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Abstracts

1.1

The Long-Term Future of Long-Term Potentiation

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The evidence that LTP and LTD are exploited for the storage of hippocampus-dependent memories in the rodent is now very strong. Yet we remain a long way from an understanding how memories are represented across the three principal neural networks of hippocampal neurons - the subfields of the dentate granule cells, and CA3 and CA1 pyramidal cells. The exploration of the network functions of the hippocampus and other areas of the brain is the next major challenge in memory research, and in this talk I will outline some possible approaches that may provide insight into the structural organization and functional principles which underlie the storage of learned information in the hippocampus in the behaving animal.

1.2

Creating a Neurogenic Environment: The Role of BDNF and FGF2

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Regional environmental cues present in the adult brain determine the fate of adult neural progenitor cells. To determine whether the growth factors BDNF or FGF2 can create a neurogenic environment outside the SVZ, we used $AAV_{1/2}$-mediated gene transfer to produce ectopic BDNF or FGF2 expression in the normal adult rat striatum, and transplanted SVZ-derived progenitor cells into this region. We observed that ectopic expression of BDNF in the striatum promoted neuronal differentiation of transplanted adult neural progenitor cells, while FGF2 expression supported the survival and proliferation of transplanted progenitor cells in the adult striatum. In contrast, adult neural progenitor cells transplanted in the normal adult striatum in the absence of BDNF or FGF2 exhibited low cell survival and glial differentiation. However, region-specific neuronal differentiation of transplanted progenitor cells was not observed in the adult striatum, suggesting ectopic BDNF or FGF2 expression was insufficient for the generation of mature neuronal phenotypes. This study provides direct *in vivo* evidence that ectopic striatal expression of either BDNF or FGF2 can induce neurogenesis in non-neurogenic regions of the adult brain. By understanding the conditions under which neurogenesis can be induced in non-neurogenic regions of the adult CNS, the repair of neural circuitry by manipulation of neurogenesis may become a possibility.

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1.3

Dynamics of SAP97 Isoforms in Spines and Functional Effects on Synaptic Transmission

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The postsynaptic density of excitatory synapses contains numerous synaptic scaffold proteins that are thought to play critical roles in maintaining synaptic structural integrity, targeting ion channels and activating downstream second messenger pathways. The Synapse Associated Protein SAP97, a member of the postsynaptic density protein family, binds both AMPA and NMDA receptors through PDZ domain interactions. SAP97 possesses a long N-terminus that contains an L-27 domain that is important for hetero- and homomultimerisation. This N-terminus is subject to alternative splicing resulting in isoforms that possess (beta) or lack (alpha) at this L27 site and results in differential possession of a palmitolyation site. Using *in vitro* dissociated hippocampal cultures expressing GFP-tagged SAP97 alpha or beta-SAP97, we have identified that the presence or absence of the L27 domain and palmitoylation sequence alters the stability of SAP97 expression at synapses as revealed by triton extraction. N-terminal splicing also alters the turnover of SAP97 in spines: fluorescence recovery after photobleaching (FRAP) revealed alpha-SAP97 has a very rapid turnover at spines compared beta-SAP97. Moreover the stability and turnover of alpha and beta-SAP97 directly affects the stability and turnover of glutamate receptors at synapses. Functionally, these changes in stability and turnover result in changes in the amplitude and frequency of AMPA receptor-mediated synaptic transmission. Together these data show that the L27 and palmitoylation sequences in the N-terminus of SAP97 dictates the stability of SAP97 and AMPA receptors in the postsynaptic density and this directly alters the properties of synaptic transmission at hippocampal synapses.

1.4

Functional Incorporation of New Brain Cells into Existing Neuronal Networks

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The brain continues to produce newborn neurons throughout development and into adulthood. The production of newborn neurons increases in response to neurodegenerative disease, however due to poor survival and functional incorporation newborn neurons cannot replace the cells lost. It is known that synapses formed onto new neurons have unique properties but the synapses formed by new neurons onto mature neurons have not been studied. The formation of these synaptic connections is critical for complete integration of newborn neurons. Here we report a new model system for studying newborn neuron integration. We have found that primary dissociated hippocampal cultures continue to produce newborn neurons. BrdU incorporation paired with immunocytochemistry of neuronal markers revealed that the production of newborn neurons occurs at a surprisingly high rate. At 3 days *in vitro* (DIV), 45.3 ± 0.06% of the total neurons in the culture dish were newborn neurons. The production of newborn neurons increased with DIV such that by 10 DIV 61.5 ± 0.04% of total neurons growing *in vitro* were newborn neurons. Newborn neurons showed altered morphology, smaller cell bodies, changes in synaptic protein expression and significantly less dendritic branching suggesting they exhibit a slower maturation process. These data show that dissociated hippocampal cultures are a useful model system in which to study the integration of newborn neurons into existing neuronal circuits.

1.5

Hippocampal Involvement in Cost/Benefit Analysis

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We propose that the hippocampus is involved in cost/benefit decision-making when a task is solved spatially, and that hippocampal cells encoding position within an environment ("place cells") also encode cost/benefit information. Rats were trained to run continuously in a figure-of-eight maze with free choice at the decision point. One arm was associated with low reward and low cost; the other with high reward but high cost. Rats were trained from various starting points and running directions, with the maze at different orientations, and quickly learned to rely on a spatial strategy to locate the high reward, suggesting hippocampal involvement. The activity of place cells was then recorded while rats performed the task, with cost/benefit ratios altered for each of five blocks of 20 trials. Pilot data from nine place cells with 13 place fields located in the central stem showed that 31% were highly biased (>0.6 on a 0-1 scale) to fire preferentially for one turn direction. Additionally, 46% showed a strong correlation (r>0.75) between firing rate on the first pass through the stem in a block of trials, and the rats' subsequent arm-choice behaviour within that block. In some cases this correlation was very high (e.g. r=0.94). Cells that were highly biased also tended to be most predictive of future choices. These data suggest that "place cells" also encode cost/benefit information.

1.6

Shedding a Light on Positive Reinforcement Mechanisms in the Striatum

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The striatum is a site of integration of neural pathways involved in positive reinforcement. Inputs from the cerebral cortex communicate information about ongoing actions to striatal spiny neurons. These excitatory inputs converge with neuromodulatory inputs from midbrain dopamine neurons, which signal the occurrence of salient, and often desirable, stimuli. Dopamine-related positive reinforcement could promote the learning of actions that reliably cause the arrival of such stimuli, by a process represented at individual spiny neurons by potentiation at activated corticostriatal synapses. Results from our experiments in urethane-anaesthetised rats suggest that corticostriatal activity and activation of dopamine neurons are necessary for corticostriatal potentiation. Surprisingly, potentiation was induced most reliably when dopamine cells were phasically activated during the spiny neuron's 'Down' state, the period of minimum endogenous corticostriatal activity. However, it remained necessary to depolarise the neuron to 'Up' state levels during dopamine-cell activation using somatic current injection. These results suggest that during learning, an additional source of excitation is required to induce corticostriatal potentiation, one which is temporally contiguous with phasic dopamine cell activity but independent of corticostriatal activation. We have identified a light-activated afferent pathway involving the superior colliculus and thalamus, which depolarises spiny neurons to the 'Up state', accompanied by phasic dopamine release. We propose a model where phasic dopamine release and simultaneous spiny neuron depolarisation by thalamic activation would favour the induction of potentiation at recently active corticostriatal inputs.

2.1

A Choice Reaction Time Task to Assess Memory Processes in Clinical Populations

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Traditionally, there have been two main approaches to the psychological assessment of clinical populations: the *psychological testing approach*, which employs psychometric tests to identify individual differences in constructs such as short-term memory, and the *information processing approach*, which uses theoretically-based, analytical tasks to identify more elementary cognitive processes that underlie these constructs. The present study examined memory processes by using a choice reaction time (CRT) task which incorporated the manipulation of four task variables (stimulus quality, memory set size, response set size, and response complexity) in order to operationalise processes involving stimulus encoding, memory comparison, response selection, motor programming, and response execution. Participants were required to memorize sets of two, four, or six concrete nouns (memory set) and then identify, after a brief delay, a repeated item (target) within a further set of two, four, or six items (response set). The results provided support for employing this CRT task to measure stimulus encoding, memory comparison, response selection and motor programming processes. A further study of patients with posterior and anterior brain damage showed that changes in stimulus quality and memory set size had the greatest impact upon patients with posterior brain damage, suggesting selective weaknesses in stimulus encoding and memory comparison processes. Changes in response set size had the greatest impact upon patients with anterior damage, consistent with a selective impairment in response selection processes. This double dissociation attests to the potential clinical utility of the CRT method to assess elementary cognitive processes and its use for the design of remediation programs.

2.2

Bradyphrenia on a Visual Inspection Time Task in Parkinson's Disease ON and OFF L-dopa

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Thinking slows with normal aging, but bradyphrenia (slowed thinking) is also a possible, but contentious, symptom of Parkinson's disease. We compared 28 non-depressed, non-demented PD participants (mean age 66.9yrs), both ON and OFF L-dopa, with 28 age and pre-morbid IQ case-matched Controls on an Inspection Time (IT) task that circumvents the necessity for a motor response. The mean Unified Parkinson's Disease Rating Scale for motor symptoms (UPDRSm) for the PD gp was 21.95 ON and 30.25 OFF L-dopa. Participants judged which leg of a Pi symbol was shorter, after it was flashed on a computer screen followed by a mask. There were 20 trials for each of nine time intervals from 20 to 250 ms, with the IT taken as the time interval where 80% accuracy was achieved. A repeated measures ANOVA with IT as the dependent variable and controlling for gender demonstrated a significant Group effect with the PD group having longer ITs than Controls in both ON and OFF conditions ($p = .002$), and a significant status (ON/OFF) x group interaction, with only the PD group showing longer ITs in the OFF versus ON condition ($p = .024$). No significant correlations were found between motor symptom severity and ITs ON or OFF L-dopa. In summary, PD participants demonstrated bradyphrenia both ON and OFF L-dopa, independently of age. Bradyphrenia was not correlated with motor symptoms but was reduced to some degree by L-dopa.

2.3

"His face *doesn't* ring a bell!" Prosopagnosia and Human Facial Recognition

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Despite considerable attention in the literature, the processes underlying face recognition and prosopagnosia are not yet well understood. Argument continues over the specificity of faces as a visual stimulus and the role of perceptual impairments in the traditional taxonomy of apperceptive and associative subtypes of prosopagnosia. This paper aims to further inform these debates by profiling the impairments of a single patient in terms of the specificity of her deficit with particular reference to the traditional apperceptive/associative taxonomy. A single patient (CW: listed with www.faceblind.org) and a control group of five matched, unimpaired, participants completed a comprehensive assessment of basic face and object perception, familiar and unfamiliar face and object recognition, and higher-order perceptual processing. Results showed that CW's impairment was specific to faces. She passed all tests of basic object perception and tests involving discrimination and recognition of visually complex non-facial stimuli. However, CW showed impairments in the recognition and recall of unfamiliar faces, famous faces, real faces (but not photographs), and any face-stimuli requiring holistic processing (CW showed no face inversion decrement). The evidence that visual recognition deficits can be restricted to faces without associated difficulties in recognising objects suggests that faces uniquely, or disproportionately, engage a holistic processing mechanism. This questions the usefulness of the associative/apperceptive taxonomy and the current neuropsychological assessment procedures that are employed to assess face recognition and perceptual impairments.

2.4

Automatic and Controlled Processing after Mild Traumatic Brain Injury

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Whether the consequences of a mild traumatic brain injury (TBI) are sufficient to produce chronic disability remains a point of contention, although it has been proposed that mild TBI may result in subtle higher-order attentional impairments. The purpose of this experiment was to compare the automization of controlled processes in clients who had sustained a prior mild TBI against a matched healthy control group, using event-related potentials (ERPs). Ten individuals who had sustained mild TBI and 10 age-, gender-, and education-matched controls were trained on the Paced Auditory Serial Addition Task, and ERPs were simultaneously recorded during task performance. Training was associated with significant improvements in behavioural performance in both groups. Controls demonstrated a significant reduction in amplitude of the late processing negativity (PN) component of the event-related potential waveform following training, which was not observed in the mild TBI group ($p < .05$). These results suggest that mild TBI may lead to impairments with the gradual withdrawal of attentional control and the strengthening of associative connections within information processing networks following training.

2.5

Functional Improvement in Chronic Stroke Patients Depends on Corticospinal Integrity: A Diffusion Tensor Imaging Study

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Diffusion Tensor Magnetic Resonance Imaging (DTI) is a recently-developed technique that can image *in vivo* the white matter pathways of the central nervous system. This study used 12-direction diffusion-weighted MRI data from nine stroke patients acquired as part of a three-year stroke rehabilitation study coordinated by the Movement Neuroscience Laboratory at the University of Auckland. DTI was used to investigate corticospinal connectivity. From the FA maps, it was found that in those patients whose motor connectivity has been compromised by the stroke to the extent that no motor evoked potential (MEP) can be elicited from a selected affected muscle group, the asymmetry in mean FA values in the posterior limbs of the internal capsules (PLICs) is correlated with functional recovery as measured by the Fugl-Meyer clinical score. Probabilistic tractography in the contralesional hemisphere produced CST location and somatotopy results consistent with those of previous studies. However, in the ipsilesional hemisphere, connectivity results were highly variable. A measure of change in symmetry of mean connectivity is found to correlate with functional recovery as measured by change in FM score. This supports previous work which has correlated CST integrity and functional improvement and it supports the theory that functional recovery after stroke depends on the extent to which motor CNS symmetry can be regained in the new post-stroke architecture. It also suggests that the movement of the fMRI activations occurs in such a way as to make the most of the preserved white matter connectivity.

2.6

Illusory Conjunctions are Biased by Synaesthesia

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In normal vision, visual features such as shape and colour are processed in functionally independent channels which are subsequently bound to produce a unified percept. When attentional resources are limited this binding can be subject to error. For example, letters and colours may be mismatched, producing illusory conjunctions. In colour-grapheme synaesthesia, letters and numbers are involuntarily associated with vivid colour experiences, with each grapheme corresponding consistently to a particular colour. Here we investigated whether synaesthesia can influence the outcome of illusory conjunctions, so that the synaesthetic colour of a letter is more likely to be bound to it than any other letter. Nine colour-grapheme synaesthetes and 9 yoked controls were shown brief displays of 3 letters. Each letter was presented in a different colour that was drawn from the set of the participant's synaesthetic colours for the letters presented. This display was followed by a single probe letter which was one of the three display letters. Participants responded 'same' if they thought the probe was coloured the same as the corresponding letter in the prior display, or 'different' if they thought it had been a different colour. Synaesthetes were significantly more likely to report 'same' if the probe was presented in its synaesthetic colour, while controls showed no response biases. This suggests that when synaesthetes make illusory conjunctions, they are more likely to bind a letter's synaesthetic colour to it over any other incorrect colour.

3.1

The Role of MAPK Signaling Pathway in the Metabotropic Action of Kainate Receptors in Rat CA1 Pyramidal Neurones

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Hippocampal pyramidal neurones display a Ca^{++} dependent K^+ current responsible for the slow afterhyperpolarization (/sAHP), a prominent regulator of excitability. There is considerable transmitter convergence onto /sAHP but little information about the interplay between the kinase-based transduction mechanisms underlying transmitter action. We have added to existing information about the role of protein kinase C (PKC) in kainate receptor actions by demonstrating that direct postsynaptic activation of PKC with either 1-oleoyl-2-acethylsn- glycerol (OAG) or indolactam is sufficient to inhibit /sAHP. The physiological correlate of this action – activation of PKC by kainate receptors – requires Gαi/o proteins. The cAMP/PKA system is well documented to subserve the actions of monoamine transmitters.We have found an additional role for the cAMP/PKA system as a requirement for kainate receptor-mediated inhibition of /sAHP. Inhibition of adenylyl cyclase with dideoxyadenosine or PKA with either H89 or RpcAMPs blocked kainate receptor-mediated actions but did not prevent the actions of direct PKC activation with either OAG or indolactam. We therefore propose that the PKA requirement is upstream from the actions of PKC.We additionally report a downstream link in the form of increased mitogen-activated protein (MAP) kinase activity, which may explain the long duration of metabotropic actions of kainate receptors on /sAHP.

3.2

Activity-Dependent Induction of Synaptotagmin 4 Retrograde Signaling Regulates Synaptic Growth

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Calcium influx into both pre- and post-synaptic neurons is a key step in synaptic transmission and synaptic plasticity. Although communication from the presynaptic neuron via Ca^{++}-dependent synaptic vesicle fusion has been well characterized, the molecular mechanisms that allow postsynaptic release of retrograde signals are relatively unknown. In the presynaptic terminal, the conserved vesicular protein Synaptotagmin 1 acts as a Ca^{++} sensor for fast synchronous vesicular fusion following an action potential. Recently, we identified another conserved member of the Synaptotagmin family, Synaptotagmin 4 (Syt 4), which localizes to a postsynaptic vesicle population in *Drosophila* neuromuscular junctions (NMJ) (Adolfsen, 2004). This suggested a potential role for Syt 4 in coupling postsynaptic Ca^{++} influx to retrograde synaptic signaling. Using transgenic expression of Syt 4, as well as a Syt 4 null mutant, we have determined that postsynaptic Syt 4 levels directly regulate synapse number. Using western blot and RT-PCR analysis, as well as a GFP-Syt 4 promoter fusion construct, we have demonstrated that activity-dependent regulation of Syt 4 protein and mRNA levels occurs in *Drosophila* temperature-sensitive activity mutants. We have also demonstrated that known forms of activity-dependent NMJ structural plasticity are impaired in Syt 4 null mutants, suggesting Syt 4-regulated retrograde signaling controls synaptic growth in response to activity. Our findings indicate that activity-regulated expression of Syt 4 may be a conserved mechanism for modulation of synaptic growth and function.

3.3

Effects of Aging on Agmatine Levels in Memory-Associated Brain Structures

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Increasing evidence suggests that agmatine, a metabolite of L-arginine, is a novel neurotransmitter. It binds to α-adrenergic and imidazoline receptors, modulates the N-methyl-D-aspartate receptor function and regulates the production of nitric oxide. The present study investigated age-related changes in agmatine levels in several memory-associated brain structures in male Sprague Dawley rats. Aged rats (24-month-old) displayed significantly reduced exploratory and locomotor activity in the open field, and were significantly impaired in the water maze task relative to the adult controls (4-month-old). The agmatine levels were measured by liquid chromatography/mass spectrometry. A significant decrease in agmatine level was found in the CA2/3 ($p < 0.05$), but not CA1 or dentate gyrus, sub-region of the hippocampus in aged rats. There were significantly increased levels of agmatine in the entorhinal ($p < 0.0005$) and perirhinal ($p < 0.01$) cortices, but not the postrhinal and prefrontal cortices, in aged rats. These results, for the first time, demonstrate age-related region-specific changes in agmatine in these memory-associated brain regions. The functional significance of these changes will be further investigated.

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3.4

Manipulating Notch Signaling Enhances Neuronal Regeneration in Adult Rat Hippocampal CA1 After Transient Global Ischemia

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Notch signaling regulates neural stem cells (NSCs) in embryonal and adult mammalian brains. Recent studies suggest this signaling also regulates damage-repair in adult mammalian brains. A problem with regenerative therapy using endogenous NSCs is the slight restoration achieved. We therefore investigated the potential of Notch signaling to augment neuronal regeneration. Wistar rats (8 weeks of age) were subjected to 6 min global ischemia, and received intracerebroventricular epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF2) on days 3-5 after ischemia. Additionally, some rats were administered a gamma-secretase inhibitor on days 6-12 to inhibit Notch signaling. Hippocampal CA1 neurons were reduced to 6 % of the number in control rats on day 28, which was partially restored to 22% of the control rats by newly generated cells induced by the EGF/FGF2 treatment. On day 5, Notch-positive NSCs and progenitors were increased in the posterior periventricle of the treated rats. Notch signaling was activated in the CA1 during the first 5 days, and then returned to the normal level by day 10. When the inhibitor suppressed Notch signaling, CA1 neurons exhibited a 36% increase compared to the rats not receiving the inhibitor treatment. In conclusion, Notch signaling was activated in the acute phase after transient global ischemia, presumably reflecting a proliferation of NSCs and progenitors. Suppression of Notch signaling in the subacute phase promotes the differentiation of progenitors into neurons.

3.5

NMDA Receptor Trafficking: Multiple Ways for Reaching and Leaving the Synapse

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Synapse plasticity, defined as a the modulation of the strength of synapses, is thought to be one of the mechanisms that underlies learning and memory. At a cellular level, the N-methyl-D-aspartate (NMDA) receptor plays a pivotal role in triggering and controlling synapse plasticity. Therefore, the trafficking of NMDA-type glutamate receptor to and from synapses will control the ability of synapses to change their strength of excitatory synaptic transmission. Very little is known about the secretory transport pathways in neurons that traffic NMDA receptors from the soma to synaptic junction and how these pathways are regulated. Our live cell imaging data of double transfected hippocampal neurons with GFP-NR1 (the obligatory NMDA receptor subunit) and DsRed-ER show that distinct, highly mobile transport vesicles with different transport velocities reach synaptic junctions. Together with the scaffold protein SAP97, NMDA receptors can leave the soma via endoplasmic reticulum (ER) – derived transport vesicles, showing that sorting of membrane-bound cargo can occur in the ER and not just at the Golgi. Knockdown of SAP97 with short hairpin RNA results in depleted synaptic NMDA receptor expression. However, in the presence of shRNA-SAP97, a significant proportion of NMDA receptors can still reach the synapse. SAP102, another NMDA receptor binding protein, traffics at an independent speed compared to SAP97 may independently traffic NMDA receptors through a distinct pathway. Together these data suggest that multiple trafficking pathways could exist for targeting NMDA receptors to synapses.

3.6

Potentiation of AMPAR and NMDAR EPSCs is Modulated by Pattern of Stimulation via Protein Phosphatase 1

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Memory of information is dependent on how we learn and training patterns can strengthen or dampen memory. When Protein Phosphatase 1 (PP1) is inhibited during learning, short intervals between training episodes are sufficient for optimal performance. Synaptic plasticity is a well defined neuronal model of learning and memory. We have examined synapse plasticity in the CA3 region of hippocampus, a region known to play a crucial role in spatial memory. In hippocampal organotypic slices, paired whole cell recordings were used to examine the frequency and space stimulation in synapse plasticity. Here, we show different patterns of LTP are dependent on different stimulation patterns. We have found that pairing 60 pulses at 1 Hz elicits Long-Term Potentation (LTP) of not only the AMPA receptor mediated excitatory postsynaptic current (EPSC) but also LTP of the NMDA receptor-mediated EPSC. Increasing the frequency of stimulation induces a distinct form of synapse plasticity that alters both AMPA and NMDA receptors-mediated currents. Inhibition of Protein Phosphatase 1 (PP1) results in the reappearance of plasticity-induced changes in NMDA receptor mediated currents. As well, widely spaced stimulation fails to elicit LTP or LTD of AMPAR EPSCs. This process involves an active suppression by PP1. These data show that potentiation of AMPA and NMDA receptor EPSCs is modulated by the pattern of stimulation via Protein Phosphatase 1.

3.7

Neuronal Circuits Underlying Interesting Behavioral Traits

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To determine the causal mechanisms that underlie behavioural phenomena such as instinct, learning, and memory formation the neuronal circuit that mediates the behaviour must be known. A 3-neuron circuit whose sufficiency and necessity has been experimentally demonstrated drives aerial respiration in *Lymnaea*. This behaviour is easily observable, can be operantly conditioned and it forms long-term memory (LTM). The necessary molecular events (altered gene activity and new protein synthesis) that underlie LTM formation occur within a single neuron, RPeD1. If we remove RPeD1's soma before training the snail learns and can form a 3h memory but not LTM. Moreover, if we remove RPeD1's soma after LTM formation the snail does not forget the learned behaviour. Thus, forgetting is also an active process. Finally, we have determined that our lab-reared population of *Lymnaea* (originally derived from the polders of The Netherlands) responds to the scent of a predator - crayfish. When snails sense the predator their ability to form LTM is enhanced up to 8-fold. This occurs even in snails that have never experienced the scent of the predator for over 200 generations. The same species of snail exists in Alberta, but crayfish are not present. We found that the Alberta snails do not respond to the presence of a crayfish with enhanced memory formation. Thus we may be able to study how instinct is encoded in neurons such as RPeD1 by comparing the properties of this neuron between the 2 populations of snails.

Poster 4.1

The Effect of Coordination Mode on Use-Dependent Plasticity

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Motor practice can promote use-dependent plasticity (UDP) in primary motor cortex (M1) of patients following stroke. The aim of this study was to evaluate the role of coordination mode on the generation of UDP to determine if changes in M1 excitability and UDP would dissociate. Ten healthy volunteers performed brisk repetitive thumb movements for 30 minutes in the opposite direction to those evoked by transcranial magnetic stimulation (TMS) prior to training. This practice was synchronized or syncopated with a 1 Hz auditory metronome in two separate sessions. Motor evoked potentials (MEPs) were recorded from 3 intrinsic thumb muscles, to assess changes in corticomotor excitability. Both synchronized and syncopated motor practice induced changes in the direction of TMS-evoked thumb movements, away from the baseline direction toward the trained direction. MEP amplitude increased following synchronized, but not syncopated, motor practice. Changes in movement direction and corticomotor excitability lasted for at least 30 minutes. Motor practice that is synchronized with external pacing may promote UDP and facilitate corticomotor excitability in patient populations with reduced corticomotor output, such as stroke. Training that is syncopated with external pacing may promote UDP without increasing corticomotor excitability. This could be relevant for individuals with disorders characterized by maladaptive plasticity.

Poster 4.2

Glutamate-Sensitive Non-Mitochondrial Carboxylase Distribution in Developing Chick Brain

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Glutamate-sensitive non-mitochondrial carboxylase (GSNMC) was found in chick retina. The synthesis of the GSNMC commenced at a few days before hatching. GSNMC was also found in the brain homogenate, but the specific site was not known. Therefore, the objective of this study was to determine the distribution of the GSNMC in various parts of the embryonic and post-hatched chick brain. Embryonic chicks (E14, E17, E18, E21) and post-hatched (D1, D3, D6, D9, D12) chicks were used. Crude protein extracts were prepared from various parts of the brain including alfactory bulb, cerebral cortex, hippocampus, cerebellum and optic tectum. They were separated on 12% SDS-PAGE and transferred to a nitrocellulose membrane. The antiserum against the GSNMC from chick retina was produced in mice and used as a probe in Western immunoblotting. The results showed that the GSNMC was distributed in all part of the brain tested. The synthesis of the GSNMC in the brain had a similar pattern to that of in the retina. As GSNMC was widely found and was increasing along the development of the brain, the widely distribution of the GSNMC in the brain might correlate with the distribution of glutamate and suggesting the possible role(s) of GSNMC in the glutamate actions.

Poster 4.3

A Randomised Controlled Trial of Attention Process Training Post-Stroke: A Rationale and Design of the START Study, 2006-2009

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Impairments in attention contribute to poor outcomes, and attention is the basis for other areas of cognition (memory, communication). In small samples Attention Process Training (APT) has been shown to reduce attention deficits in persons with traumatic brain injury. APT materials consist of a group of hierarchically organised tasks that exercise different components of attention, including sustained, selective, alternating, and divided attention. There is no robust evidence for the effectiveness of APT in stroke patients. The aim is to examine effectiveness of APT in improving attention and health related quality of life (HRQoL) in stroke survivors at 6-months after the stroke. Secondary aims are to determine the impact of APT on: (a) disability and handicap 6-month post stroke; and (b) other neuropsychological functions in stroke survivors 6-months post stroke. The 160 participants will include survivors of first-ever stroke admitted to acute rehabilitation units of Auckland hospitals across an 18-month period, identified via neuropsychological assessment as having an attention deficit. Exclusion criteria: (1) inability to give informed consent; (2) severe cognitive deficits precluding participation; (3) medically unstable; (4) not fluent in English, as tests requires English fluency; or (5) another condition that could impact results. The findings will be of significance to evidence-based planning of rehabilitation and improving stroke outcomes. If APT is an effective means of improving attention and HRQoL post-stroke, this trial will provide a new direction for rehabilitation efforts, which have traditionally focussed on motor functioning, language and activities of daily living.

Poster 4.4

Anatomic Approach to Volumetry of the Amygdala

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A striking feature of studies that have addressed the measurement of the amygdala is the wide range of volumes encountered, with reports of volumes ranging from 1 to almost 4cm^3. Another striking feature is the number of discrepancies in the landmarks adopted for manual segmentation in MRI. The goals of our study were to elaborate the methodology of its measurement in MRI images on the basis of amygdalar cytoarchitecture and to determine the volumes of the amygdala. In spite of the fact that it is not possible for clinicians to measure all necessary dimensions, another goal was to find a simplified measurement technique, which could serve as an indicator of the actual size of the amygdala. The methodology of amygdalar measurement and its volumetric estimation was elaborated by means of classical anatomical methods and MRI examinations in a sample of 51 healthy adults (18 – 99 years of age). Neither volumetric differences between two sexes nor interhemispheric differences were significant for absolute volumes of amygdala. A significant correlation between the size and age of the amygdala was not found. From a wide variety of approaches to simplify the estimation of the amygdalar volume, a single measurement of the plane in the level of the most anterior tip of the hippocampus is very promising.

This study was supported by IGA MZ 2006, NR8931-4.

Poster 4.5

Aging Does Not Effect Theta Phase Precession During the First Pass Through a Place Field in a Familiar Environment

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In all subregions of the hippocampus the timing of spikes shows a dynamic relationship to the hippocampal theta rhythm. As a rat passes through a principal cell's place field, the timing of spikes shift relative to the local theta rhythm such that the spike timing occurs at earlier phases of the theta cycle. In both young and old rats, for the majority of CA1 pyramidal cells, this "theta phase precession" covers approximately 360 degrees or a complete theta cycle. In old rats, however, the rate of theta phase precession is faster compared to young rats. While this is likely due to the lack of experience-dependent place field expansion plasticity in old rats, it is unclear if there are differences in theta phase precession between young and old rats during the first pass through a place field (i.e. before the place field has expanded). Neurons from CA1 were recorded from young (9-12 month) and old rats (25-30 months) as they traversed a circular track in a familiar environment. In the old rats the NMDA receptor was modulated by the activity-dependent non-competitive antagonist memantine, which has been shown to restore experience-dependent plasticity. Neurons showing place-specific firing during the first pass through a place field exhibited a full 360 degrees of theta phase precession. This was consistent between young and old rats administered saline or memantine suggesting that prior to experience-dependent place field expansion theta phase precession is not altered with age.

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Poster 4.6

Classifying Alzheimer's Disease Through Multigene Expression Signature Profiling

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The NINCDS-ADRDA and DSM-IV criteria are widely used for diagnosis of probable-AD. These have a number of limitations, including lack of specificity and sensitivity, and an error rate of ~10% even in academic centers. Furthermore, such diagnoses can only be made post-symptomatically, when medications will likely be less effective. Imaging and individual biomarker methods have additional drawbacks in their need for specialized equipment, and specificity and sensitivity respectively, and may not be useful for early screening. There is growing evidence of peripheral responses in AD, e.g. T-cell CD45 isoforms, HO1 and HSP70 RNA levels. We have hypothesized that leukocyte gene expression changes, induced by AD, can be utilized to form a biological classifier of the disease. We have tested this hypothesis via microarray analysis of ~40,000 RNA transcripts in peripheral blood leukocytes from our initial sample of AD patients and matched controls. Our preliminary results for female AD (n=11) and control subjects (n=9) showed 94% prediction accuracy using a 1-nearest-neighbor classification algorithm (p=.0196). These data suggest leukocyte expression can be employed for AD classification. We believe the larger numbers (n=60) being recruited will increase the significance of these results. The findings of our larger study may be of significance for improving clinical AD diagnosis.

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Poster 4.7

Anterior but not Laterodorsal Thalamic Nuclei Lesions Impair Continuous Recognition in a Radial Arm Maze

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The role of different thalamic nuclei in diencephalic amnesia is uncertain. The anterior thalamic nuclei (ATN) have been emphasised, but the adjacent laterodorsal nucleus (LD) may also be part of an extended ATN complex. Frontal and limbic system connections overlap across the ATN and the LD, but the LD are distinguished by prominent connections with the parietal cortex. Parietal cortex and hippocampal system injury impair spatial memory, but dissociations across tasks have been reported. Specifically, hippocampal but not parietal cortex lesions produce severe impairments for differential reinforcement in a continuous recognition procedure in which twelve arm visits are provided in a radial maze but reward is absent on any repeated arm. In intact rats, the delay in entering a repeated arm decreases as the number of intervening arms increases (lags of 0-6 arms). Following preoperative acquisition, three matched groups of rats received either AT, LD or sham surgery. Initial findings indicate that the ATN group exhibited a mild impairment whereas the LD group was not impaired. If detailed histology confirms the specificity of the lesions, then this study will provide the first evidence of a dissociation between the effects of LD and AT lesions.

Support from the Neurological Foundation (NZ) is gratefully acknowledged.

Poster 4.8

The Plant Convulsant Tutin Does Not Directly Activate Glutamate Receptors

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Tutin is a natural convulsant compound found in the New Zealand native tutu tree as well as other members the *Coriaria* genus worldwide. Unpublished data from our lab shows that the dose of tutin used here significantly decreased evoked GABA currents to 63 ± 5.92% of control. However it has been suggested that tutin is convulsant through a direct activation of glutamate ((particularly α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)) receptors. To test this hypothesis we used whole cell voltage-clamp in primary cortical neuronal cultures from E16-E18 rats and evoked glutamate receptor mediated currents using either AMPA or N-methyl-D-aspartate (NMDA). Agonists were applied directly onto the cell soma for 500 msec at the concentration evoking 50% of the maximal response (EC50; 8 μM AMPA and 10 μM NMDA). In all cells we recorded evoked currents before, during and after perfusion of tutin at 10 μM. Tutin did not significantly alter peak AMPA-induced currents (103.5 ± 1.7 % of control) or peak NMDA-induced currents (97.3 ± 3.5 % of control) according to two-tailed paired *t*-tests ($P < 0.05$ significant). We conclude that tutin does not exert its excitatory effects by modulating ionotropic glutamate receptors.

Poster 4.9

Environmental Enrichment Increases the Sparseness of Spatial Representations in the Hippocampus

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Complex environments improve cognitive functions including hippocampus-dependent tasks but the mechanisms underlying these enhancements are poorly understood. Previous studies of hippocampal physiology following exposure to complex environments have yielded mixed results. Indeed, we observed no differences in basic hippocampal physiology following a 3-4 month period of environmental enrichment. To explore this issue further, we exposed enriched and control rats to a novel environment for 5 min and then processed their hippocampi for immunohistochemical labeling of the immediate early gene ARC, a marker of recent neural activity, and NeuN, a marker for all neurons. Using a confocal microscope, the number of ARC positive neurons in CA1 was then quantified. Enriched rats had significantly *fewer* ARC positive neurons (10% ARC positive neurons) following the novel environment exposure than did control animals (36%) suggesting that the enriched animals are using a more sparse code to store a spatial representation. This effect was not due to changes in overall neuron density or width of the cell body layer in CA1. A sparse code would theoretically increase the storage capacity and enhance the pattern discrimination power of enriched animals' hippocampal network. In support of this hypothesis, when the animals were tested behaviourally, enriched animals were more sensitive to a change in the environment compared with controls.

Supported by the New Zealand Marsden Fund.

Poster 4.10

The Plasma Membrane Ca^{++} ATPase, PMCA2, Contributes to Pre-Synaptic Ca^{++} Dynamics and Short Term Plasticity at the Cerebellar Parallel Fibre to Purkinje Neurone Synapse

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PMCA2 is a fast, highly effective mechanism to control (by extrusion) resting cytosolic Ca^{++} and Ca^{++} excursions in neurones and other excitable cells. The strong expression of PMCA2 in the cerebellum and the cerebellar behavioural deficits presented by PMCA2-/- knockout mice all point to its importance for cerebellar circuit dynamics. The aim was to provide direct functional evidence for the influence of pre-synaptic PMCA2 mediated Ca^{2+} extrusion for short term plasticity at cerebellar parallel fibre to Purkinje neurone synapses. Whole cell patch clamp recordings from Purkinje neurones (PNs) within cerebellar slices from wild type (wt) and PMCA2-/- mice revealed enhanced paired pulse facilitation (PPF) of parallel fibre (PF) evoked EPSCs from PMCA2-/- PNs, that also took longer to return to baseline. Similar results were obtained in the presence of the PMCA inhibitor, carboxyeosin, but eosin was ineffective in PMCA2-/- cells. Additional results from intracellular Ca^{++} measurements from bundles of pre-synaptic PFs showed that the decay of the PF Ca^{++} transient was also enhanced in slices from PMCA2-/- slices compared with wt. Our results provide strong functional evidence for a contribution by PMCA2 to the clearance of Ca^{++} from the PF pre-synaptic compartment to influence short term plasticity at the PF-PN synapse.

Poster 4.11

Assessing Cognitive Function in Neuropsychiatric Systemic Lupus Erythematosus; A Functional MRI Study

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Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect the nervous system causing neuropsychiatric SLE (NP-SLE). NP-SLE is characterised by the disruption of neurological and psychiatric functioning with cognitive dysfunction being a common manifestation. To date, no functional magnetic resonance imaging (fMRI) investigations of cognitive function in NP-SLE have been undertaken. Here we used fMRI to investigate brain activation in people with NP-SLE during a working memory task (the n-back). It was hypothesised that atypical neuronal function would be demonstrated in the NP-SLE group, relative to control groups, during performance of the n-back. In the n-back task, participants were required to identify if a presented letter was the same as that seen n trials beforehand. Neuronal activation in the 0-back and 2-back conditions was compared in 27 participants (9 NP-SLE patients, 9 rheumatoid arthritis (RA) controls and 9 healthy controls (HC). It was found that the NP-SLE group showed working memory load-related activation in the combined hemispheres of the posterior inferior parietal lobule (BA 7) that was significantly greater than the two control groups. This result confirms that NP-SLE patients demonstrate an abnormal pattern of increased working memory load-related activation, relative to controls.

Poster 4.12

The Temporal Link Between Chemokine Expression and Migration of Subventricular Zone Neuroblasts following Striatal Cell Death

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A number of studies have demonstrated directed migration of neural progenitor cells to sites of brain injury. This study examined the temporal correlation between progenitor cell proliferation ("birth") and neuroblast migratory response following quinolinic acid (QA) lesioning of the adult rat striatum. Retroviral labelling of subventricular zone (SVZ)-derived progenitor cells demonstrated that the majority of doublecortin cells present in the damaged striatum were generated from progenitor cells dividing within 2 days either prior to or following the QA lesion. In contrast, cells dividing 2 or more days following QA lesioning, migrated into the striatum but exhibited a glial phenotype. These results demonstrate that directed migration of SVZ-derived progenitor cells and neuroblast differentiation in response to QA lesioning of the striatum is acute and transient. To establish a relationship between the temporal profile of SVZ progenitor cell migration and chemokine protein expression following QA lesioning, we performed a large scale screening approach investigating a panel of chemokines. Of this panel, MCP-1, MIP-1α and GROα were found to be significantly increased in the striatum for the first 2 days following the lesion, with protein levels ranging from 25-63 fold over normal. This suggests a strong temporal correlation between increased striatal chemokine protein expression and SVZ progenitor migration. We therefore propose that lesion-induced expression of the chemokines MCP-1, MIP-1α and GROα act to attract SVZ progenitor cells into the QA lesioned striatum.

Poster 4.13

Heterosynaptic Inhibitory Priming of LTP in Area CA1 of the Hippocampus

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In the BCM model of experience-dependent plasticity, the modification threshold (θ_M) is regulated by the cell-wide previous history of postsynaptic activity. The aim of this research was to investigate the mechanisms by which strong high-frequency priming stimulation reduces the level of long-term potentiation (LTP) later induced on an independent but converging pathway. Field excitatory postsynaptic potentials were recorded in area CA1 following stimulation of the Schaffer collaterals of acute hippocampal slices from 6-7 week male Sprague-Dawley rats. Priming one pathway reduced the level of LTP induced 30 min later by either 50 Hz or 100 Hz stimulation of the heterosynaptic pathway. This effect was not mediated by increases in GABAergic inhibition as the addition of 100 μM picrotoxin and 1 μM CGP did not prevent priming. Two key predictions of the BCM model are that changes in θ_M occur cell-wide and are determined by the levels of previous cell firing. Priming stimulation of the stratum oriens inhibited LTP induced in the stratum radiatum, supporting the hypothesis of cell-wide changes in θ_M. We found, using sharp electrode intracellular recordings, that hyperpolarising cells during priming to completely prevent somatic action potentials, did not prevent priming. Furthermore, there was little if any postsynaptic cell firing during the normal priming stimulation. These results suggest that synaptic plasticity is homeostatically regulated by the cell-wide history of activity, but that postsynaptic cell firing is not necessary for such regulation to occur.

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Poster 4.14

Neural Substrates of a Visual Illusion: Evidence for Visual Cortex Plasticity in the McCollough Effect?

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The McCollough effect (ME) is a long-lasting orientation-contingent colour aftereffect in which colourless gratings appear coloured following exposure to chromatic gratings in which a colour is paired with a particular line orientation. The neuronal mechanisms that underpin the ME remain unclear. While early explanations involved neuronal fatigue, recent proposals implicate synaptic plasticity (long-term potentiation; LTP; and long-term depression; LTD). This exploratory study investigated whether systematically varying the rate of presentation of ME induction stimuli across rates that have been shown to differentially impact on sensory-induced plasticity in visual cortex would also affect the ME, both behaviourally and neurophysiologically. We measured visual evoked potentials (VEPs) elicited by achromatic gratings before and after ME induction at one of three stimulation rates, as well as measuring the effect of stimulation rate on the perceived aftereffect. Behaviourally, the aftereffect was not influenced by the rate of induction stimulation, but the neurophysiological changes accompanying the ME were affected. Very high-frequency stimulation (18 Hz) led to an increase in the amplitude of a late positive VEP component, while low-frequency stimulation (1 Hz) decreased the amplitude of the same component. Source estimation analyses suggested that changes originated in different regions of visual cortex following the different rates of stimulation.

Poster 4.15

The Acute Effects of Trifluoromethylphenylpiperazine (TFMPP) Administration on the Amplitude of the P300 in Healthy Adult Right Handed Human Males

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Trifluoromethylphenylpiperazine (TFMPP) is a new designer drug reported to have psychoactive effects in rodents and humans similar to methamphetamine (MA) and 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). The combination of TFMPP and another piperazine analogue benzylpiperazine (BZP) are legal and widely available in New Zealand. These compounds have become a popular alternative to MDMA and MA. Despite conservative estimates that 150,000 doses/month of Party Pills are sold in New Zealand, little information is available describing the acute effects of these drugs which appear to be amphetamine-type stimulants. This double-blind, placebo-controlled study investigated the effects of TFMPP on event-related potentials (ERP) during an auditory odd-ball task. The N100 and P300 components of the human ERP can provide insights into information processing, attention allocation and immediate memory processes. Healthy, right-handed males (25 ± 5.6 years old) were given placebo (n= 16) or TFMPP (0.94mg/kg, oral, n=15) and tested pre- and 1.5-2 hr post-drug administration. There was no effect of TFMPP on the N100 ($F_{(1,29)} = 0.75$; n.s.). Simple effects analyses revealed that the P300 amplitude was significantly reduced after administration of TFMPP (Pre: 3.18 ± 0.24μV, Post: 2.82 ± 0.28μV; $p<0.05$). The results show that TFMPP reduces the components involved in attention allocation and immediate memory processing whilst not affecting basic information processing. The effect of TFMPP on the oddball-evoked ERP is similar to cocaine, suggesting that their effects on cognitive processes may also be alike. This suggests that, in general, their effects on cognitive processes may also be similar.

Poster 4.16

Recording of Cerebral Oxygen Saturation Using Near Infrared Spectroscopy in an Ischemic Rat Model

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Near infrared spectroscopy (NIRS) has been developed as a noninvasive technique to measure the changes in concentrations of oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb) and total hemoglobin (HbT) as well as cerebral oxygen saturation (StO_2). Recently, NIRS has been utilized to assess cerebral oxygenation, hemodynamics and neuronal activity in humans. However, the clinical value of NIRS-parameters in ischemic stroke is still uncertain. In the present study, we investigated the changes in cerebral blood flow (CBF) using laser-Doppler Flowmetry (LDF) and NIRS in rats subjected to temporary (60-mins) middle cerebral artery occlusion (MCAO). In addition, NIRS-parameters were recorded from the initial ischemic events up to 4 weeks after the MCAO operation in rats. Ischemic changes, averaged over the 60 minutes of occlusion, were follows: CBF = -52.41 ± 9.77%, StO_2 = -24.67 ± 10.85%, HbT = -13.17 ± 18.56%, HbO_2 = -33.09 ± 23.21%, Hb = 21.06 ± 11.47%. Our results revealed that the changes of flow were similar to the changes in concentration of HbO_2 and in StO_2. In addition, mismatch between cerebral blood flow and volume was found. The results of time-course monitoring on the ischemic stroke rat also showed that NIRS might be used for monitoring the condition of ischemic stroke and could be a practical tool for predicting the functional outcome after stroke.

Poster 4.17

Evidence of Neurogenesis in the Temporal Cortex of the Adult Human Epilepsy Brain

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Endogenous progenitor cells exist in the adult human brain and have the potential to proliferate and generate new neurons (Eriksson et al., 1998). Recently, increased numbers of proliferating cells and the presence of new neurons have been observed in the adult human Huntington's diseased brain (Curtis et al., 2004), demonstrating that the adult human brain has the potential to produce new neurons in response to progressive cell loss. Extending these observations, this study aimed to investigate the regenerative potential of the adult human brain in response to cell loss associated with temporal lobe epilepsy. Using immunohistochemical techniques and a marker for migrating immature neurons, doublecortin, this study showed increased numbers of migrating immature neurons in the temporal cortex of the adult human epilepsy brain compared to the control brains. Antibody specificity was confirmed using Western blot analysis. Most importantly, triple immunofluorescence labelling using the markers doublecortin, proliferating cell nuclear antigen (PCNA) (a proliferative cell marker) and βIII-tubulin (an early neuronal marker) demonstrated that a population of cells immunopositive for doublecortin co-express both PCNA and βIII-tubulin indicating that cells have undergone proliferation to generate new immature neurons. These findings provide evidence of neurogenesis in the temporal cortex of the adult human epilepsy brain.

Poster 4.18

Neuropsychological Sequelae of an Electrocution Accident: Assessment and Treatment Considerations

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Electrical injuries present a growing concern in residential and occupational settings. About 1000 deaths per year result from electrical injury (EI) in the US. An Australian retrospective study of electrocution deaths reported the following data: male (91%), female (9%), accidents (69%), suicides (29%), low-voltage (<1000V) (83%), high-voltage (>1000V) (16%), and lightening (1%). EI survivors typically report physical injuries (e.g., burns, respiratory arrest, cardiovascular abnormalities) and neurologic damage (e.g., sensory deficits, transient paralysis, and cerebral infarction). While there has been a growing interest in the neuropsychological sequelae of EI in recent years, there is no distinct model for its assessment and treatment. The present case study involves a 42 year-old woman, who was cleaning irrigation pipes with her boss, when a raised pipe hit 3-phase 24,000V overhead powerlines, causing their electrocution. She lost consciousness and/or suffered post-traumatic amnesia for 15-20 minutes, and was treated for hands burns and right ankle haematoma. Following the accident, she reported multiple physiological, psychological and neuropsychological symptoms, often resulting in psychiatric admissions. Neuropsychological assessment (2003) suggested that she might have acquired mild brain dysfunction due to her electrocution, which was difficult to separate from her psychiatric symptomatology (including PTSD). A follow-up assessment (2007) showed significant deterioration in psychological functioning, but only selectively neuropsychologically. It is suggested that attention/concentration, memory, processing speed, and executive functioning as well as emotional sensitivity, moodiness, anxiety and depression are more vulnerable to electrocution, and should be properly assessed and treated.

Poster 4.19

Variation in Hippocampal Theta Shoulders Along the Longitudinal Axis of the Hippocampal CA1 Subregion

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The hippocampal theta oscillation is typically not purely sinusoidal. In many recordings, a distinct shoulder appears on each theta wave, which likely gives rise to the second harmonic component often seen in hippocampal EEG power spectra from behaving animals. Terrazas et al (2005) showed that the amplitude of the theta shoulder is more strongly dependent on running speed than the fundamental wave, and thus the waveshape changes substantively with running speed. Maurer et al (2005) showed that both theta amplitude and neuronal firing rates increased more steeply with running speed in the dorsal, compared to the middle hippocampus, suggesting that the gain of some self-motion signal might vary systematically along this axis, leading to a change in the scale of the spatial representations (place fields). Further analysis of the data from Maurer et al. (2005) now shows that the shoulder component of the theta wave is much weaker in the middle region of the CA1 field than more dorsally, suggesting that this component may be the primary factor in the septotemporal variation in slope of the theta amplitude versus running-speed function.

Poster 4.20

Insulin-Like Growth Factor-1 (IGF-1) Acts as a Chemoattractant For Adult Neural Progenitor Cells in the Normal Adult Rodent Brain

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The migration of subventricular zone (SVZ)-derived neural progenitor cells along the rostral migratory stream (RMS) to the olfactory bulbs is tightly regulated by a number of local microenvironmental cues. Using *in vivo* gene transfer, we investigated whether IGF-1 could redirect the migration of neural progenitor cells from the RMS into the normal adult rat striatum. IGF-1 was overexpressed in adult Wistar rats by unilateral striatal injection of the viral vector, $AAV_{1/2}$-IGF-1. Control animals received $AAV_{1/2}$-Luciferase. Animals received daily injections of the mitotic marker BrdU from18 to 28 days after $AAV_{1/2}$ injection to label proliferating progenitor cells. Animals were killed 4 or 8 weeks after $AAV_{1/2}$ injection. Migrating neural progenitor cells were visualised by immunocytochemistry using the immature neuronal marker doublecortin (Dcx) and the number of Dcx positive cells and the extent of cell migration quantified. Neuronal differentiation was examined 8 weeks after $AAV_{1/2}$ injection by investigating the degree of colocalisation for BrdU and neuronal markers including NeuN, calbindin and DARPP32. We observed no difference in the number of Dcx positive cells within the striatum of $AAV_{1/2}$-IGF-1 and $AAV_{1/2}$-Luciferase treated animals 4 weeks after viral vector injection. In contrast, the number of Dcx positive cells, and the extent of their migration into the striatum was significantly increased in $AAV_{1/2}$ -IGF-1 treated animal compared to control animals 8 weeks after injection. A small proportion of these cells were found to double label with BrdU/NeuN. These results demonstrate that IGF-1 can redirect the migration of neural progenitor cells from the SVZ/RMS into the normal adult rat striatum and may have potential in enhancing progenitor cell migration to sites of brain injury.

Poster 4.21

The Effects of a Calcineurin Inhibitor on Vestibular Compensation

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Several lines of evidence suggest an important role of calcium in vestibular compensation, the process of behavioural recovery that occurs following peripheral vestibular damage. Our previous results from real-time PCR studies revealed an up-regulation of molecules relating to calcium-mediated intracellular signaling cascades in the ipsilateral vestibular nucleus complex (VNC) 6 hs after unilateral vestibular deafferentation (UVD). In this study, to further confirm the role of calcineurin in the development of vestibular compensation after UVD, we investigated the effects of pre-treatment of FK506, a calcineurin inhibitor (1,5, or 10 mg/kg i.p.), by measuring the number of spontaneous nystagmus beats following UVD until 48hs post-op. We also assayed the activity of calcineurin by measuring free phosphate in the VNC 24hs after FK506 10mg/kg i.p., which is reported to show its maximum effect in the whole blood, to confirm the effect of FK506 on calcineurin in the VNC. Among FK506-treated animals, the groups treated with 5 or 10 mg/kg showed a significantly higher number of spontaneous nystagmus beats at 12 hs and 18 hs post-UVD compared to those in the 1 mg/kg group ($p < 0.01$). The amount of free phosphate, representing the activity of calcineurin, was suppressed to 2.7 nmol/mg/min in the FK506 treated group compared to 5.4 nmol/mg/min in the control group ($p<0.05$). The dose-dependent pattern of the effects of FK506 strongly suggests that a calcineurin inhibitor decelerates vestibular compensation, suggesting that calcineurin might induce vestibular compensation by acting on the phosphorylation state of target proteins in the VNC after UVD.

Poster 4.22

CaMKII Contribution to Protein Synthesis-Dependent mGluR-mediated LTD in Rat Hippocampus

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The mechanisms by which group 1 mGluR-mediated LTD is induced have not yet been fully elucidated, although it is known to be protein synthesis dependent in adult animals. Biochemical studies in our lab have suggested that mGluR-dependent protein synthesis is mediated by calcium/calmodulin-dependent protein kinase II (CaMKII). The present study tested whether mGluR-depdendent LTD has a similar dependence on CaMKII. Hippocampal slices with CA3 removed were prepared from 6-7 wk male Sprague-Dawley rats. Field EPSPs were recorded in area CA1 and the initial slope was measured. The group 1 mGluR specific agonist DHPG (100 μM, 10 min) induced an LTD (-36 ± 3%, n=7) that was only partially blocked by the protein synthesis inhibitor cycloheximide (60 μM, -20 ± 6%, n=5; $p<0.05$). Similarly, inhibition of CaMKII with KN62 (10 μM) partially blocked the induction of LTD (-14 ± 5%, n=11, $p<0.005$). Because KN62 by itself induced a depression, the effect on DHPG-induced LTD was only revealed when the average KN62 effect was subtracted from individual DHPG experiments. In contrast, the LTD was not blocked by inhibitors of the classical Group I mGluR signaling pathway such as U73122 (10 μM, phospholipase C inhibitor), which actually facilitated LTD induction (-51 ± 3%, n=4 $p<0.005$), or chelerythrine (10 μM, protein kinase C inhibitor, -37 ± 5%, n=7). We suggest that group 1 mGluR-mediated LTD is only partially dependent on new protein synthesis and that this mechanism involves CaMKII activation.

Supported by the NZ Health Research Council.

Poster 4.23

Apoptotic Cell Death in the Cingulate Cortex Ten Hours After a Single Exposure to Ethanol on Postnatal Day 7

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This study investigated the acute effects of a single binge ethanol exposure on the cingulate cortex of the neonatal rat. Long Evans rat pups, 7 days of age, were exposed to ethanol (AI - 4.5g/kg/day ethanol in 2 feeds, 2 hours apart via intubation) or sham intubated (IC - control group). Pups were killed ten hours following ethanol delivery to investigate acute apoptotic cell death. The forebrain was frozen and serially sectioned at 40μm. Matched, coded sections were stained with either Hoescht 33342, Haematoxylin or immuno-stained to detect GFAP, Neu-N and active caspase-3. Stereological methods were used to determine the total number of apoptotic nuclei within the cingulate cortex. Immuno-staining was used to phenotype apoptotic cells. Peak blood ethanol concentration 3.5 hours after ethanol feeding was 382.79 ± 57.29mg/dl (*mean* ± *sd*). ANOVA with posthoc analysis (SPSS) found significantly more apoptotic cells in the cingulate cortex of the AI group compared to the IC group (F=78.53, $p<0.001$). Immuno-staining showed apoptotic cells belonged to neuronal and astrocytic populations. This acute cell death indicates that both neurons and glia cells are susceptible to ethanol-induced cell death. This cell death may affect the normal development of neuronal connections within the cingulate cortex. This experimental paradigm models the late third trimester of human development and thus suggests that single binge alcohol exposure may affect the developing human fetus in a similar manner.

Poster 4.24

Developing a Pharmacology of Epigenetics

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There is increasing evidence of altered epigenetic control of genes in brain disorders like Alzheimer's. Valproic acid (VPA) is a drug widely used for the treatment of bipolar disorder and epilepsy. Recent studies have shown that VPA also acts as a histone deacetylase (HDAC) inhibitor, thus maintaining the N-terminals of susceptible histones in an acetylated and transcriptionally active state. We sought to develop a high content assay to measure histone acetylation in response to VPA treatment using human neural cells in an attempt to characterize the pharmacology of its actions on the epigenome. We studied the effects of VPA on acetylation for histone H3 in SK-N-SH cells. Histone acetylation was measured using immuno-cytochemistry, high content imaging and analysis of staining intensity distributions, where the intensity values of every cell in the population were accounted for. VPA increased histone H3 acetylation in a concentration- and time-dependent manner. To confirm these results and validate our high content assay we performed experiments using a known HDAC inhibitor, trichostatin A (TSA) and Western blotting. TSA had a similar profile of action to VPA and Western blotting validated the high content assay as a method for studying histone actelyation. Our findings demonstrate an important role for VPA in controlling epigenetic processes. This assay can be used to investigate how various pharmacological agents alter neuronal epigenetics and help in the development of a pharmacology of epigenetics.

Supported by the National Research Centre for Growth and Development.

Poster 4.25

Benzylpiperazine (BZP) Decreases the Amplitude of the P300 Event-Related Potential (ERP) in Healthy Adult Right-Handed Human Males

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Party pills containing benzylpiperazine (BZP) are widely, and legally, available in New Zealand. Early research has found similarities between BZP and dexamphetamine. In a double-blind, placebo-controlled study, the electrophysiological effects of BZP were investigated in right-handed 18-40 year old male volunteers. Twelve participants per group (mean age 25.8 ± 5.8 years) were tested before and 1.5–2 hrs after administration of a single oral dose of BZP (250 mg) in controlled laboratory conditions. A 128-channel electroencephalogram (EEG) was employed to record the P300 potential evoked in an auditory oddball task before and after drug administration. A group by time split-plot ANOVA was performed on the amplitude and the latency of the P300 ERP. For amplitude, the time (pre v post) by group (BZP v placebo) interaction approached significance, $F_{(1,18)}$= 3.49, p = .078. Simple effects tests demonstrated that amplitude was significantly lower in the BZP group post administration compared to pre administration (2.79 ± 1.01 μV post, 3.17±1.03 μV pre; $F_{(1,18)}$=8.56, p=.009). There was no significant change in the control group and there was no significant drug-induced effect on the latency of the P300 component for either group. This suggests that BZP is in a similar category to other psychostimulants such as cocaine and caffeine, which are known to reduce the amplitude of the P300 ERP.

Poster 4.26

Precued Parameters: Effects of Knowing Hand, Direction and Muscle on Motor Preparation

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Precue information about an upcoming movement affects reaction time (RT). As uncertainty about the nature or number of parameters increases, RT becomes longer. The effect of precued parameters on motor preparation was investigated by measuring changes in cortical and muscle activity and RT. Twelve participants each performed 1280 trials. Five precue conditions comprised simple, two- and four-choice RT tasks. Before stimulus onset, a precue provided information about the hand (left or right), direction (left or right) or homologous muscles (pronators or supinators, in an ambiguous precue condition where neither hand nor direction were specified) associated with one, two or four targets. A variable foreperiod was followed by an imperative stimulus. RT increased as a function of the number of precued parameters ($p < .05$). Within the three 2-choice RT conditions, RT was longer when the precue specified direction compared to the ambiguous and hand precue conditions. Amplitude of the contingent negative variation (CNV) decreased when uncertainty increased. CNV amplitude was greater in the contralateral hemisphere. Within each hand, the effect of the nature of the parameter was observed at the ipsilateral recording site; CNV amplitudes were greater ($p < .05$) when the precue was ambiguous or specified direction. Amplitude of the foreperiod lateralised readiness potential (LRP) was greater when complete rather than partial information was precued ($p < .05$). Precuing effects reflect central (non-motoric) mechanisms of motor preparation whereby hand and direction parameters are programmed in series, and, hand and muscle appear to be programmed in parallel.

Supported by a University of Otago Postgraduate Award to R Scott.

Poster 4.27

Interleukin-10 Release from Spinal Cord Microglia and Astrocytes After Toll-Like Receptor 4 Stimulation is Enhanced by Glutamate

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Neuropathic pain involves activation of the Toll-like receptor 4 (TLR4) on spinal cord glia, leading to the release of a variety of cytokines (Tanga et al (2005) PNAS 102(16):5856-61). One released cytokine is interleukin-10 (IL10) which blocks the action of pro-inflammatory cytokines. The question arises as to whether excitatory synaptic transmission using glutamate can modulate this protective mechanism. Enzyme-linked immunosorbent assay was used to quantify IL10 release from cultured spinal cord microglia and astrocytes. RT-PCR was used to measure IL10 mRNA expression. Lipopolysaccharide (LPS) was used as a TLR4 agonist. Glutamate (1 mM) significantly increased LPS-stimulated IL10 release from astrocytes by 168% and from microglia by 140% ($p < 0.01$). Correspondingly, glutamate enhanced LPS-stimulated transcription of IL10 mRNA in both types of glial cells. The effect of glutamate on IL10 release was dependent on the concentration of glutamate used (EC_{50} for astrocytes was 363 μM and EC_{50} for microglia was 280 μM). Maximum potentiation occurred when glutamate and LPS were co-applied for 16 h. A metabotropic glutamate receptor group I/II agonist mimicked the effect of glutamate on microglia and astrocytes while agonists to other glutamate receptor subtypes had no effect. These results show that glutamate substantially increases the release of an anti-inflammatory cytokine from TLR4-activated astrocytes and microglia. This implicates excitatory transmission in the spinal cord in the release of anti-inflammatory cytokines.

Poster 4.28

Development of a Stable Cell Line Expressing the Human M3 Muscarinic Receptor

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Muscarinic acetylcholine receptors are involved in many processes including memory formation and cell survival. To study the pharmacology and function of the human M3 muscarinic receptor we have developed a stable HA-tagged M3-HEK 293 cell line. To characterize this stable cell line we performed immunocytochemical and western blot analysis and functional reporter assays. Immunocytochemistry using two different antibodies to the M3 receptor, directed at different epitopes, detected predominantly cell membrane-bound M3 receptor which internalized 1 h after agonist (carbachol) exposure. Immunocytochemical localization of HA showed a similar pattern of staining to the M3 receptor antisera. Western blot analysis confirmed the immunocytochemical results. We also performed functional signaling assays to determine whether transcription factors CREB and Krox24, known to be induced by activation of endogenous M3 receptors on human neuroblastoma cells, were activated in HA-tagged M3-HEK293 cells. Both CREB (activated by phosphorylation) and Krox24 were strongly activated in HA-tagged M3-HEK293 cells. Additionally, there was a carbachol-mediated low level CREB and Krox24 activation in wild-type HEK293 cells indicating that wild-type HEK cells express endogenous muscarinic receptors. We have developed a stable human M3 receptor expressing HEK293 cell line for use in studies of the pharmacology and function of this receptor.

Supported by a grant from the Health Research Council of New Zealand.

Poster 4.29

Investigation of Sleep Cycle Maturation and Brain-State Phase Transitions in Fetal Sheep

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The present project is to apply the Waikato mean-field model—which predicts that the adult human brain-state transition between slow-wave sleep (SWS) and rapid-eye movement (REM) sleep can be analysed as a first-order phase transition—to the maturing brain of the fetal sheep. Correlation time (τ), singular-value decomposition (SVD) entropy and spectral-edge frequency (SEF) analysis of fetal sheep EEG recordings indicate that before 125-day gestational age (dGA), the EEG shows no organized stable state. After 125 dGA, two stable cyclic SWS and REM states are established: the SWS state has higher average power, longer τ and smaller entropy than the REM state. With increasing age, for SWS state, τ increases, and entropy and SEF decrease. For REM state, τ decreases with age, while entropy and spectral edge increase, indicating that REM state has broader spectrum with less-synchronized voltage fluctuations. Therefore, we see a progressively increasing contrast between SWS and REM states with advancing age. Furthermore, the brain-state transition from SWS to REM is much more abrupt than the transition from REM to SWS. These observations suggest that the "up" transition from SWS to REM can be modeled as a first-order (discontinuous) phase change in cortical state, while the "down" transition from REM to SWS is a second-order (continuous) phase change.

Poster 4.30

Regulation of N-Methyl-D-Aspartate Receptor Subunits NR1 and NR2A Expression *in vitro*

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Ionotropic N-methyl-D-aspartate receptor (NMDAR) activation is essential for long-term potentiation (LTP). Expression of specific NMDAR subunits, NR1 and NR2A-B, is up-regulated during late phase of LTP *in vivo*. Interestingly, only NR2 subunits expression was sensitive to pre-existing NMDAR blockade, it appeared that different signalling pathways regulate NR1 and NR2A-B expression. This study investigated which signalling pathways may control NR1 and NR2A promoter transcription by transfecting differentiated SH-SY5Y neuroblastoma cells with pGL3 vector (Promega) containing either NR1 or NR2A promoters cloned upstream of the luciferase reporter gene. Using this assay we found significant increases in luciferase activity for both pGL3-NR1 (32 ± 7%; mean ± S.E.M., n = 12; $p < 0.01$) and pGL3-NR2A (18 ± 5%, n = 9; $p < 0.01$) following 24-hour treatment with 50 μM glutamate. The glutamate-induced NR2A promoter activity increase was attenuated when incubated with NMDAR antagonist, CPP (pGL3-NR2A -7 ± 5%, n = 6) but NR1 promoter activity was unaffected (26 ± 16%, n = 7). In contrast, incubation with group 1 metabotropic glutamate receptor antagonist, LY-341495, blocked glutamate-induced activity of both NR1 and NR2A promoters (pGL3-NR1 10 ± 3%, n = 7; pGL3-NR2A 5 ± 2%, n = 7). These results confirm our hypothesis that pre-existing NMDARs control expression of NR2A, but are not required for NR1 expression, which is likely controlled by metabotropic receptors-linked signalling pathways.

5.1

25 Years of Motor Control and Learning Research: The Paradigm Crisis Resolved?

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The 25 years since the inaugural meeting of AWCBR has been a period of rapid change in the field of motor control. Of particular significance has been the emergence of the ecological approach to perception and action that, to some, placed the motor control and learning field in the midst of a full scale Kuhnian (1962) paradigm crisis. In recent years, differences in how the relation between perception and action should be conceptualised have led to a bifurcation between researchers remaining within the ecological psychology umbrella and researchers adopting dynamical systems theory. This presentation will trace the developments in the field over the past 25 years with particular reference to my own area of research, interlimb coordination. Our research has focused on the interaction between cognition and dynamics in the learning and control of coordination patterns. In the second part of the talk the recent shift to identifying the neural correlates of coordinated behaviour will be discussed and future directions outlined.

5.2

Lateralisation of Motor Imagery Following Stroke

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In people recovering from stroke, motor imagery may activate the primary motor cortex (M1) of the stroke-affected hemisphere. We investigated whether the hemisphere affected by stroke affects the ability to perform motor imagery and the facilitation of M1 activity. Experiment one assessed the speed and ease of actual and imagined motor performance. Experiment two measured corticomotor excitability during imagined movement of each hand separately, and both hands together, using transcranial magnetic stimulation. Control participants imagined movements more slowly than actual performance, and MEPs were facilitated in the right hand when they imagined moving their right hand and both hands together. Stroke patients reported that they were able to imagine movements with either hand, despite no measurable facilitation of MEPs in the stroke-affected hand. In left hemisphere stroke patients, MEPs were facilitated in the left hand during imagery of both hands together. In contrast, motor imagery did not facilitate MEPs in either hand of right hemisphere patients. We speculate that input from regions of the right hemisphere are required to facilitate left M1 excitability during motor imagery, and this is prevented by damage to the right parietal cortex.

5.3

Effects of Stimulus Modality, Foreperiod Duration and Memorisation on Brain Event Related Potentials and Reaction Time

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In monkeys, memorisation of target location is associated with faster reaction time (RT). Results from our laboratory indicate that in humans RT is shorter when memorisation is not required and longer when the location of the target must be remembered until the "GO" signal. One hypothesis is that in the "memorise" condition participants shift visual attention between the source of the visual "GO" signal and the location of the precued (but not illuminated) target. In this experiment we replaced the visual with an auditory stimulus. Ten participants performed 48 trials to each of four targets in three foreperiod and two memorisation conditions, (a total of 1152 trials). On each trial, participants moved their index finger in response to an auditory "GO" signal, from a central switch to one of the targets. RT was measured from the "GO" signal to switch release. A precue 750 - 1050 ms before the "GO" signal indicated the correct target. The target either remained illuminated during the foreperiod (non-memorisation condition) or was extinguished after 300 ms (memorisation condition). EEG data were recorded from scalp surface electrodes. RT was significantly faster ($p < .001$) for non-memorisation (M = 210 ms) than memorisation (M = 216 ms). Brain electrical activity, represented as a contingent negative variation (CNV) was increased over the contralateral (C3') motor cortex and, paradoxically greater in the memorisation condition in which RT was longer. While the magnitude of the CNV amplitude (C3') is robust evidence of motor preparation per se, it does not appear to predict the speed of preparation in this experiment.

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5.4

Functional Connectivity Between Primary and Secondary Motor Areas During Interlimb Coordination

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Coordination of coincident hand and foot movement is direction-dependent regardless of the musculature used to execute the movement. Previously in this forum it was reported that excitability of forearm representations within primary motor cortex (M1) are modulated by foot movement direction. In a new experiment the neural basis of the isodirectional movement preference was explored by probing "secondary" motor areas that interact functionally with M1. Targeted dual-coil paired-pulse transcranial magnetic stimulation (TMS) was combined with electromyography (EMG) to examine the interaction between dorsal premotor cortex (PMd), ventral premotor cortex (PMv) and supplementary motor area (SMA) on the excitability of arm muscle representations within M1. Using a range of conditioning stimulation intensities applied over secondary motor areas, we examined the size of motor evoked potentials (MEPs) in EMG of forearm flexor (FCR) and extensor (ECR) in eight participants tested at rest, and during voluntary ipsilateral ankle plantarflexion and dorsiflexion movement. Consistent with previous findings, a direction-dependent and reciprocal facilitation of FCR and ECR MEPs was observed using single-pulse TMS. With dual-coil paired-pulse TMS, conditioning of PMv had no bearing on MEP amplitude across all conditions. At rest, conditioning of SMA revealed an early phase of inhibition in MEPs consistent with previous reports, but was abolished during both plantarflexion and dorsiflexion, suggesting that SMA-M1 networks may be involved in the maintenance of posture. Conditioning of PMd revealed two distinct phases of MEP facilitation during foot movement compared to inhibition at rest. The facilitation promoted hand movement in the same direction of the foot. Networks within PMd may functionally stabilise preferred patterns of interlimb coordination by modulating intracortical elements within M1 through divergent cortico-cortical networks.

5.5

Wave Like Behaviour of Skeletal Muscle Under Gentle Compression

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The aim was to explain wave like behaviour of skeletal muscle during its compression. Skeletal muscle was gently compressed using the device with interpretive software. The sensor was compressing the muscle at a constant rate- 0.5 mm/s. The instantaneous forces of resistance and the level of vertical deflection as well as the period of deformation were measured from the 200-400 points. The experimental session includes *in-vivo* and *in-vitro* approaches. *In vivo* we tested adductors of thumb of 10 untrained young males. *In vitro* we used 6 samples of fresh meat (beef) - 12 points in each sample. There were three data acquisitions per each tested point. Each sample of meat was tested twice before and after artificial drying (up to 65 % of its initial mass). Stiffness was analysed over each step of 0.05 mm of compression. In each case we calculated the frequency of fluctuation of momentary stiffness over the total plot of compression. *In vivo* inspection muscle showed a narrow range of frequencies from 6.73 to 7.44 Hz. (7.15 + 0.24 Hz). Close range of frequencies, was demonstrated also on the fresh meat, but the results of the dry tissues demonstrated significantly lower level of frequencies (5.27+0.31). These results may be due to compressive distribution of the fluids within muscular compartments. We speculate that the close ranges of frequency *in vivo* and *in vitro* (intact muscle) may reflect the same patterns in extra cellular liquid currents. Consequently our next study will examine the patterns of fluctuation of stiffness on the degenerated or inflamed muscles, to determine the different amount of fluid in their compartments.

5.6

Measurement of Neural Drive During Voluntary Efforts With Transcranial Magnetic Stimulation is Insensitive to Inadvertent Activation of the Antagonist Muscles

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Single pulse transcranial magnetic stimulation (TMS) has been used recently to provide reliable measurements of voluntary activation for the elbow flexors and the wrist extensors in humans. Although this technique has been shown to give reproducible measurements across days, it has been criticized for its potential limitation associated with inadvertent activation of the antagonists. Co-activation of the antagonists may give an overestimation of voluntary activation. Here, for the first time, we formally examined the sensitivity of this twitch interpolation technique using a muscle twitch potentiation method. We measured voluntary activation of the wrist extensors with TMS in 6 healthy volunteers with and without prior antagonist potentiation, achieved via a brief maximal wrist flexion contraction. Cortical voluntary activation is measured with a method proposed by Todd et al (2003). Brief maximal flexion contractions increased the resting wrist flexor twitch force produced by supramaximal median nerve stimulation by approximately 205% ($p=0.002$) but did not change the estimation of wrist extension voluntary activation ($p=0.013$, test of equivalence). We conclude that TMS can be used to provide valid and reliable measurement of voluntary activation for the wrist extensors and suggest that the technique may be applicable to other muscle groups.

5.7

Time-Course Analysis of Muscle Tone in Spinal Cord Injury and Parkinson's Disease Rat Models

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Spasticity and rigidity are often seen in neurological deficits associated with spinal cord injury (SCI) or Parkinson's disease (PD). The purpose of this study was to apply a quantitative device to assess the spasticity and rigidity changes for animals following SCI caused by T8 spinal cord hemisection and PD after unilateral infusion of the neurotoxin 6-hydroxydopamine (6-OHDA) into the medial forbrain bundle (MFB), respectively. The miniature manual stretching device measured the reactive torque and angular displacement at different stretching frequencies (1/3, 1/2, 1, 3/2 and 2 Hz). The viscous and elastic components were derived to represent the viscosity (B) and stiffness of rat's ankle joint. In SCI rat, the viscosity and stiffness reached a peak value around 3 weeks post-injury and slightly decreased afterwards. In PD rat, the biomechanical measurements showed not only increase in stiffness but also increase in viscous components in the contralateral side. Furthermore, both elastic and viscous components of PD rat were decreased after apomorphine injection. In conclusion, the present study used well-defined animal models to demonstrate the development of muscle tone in SCI and PD rats. The developed quantitatively biomechanical parameters can provide objective assessment methods for investigating the changes of abnormal muscle tone in rat models of SCI and PD that will be useful for evaluating novel treatments.

6.1

The Distinct Neural Network Involved in Pitch Labelling of Absolute Pitch Musicians

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Musicians with absolute pitch (AP) possess the rare ability to immediately recognise or reproduce tones of specific pitch without the aid of an external reference tone. Research on the neural substrates of AP has relevance for understanding the capabilities of the human brain for plasticity in general. The present study used electroencephalography (EEG) to investigate the auditory evoked potentials of AP musicians, non-AP musicians and non-musicians. The N1 component was compared across groups in musical tone labelling tasks with and without presentation of a reference tone. Source localisation differences examined using low-resolution electromagnetic tomography (LORETA) revealed that in the labelling task which did not give a reference tone, AP musicians demonstrated more activation than non-AP musicians in both left and right auditory regions, with a greater increase in the left hemisphere. This suggests that the two hemispheres may have separate roles for pitch processing, and additionally that AP musicians are able to recognise and assign labels spontaneously and thus are able to recruit left auditory regions effectively. The current findings suggest that when required to label tones without the aid of a reference note, AP musicians utilise the neural network involved in pitch processing with greater efficiency than non-AP pitch musicians and non-musicians.

6.2

Event-Related Potentials Reveal Age-Related Changes in Working Memory

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Performance measures and event related potentials (ERPs) were recorded during two working memory tasks from younger and older adults. For both tasks, digits were presented, visually, in strings from 4-11 numbers. In one task, participants were required to match the first four digits of a string to a subsequent 4-digit number (delayed-matching-to-sample task, DMST). In the other task, participants were required to match the last four digits of a string to a subsequent 4-digit number (Updating Task, UT). Performance for both age groups was better for the DMST than for the UT, but younger adults performed better than the older adults on the UT. ERP analyses revealed that neural inhibition of task-irrelevant digits was greater for younger than older adults regardless of whether there were differences in task performance between the age groups. ERP analyses also revealed that indices of proactive interference were greater for older than younger adults during the UT. Furthermore, ERP scalp distribution, during the UT, showed a stronger frontal focus for older adults. Thus, even though older adults showed a decline in the efficacy of neural inhibition, they were able to maintain task performance, within limits, in the face of distracting stimuli.

6.3

Dissociating Action and Linguistic Knowledge For Functional Objects

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People can learn to categorize new objects based on pragmatic experience with these objects, and not just the objects' appearance. Studies attempting to localize neural substrates for tool identification or use may be confounding linguistic and action knowledge. The present study addresses this issue by manipulating participants' experience with creating and naming novel objects, specifically, knots. Thirty participants spent 5 days learning how to tie or name 40 different knots. Before and after training, fMRI images were acquired while participants performed a perceptual discrimination task on pairs of knots. Imaging data indicate that when participants performed this task on knots they learned to tie, activity increased in brain regions associated with object manipulation and goal-oriented action, such as left inferior parietal lobule (IPL). Observation of knots whose names were learned resulted in activation of posterior cingulate and inferior temporal regions. Repetitive transcranial magnetic stimulation of IPL and ventral premotor cortex (PMv) on 15 of the participants revealed that stimulation of IPL had more of an effect than PMv stimulation on perceptual discrimination performance, particularly for knots that participants had learned to tie. We conclude that, with training, novel objects such as knots can take on tool-like functional properties that are mediated by inferior parietal areas rather than ventral stream areas for object identification.

6.4

Cognitus Interruptus: Inhibitory Control of Thought and Action

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The study of stopping serves as a model for how thought and action are controlled in the brain, and for how movement disorders arise and might be treated. Preventing a planned action involves a network of structures within the brain. Their output influences neurons within the primary motor cortex (M1), where descending commands for voluntary movement originate. This presentation will summarise our recent studies of motor system activity during selective prevention of movement. These studies demonstrate that it is easier to prevent two movements that were prepared for synchronous performance, than to prevent one movement while performing the other. The latter involves a generalised inhibition of both movements, followed by delayed performance of the desired movement. Thirteen participants completed an event-related functional MRI study of stopping behaviour. Performing the unimanual task engaged contralateral primary sensorimotor cortex and ipsilateral cerebellum. Rapidly preventing task performance engaged a predominantly right hemisphere frontoparietal network, including the inferior frontal gyrus. Selectively preventing one component of the task, while simultaneously performing another, led to additional activation of medial frontal cortex. The relationship between these findings and similar studies of stopping behaviour in people with Attention Deficit Hyperactivity Disorder will be discussed.

6.5

Conflict-Specific Theta Activation of Right Frontal Cortex - A Region Involved in Behavioural Inhibition

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Conflict resolution often requires that pre-potent behaviours be inhibited so that risk assessment or alternative actions can take their place. While conflict is likely to occur in tasks such as the Stroop, the Go/NoGo and the Stop Signal, it is likely to be accompanied by competition for attention, working memory or planning resources. To minimise task demands and separate out goal-conflict specific activations, we created a paradigm that uses simple stimuli and responses. We held monetary reward of a left key-press constant while varying the level of monetary punishment with: a) net reward greater than punishment to motivate participants to make a left key press; b) reward and punishment equally balanced; and c) net punishment greater than reward to motivate participants to avoid a left key press by making a right key press that had no monetary consequences. Condition 'b' had maximal goal-conflict, less net reward than condition 'a' and less punishment than condition 'b'. Condition 'b' produced more low band theta (4-5Hz) than 'a' or 'c'; and did so consistently in right frontal regions. This is not only consistent with previous studies implicating the prefrontal cortex and the right hemisphere in inhibition but also suggests that goal-conflict contributes to the activations observed during behavioural inhibition in these studies as opposed to simple reward and punishment processes and task demands such as memory.

6.6

The Effects of Handedness on Interhemispheric Communication

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Each cerebral hemisphere is considered to be specialised for particular cognitive processes. However, in many cognitive tasks, in order for efficient processing to occur, information must also be transferred between the hemispheres. It has been previously demonstrated that this transfer is faster from the right-hemisphere to the left, than from the left to the right, in healthy right-handed individuals. This may be due to there being a larger number of rapidly conducting neurons in the right hemisphere. To date, it is not known whether this asymmetrical transfer is also seen in left-handed individuals. In the current study, we used a visual detection task (the Poffenberger) coupled with electroencephalography (EEG) to investigate if there are interhemispheric transfer differences between left- and right-handed males. Our results yielded an interaction between transfer direction and handedness. Further exploration revealed that while right-handers demonstrated faster transfer from the right hemisphere to the left, left-handers showed equivalent speed in both transfer directions. The different patterns of interhemispheric transfer between left- and right-handed males may be explained with reference to anatomical differences of the brain. To further investigate this, we are using diffusion tensor imaging (DTI) to compare the microstructure of the interhemispheric callosal pathways in left- and right-handed males.

6.7

Amusia is Associated with Deficits in Spatial Processing

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Amusia (commonly referred to as tone-deafness) is a difficulty in discriminating pitch changes in melodies that affects around 4% of the human population. Amusia cannot be explained as a simple sensory impairment. Here we show that amusia is strongly related to a deficit in spatial processing in adults. Compared to two matched control groups (musicians and non-musicians), participants in the amusic group were significantly impaired on a visually presented mental rotation task. Amusic subjects were also less prone to interference in a spatial stimulus-response incompatibility task and performed significantly faster than controls in an interference task in which they were required to make simple pitch discriminations while concurrently performing a mental rotation task. This indicates that the processing of pitch in music normally depends on the cognitive mechanisms that are used to process spatial representations in other modalities.

7.1

Dopaminergic Mechanisms of MDMA-Produced Drug-Seeking

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Drug-seeking can be produced in laboratory animals following exposure to either stimuli that were previously paired with self-administered drugs or to selective drug primes. In the present study, we first trained rats to intravenously self-administer MDMA ("ecstasy"; 0.5 mg/kg/infusion). Once reliable self-administration was produced, a recurring series of 5-day tests was conducted. During the first 2 days, MDMA was available for self-administration. During the next 2 days, the MDMA solution was replaced with vehicle solution and operant responding extinguished. On Day 5, rats received an injection of a drug prior to being placed in the self-administration chambers. On this test day, only vehicle solution reinforced operant responding and the ability of the drug prime to reinstate extinguished responding was measured. MDMA (0-10.0 mg/kg, IP), cocaine (0.0-10.0 mg/kg, IP) and the dopamine uptake inhibitor, GBR 12909 (0.0-10.0 mg/kg, IP) dose-dependently reinstated extinguished drug-taking but the direct dopamine agonists SKF 81297 (0.0-4.0 mg/kg, IP) or apomorphine (0.0 – 4.0 mg/kg) were ineffective. The effects of MDMA were dose-dependently blocked by pretreatment with the dopamine D1-like antagonist, SCH 23390 (0.0 – 0.02 mg/kg, SC). These data support a role of the dopamine transporter in relapse to MDMA use.

7,.2

Expression of Cannabinoid Receptors in the Hindbrain

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For over a decade, it was thought that the cannabinoid CB1 receptors were expressed mainly in the brain, while CB2 receptors were found only in peripheral tissues. Contrary to the idea that CB2 receptors are restricted to peripheral tissues and are expressed predominantly in immune cells, it has been reported recently that CB2 receptors are also localized in various parts of the brain including the brainstem and cerebellum. Using immunohistochemistry, we were able to detect very specific labeling of CB2 receptor-positive Purkinje cells as well as granule cells in the cerebellum. We also examined other areas of the hindbrain including the vestibular nucleus and cochlear nucleus for CB2 receptor expression. There is very little evidence regarding the co-expression of CB1 and CB2 receptors in the brain. For this reason, we have undertaken the double labeling study of CB1 and CB2 receptors. The results from this study will provide further insights into the broader roles of CB2 receptors in the central nervous system (CNS). Furthermore, CB2 receptors may become a new target for the treatment of CNS-related illnesses.

7.3

Behavioural Effects of Intracerebroventricular Microinfusion of Difluoromethyl Ornithine in Rats

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The polyamines putrescine, spermidine and spermine are widely distributed in mammalian tissues and play essential roles in cellular proliferation and differentiation processes. Although the modulatory role of polyamines in the N-Methyl-D-aspartate receptor function has been long known, their effects on learning and memory have only recently been examined. The present study investigated the effects of intracerebroventricular microinfusion of difluoromethyl ornithine (DFMO), an inhibitor of putrescine synthesis, in the elevated plus maze, open field and water maze tasks in adult rats. All of the behavioural tests were conducted 50 minutes after the infusion. Rats with low (25 μg/5 μl) and high (50 μg/5 μl) doses of DFMO spent significantly more time on the enclosed arm (all $p < 0.05$) and less time on the open arm (all $p < 0.01$) relative to the controls in the elevated plus maze. All three groups performed similarly in the open field task. In the water maze task, DFMO at both doses did not significantly affect animals' performance. The present study demonstrates that DFMO at these doses has an anxiogenic effect without affecting animals' locomotor and exploratory activities and spatial learning. We are currently measuring the concentrations of polyamines in different brain regions following intracerebroventricular microinfusion of DFMO and the relationship with animals' behaviour will be analyzed.

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7.4

Ethanol and the Human EEG During Continuous Discrimination: Opposite Effects at Frontal and Midline Sites Compared to Posterior and Lateral Sites

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High dose alcohol increases human frontal theta rhythm but decreases rat hippocampal "theta". We looked for opposite effects of alcohol on the human EEG at different sites. We used continuous discrimination tasks that in rats generate hippocampal theta. Squares were regularly presented and a left or right response made to each. Choice depended either on whether the square was small or large (reference memory) or on whether it was the same or different size from the previously presented one (working memory). At peak breath alcohol concentration (BAC), there was an inverted U relationship between BAC and task performance. Both tasks showed a normal U relationship of BAC with frontal power in the low theta band (4-6Hz) and to a lesser extent in the upper alpha band (12-14Hz). Posterior midline power showed this effect across the full theta-alpha range. This is consistent with previous reports of increased power with higher doses of alcohol than were used by us. Both tasks produced an inverted U above left mid-temporal cortex across the full theta and alpha range. The working memory task produced an additional inverted U above left posterior-temporal cortex but only at times close to stimulus presentation and only in the 8-10Hz band. There are therefore at least two anatomically and functionally distinct components of lower frequency human EEG that show homologous alcohol responses to those of rat hippocampal theta; in contrast to frontal and midline components that show the opposite.

7.5

What Turns Dopamine Cells Off ?

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Several models of reward-learning propose that dopamine cells are under joint excitatory-inhibitory control and that modulation of inhibitory input contributes to rapid fluctuation in response according to cue-reward contingencies. One candidate structure for inhibitory input is the striatum. We are recording responses of single striatal neurons to cue signals in freely moving rats under two, previously trained cue – reward contingencies. In the no-reward condition, the house light is continuously on and a cue (2.5 kHz tone, 0.5 s) occurs alone, at pseudo-random intertrial intervals. In the reward condition, the room is dark and the same cue is followed (1 or 2 s following the cue offset) by delivery of sweetened water reward. To date, 15/32 recorded cells showed a short-latency (28 ± 12 ms) excitatory response to cue onset in the non-reward condition. In the rewarded condition 10/15 cells completely lost the excitatory response, including 3 that showed an inhibitory trough instead. No cells showed the opposite context selectivity. Striatal activity is thus appropriately patterned and timed to gate the conditioned responses of midbrain dopamine cells to cues depending on their relationship to rewards.

7.6

The Effects of Benzylpiperazine (BZP) Administration on the Poffenberger Paradigm of Interhemispheric Transfer in Healthy Adult Right Handed Males

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Benzylpiperazine (BZP) containing party pills are widely available in NZ (approx.150,000 doses sold per month). The only published human trials of BZP, conducted in the 1970s, found physiological and psychological similarities to dexamphetamine. We employed high-density (128-channel) EEG as participants carried out a simple signal detection task (the Poffenberger). Measuring the latencies of the lateralised N160 component in each cerebral hemisphere gives estimates of cortical registration of stimuli, and of interhemispheric transfer time (IHTT). Using a randomised, double-blind, placebo-controlled design, the effects of BZP were investigated in healthy right-handed 18-40 year-old males (mean age 25.8 ± 5.8 years). Two groups (n=9 drug, n=11 placebo) were tested before, and two hours after administration of a single oral dose of either BZP (250mg) or placebo. The N160 appeared earlier in the parietal visual cortex for the BZP group relative to the placebo group. Simple effects test revealed this relationship was significant, $F_{(1,18)} = 4.604$, p= .046. $F_{(1,18)} = 8.39$, $p = .01$, indicating the drug sped information transfer along visual pathways. The drug had no significant effect on IHTT. Thus BZP appears to interact with the neurotransmitter system involved in the generation of the N160, but not that involved in IHTT.

8.1

Purinergic Regulation of the Endocochlear Potential in the Mouse and Changes with Age

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Sound transduction in the cochlear sensory cells is driven by the positive endocochlear potential (EP, +100mV) in the endolymph that bathes the surface of hair cells. We have shown that adenosine triphosphate (ATP) secreted into the cochlear endolymph regulates the EP via ATP-gated ion channels (P2X receptors) in cells lining the endolymphatic space of the guinea-pig (Thorne et al., 2004 JARO, 5:58-65). In this study we have investigated the influence of ATP in the regulation of EP in the mouse. The EP and cochlear partition resistance (CoPR: change in voltage resulting from 1 µA current pulses introduced into endolymph) were measured from glass pipettes in scala media (first turn) of anaesthetised (Urethane, 1.25g/Kg) CBA/CAJ mice. Introduction of ATP into endolymph caused a dose-dependent reduction of EP and CoPR due to activation of P2X2 receptors in tissues lining the endolymphatic compartment. This indicates that ATP in endolymph also regulates EP in mouse by activating a P2X2-mediated shunt conductance in the endolymphatic compartment. The dynamics of the responses were similar to guinea-pigs in that EP recovered faster than resistance. Preliminary data suggests that EP is lower in aged animals (15-18mths) although they still showed a response to ATP. These data provide further support for a role of ATP in regulation of EP and consequently humoral regulation of hearing sensitivity under stress conditions.

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8.2

Auditory Phenotype of CD39 Deficient Mice

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Signalling actions of extracellular nucleotides influence cellular function in most tissues acting on P2 receptors. In the inner ear, P2 receptor signaling is involved in regulation of cochlear electrochemical homeostasis and hearing sensitivity. CD39 (NTPDase1) is an ecto-nucleotidase (ecto-nucleoside triphosphate diphosphohydrolase) that can hydrolyse nucleoside tri- and diphosphates to generate monophosphates of purine and pyrimidine nucleosides. Mice with the NTPDase1 gene deleted exhibit major alterations in haemostasis and profound alterations in inflammatory and thrombotic reactions. Imaging studies in the cochlea have suggested the involvement of NTPDase1 in regulation of blood flow and auditory neurotransmission. Our study aimed to determine auditory phenotype of these NTPDase1 null mice. Auditory brainstem responses (ABR) and distortion product otoacoustic emissions (DPOAE) were unaffected in NTPDase1 deficient mice across the range of test frequencies, suggesting normal neural and outer hair cell function. Mutant mice, however, showed increased vulnerability to acoustic trauma. Gene expression analysis of other membrane-bound NTPDases with comparable hydrolytic activity demonstrated an up-regulation of NTPDase2 and 8 in the cochleae of NTPDase1 deficient mice, which was confirmed by analysis of protein expression. These results demonstrate that the loss of NTPDase1 can modify cochlear response to noise, but other surface located NTPDases can offset further alterations of cochlear homeostasis.

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8.3

Changes in Postsynaptic Protein Expression in the Cochlea During Synapse Remodeling

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The afferent innervation in the developing cochlea undergoes dramatic remodelling prior to the onset of hearing. Our recent data have demonstrated that the primary auditory neurones exhibit precisely timed neurite outgrowth, neurite refinement and neurite retraction to establish the mature innervation pattern (Huang et al., 2007) in press. However, the mechanisms driving this process of synapse remodelling remain elusive. One theory is that the molecular makeup of the afferent synapse may determine synapse elimination or survival, leading to neurite retraction. In the cochlea, glutamate is recognized as the primary neurotransmitter for sound transduction, and the postsynaptic expression of glutamatergic receptor subunits have been identified. In other brain regions, postsynaptic density proteins have been known to interact with glutamatergic receptors and regulate the trafficking of receptors to the synapse. However, it is currently unknown if these proteins are expressed in the developing cochlea nor what role they could play in synapse function. In this study, we have identified the expression of GRIP, PICK1, PSD93 and SAP97 in the developing mouse cochlea using confocal immunofluorescence. The expression of these postsynaptic proteins was found in the nerve terminals innervating both types of sensory hair cells. The expression of these proteins reached maximal levels at P6 and then was down-regulated at P12. This differentially-regulated expression of postsynaptic proteins alters the molecular composition of developing synapses during synapse remodelling and may thus be involved in regulating synapse elimination and neurite retraction in the developing cochlea.

8.4

Effects of Bilateral Vestibular Deafferentation on Open Field Activity in Rats

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Over the last decade, spatial learning and memory deficits following bilateral peripheral vestibular damage have been reported in both animals and humans. Although there is a general notion that animals with bilateral vestibular deafferentation (BVD) are hyperactive, general locomotor activity and exploratory behavior in these animals have never been investigated systematically. In the present study, rats with BVD (n = 18) or sham surgery (n =17) were tested in an open field for a 5 min session at 3 weeks, 3 months and 5 months following the surgery. For all 3 time points, BVD rats spent significantly more time engaged in movement, travelled farther and did so at a higher velocity than the sham rats. BVD rats also exhibited reduced thigmotaxis and wall supported rearing compared to sham rats. However, when overall stopping behavior was analysed, the incidence of stops was not only significantly more frequent, but also longer in duration in BVD rats compared to sham rats. Although BVD resulted in significant changes in locomotor activity and exploratory behaviour, temporal analysis of these measurements revealed a similar pattern for both sham and BVD rats over the 5 min test session. The results are discussed in terms of their possible significance for spatial navigation and emotional behavior.

8.5

Neurochemical Changes in the Hippocampus Following Bilateral Vestibular Damage

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Complete loss of vestibular function results in severe impairments in spatial learning and memory. Bilateral vestibular damage causes place cell dysfunction, a decrease in the power of theta activity and a loss of electrical excitability in the hippocampus. Most recently it has been shown that patients with long-term bilateral vestibular loss exhibit a selective hippocampal atrophy that correlates with their spatial memory deficits. In the current study we sought to investigate the neurochemical basis of the electrophysiological deficits that occur in the hippocampus following vestibular damage in rats, using a combination of western blotting and immunohistochemistry with selective antibodies for the synaptic proteins, synaptophysin and SNAP-25. At 6 months following bilateral vestibular deafferentation, there were no significant changes in synaptophysin expression in the CA1 region of the hippocampus or the dentate gyrus, compared to sham controls; however, there was a significant decrease in SNAP-25 expression in the dentate gyrus but not CA1. SNAP-25 expression was unchanged in the perirhinal, entorhinal and frontal cortices; however, synaptophysin expression was significantly reduced in the frontal cortex but not in the other cortical regions. Together with previous studies indicating a down-regulation of NMDA receptor subunits and neuronal nitric oxide synthase, these results suggest that the hippocampus undergoes a series of subregion-specific neurochemical changes following vestibular loss that may explain the electrophysiological deficits that have been described.

8.6

Carbamazepine Reduces the Behavioural Manifestations of Tinnitus Following Salicylate Treatment in Rats

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Carbarmazepine (CBZ) is one of a number of anti-epileptic drugs that is used for the treatment of chronic subjective tinnitus. Despite this, there are relatively few clinical trials or preclinical studies that have investigated its efficacy. In this study, we used a conditioned response task in which the rats learned to associate the offset of a 10 kHz, 50 dB tone, with a mild foot shock (0.1 to 0.5 mA), to confirm that rats receiving a 350 mg/kg i.p. injection of salicylate, experienced tinnitus. We then investigated the effects of 3 doses of CBZ, 5, 15 or 30 mg/kg i.p., on the behavioural manifestations of tinnitus in this task. We found that 15 mg/kg, but not 5 mg/kg or 30 mg/kg, significantly suppressed tinnitus compared to the vehicle group ($P < 0.05$). CBZ on its own did not have any significant effect at the15 mg/kg dose. A 15 mg/kg dose of CBZ corresponds approximately to a 600-1000 mg dose for a 70 kg human, which is the dose range that has been found to be effective for the treatment of tinnitus. Therefore, these results are consistent with the hypothesis that CBZ has efficacy against tinnitus in humans.

8.7

Auditory Processing Maturation Assessed with Event-Related Potentials (ERPs)

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The N1 component of the auditory ERP is attenuated following repetition of stimuli, argued to reflect refractoriness of neurons in the auditory cortex or an inhibitory circuit. The present study examined whether N1 amplitude modulation reflected refractoriness or latent inhibition, and whether this showed a developmental function. ERPs to tone pairs separated by ISIs of 100, 200, 400, or 800 ms were recorded. In the first study adults were assessed, and in the second study children aged 7-9 years were assessed. In adults, the amplitude of the N1 to the second tone in the pair was smaller than the N1 elicited by single tones at 800 ms ISIs, suggesting that N1 attenuation reflects latent inhibition. N1 amplitude was larger to the second tone than to single tones at 100 ms ISIs, reflecting perceptual integration of successive stimuli. In children, N1 amplitude following the 800 ms delay was not attenuated, and there was an enhancement of N1 amplitude to the second tone of the pair when separated by 400 ms. These results indicate that there is maturation of auditory processing from childhood to adulthood in two processes, with a reduction in the temporal window over which successive stimuli are integrated, as well as enhancement of a top-down inhibitory neural circuit that modulates auditory processing.

9.1

The Life and Death of Human Brain Cells

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Human neurodegenerative disorders such as Alzheimer's, Parkinson's and Stroke are currently only treatable with symptomatic medications. Despite a plethora of positive pre-clinical studies, no neuroprotective or neurorestorative treatment has yet worked in humans. We have taken the view that one reason for this failure to translate lab research to the clinic is that human brain cells are significantly different from other mammals. Therefore, we have focused our studies on molecular pathological studies of normal and diseased human brain material and studies using human brain cells in tissue culture. In this presentation I will describe the establishment of our human brain cell culture facility and an associated high content cell and tissue analysis facility. These facilities are now being used to study the life and death (ecology) of human brain cells in tissue culture and to analyze human brain cells at high throughput in tissue sections. We hope to unravel processes involved in neurodegeneration, neuroprotection and repair in the human brain.

9.2

Altered $GABA_A$ Function in Stargazer Epileptic Mice

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Absence epilepsy is a neurological disorder characterized by brief non-convulsive events accompanied by a loss of consciousness and 2.5-4Hz "spike-wave discharge" (SWD). Stargazer mice are a model of absence epilepsy, which show SWDs during periods of behavioral arrest, and these absence-like events are reduced by anti-absence medication. Drugs which enhance the action of the neurotransmitter GABA can worsen absence epilepsy, indicating the importance of GABA in the pathophysiology of absence. Aside from the classical phasic inhibition GABA release produces, it can also act via volume transmission to produce a tonic inhibitory conductance, usually mediated by α4/6βδ subunit containing $GABA_A$ receptors.We investigated whether epileptic stargazer mice (*stg*) had altered levels of tonic $GABA_A$ current in comparison to their non-epileptic littermates (+/+). In dentate gyrus granule cells (DGGCs) there was no difference in phasic GABA action between *stg* and +/+ mice. However *stg* mice showed significantly less tonic $GABA_A$ current, and this tonic current was significantly less enhanced by the δ-selective positive modulator THDOC; indicating that stg mice had less α4/6βδ receptors than +/+ mice on the DGGC. We believe that subunit change is a result of the excitatory bombardment DGGCs receive during SWDs. As a control we also investigated the level of inhibition in cerebellar granule cells which are not excited during absence events. Here there was no apparent difference in the level of tonic $GABA_A$ mediated current.

9.3

Regulation of NMDA Receptor Function by Secreted Amyloid Precursor Protein-α

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Alzheimer's disease is characterised by aberrant processing of amyloid precursor protein (APP), one result of which is abnormally low levels of a neuroprotective protein, secreted amyloid precursor protein-alpha (sAPPα). sAPPα has been shown to facilitate long-term potentiation (LTP) in the dentate gyrus *in vivo* but the underlying mechanisms are unclear. Given the critical role of NMDA receptors (NMDARs) in hippocampal LTP we hypothesized that sAPPα would enhance NMDAR function. Whole-cell patch-clamp recordings were made from young adult rat dentate granule cells in acute hippocampal slices maintained *in vitro* at 32°C. The effects of different concentrations of exogenous sAPPα were tested on pharmacologically isolated, synaptically evoked NMDAR excitatory postsynaptic currents (EPSCs). These were recorded during a high-frequency (400 Hz) tetanus capable of inducing LTP in the dentate gyrus *in vivo*. At a low concentration (0.03 nM) sAPPα increased the peak amplitude and decay time of the tetanic NMDAR EPSCs, and consequently increased the total charge transfer through the NMDARs. Higher concentrations of sAPPα had no effect, consistent with the inverted U-shaped concentration-dependence of the facilitation of LTP *in vivo* by sAPPα. Interestingly, the effects of sAPPα were not accompanied by changes in NMDAR EPSCs evoked by single synaptic stimuli. These data suggest that one mechanism by which sAPPα could facilitate LTP induction *in vivo* is through an up-regulation of NMDAR function during tetanic stimulation.

Supported by the New Zealand Health Research Council.

9.4

Ceftriaxone Increases the Activity of Glutamate Transporters – Implications for Neuroprotection in Stroke

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Astrocytic glutamate transporters are considered an important target for neuroprotective therapies as the function of these transporters is abnormal in stroke and other neurological disorders associated with excitotoxicity. Recently, Rothstein et al. (Nature 433:73 77, 2005) reported that β-lactam antibiotics (including ceftriaxone, which easily crosses the blood brain barrier) increase glutamate transporter 1 (GLT 1) expression and reduce cell death resulting from oxygen-glucose deprivation (OGD) in dissociated embryonic cortical cultures. To determine whether a similar neuroprotective mechanism operates in more mature neurons, which show a different pattern of response to ischemia than primary cultures, we performed electrophysiological assessment of glutamate transporter function in acute hippocampal slices obtained from Wistar rats (P21 27) treated with ceftriaxone for 5 days (200 mg/kg; i.p.). Whole-cell patch clamp recording of glutamate-induced *N*-methyl-D-aspartate (NMDA) receptor currents, from CA1 pyramidal neurons, showed a larger potentiation of these currents after application of 15 μM DL-threo-β-benzyloxyaspartic acid (TBOA; a potent glutamate transporter blocker) in ceftriaxone injected animals than in untreated animals, indicating increased glutamate transporter activity. In addition, the delay to OGD induced hypoxic spreading depression (HSD) recorded in slices obtained from ceftriaxone treated rats was longer (6.3 ± 0.2 vs. 5.2 ± 0.2 min; $p<0.001$) than that in the control group. These data indicate that ceftriaxone treatment increases the activity of TBOA sensitive glutamate transporters also in postnatal tissue, and show a neuroprotective effect of this antibiotic in our model.

9.5

Convulsants and Depolarisation Evoke Ca^{++}-dependent Release of the Sleep Lipid Oleamide

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cis-9,10-Octadecenoamide or "oleamide" accumulates in the CSF of sleep deprived animals and synthetic oleamide promotes physiological sleep. Factors regulating the release of the lipid from rat cortical cells grown in primary culture were investigated using GC-MS. Release from cellular monolayers was increased *circa* four fold ($p<0.05$) upon exposure to 50mM K^+ in aCSF. Removal of Ca^{++} from aCSF reduced the passive release of oleamide ($p>0.05$) and completely abolished K^+-evoked-release under depolarizing conditions. Incubation of cultures with the FAAH inhibitor PMSF (100 µM) significantly increased both the passive and depolarisation-evoked release of oleamide. The convulsants bicuculline (40 µM) and kainic acid (100 µM) evoked paroxysmal epileptiform bursts and sustained inward currents, respectively, in cultured cortical pyramidal cells. Bicuculline evoked a *circa* 8fold increase in the secretion of oleamide ($p = 0.001$) which was completely occluded by 100 nM tetrodotoxin (TTX). Kainic acid (which directly gates calcium permeant ion channels) resulted in TTX-insensensitive oleamide release (>10 fold enhancement of extracellular concentrations; $p<0.001$) from the neuroglial cultures. We have previously shown that oleamide promotes inhibitory currents through benzodiazepine sensitive GABAa receptors and reduces membrane excitability by blocking voltage-gated sodium channels by promoting fast inactivation. We conclude that Ca^{++} entry following depolarization or epileptiform activation of neuroglial cells is a trigger for oleamide release and that the lipid may act as an endogenous anticonvulsant.

10.1

Mood Disorders, Personality and Genes

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To understand the nature of mood disorders requires a better understanding of both aetiology and outcomes. Genes are relevant to understanding a wide variety of factors related to mood disorders. The inclusion of personality is due to increasing evidence that the genes from the personality traits of negative affect (neuroticism or harm avoidance) may be the same genes that confer vulnerability to mood disorders, especially depression. In this talk data will be presented showing how different genetic polymorphisms may be: Relevant to aetiology of depression; Overlap with genes for personality; Influence symptom presentation in depression; Predict antidepressant response; and Predict antidepressant side effects. The presentation will also link current clinical diagnostic systems with Cloninger's Psychobiological Model of Personality.

10.2

Dopaminergic Neurons of the Substantia Nigra Express Functional TRPM2 Channels

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Parkinson's disease is one of the most common neurodegenerative disorders, and is associated with a loss of dopamine releasing neurons of the substantia nigra pars compacta (SNc). The reason for the specific vulnerability of these neurons remains unclear, although many hypotheses propose an involvement of oxidative stress. TRPM2, a member of the TRP protein family, has been described as an oxidative stress sensor. TRPM2 is activated by hydrogen peroxide and is a calcium permeable, non-selective cation channel protein. The aim of this study was to determine whether TRPM2 channels are functionally expressed in dopaminergic neurons of the SNc. Rat midbrain slices labelled with antibodies against tyrosine hydroxlyase and TRPM2 were imaged with confocal microscopy. TRPM2 immunoreactivity was observed in the SNc in both dopaminergic and non-dopaminergic neurons. To assess channel functionality, whole-cell patch-clamp recordings and calcium imaging (fura-2) were performed on midbrain slices *in vitro*. ADP-ribose, an intracellular agonist of TRPM2 channels, produced a concentration dependent increase in the inward current and intracellular calcium levels (50, 200 and 400 μM; ANOVA, $p<0.05$, $n=53$). Both effects were inhibited in the presence of clotrimazole (5 μM; $p<0.05$, $n=12$), a non-specific blocker of TRPM2. These results provide the first evidence for the functional expression of TRPM2 channels in the dopaminergic neurons of the SNc. It remains to be determined whether these channels play a role in oxidative stress-induced damage of SNc neurons.

10.3

Neuronal Ceroid-Lipofuscinosis in Borderdale Sheep is Caused by a Nucleotide Substitution at a Consensus Splice Site in the *CLN5* Gene

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Batten disease (neuronal ceroid lipofuscinoses, NCLs) refers to a group of inherited childhood diseases resulting in severe brain atrophy, blindness and seizures of increasing severity, leading to the premature death of about 1 per 12,500 births world-wide. At least seven genes are responsible for different forms of the disease and there are no effective therapies. Large animal models are invaluable for studying these diseases and a form was found in New Zealand Borderdale sheep. Mapping and gene sequencing studies revealed *CLN5* as the disease-causing gene. The disease causing mutation is a substitution at a consensus splice site (c.571+G>A) leading to the splicing of exon 3 and resulting in a shorter putative protein with reduced or lack of biological effect. Analysis of storage body proteins showed that subunit c of ATP synthase is the major component. *CLN5* codes for a soluble lysosomal protein and thus is more indicated for gene therapies. Preclinical studies in the CLN6 form affecting New Zealand South Hampshire sheep revealed that changes to the brain began prenatally with detection of an early inflammation. If occurring in Borderdale sheep, this will indicate that is a general property of different forms of Batten disease and place the Borderdales as ideal for testing combinations of anti-inflammatory and gene therapies.

10.4

Hippocampal Dysfunction in an Animal Model of Schizophrenia

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Cognitive impairments are recognised as a key aspect of schizophrenia and may result from deficits in the formation and maintenance of contextual representations. Previous research has demonstrated that the hippocampus processes contextual information and that hippocampal function is abnormal in schizophrenia. This study tested the hypothesis that contextual deficits are associated with hippocampal dysfunction using a recently developed maternal immune activation (MIA) animal model of schizophrenia, in which a cytokine activator (polyriboinosinic-polyribocytidilic acid) is administered to pregnant rat dams during mid-gestation. MIA offspring were examined in a number of tasks known to require the hippocampus. MIA offspring displayed increased thigmotaxis and hyperlocomotion during open-field exploration. These changes in exploration were observed in adult (3 month), but not juvenile (37 Day) MIA offspring, mimicking the post-pubertal emergence of schizophrenia. Adult MIA offspring also displayed reduced habituation with repeated exposure to a familiar context. Furthermore, rearing in response to contextual change was greater in controls than MIA offspring. Despite normal object discrimination performance, adult MIA offspring spent less time exploring objects in an open-field and the proportion of time exploring novel rather than familiar objects was less than in controls. Reversal learning in a T-maze was also enhanced in MIA offspring relative to controls. As damage to the hippocampal/parahippocampal region produces a similar pattern of deficits, the results suggest that impaired contextual processing in schizophrenia may result from abnormalities in the hippocampal formation or its input structures.

10.5

Connexin43 Localisation is Altered in Parkinson's Disease Brains

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Recent studies indicate that both the neurological immune response and inflammation play an important role in the dopaminergic cell death in Parkinson's Disease. Under inflammatory conditions the central nervous system's (CNS) innate immune response is activated by microglia that are attracted to the site of injury. Once activated, microglia produce inflammatory cytokines, including TNFα that are in turn capable of altering the expression of cell-to-cell coupling proteins called connexins. Connexins are the molecular subunits of Gap junctions and are widely expressed in various cell types of the CNS. We investigated the expression and cellular localisation of Connexin43 (Cx43) protein in the substantia nigra of normal and Parkinson's Disease human brain using immunohistochemistry and Image J Software. Our results showed that while the total level of Cx43 expressed by all cell types was not altered in the substantia nigra of Parkinson's Disease brains compared to controls, there was a significant difference in cellular localisation of Cx43. In controls, Cx43 was expressed primarily on neurons and astrocytes while in the substantia nigra of Parkinson's Disease brains the percentage of microglia cells expressing Cx43 was dramatically increased. This increase in microglia Cx43 expression may enhance Gap junction cell-to-cell coupling, leading to further recruitment and activation of microglia. Determining the role of connexins in microglial activation and inflammation may therefore provide a future basis for understanding the complexities of Parkinson's Disease.

11.1

Transplacental, *in utero* Gene Delivery to the Fetal Mouse Brain after Intravenous Injection into the Maternal Circulation

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Prior studies have established that after i.v. injection, pegylated immunoliposomes (PILs) can deliver a gene across multiple biological barriers to a remote target site (e.g. see Lancet Neurol 1, 306-315, 2002). These studies predicted that gene delivery across the placenta and fetal blood-brain barrier (BBB) could be achieved using receptor-mediated immunoliposome delivery systems. We tested this hypothesis by intravenously injecting PILs (containing firefly luciferase DNA) into near-term pregnant mice. Pups were born the following day, and at 48-hours post-injection, CNS tissue luciferase expression was assayed using a luminometric procedure. We successfully delivered PILs containing the luciferase transgene into Lafora wild type mice and demonstrated the expression of protein days later. In utero delivery of the pGL3 DNA has also been shown after a single i.v. injection into pregnant Lafora Knockout (EPM2a null-mutant) female mice, by demonstrating luciferase activity days later in the newborn pups. Adult mouse CNS tissues (receiving i.v. plasmid DNA which was not encapsulated in PILs) served as controls; luciferase activity was not significantly different from zero. These studies demonstrate for the first time that receptor-mediated transport of PILs across both the placental barrier, as well as the fetal BBB in utero, has been achieved. It has also been confirmed in a mouse-model of an invariably fatal human disease. Preliminary studies wherein Lafora-knockout mice have which have received gene therapy treatments (immunoliposome-delivered EPM2a) will be discussed.

11.2

The MIS Type-II Receptor, MISRII, Has Splice Variants in the CNS

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We have recently shown that Müllerian Inhibitory Substance (MIS) is a survival factor for embryonic motoneurons. During development, MIS is a male-specific gonadal hormone that contributes to the masculinization of the brain. However, post-puberty MIS ceases to be dimorphic and is produced by motoneurons and the gonads of both sexes. Most neurons bind anti-MISRII and are lacZ positive in MISRII-promoter-LacZ knock-in mice, suggesting that MIS may be a broad regulator of the brain. Classical MIS signaling occur in the Müllerian ducts and gonads. Even though these tissues have a higher abundance of MISRII than motoneurons, they are less sensitive to MIS, raising the possibility that neurons may express a distinct MISRII form. The use of qualitative and quantitative RT-PCR analyses confirmed the presence of two novel splice variants in addition to the MISRII full-form in the CNS: the first variant was missing a large part of the extracellular ligand binding domain (exon 2), while the second was missing a large portion of the kinase domain (exons 9 & 10). These results confirm the presence of splice variants in the CNS and provide a possible mechanism for tissue-specific diversity in MIS sensitivity.

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11.3

MIS$^{-/-}$ Mice Have Cryptic Neurological Deficiencies

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Müllerian Inhibitory Substance (MIS) is a male-specific gonadal hormone during development, but is produced by the gonads and some neurons of both adult males and females. The receptors for MIS are present on all neurons, but young adult MIS$^{-/-}$ mice are viable and do not exhibit overt neurological symptoms. We have recently shown that MIS$^{-/-}$ mice have a mild male-specific deficiency in the number of spinal motoneurons, which is subclinical. This raises the possibility that the MIS$^{-/-}$ mice have other cryptic neurological abnormalities. Sleeping time in response to nembutal is sexually dimorphic, with males sleeping longer than females. We confirm this sex difference here ($p=0.000$). Male and female MIS$^{-/-}$ slept for a shorter time than sex-matched congenic MIS$^{+/+}$ mice, but this effect was only statistically significant for male mice ($p=0.042$). The sleep time of male MIS$^{-/-}$ mice was not different to female MIS$^{-/-}$ or MIS$^{+/+}$ mice. This suggests that MIS contributes to sex-differences in GABAergic signalling, as nembutal acts on GABAA receptors. The MIS$^{-/-}$ mice of both sexes travelled less distance in an open field test than congenic MIS$^{+/+}$ mice ($p=0.025$), as they spent more time resting ($p=0.024$). Female mice are not exposed to MIS during development, and this observation is thus consistent with the MIS present in adults regulating brain function.

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11.4

A Mathematical Model of Cerebral Mass Vessels Using Krogh Cylinder

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The cerebral mass is supplied by an arterial network, called the Circle of Willis (CoW), that distributes incoming oxygen rich blood from the internal carotid and basilar arteries. Approximately 50% of the population have an incomplete CoW. If there is a shortage in the blood supply due to certain pathological conditions such as occlusion or stenosis in one or more supplying arteries, stroke-like symptoms can result in an individual with an incomplete CoW. The mathematical model of the CoW (Moore et al, 2005) is developed to include the myogenic response based on the distribution of open ion channels across the vessel walls (Gonzalez-Fernandez et al, 1994). We have developed a model to include the structure of the arterial tree representing the arterial network of the cerebral mass down to the capillary level. The model utilizes the Krogh cylinder (McGuire et al, 2001), a representation of the capillary-tissue region. Through this model, changes in the CoW geometry and/or pathological conditions affect the vasomotion and mean diameter of arterioles downstream of the CoW; in turn affecting the blood flow, and therefore, the oxygen diffused to brain tissue. The model replicated the behaviour of cerebral auto-regulation under a variety of conditions of perfusion pressure reduction and thus a representation of stroke and at-risk patients providing more insight on how the brain regulates its own blood supply. The main areas for risk seem to be the absence of the ACoA under ipsilateral occlusion of the ICA.

11.5

Enhanced Axonal Regeneration After Spinal Cord Injury in an *ex vivo* Model

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Each year there are 70 new cases of spinal cord injury in New Zealand. Spinal cord injury is characterised by primary irreversible mechanical damage and the subsequent secondary injury spread. Peripheral nerve grafting into the site of injury has proved to be successful in promoting axonal regeneration from the spinal cord itself, but regeneration is limited due to the development of an astrocytic scar at the site of injury. Connexin 43 specific antisense (Cx43AS) has been shown to reduce lesion spread and inflammation. This study investigates the use of Cx43AS for enhancing spinal cord repair in conjunction with peripheral nerve grafting. An *ex vivo* spinal cord segment culture model was established utilizing rat spinal cords cultured in media for five days. After incubation, spinal cords were cryo-sectioned and stained immunohistochemically. Fresh peripheral nerves were grafted into the spinal cord segments with Cx43AS applied concomitantly, followed by five days of culture and subsequent processing as above. Results showed that initial swelling and inflammation at the sites of damage in the spinal cord segments were reduced effectively by Cx43AS application. Neuronal survival at neighbouring sites was enhanced five days post-operation. Spinal cord neuronal outgrowth entering the peripheral nerve was observed, and this was further enhanced by Cx43AS treatment.

11.6

Transplantation of Human Embryonic Stem Cell-Derived Neural Precursors into the Quinolinic Acid Lesion Rat Model of Huntington's Disease

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Cell transplantation therapy may offer a viable treatment strategy for patients with Huntington's disease (HD) by providing new cells to replace those lost through disease. This study examines the potential therapeutic use of neural precursors (NP) derived from human embryonic stem cells (hESC) in the treatment of HD. NP cultures were derived from the hES cell line Envy and cultured with or without Noggin. The characteristics of Noggin-induced and spontaneously-derived NP cells were evaluated 4 and 8 weeks after transplantation in the quinolinic acid (QA) lesion rat model of HD. Adult male Wistar rats received a unilateral intrastriatal infusion of QA in order to mimic the selective loss of striatal neurons observed in HD. One week after QA injection, rats were transplanted either with Noggin-induced or spontaneously-derived Envy NP cells in the QA lesioned striatum. Envy NP cells survived transplant and migrated extensively within the QA lesioned striatum as well as throughout the CNS. Immunohistochemical analysis showed that transplanted Envy NP cells differentiated into mature neurons, as demonstrated by NeuN co-expression eight weeks after transplantation. The results of this study demonstrate the potential use of hESC-derived NP cells for cell replacement therapy for the treatment of HD.