a potential to be developed as a clinical otological treatment using both local and systemic administration routes.

Poster 7.41

The role of P2 receptor signalling in hair cell survival under stress

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Mammalian hair cells show no spontaneous or injury-induced regeneration; hence their loss resulting from environmental stress and diseases has been considered irreversible leading to permanent sensorineural hearing loss. We and others have shown that extracellular nucleotides acting via purinergic receptors (P2 receptors) regulate aspects of normal cochlear function and its response to stress. The current study aimed to determine the effect of P2 receptor signalling on survival of cochlear sensory hair cells after exposure to ototoxic aminoglycoside antibiotic neomycin. Cochlear explants were obtained from C57BL/6 mice at postnatal day 7. The explants were pre-incubated with ATP (non-selective P2 receptor agonist) or its non-hydrolysable analogue ATPγS in normal culture medium for 18 hours before exposing cochlear tissues to neomycin (1 mM) for 6 hours. This was followed by 18 hours of incubation with the normal culture medium containing ATP or ATPγS. The explants were fixed in 4% PFA, hair cells stained with Alexa 488-Phalloidin, and counted under the epifluorescence microscope. In the control explants incubated in the normal culture medium the cochleae were well preserved with minimal hair cell loss (2.27±0.35%). In neomycin-treated explants, the hair cell loss increased to 26.32±5.19%. Culture medium enriched with ATP showed no effect on OHC survival, whereas ATPγS addition to the culture medium contributed to greater loss of hair cells (36.67±12.93), suggesting a cytotoxic effect of ATPγS. This study demonstrates that ATP does not affect hair cell survival in the cochlea exposed to neomycin, however ATPγS shows significant cytotoxicity due to prolonged stimulation of P2 receptors. In contrast, ATP hydrolysis to adenosine by ectonucleotidases prevents ATP cytotoxicity.

Poster 7.42

Noise-induced inflammatory response in the cochlea

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Hearing loss is the most common sensory disability with considerable social and economic implications. Exposure to excessive noise is one of the major causes of hearing loss. Recent studies have suggested that excessive noise induces cochlear inflammation which contributes to the overall pathogenesis of cochlear injury and hearing loss. The present study examined changes in expression levels of proinflammatory cytokines, chemokines and adhesion molecules in the mouse cochlea following acute exposure to traumatic noise (24h, 100dBSPL, 8-16 kHz). Cochleae were collected from adult C57BL/6 mice at various intervals after noise exposure to assess the dynamics of the inflammatory response. Inflammatory markers in the noise-exposed cochleae were studied using immunohistochemistry and quantitative real-time RT-PCR. Increased immunoexpression of adhesion molecules was detected 1-3 days post-noise. Intercellular adhesion molecule-1 (ICAM-1) was expressed primarily by fibrocytes and endothelial cells in the inferior region of the spiral ligament, while platelet endothelial cell adhesion molecule-1 (PECAM-1) was confined to blood vessels in the spiral ligament, stria vascularis, spiral limbus and spiral ganglion. Real-time RT-PCR demonstrated markedly elevated mRNA levels of TNF-α, chemokine (C-C motif) ligand-2 (CCL2) and ICAM-1 after noise exposure. All genes displayed similar dynamics of expression, with an initial up-regulation at six hours post-noise and a second peak at seven days. These findings suggests that these cytokines and adhesion molecules initiate noise-induced inflammation in the cochlea by mediating the recruitment and extravasation of inflammatory cells, the stage associated with the development of noise-induced cochlear injury. However, the later peak in expression may be associated with reparative processes. Better understanding of the inflammatory processes and pathways may lead to pharmacological interventions to mitigate noise-induced hearing loss.

Poster 7.43

Influence of sound stress on cochlear function and endolymph electrochemistry in aging C57BL/6 mice

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Age-related hearing loss is a significant disability affecting a large proportion of the population. There is some evidence that the hearing loss is exacerbated by noise exposure, but the interaction between noise and aging on hearing is not well understood. One hypothesis is that ageing affects the tissues responsible for maintaining the essential ion concentrations in the cochlea and changes in ionic homeostasis may increase the cochlear stress with high sound stimulation. The present study aimed to determine the influence of noise stress on cochlear function and endolymph electrochemistry in ageing C57BL/6 mice. The mice (1-12m) were exposed to noise (80, 90 or 100dBSPL; 8-16kHz; 2hrs) and auditory function was measured using the auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE). The endocochlear potential (EP) and endolymph K^+ concentration were also measured. The ABR and DPOAE thresholds elevated significantly with age, most prominently at higher frequencies (16-32kHz). Noise caused an increase in thresholds which was greater in 1mth-old mice at lower frequencies than in older animals, which showed similar threshold shifts at different ages. These data indicate that younger mice may be more susceptible to noise, but that aging does not increase the susceptibility to noise exposure. Despite an observed atrophy of the secretory tissues in the cochlea with age, there was no significant difference in the EP or K^+ concentration with age, indicating that aging does not affection homeostasis in endolymph. These data suggest that the cochlea maintains the ionic homeostatic capacity with age and that aging does not make the cochlea more vulnerable to noise-induced hearing loss.

Poster 7.44

Development of a Golgi staining method for human post-mortem brain tissue to facilitate investigations into neurogenesis in Alzheimer's disease

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The Golgi staining method reveals the detailed structure of whole neurons and glia. The selective nature of the stain allows clear visualisation of individual neurons, including delicate processes and dendritic spines, without neighbouring cell processes obscuring their structure. The Golgi stain has facilitated the study of nervous tissue structure and function in mammalian tissue for over 100 years. Despite this, there have been few studies utilising this technique for human brain tissue analysis. This study aimed to develop a Golgi staining technique specifically for human post-mortem tissue to facilitate studies investigating neurogenesis in Alzheimer's disease. Modification of existing Golgi-staining methods were performed on fresh (not frozen), fresh-frozen, fixed-frozen and fresh-fixed (not frozen) human hippocampus from control, Alzheimer's disease and Huntington's Disease brains. Qualitative analysis of dendritic branching, clarity of dendritic spine staining and background crystallisation was performed and compared to that of Golgi-stained sheep hippocampus in order to determine the optimal method of tissue preparation and staining. Neurons were not successfully stained in frozen tissue, either fresh or fixed. However neuronal staining was achieved and optimised in fresh and fresh-fixed tissue. Comparison with sheep tissue showed the fresh-fixed tissue procedure produced the most reliable staining of neuronal processes and dendritic spines. The success of this staining has allowed the development of immunofluorescent Golgi-staining techniques which will enable us to assess the neurochemical properties of Golgi-stained neurons. By pairing these two techniques it will be possible to selectively assess structural characteristics of maturing neurons in the subgranular zone of the hippocampus in humans.

Poster 7.45

fMRI of the dorsal extrastriate visual cortex in children

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There is growing evidence that the dorsal visual cortical stream is particularly susceptible to abnormal development, a phenomenon known as dorsal stream vulnerability. To date, dorsal stream function in children has been measured using psychophysical tasks and visual evoked potentials. The aim of this study was to assess the feasibility of using functional magnetic resonance imaging (fMRI) to measure activity within the dorsal stream of MRI-naïve 7-year old children with risk factors for abnormal neurodevelopment (preterm birth, neonatal hyperglycaemia\hypoglycaemia). Scanning sessions included anatomical MRI, diffusion tensor imaging and fMRI protocols. During fMRI, blocks of coherent and incoherent random-dot kinematograms were presented interleaved with baseline blocks of limited-lifetime non-directional dot fields. Participants fixated on stationary images of cartoon characters presented in the centre of the screen and responded whenever a specific character appeared. The fMRI scan lasted 260 seconds. Psychophysical measures of global motion perception were performed separately in a laboratory setting. fMRI was attempted with 14 children and significant activation in dorsal extrastriate area V5 was observed in 8 children. The remaining children either lost attention or exhibited excessive head movement. These results demonstrate that fMRI of the dorsal stream is possible in some children with risk factors for abnormal neurodevelopment. Techniques such as habituation to the scanner environment may improve the proportion of successful scans.

Poster 7.46

Birthdating two cohorts of adult-born granule cells within-animal for comparisons of maturity-dependent cell excitability

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Neurogenesis occurs throughout adulthood in mammals, and the behavioural importance of these adult-born cells has been debated. Most studies of cell activity have compared adult-born neurons (4-8 weeks of age) with presumed, but not specifically identified neurons born during development. In the present study, we aimed to develop a double-labelling technique which would time-stamp new cells at 8 months and 12, 6 and 4 weeks prior to study at 10 months of age. We dated in male Sprague-Dawley rats two cohorts of new neurons in each animal by injecting one of two thymidine analogues (iododeoxyuridine (IdU) or chlorodeoxyuridine (CldU)) at the chosen time point. We then used immunofluorescence techniques to label cells for calbindin, the immediate early gene Zif/268, and the desired thymidine analogue. After exposing the animal to a novel environment for 5 minutes one hour prior to death, we examined the proportion of the early- or late-born neurons that were also "active" as indicated by Zif/268 co-labelling. We found it necessary to use highly cross-adsorbed secondary antibodies (Alexa Fluor 555 goat anti-mouse (A21424) and anti-rat (A21434)) to reduce the co-labelling of the IdU and CldU from nearly 100% to less than 6%. Preliminary results also showed a trend that neurons born at 6 weeks are twice as likely as those born at 12 weeks to be co-labelled with Zif/268 (2.04% vs 1.02%). Development of this technology will permit specific testing of the hypothesis that dentate granule cells "retire" as they age.

Supported by a grant from the Marsden Fund.

Poster 7.47

Antenatal maternal stress and the catechol-O-methyltransferase (COMT) Rs165599 polymorphism interact to influence childhood IQ

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While antenatal maternal stress has been associated with a range of adverse outcomes in offspring, there is considerable individual variation in the presence and severity of these. The Catechol-O-Methyltransferase (COMT) gene has been linked to differential susceptibility to the consequences of antenatal stress. This study examined a functional polymorphism of the COMT gene (Rs165599) in relation to maternal perceived stress and childhood cognitive performance, using data from the longitudinal Auckland Birthweight Collaborative (ABC) study. At age 11, a total of 546 DNA samples were collected from the children. The main independent variable was maternal perceived stress over the prior month, measured at birth, 3.5 and 7 years. Full-Scale IQ (FSIQ), the outcome, was measured at ages 7 and 11. The analysis revealed significant main effects of antenatal maternal stress, maternal stress at 3.5 years and maternal stress at 7 years on offspring FSIQ. A significant interaction also showed that children exposed to high maternal antenatal stress had significantly lower FSIQ scores at both 7 and 11 years of age when compared to those exposed to low stress, only when they had at least one copy of the Rs165599 G allele. At each age, this difference was of approximately five IQ points. The G allele of the Rs165599 polymorphism may confer genetic susceptibility to negative cognitive outcomes arising from exposure to antenatal stress. This finding highlights the need to consider gene-environment interactions when investigating the outcomes of antenatal stress exposure.

Poster 7.48

Perlecan domain V reduces the levels of tissue plasminogen activator in astrocyte-neuron co-culture

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The only approved pharmacological treatment for ischemic stroke is tissue plasminogen activator (tPA). tPA is a serine protease with thrombolytic activity permitting the breakdown of blood clots. Unfortunately, tPA therapy is restricted to 6hr after stroke. In fact tPA contributes to the degradation of the extracellular matrix and breakdown of the blood-brain barrier which increases brain edema. Perlecan, a heparan sulphate proteoglycan, is the most protease-sensitive matrix component and proteolysis of perlecan occurs within hours following stroke. We hypothesized that the proteolytic by-product of perlecan, domain V (DV), could inhibit endogenous tPA release as part of a proteolytic negative feedback. To that end, we measured the effects of DV, on the extracellular tPA levels in astrocyte-neuron co-culture under stress and control conditions. In stress conditions, astrocytes were mechanically stretched to render them reactive, and then cortical neurons were plated on top. Under these conditions of stress, reactive astrocytes impaired neurite outgrowth, similar to that observed for reactive gliosis in vivo. ELISA measurements of active tPA in cell culture media revealed elevated tPA levels in the stretched compared to non-stretched conditions (control = 0.99 ng/ml; stretched = 1.74 ng/ml). Administration of DV to the media resulted in a significant decrease in tPA levels in both control and stretch conditions (control+DV = 0.13 ng/ml; trauma+DV = 0.17 ng/ml). This decrease in tPA corresponds to a small increase in neurite outgrowth. DV-mediated regulation of the proteolysis is further evidence that DV may be beneficial in neuroreparative processes.

Poster 7.49

MicroRNA, miR-28-5p, is down-regulated at dentate gyrus synapses after long-term potentiation induction *in vivo*

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MicroRNA are non-coding RNA which repress translation of groups of mRNA related by target sequences. Consequently, microRNA are considered important coordinators of gene expression. Coordinated gene expression underpins the persistence of long-term potentiation (LTP), a model of memory processes. Translation of synaptic mRNA is likely to contribute to the altered synaptic proteome necessary to consolidate memory processes. As specific microRNA are synaptically-located, we propose that they are ideally suited to couple synaptic activation, translational regulation and LTP persistence. This study aimed to identify microRNA regulated at dentate gyrus synapses during LTP. LTP was induced unilaterally at medial perforant path synapses in awake adult male Sprague-Dawley rats (n=4) using high frequency stimulation. Five hours later, the dentate gyrus middle molecular layer, containing the activated synapses, was laser-microdissected from coronal cryosections. Total RNA, including microRNA, was isolated (Norgen) from matched control and stimulated tissue. MicroRNA expression was profiled using TaqMan Low Density microRNA Microarrays (TLDAs; Life Technologies). Eight normalisation strategies were compared to determine which decreased technical variance most successfully. One-sample t-tests (fold change ± 15%; $p<0.05$) were used to identify differentially expressed microRNA. TaqMan assays were used to verify predictions from TLDAs. Normalisation using miR-301b was optimal. TLDA analysis predicted regulation of eight microRNA at synapses 5 h post-LTP induction. To date, down-regulation of miR-28-5p has been confirmed using individual TaqMan assays (fold change = 0.88 ± 0.04; $p<0.05$). This is intriguing because bioinformatics predict that miR-28-5p regulates synthesis of proteins involved in synapse-nucleus communication. These results support the hypothesis that synaptic, LTP-responsive microRNA contribute to LTP persistence via regulation of the synaptic proteome.

Poster 7.50

Super resolution imaging of hippocampal synapses

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The postsynaptic density (PSD) is a dense region of protein that lies beneath the postsynaptic membrane of excitatory glutamatergic synapses. Understanding the 'molecular architecture' of the PSD scaffolding proteins may reveal whether structural changes in architecture are correlated with synaptic plasticity. Of particular interest are two N-terminal isoforms of SAP97 that are thought to regulate surface expression of glutamate receptors. However, the ~200 nm resolution limit of traditional optical microscopy has greatly complicated detailed study of protein arrangements within the densely packed PSD. Recently developed super resolution imaging techniques have overcome these limitations. We have applied a single molecule localisation method of super resolution imaging known as dSTORM to image the distribution of synaptic proteins in cultured rat hippocampal neurons. Super resolution imaging of Homer, Bassoon, α-actinin, Shank, PSD-95, and GluR1 reveals physically discernible distributions that are not resolvable with conventional optical microscopy. Transient overexpression of the SAP97 isoforms alters synapse morphology and protein distribution, a process thought to underlie synaptic plasticity. Dendritic spine morphology can be resolved using super resolution imaging of antibodies targeting transiently expressed EGFP. Our data reveal heterogeneity in synaptic protein distribution at super resolution which could dictate diverse functional roles in the PSD.

Poster 7.51

Cell proliferation dynamics in the adult sheep and human neurogenic niches

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Progenitor cell proliferation in transgenic rodent models of Huntington's disease (HD) have not reflected observations made in the human HD brain. In the subventricular zone (SVZ), animal models of HD have demonstrated no change in proliferation, while in humans there is a prominent increase in proliferation in HD cases. However, no previous study reports on proliferation in the human subgranular zone (SGZ) of the hippocampus in HD, despite numerous transgenic mouse models of HD showing decreased SGZ proliferation. Furthermore, to obtain better animal models we are developing a transgenic HD sheep; with its gyrencephalic brain it may more closely resemble the human proliferative regions compared to the rodent. In this study we examined SGZ proliferation in 14 HD and 8 normal human brains, and SGZ and SVZ proliferation in 8 normal sheep brains (4 young, 4 old) using a range of cell-cycle protein markers including proliferating cell nuclear antigen and bromodeoxyuridine in sheep. The results showed minimal proliferation in the human SGZ, comparable with previous studies on human hippocampal proliferation. Additionally, no significant difference in SGZ proliferation between normal and HD cases was observed. Like humans, the sheep SGZ is less proliferative than the SVZ and proliferation in the sheep SVZ resembles that reported in the human SVZ supporting the idea that sheep are a good model of progenitor proliferation in humans. Moreover, due to the rarity of proliferation in the human hippocampus, hippocampal plasticity in humans may not primarily involve cell proliferation.

Poster 7.52

C/EBPδ expression in human brain glial cells

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The transcription factor C/EBPδ contributes significantly to the innate immune response and associated inflammation through the induction of pro-inflammatory gene expression. Whilst this pro-inflammatory nature of C/EBPδ has been studied in several organ systems the role of the transcription factor in the human brain and associated neuroinflammation remains unclear. Previous studies have identified C/EBPδ expression in rodent brain glial cells (microglia and astrocytes); however, significant differences exist in their inflammatory response when contrasted with humans. We therefore sought to examine the expression of C/EBPδ using primary mixed glial cultures obtained from human biopsy tissue. We show here that C/EBPδ displays a low basal expression in primary human glial cultures. However, nuclear expression of C/EBPδ was strongly induced by immunogenic stimuli including the inflammatory cytokines TNF-α, IL-1β and IFN-γ and the bacterial component LPS. With IL-1β this induction was concentration-dependent starting at the pg/mL range. Consistent with rodent literature, a significant induction of C/EBPδ in astrocytes was observed. C/EBPδ expression in human microglia however remained largely unchanged, which differs from previous work in rodents. We also identified a significant induction of C/EBPδ in pericytes, a cell type responsible for cross-talk between cerebral and peripheral inflammation and shown to be immunoactive in culture. Using RNAi techniques the IL-1β induced expression of C/EBPδ can be attenuated allowing for further studies to identify the functional role of C/EBPδ induction following inflammatory responses in these mixed human glial cultures.

Poster 7.53

Disruption of MDMA-produced reinforcement following forced abstinence

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Extended MDMA self-administration produces dose- and time-dependent reductions in various indices of 5HT neurotransmission. In particular, tissue levels of 5HT were decreased following 5 days, but not 14 days, of withdrawal (Do & Schenk, 2011). Because 5HT is inhibitory to self-administration and because MDMA preferentially increases 5HT, we have suggested that MDMA self-administration is initially inhibited by the pronounced increase in synaptic 5HT. As self-administration progresses, substantial deficits in the 5HT response are produced and we have hypothesised that this underlies the development of reliable self-administration. If so, then MDMA self-administration should decrease following a 14 day withdrawal from the drug when 5HT levels have been restored. To test this idea, we measured MDMA self-administration prior to, and following, a 14-day withdrawal period.The initial self-administration phase continued until a total intake of 165 mg/kg MDMA was reached (mean number of days to meet criterion=26.46, range=19-34). The group was then split into two subgroups: one group remained in the home-cages for 14 days before recommencing MDMA self-administration; and another group continued to self-administer MDMA. Responding over days was stable for the group that continued to self-administer MDMA but responding from the group that underwent forced abstinence for 14 days decreased and then increased to baseline rates within 9 days. These data are consistent with the idea that MDMA-induced increase in 5HT is inhibitory to MDMA self-administration.

9.1

Activation of trace amine-associated receptor 1 prevents relapse to cocaine seeking

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Addiction to cocaine is a major burden to society worldwide and its treatment remains an important challenge. The availability of pharmacotherapies is limited and, to date, there is no pharmacological agent that appears to be effective for the treatment of cocaine dependence. The trace amine-associated receptor 1 (TAAR1) has emerged as a promising target for medication development in addiction due to its ability to regulate dopamine (DA) function. Here, we tested in rats the efficacy of RO5203648 and RO5256390, partial and full TAAR1 agonists, respectively, in models of cocaine relapse. Using a model of context-induced relapse, both RO5203648 and RO5256390 dose-dependently blocked cocaine seeking after a 2-week period of withdrawal from chronic cocaine self-administration. In a model of extinction-reinstatement, RO5203648 was able to inhibit cocaine-primed reinstatement of cocaine seeking. At "therapeutic" doses neither RO5203648 nor RO5256390 altered responding for a natural reward, suggesting that the agonists spared motoric and motivational function. Fast-scan cyclic voltammetry data showed that RO5203648 prevented cocaine-induced DA overflow in slices through the nucleus accumbens, but did not alter DA half-life, suggesting that the partial agonist blocks cocaine-stimulated DA overflow by mechanisms other than direct interference with DA uptake. Taken together, these data provide strong evidence in support of TAAR1 pharmacological agents as leads for the treatment of cocaine addiction.

9.2

Identifying cellular changes in the reward system following methamphetamine self-administration in rats using a multi-omics approach

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Drug addiction is a chronic, relapsing brain disorder where a user continues to seek and take drugs despite a range of known adverse consequences. Addiction involves changes to epigenetics, mRNA, microRNA (miRNA), neurotransmitters, and protein expression. The detail of the molecular aspects that regulate the transition between the controlled intake of drug and uncontrolled intake distinguishing addiction is not completely understood. Our study focused on the ventral tegmental area (VTA), which is a brain region that contains dopaminergic cell bodies and is required for a number of addiction-related behaviours. We performed microarray analysis on the VTA of rats that had undergone methamphetamine self-administration followed by 14 days of abstinence. A total of 78 significantly different miRNA and 49 differentially-expressed mRNA were identified, which are related to neuroplasticity, neuroprotection, oxidative stress and drug addiction behaviours. In addition, the work performed in this area has some links to previous proteomics work done in another region of the reward system, the striatum. The proteomics work identified 27 differentially-regulated proteins in striatal synaptosomes, which are involved in cytoskeletal rearrangement, cell signalling and neuroprotection. Unravelling the molecular complexity of drug addiction using a relevant behavioural model is likely to allow for better design of addiction pharmacotherapies, as well as identify individuals with increased vulnerability to drug addiction.

9.3

Behavioural and cellular effects of AL-1-99, a novel kappa opioid receptor agonist

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Psychostimulant abuse is a serious health and social problem throughout the world, particularly in New Zealand. The use of amphetamine type stimulants in Australia and New Zealand is much higher than the rest of the world (2 - 2.7% compared to the global average of 0.7 - 1.3%; UNODC 2013). Development of pharmacotherapies to treat addiction is of global significance as there are no current FDA approved therapies for psychostimulant abuse. With the aim of furthering research into novel pharmacotherapies to treat drug addiction, we tested a novel kappa agonist AL-1-99 for its ability to reduce reinstatement of extinguished cocaine-seeking in rats. We found that AL-1-99 (1 mg/kg) significantly reduced cocaine-primed reinstatement of drug seeking compared to the vehicle ($p<0.05$) and these effects were reversed by kappa antagonist nor-BNI. The effects of AL-1-99 on dopamine transporter function were also investigated using a cellular model. AL-1-99 showed a significant increase in dopamine transporter function at 10 µM ($p<0.05$), which may contribute to the anti-addictive properties of this kappa agonist. Using HEK-293 cells and Western blotting, we studied the possible pathways via which kappa agonists signal and discovered that AL-1-99 (10 µM) significantly activated the mitogen activated protein kinases/extracellular regulated kinases (MAPK/ERK) pathway after 10 min ($p<0.05$). Findings from this ongoing study will provide more information on the behavioural and molecular action of novel kappa opioid receptor agonists, which may be useful to develop effective pharmacotherapies.

9.4

Tobacco particulate self-administration in rats: A role for non-nicotinic constituents in tobacco dependence

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Nicotine self-administration in rats is the most widely used animal model of tobacco dependence. There is increasing evidence, however, that non-nicotinic constituents in tobacco smoke contribute to addiction and that different tobacco products contain varying levels of these constituents. The present study firstly sought to compare self-administration of pure nicotine to tobacco particulate matter (TPM) to determine if there were differences in reward-efficacy attributable to the non-nicotine constituents. Secondly, cigarette and roll-your-own (RYO) TPM groups were included and compared to determine whether different formulations of non-nicotinic constituents could impact reward. Briefly, male Sprague Dawley rats were implanted with indwelling jugular catheters for self-administration (n=76). The reinforcing efficacy of infusions of nicotine (0.0 or 30.0µg /kg/inf) versus cigarette/RYO TPM (with matched nicotine content) were determined using spontaneous acquisition of self-administration on a fixed ratio (FR) schedule. The progressive ratio (PR) schedule was then employed to determine the motivation to receive each drug and within subjects dose-response curves were also produced (7.5, 15.0, 30.0 and 60.0µg/kg/inf nicotine). The main finding was that the RYO TPM was more reinforcing and produced a different profile of reward-related behaviour compared to both the nicotine and cigarette TPM groups. The conclusions were that non-nicotinic components have a role in tobacco dependence and that some tobacco products could have higher abuse liability, irrespective of nicotine levels.

9.5

MDMA self-administration attenuates the adipsic effect of a 5-HT$_{1b}$ agonist in rats

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MDMA is a preferential serotonin (5-HT) releaser and many behavioural effects of the drug have been attributed to serotonergic mechanisms. Repeated exposure to MDMA causes a number of neuroadaptations that might explain changes in the drug response. Among the changes that might be expected to occur are alterations in the sensitivity of various receptor subtypes. This study investigated effects of exposure to MDMA via self-administration on 5-HT$_{1b}$ receptor mechanisms. The 5-HT$_{1b/1a}$ agonist, RU 24969, dose dependently decreased water consumption in drug naïve rats. This effect was reversed by the administration of the 5-HT$_{1b}$ antagonist GR 127935 but not the 5-HT$_{1a}$ antagonist WAY 100635. Following the self-administration of MDMA or cocaine the effect of RU 24969 on drinking was measured. The response to RU 24969 was attenuated following self-administration of MDMA but not cocaine. These data suggest a selective impairment of the 5-HT$_{1b}$ receptor as a result of exposure to MDMA.

10.1

Towards dementia prevention by activating cognitive lifestyles

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Cognitive lifestyle refers to lifelong patterns of complex mental activity – a challenging concept to measure. We developed and validated the *Lifetime of Experience Questionnaire* (LEQ) as a way of quantifying individual differences in cognitive lifestyle amongst older cognitively intact persons. In collaboration with several population-based cohorts, we are beginning to build a picture of what is a 'normal' cognitive lifestyle amongst older Australians, British and French individuals. In addition, we have shown that a more active cognitive lifestyle is not only associated with reduced risk for long term incident dementia, but also with increased chances of cognitive recovery from mild cognitive dysfunction to normal cognition. Further data supports the idea that cognitive lifestyle leads to a compression of cognitive morbidity, with important socioeconomic and health implications. What could be the biological basis for this protective effect? By combining *in vivo* neuroimaging and *post mortem* histological analyses we are starting to understand the cumulative effect of multiple potential disease-modifying, neuroplastic and neuroprotective processes – mechanisms that may ultimately help prevent or delay dementia. From a health prevention perspective, our group has also now carried out two major randomized clinical trials that attempt to translate these insights into effective cognitive lifestyle interventions. New results from the Timecourse Trial will be presented, indicating that it is indeed possible to protect and enhance cognitive function in older at-risk individuals.

10.2

Altered expression of plasma microRNA in sporadic Alzheimer's disease

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Alzheimer's disease is a progressive neurodegenerative disorder with the underlying pathological changes occurring in the brain years before the characteristic symptoms of memory loss become acknowledged by the individuals afflicted by the disease and their families. There is a pressing need to be able to predict the onset of the Alzheimer's disease process, to allow appropriate therapeutic interventions to be carried out before damage to the brain becomes irreversible. The aim of this work was to determine if altered levels of microRNA in blood plasma might act as a marker of for the disease process potentially allowing early detection of Alzheimer's disease. Here we have profiled the expression of plasma microRNA in Alzheimer's-affected (n=9) and gender and aged-matched elderly participants (n=12). Using TaqMan Low Density Arrays (TLDAs) we were able to reliably detect 156 microRNA (Ct <33, present in all samples). Following data normalisation, using the 3 most invariant microRNA (as determined by "Normfinder"; HTqPCR package), differentially expressed microRNA were identified using unpaired *t*-tests and *p*-values adjusted using the Benjamini and Hochberg procedure to control for false discovery. Following this procedure 3 microRNA were identified as upregulated in the Alzheimer's group. These promising early studies indicate that the Alzheimer's disease process may be reflected in altered microRNA levels in blood plasma.

Supported by a grant from the Health Research Council.

10.3

Where the papers meet the patient

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People newly presenting to a clinic come with no diagnostic label, but a wish for help, insight, prognosis and comfort, among many things. Their loved ones (or not so loved ones) add a further dimension to the situation. The clinician comes to clinic with a wide range of knowledge, experience and preconceived ideas. Somehow they come to an agreement and settle on a plan. So where does the scientist fit in? Integration of preclinical and clinical science is actually in the clinic, and without scientists the art of medicine takes over but soon runs out of momentum. I will outline some of the more important challenges that face the clinical side of Alzheimer's and other dementias. As time allows we will touch on how prodromal Alzheimer's disease has become of particularly topical, and include any recent snippets of information from the AAIC meeting in Boston, July 2013. The practical implication of these will be explored. An outline of the Recent National Framework for Dementia Care will be touched on, and where the scientific community may have a part in this.

10.4

Altered arginine metabolism in Alzheimer's brains

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss with aging as a major risk factor. L-arginine is a metabolically versatile amino acid with a number of bioactive metabolites, and altered arginine metabolism has been implicated in AD pathogenesis. This study, for the first time, systematically determined the arginine metabolic profiles in the superior frontal gyrus in normal cases with an average age of 60 or 80 years and in AD cases with an average age of 80 years, using enzyme assays, Western blot, liquid chromatography mass spectroscopy and high-performance liquid chromatography. We found significantly reduced activity and protein expression of nitric oxide synthase, and increased arginase activity and arginase II protein expression in the AD group relative to the two control groups. The level of L-ornithine was dramatically decreased in the AD group only, accompanied with increased L-arginine and glutamine levels. There were also AD- and age-related reductions in the agmatine, putrescine and spermidine levels, with no significant changes in L-citrulline, spermine, glutamate and γ-aminobutyric acid. Cluster analyses revealed that L-arginine and its downstream metabolites formed distinct groups, which changed differentially as a function of advanced aging or AD. These findings demonstrate dramatically altered arginine metabolism in the superior frontal gyrus of AD brains, which supports the prominent role of arginine metabolism in AD pathogenesis.

Supported by the Health Research Council of New Zealand.

10.4

Genetic approaches to dissecting Alzheimer's disease

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A small proportion of Alzheimer's disease (AD) is attributable to several well-defined mutations in genes known to be involved in amyloid beta production. The remainder of AD cases have a largely unknown genetic background that is partially defined by a small number of variations in 'risk factor' genes. It is likely that further genetic abnormalities associated with AD are yet to be identified. In this seminar I will present current work from our lab investigating somatic mosaicism of aneuploid cells in the AD brain. I will then describe our other research using C. elegans as a model to investigate the interaction between amyloid beta and polyglutamine proteins. Finally, I will look to the future of AD research in our lab.

11.1

Glutamate receptors and synaptic plasticity in health and disease

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We are interested in identifying some of the signalling cascades that are activated by NMDARs and result in AMPAR internalisation during LTD in the hippocampus. First we identified a role for the ser/thr kinase, glycogen synthase kinase-3 beta (GSK-3β). We found that it was activated by a protein phosphatase cascade that led to dephosphorylation of ser9 by protein phosphatase 1 (PP1) and that this activation was required for LTD [1]. We also found that during LTP, the activation of PI3K and Akt resulted in phosphorylation of ser9 to inhibit GSK-3β and that by this mechanism LTP is able to inhibit LTD. Since GSK-3β is implicated in Alzheimer's disease (AD) and since cognitive decline and a loss of synapses is an early feature of AD we wondered whether this disease might be triggered by a dysregulation of GSK-3β leading to excessive LTD and synapse elimination. As an initial test of this hypothesis, we examined the ability of a GSK-3 inhibitor to restore the Aβ-induced inhibition of LTP. Consistent with this idea, we found, in two-input experiments, that the selective inhibitor CT-99021 could reverse the LTP deficit. If AD is indeed caused by aberrant LTD, then it may be possible to relate other hall mark features of the disease, such as caspase activation, gliosis and the hyperphosphorylation of tau, to LTD mechanisms. As a first step, we are now trying to identify other components of the LTD cascade. These will be discussed.

[1] Peineau S, Taghibiglou C, Bradley C, Wong TP, Liu L, Lu J, et al. (2007). *LTP inhibits LTD in the hippocampus via regulation of GSK3beta.* Neuron. 53: 703–17.

11.2

Alterations in synaptic function and plasticity in neurons expressing Autism-associated mutations in Shank3

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Autism Spectrum Disorders (ASD) are a set of neurodevelopmental disorders characterised by impaired communication, social behaviour, learning difficulties, as well as by repetitive or stereotyped behaviours. Mutations in multiple genes have been linked to autism and many of these encode proteins that are found at excitatory glutamatergic synapses. We have focussed on the Shank family of proteins (Shank1, Shank2 and Shank3), which are highly expressed within the hippocampus and cortex. Shank proteins have emerged as central regulators of postsynaptic function, interacting via their multiple binding domains to a large number of postsynaptic molecules including glutamate receptors, structural proteins and the actin cytoskeleton. ASD-mutations have been reported in all Shank proteins, e.g. multiple point mutations and several copy number variations have been identified in the Shank3 gene in patients with ASD. Our data show that ASD-associated mutations in Shank3 result in significant weakening of glutamatergic synaptic transmission between neurons. This is caused both by a decrease in AMPA and NMDA receptor-mediated currents and a presynaptic decrease in glutamate release. These Shank3 ASD mutations disable Shank3 from signalling across the synapse via the trans-synaptic complex formed by presynaptic neurexin and postsynaptic neuroligin. Neurons expressing Shank3 ASD-associaited mutations are also unable to undergo long-term potentiation (LTP), the cellular correlate of learning and memory. These data indicate that ASD-associated mutations in a subset of synaptic proteins may target core cellular pathways that coordinate the functional matching, maturation and plasticity of excitatory synapses in the central nervous system.

11.3

Regulation of microRNA following induction of long-term potentiation *in vivo*

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MicroRNA are small noncoding RNA that can function as coordinators of the expression of groups of genes. This occurs through microRNA recognition of specific seed sites within target mRNA, and results in translation arrest or mRNA degradation. Coordinated regulation of protein synthesis and gene expression is essential for the consolidation of long-term potentiation (LTP), a well-accepted model of the memory mechanisms. Interestingly, recent studies have suggested that LTP induction results in regulation of the levels of specific microRNA, suggesting that they may contribute to the regulation of the LTP-induced gene response. As LTP induction promotes a rapid generalised rapid up-regulation of gene expression, we predicted that there might be a concomitant rapid down-regulation of microRNA levels. Accordingly, we carried out global microRNA expression profiling in the rat dentate gyrus 20 min following LTP induction. We found that the majority of differentially expressed microRNA were down-regulated. Further analysis of selected plasticity-related microRNA, miR-34a and miR-132, revealed that the down-regulation was specific to these early time points and that blockade of the NMDA subtype of glutamate receptor not only prevented the down-regulation but released an activity-associated inhibitory mechanism. Furthermore, we found that the pri-miR-132 transcript was dramatically up-regulated, suggesting that the observed down-regulation of mature miR-132 occurred solely by post-transcriptional mechanisms. As bioinformatics analysis highlighted AMPA, NMDA as well as metabotropic glutamate receptors subunits as putative targets of miR-34a and miR-132, it appears that these and other microRNA make a surprisingly rapid contribution to synaptic plasticity mechanisms via dis-inhibition of translation of key plasticity related molecules.

Supported by grants from the University of Otago Research Committee.

11.4

Altered hippocampal function in the maternal immune activation model of schizophrenia

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Individuals with schizophrenia display a number of structural and cytoarchitectural alterations in the hippocampus. It is currently unclear how these changes affect hippocampal function. Alterations in hippocampal activity could, for example, affect memory processes and disrupt hippocampal representations of the environment and so account for some of the cognitive symptoms of schizophrenia. Changes in neural activity in the hippocampus could also have downstream effects, resulting in a dysregulation of dopamine systems. Our goal was to determine whether environmental risk factors that have previously been associated with schizophrenia produced changes in hippocampal synaptic plasticity, spatial representations, and associated memory processes, using the maternal immune activation (MIA) animal model. To induce this model, pregnant rat dams were administered either the viral mimic Poly I:C (iv) or vehicle on GD15. The adult offspring of these animals were subsequently shown to have impaired pre-pulse inhibition, a bench-mark deficit in animal models of schizophrenia. MIA did not alter basal synaptic transmission, as measured from field potentials, in either the dentate gyrus or CA1 of freely-moving adult rats. It did, however, result in increased paired-pulse facilitation of the dentate gyrus population spike and an enhanced persistence of dentate long-term potentiation (LTP). An examination of the firing properties of the 'place cells' of region CA1 of the hippocampus, also conducted in freely moving animals, revealed no change in overall firing rate in the MIA-group cells but a decrease in the region of space within which the cells fired (their 'place field') and an altered response to a cue shift. The synchrony of firing of these cells to simultaneously recorded theta (4-12 Hz) EEG activity was also disrupted, with a marked shift of mean phase angle of firing in cells recorded from the MIA animals. MIA animals also showed a memory deficit in an object-discrimination task and altered responses to a change in context, but were unimpaired in the standard version of the water maze. The data demonstrate that MIA alters hippocampal plasticity and principal cell activity in the adult offspring. These changes are associated with alterations in some hippocampal-dependent memory tasks, but somewhat surprisingly, no deficit was observed in the standard version of the water maze, the quintessential test of hippocampal function. The results provide insight into how hippocampal function may be altered in schizophrenia, but also suggest that careful behavioural testing will be required to fully determine how the observed changes in neural function impact on cognition and behaviour.

12.1

Neural prostheses: Practical applications in neuroscience

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Neural prostheses are engineered devices that record from and/or electrically stimulate excitable tissue in order to improve health outcomes. Since the introduction of the first heart pacemaker in the 1950s, there have been a number of bionic devices approved for clinical use, resulting in a dramatic impact on the quality of life of millions of people. These technologies depend on fundamental biomedical engineering principles and a thorough understanding of the anatomy and physiology of the target neural population. I will provide an overview of the design principles of modern neural prostheses using two well-known commercial devices as examples; cochlear implants for the treatment of severe hearing loss and deep brain stimulators (DBS) designed to alleviate motor tremor associated with Parkinson's disease. Significantly, there are a large number of devices currently undergoing development, fuelling expectation that this field will undergo major expansion over the next decade. These devices include retinal prostheses to provide visual cues for the blind; functional electrical stimulation to assist paraplegics stand and walk; DBS to treat severe depression and related psychiatric disorders; vestibular prostheses to assist patients with severe balance disorders; and recording or feedback devices such as brain–computer interfaces and peripheral nerve-recording arrays to control computer-assisted devices including artificial limbs. Finally, it is important to emphasise that neural prostheses provide a relatively crude representation of the temporal and spatial patterns of neural activity observed in normal neural structures; these devices are also reliant on the plastic brain for their considerable clinical success.

Supported by the Australian Research Council, the NH&MRC and the Victorian Government.

12.2

Attenuation of sound stimulation affects the molecular make-up of excitatory synapses in the developing cochlea

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Neural activity during early development is thought to mediate the refinement of pathways in the central and peripheral nervous system. We sought to examine how sensory stimulation of our hearing organ, the cochlea, affects the consolidation of glutamatergic synapses in this organ. To investigate this we induced a unilateral conductive hearing loss at postnatal day (P) 11 in mice, prior to the onset of sound mediated stimulation of the sensory hair cells, by rupturing the tympanic membrane and dislocating the auditory ossicles in the left ear. Auditory brainstem responses from P15 and P21 mice showed a 40 – 50 dB increase in thresholds for frequencies 16 and 24 kHz in the dislocated ear (D) relative to the control (C) ear. Immunohistochemistry and confocal microscopy were subsequently used to examine the effect of this attenuation of sound stimulation on the expression of RIBEYE, which comprises the presynaptic ribbons, Shank-1, a postsynaptic scaffolding protein and GluR2/3 and 4, both subunits of the post-synaptic AMPA receptor. Our results show that the number of puncta for all synaptic proteins is the same in C and D ears, however, the size of RIBEYE, GluR4 (but not GluR2/3) and Shank-1 puncta is increased in D ears by P21. Thus it appears that sound stimulation does not affect the number of glutamatergic synapses in the cochlea, but it does affect the molecular make-up of these synapses. Up-regulation of synaptic proteins with sound attenuation may provide a compensatory increase in synaptic transmission due to the reduced sensory stimulation of the inner hair cells.

12.3

Border cells: Generators of spontaneous morphological changes in supporting cells of the developing cochlea?

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Prior to onset of hearing, developing cochlear inner hair cells (IHC) and neurons undergo spontaneous activity to retain and refine neural connections important for development in the absence of sound. This spontaneous activity is dependent on purinergic (ATP) signalling and morphological changes within epithelial cells of a transient structure known as the Kölliker's organ, lying adjacent to the IHC. These rhythmic morphological changes are thought to influence, and perhaps regulate IHC activity. This study investigated the mechanisms of spontaneous morphological changes of supporting cells. Real-time imaging was used to measure changes in optical properties of cells of Kölliker's organ as a quantitative index of morphological changes in Wistar rat cochleae between the ages of P9-11. Freshly dissected tissues were treated with purinergic P2 agonists ATP (100µM), ATP-γ-S (100µM), and antagonist Suramin (150µM). For histological analysis, tissue was resin embedded, and 1µm sections stained with Toludine-blue. The specificity of spontaneous activity to the Kölliker's organ of pre-hearing rats was first established. During real-time DIC imaging, ATP and ATP-γ-S caused a reduction in light transmittance throughout the Kölliker's organ, with subtraction imaging showing the greatest crenation at the border cell region immediately adjacent to IHCs. ATP-γ-S in particular resulted in a sustained crenation of the border cell region, during the 10 minutes of exposure which was observed histologically as a condensation of the border cells. These effects in the presence of ATP-γ-S were reversed with suramin, and suramin alone induced swelling of the border cells. These results suggest that border cells are a primary source of generation of ATP-mediated spontaneous morphological activity observed during cochlear development.

12.4

The mechanisms of misperception: Embodiment and bodily illusions

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Although our somatic experiences seem to reflect reality, many clinical cases exist in which our bodily events are misjudged or misinterpreted, resulting in distorted bodily experiences. Experimental studies have demonstrated that even healthy participants can experience such distorted somatic experiences through simple cross modal manipulations. Here, we aimed to see how manipulating the degree to which a limb is embodied might alter tactile sensitivity and the tendency to experience illusory somatic sensations. Participants were presented with digitally manipulated representations of their own hands using the MIRAGE virtual reality system. In experiment 1, participants were asked to detect the presence of a near threshold tactile stimulus while their right index fingers were presented as visually normal, 'stretched' or 'chopped off'. Though participants still reported ownership of the finger, these manipulations resulted in marked differences in the degree to which participants were able to detect the tactile stimulus and the number of times an illusory tactile stimulus was reported. In experiment 2, participants were divided into 'Low' and 'High' groups based on their tendency to experience medically unexplained symptoms (MUS), and the extent to which top-down (cognitive) or bottom -up (sensory) processes modulated perception was manipulated. Individuals in the High MUS tendency group showed significantly different response patterns in relation to these top down/bottom up manipulations, as compared to the Low MUS tendency group. It is hoped that this distinction between top-down and bottom-up processes in somatic sensory illusions may help elucidate the causes of clinical phenomena such as somatoform disorders.

12.5

Eye movements during selective electrical vestibular stimulation in rat

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One of the most important functions of the vestibular system is to stabilize the gaze through the vestibulo-ocular reflex (VOR).The role of each of the 5 vestibular receptor systems involved in the VOR have been investigated by selective electrical stimulation in cat, monkey, guinea-pig or rabbit. But some contradictory results remain, especially concerning otolithic receptor stimulation. Furthermore, no study has ever been published in rat even though it is currently one of the most common models used in the neurosciences. Hence we have developed a new model of selective electrical vestibular stimulation in rat. A new surgical approach allows us to selectively stimulate each of the 5 vestibular receptor systems under general anaesthesia. Twenty six Wistar rats were tested with a total of 14 series of stimulations of the anterior ampulla receptors, 4 series of the lateral ampulla, 11 of the posterior ampulla, 57 of the saccule and 88 of the utricle. The eye movement induced by anterior or lateral ampulla stimulations was vertical upward or horizontal, respectively, which is consistent with the results in other species. Posterior ampulla stimulation induced torsional eye movements already described in cat, but not in rabbit, monkey or human, which demonstrate vertical movements. Otolithic receptor stimulations show different types of eye movements, including some disconjugate movements never described before. These original results are discussed in relation to oculomotor muscles orientation, electrical parameters, the position of the electrode relative to the striola or anaesthetic parameters. These new data are particularly relevant for the new area of research in vestibular prosthesis. This research was supported by the Royal Society of NZ Marsden fund, and a Marie Curie International Research Staff Exchange Scheme Fellowship within the 7th European Community Framework Programme.

12.6

Statistical parametric mapping of experience-dependent immediate early gene expression in the initial phase of vocal learning

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The song template represents a central feature of songbird vocal learning, as this stored representation of the tutored song guides the sensorimotor approximation of a young male's own vocal motor output toward an imitation. Auditory forebrain regions have been proposed as a likely repository of the template. However, the boundaries of these regions are not distinct, requiring the development of spatially unbiased approaches to assess areal changes in neural activity during template acquisition. To achieve this, we have developed a method for producing 3D statistical parametric maps of immediate-early gene expression, providing a globally unbiased approach to the assessment of brain activity in the awake unrestrained animal. IEG expression was reconstructed into 3D by a processing pipeline involving transformations, smoothing, registration, and interpolation of image data. SPM5 and (and tailored SPMMouse) were used to perform voxel-based statistical comparisons across brain volumes, identifying differentially activated regions of the brain across various experimental groups. Adopting this SPM framework, we utilized a minimal training paradigm to explore the brain regions selectively activated by operant song training. Song learning can be initiated in isolate juvenile zebra finch males by a brief exposure to the model song. Global IEG activation in response to tutoring was examined using ZENK in situ hybridization to brains collected 30 minutes after first tutor song playback. We compared the expression patterns in response to a playback of the tutor song model in juvenile birds that were naïve to the operant paradigm, birds that were given a single passive playback, and birds that had previously received a single complete session of training (a maximum of 75 seconds of song playback). Groupwise comparisons between playback-induced global brain IEG expression revealed areas showing differences in regional activation based on the nature of first tutor song exposure (operant or passive) and previous experience. Unexpectedly, we identified a region of the entopallium as differentially engaged by ~2.5 seconds of operant or passive tutoring. The contribution of this region of activation to learning of the song, learning of the operant, or possible attentional processing is still being determined. Our further molecular analyses of events occurring during template encoding and subsequent rapid vocal change reveal the engagement of epigenetic processes in the striatum. Dissection of the mechanisms of song template encoding will likely illuminate conserved mechanisms involved in the formation and utilization of internal models guiding learned social behaviors, deficits in which have been proposed to underlay human disorders of social functioning such as autism and schizophrenia.

13.1

The Blood-Brain Barrier: An interface in the neuroimmune and neuroendocrine systems

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The blood-brain barrier (BBB) is often misperceived as a rigid wall separating the blood stream and the peripheral tissue it nourishes from the central nervous system (CNS). Although the vascular blood-brain barrier, which results from modifications to the capillary that nourishes the brain, does prevent the unregulated leakage of substances between the blood stream and the CNS, it also controls the highly regulated exchange of nutrients, vitamins, electrolytes, toxins, xenobiotics, and informational molecules that does occur between the blood and the brain. The exchange of informational molecules (e.g., peptides and regulatory proteins) and its regulation means that the BBB is the basis for a humoral communication that occurs between the CNS and peripheral tissues. This lecture will explore two concrete examples of this humorally based brain-body communication. The first will focus on how neuroinflammation alters BBB transport systems, including those important in the progression of alzheimer's disease. The second will examine how the BBB controls the brain's monitoring of caloric reserves and how impaired transport contributes to obesity.

13.2

Mechanisms of signalling across the Blood Brain Barrier

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The blood-brain barrier (BBB) has evolved to have many functions, including the regulation of the exchange between the blood and the brain of informational molecules, such as peptides and regulatory proteins. One area in which the BBB plays a prominent role is the transport of gastrointestinal hormones into the brain. These hormones convey information about peripheral events to the CNS. For example, serum leptin levels correlate with the amount of adipose tissue that an individual has. Leptin is transported into the brain by a saturable system and there regulates the expenditure of calories. The relation between CNS and serum leptin levels is non-linear with saturation of the transporter at levels seen in obesity. The most linear portion of the curve (and therefore the portion of the curve that is most efficient in conveying peripheral information to the brain) occurs at very low levels of leptin. Such low levels of leptin are not seen normally in Western civilization but are typical of animals living in the wild and are the levels at which leptin tends to shift caloric expenditures away from feeding motivated behaviors to those related to reproduction, immune system maintenance, and neurogenesis. Effects on cognition, synpatogenesis, and neuronal protection are common among the gastrointestinal hormones; leptin, insulin, amylin, CCK, GLP, ghrelin, and many others have these effects. We postulate that these effects on brain function evolved directly from the regulatory and informational aspects that these hormones possess due in part to their abilities to be transported across the BBB.

13.3

Hormone and metabolite signaling in the circumventricular organs

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Central nervous system (CNS) structures involved in the regulation of energy balance gather information from the variety of different peripherally derived signaling molecules that we now believe provide an integrated perspective of energy status of the organism. However, the existence of the blood brain barrier means that the CNS is theoretically unable to directly monitor many of these circulating signals such as adiponectin, amylin, cholecystokinin (CCK), glucose, ghrelin, leptin, and peptide YY (PYY) which do not freely diffuse across this barrier. A number of mechanisms have been suggested to play important roles in facilitating the ability of the CNS to monitor this essential sensory information. My presentation will describe briefly potential roles of vagal afferent signaling and peptide transporters in providing access routes for such information transfer, but will focus primarily on the potential roles of specialized CNS structures which lack the blood brain barrier known as the sensory circumventricular organs (CVOs). In particular I will highlight the complex sensory abilities of single CVO neurons in sensing multiple satiety signals and also describe the efferent projections of these neurons to essential autonomic control centres behind the blood brain barrier.

13.4

Prolactin transport into the brain does not require the prolactin receptor

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The anterior pituitary hormone, prolactin, crosses the blood-brain barrier (BBB) to exert critical physiological functions in the brain. However, the mechanism by which prolactin enters the brain is not completely understood. As a relatively large 23 kDa polypeptide, prolactin is likely to require a transporter to cross the BBB and gain access to the brain. Prolactin is found in the cerebrospinal fluid (CSF), and levels in the CSF parallel those found in the blood. Extremely high levels of prolactin receptor are found in the choroid plexus, and it has been hypothesised that this receptor in the choroid plexus may serve as a transporter by binding to prolactin in the blood and secreting it into the CSF. We aimed to test this hypothesis by measuring the transport of ^{125}I-labelled prolactin into the brain of mice lacking the prolactin receptor ($Prlr^{-/-}$) compared to wild-type controls ($Prlr^{+/+}$). We found that there was no change in the rate of ^{125}I-labelled prolactin transport into the brain in $Prlr^{-/-}$ mice, compared to control mice. The transport of prolactin into the brain was saturable, with transport effectively blocked by unlabelled ovine prolactin. A very high dose of prolactin (1 mg prolactin injected, achieving blood levels 726.6 µg ml prolactin) was required to block transport, however, suggesting that transport is unlikely to be saturated even at pathological levels of hyperprolactinaemia. These data suggest that the prolactin receptor is not required for transport of prolactin into the brain, but this function involves another, as yet unidentified, transporter molecule.

13.5

Delivering drugs to the brain via the Blood Brain Barrier

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Delivery of drugs at pharmacological levels to the brain is challenging, although clearly not impossible, given that there are drugs in the clinic for CNS disorders such as depression, anxiety, psychosis, epilepsies and degenerative disorders. Nevertheless, there are CNS disorders that are currently untreated, and many potentially useful drugs, both small organic molecules and large biologics, are excluded from the brain by the selectively permeable Blood Brain Barrier (BBB). Small lipophilic drug molecules probably cross the BBB by passive diffusion, if they are not effluxed from endothelial cells by efflux transporters (eg Pgp). Small hydrophilic molecules (eg L-Dopa) are delivered by transporters (eg LAT-1). Such transporters are stereospecific and regulated, sometimes by the drug itself. Delivery of large biopharmaceutical molecules (eg mAb) via an intact BBB is particularly challenging. One possible approach is the so-called Trojan horse, that is entrapping the biopharmaceutical in a colloidal carrier (eg iposome) tagged with a natural ligand for which there is a high capacity transporter on the BBB (eg transferrin). Alternatively, fusion molecules comprising the bioactive protein and ligand have been investigated. Some researchers have treated the surface of colloidal particles so that they, fortuitously, adsorb selected plasma proteins (eg apoE) and are then taken across the BBB via receptor mediated transcytosis (eg with LDLR). Given the central role of transporters in drug delivery via the BBB, their regulation and function is likely to be an important determinant of drug concentrations in the CNS and hence of efficacy. This presentation will discuss issues relevant to the delivery of small molecules to the brain and some of the strategies for biopharmaceuticals.