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Abstracts

1.1

Manipulating Dopamine Pathways in the Bee Brain: Impacts on Brain Function and Behaviour

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Honey bee queens produce a pheromone (queen mandibular pheromone, QMP) that has profound effects on dopamine signalling in the brain of young worker bees. Brain dopamine levels, levels of dopamine receptor gene expression, and brain tissue responses to exogenously applied dopamine are all altered by this pheromone. One interesting consequence is that aversive olfactory learning in young workers exposed to their mother's pheromone is blocked, whereas appetitive learning remains intact. Effects of the pheromone on learning are age dependent: worker bees 15 days of age and older show robust aversive learning, irrespective of whether or not they have been exposed to QMP. The selectivity of QMP's effects provides a useful tool for exploring the cellular and molecular level mechanisms that underlie the formation of associative olfactory memories that guide the behaviour of this highly social insect.

This work was supported by grants from the Royal Society of New Zealand Marsden Fund: UOO0312 and UOO0615.

1.2

Tracking the Learning of Novel Actions and Action Selection: A Behavioural Analysis of Dopamine Depletion

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The ability to discover the actions that result in a rewarding or beneficial event for an organism, and also to select appropriate actions to meaningful sensory cues are crucial for the organism's learning and survival. It has been proposed that the basal ganglia and, specifically, the dopamine neurotransmitter, are critical for this basic selection process. This study aimed to track learning of novel actions in normal controls and in people with Parkinson's disease, to investigate the behavioural effects of dopamine depletion in the patient group. In the present study, participants were instructed to move a cursor on a computer screen to learn the particular action(s) that elicit a sensory event. We refer to this as the "where task" because location of the cursor determined whether a stimulus was subsequently elicited. The task consisted of 4 conditions, (3 blocks of 40 trials per condition). In Condition 1, participants discovered the actions associated with the location that elicited a reward (a green flash worth 10 pts.); the rewarded location remained constant within a block and then changed for the next block. In Conditions 2-4, the location that elicited the reward alternated between 2 different possibilities. Those conditions were defined by the type of feedback, either eliciting a neutral stimulus (blue flash worth 0 pts.), punishing stimulus (red flash removing 2 pts.), or no-feedback (no stimulus). Participants' cursor movements, search times and switch times were recorded for all trials. All normal controls learned the actions to elicit the reward within the first block. Significant differences in switch time were found between no-feedback and the punishing and neutral conditions, but the latter two conditions did not differ, setting the stage for further testing on Parkinson's patients. The specific aim of testing patients is to provide behavioural evidence of the link between dopamine depletion and unremittent action selection.

1.3

Not Presented

1.4

The Hyperpolarisation-activated Current (Ih) Significantly Contributes to the Afterhyperpolarisation in Striatal Cholinergic Interneurons

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The striatum is an area in the basal ganglia involved in reward-related learning. Pauses in the tonic firing of striatal cholinergic interneurons emerge during such learning and are triggered by neutral cues which develop behavioural significance. We have hypothesised that these firing pauses are caused by an afterhyperpolarisation (AHP) and that this intrinsic mechanism can be engaged by excitatory inputs. To measure the effect of cortical synaptic inputs on the AHP, recordings were made from cholinergic interneurons using rat brain slices and the visualised whole-cell patch-clamp technique. Repetitive stimulation of corticostriatal fibres at 60-120 Hz evoked successively larger PSPs and the magnitude of the AHP was directly proportional to the magnitude of the preceding membrane depolarisation. This relationship was unchanged by the bath application of bicuculline (30 µM) or CGP-55845 (1 µM) to antagonise $GABA_A$ and $GABA_B$ receptors, respectively, indicating that the AHP was not due to inhibitory synaptic inputs. Since AHPs were triggered efficiently over a range of membrane potentials negative to -50 mV, we examined if the AHP following subthreshold synaptic stimulation is mediated by the temporary inactivation of hyperpolarisation and cyclic nucleotide activated (HCN) current (Ih). Bath application of the Ih antagonist ZD-7288 (50 µM) reduced the size of the AHP to 15% of controls ($p<0.01$) for depolarising PSPs of intermediate magnitude (400-600 mV.ms). In addition, the AHP magnitude was reversibly reduced following bath application of 2 mM Cs^+, which blocks Ih. Thus afferent synaptic potentiation as well as regulatory mechanisms that modulate HCN channel activity may underlie the appearance of cue-induced pauses in tonic firing of cholinergic interneurons.

1.5

Spatial Learning Results in Elevated Agmatine Levels in the Rat Brain

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Accumulating evidence suggests that agmatine, a metabolite of L-arginine by arginine decarboxylase, is a novel neurotransmitter and exogenous agmatine can modulate behaviour functions including learning and memory. However, direct evidence of its involvement in learning and memory processes is currently lacking. The present study measured agmatine levels in the hippocampus, parahippocampal region, cerebellum and vestibular nucleus in rats that were trained to find a hidden escape platform in the water maze task (WM, n = 7), or forced to swim in the pool with no platform presented (SW, n = 7), or kept in the holding box (HB, n = 7), using liquid chromatography/mass spectrometry. Compared with the SW and HB groups, agmatine levels were significantly increased in the CA1 (all $p < 0.001$) and dentate gyrus ($p < 0.05$ and 0.01, respectively) sub-regions of the hippocampus, the entorhinal cortex (all $p < 0.05$) and the vestibular nucleus (all $p < 0.01$) in the WM group. These results, for the first time, demonstrate spatial learning-induced region-specific elevation in agmatine, and raise a novel issue of the involvement of agmatine in the processes of learning and memory.

Supported by New Zealand Neurological Foundation.

1.6

Age-Related Changes in LTP-Associated Gene Expression Profiles in the Dentate Gyrus

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Long-term potentiation (LTP) is a well-accepted memory model, which persists for weeks when induced *in vivo* at perforant path synapses in adult rats. LTP persistence depends on new gene expression, and is curtailed when induced in aged animals, suggesting an ageing-related dysregulation in LTP-specific gene expression pathways. To test this hypothesis we have used DNA microarray analysis to compare LTP-associated gene expression profiles in young adult (YA; 4-6 months; *n*=5), middle aged (MA; 15 months; *n*=3) and old aged (OA; 20-25 months; *n*=5) male Sprague-Dawley rats. Unilateral stimulation of perforant path synapses resulted in robust potentiation of field potentials (YA: 25.6±6.9 (average ± S.E.M), MA: 19.8±0.8; OA: 31.4±5.2). RNA isolated from control and stimulated dentate gyri 20 min post-LTP was converted to cDNA by reverse transcription, coupled to fluorescent dyes (control: Cy3; stimulated: Cy5) and used to probe Operon Rat27K oligo DNA microarray slides. Data normalisation and statistical analyses were carried out using the TM4 microarray analysis package, and Ingenuity Pathway Analysis was used to identify age-related alterations in LTP-related gene expression pathways. Using quantitative PCR we have confirmed that Ryr3, Limk1 and Oprm1 levels (representing calcium signalling, chemokine signalling and cAMP signalling pathways respectively) were increased in OA compared to YA. These results support our hypothesis that LTP-specific gene expression patterns are altered with ageing. These changes could underlie the age-dependent reduction in LTP persistence.

Supported by a grant from the NZ Marsden Fund.

1.7

How Well Can Young People With Asperger's Disorder Identify Threat in Faces?

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This study examined the ability to detect threat in faces as function of Asperger's disorder and nonverbal cognitive ability. The ability to identify threat in facial photographs was compared between two groups of young people with Asperger's disorder and nonautistic university students (NUS, n = 17). The Asperger group was subdivided into a very high functioning Asperger (VHFA, n = 17) group whose general nonverbal cognitive ability was equivalent to the NUS group, and a high functioning Asperger (HFA, n = 12) group. Participants were given pairs of faces (one convicted murderer and one layperson) and asked which person looked more dangerous. There was no significant group difference in the ability to identify dangerousness between the VHFA group and the NUS group. However, the HFA group was at chance when identifying dangerous faces. This study indicates a graded degree of performance with the NUS group performing best, the VHFA group next, and the HFA group performing worst. These results emphasized the role of nonverbal cognitive ability play in perceiving threat in faces, and the disadvantage of Asperger's disorder in identifying threat in faces. In addition to the implicated dysfunction of the amygdala, orbiofrontal cortex, superior temporal sulcus in Asperger's disorder, this study suggested that the ability to detect threat in faces is mediated by nonverbal cognitive ability, such as perceptual relations, analogy and inductive reasoning. Training these skills might enhance the ability to recognise threat in faces in young people with Asperger's disorder.

2.1

Dentate Gyrus Subregional Analysis of Glutamate Receptor Expression Following Perforant Path LTP *In Vivo*

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Long-term potentiation (LTP) is a well-studied cellular mechanism of information storage. LTP can persist for days or longer in the rodent dentate gyrus *in vivo* but identifying biochemical and morphological correlates of LTP over this time frame has been problematic. While we have shown a late LTP-associated increase in α-amino-3-hydroxy-5-methyl-4-isoxazole receptor (AMPAR) and *N*-methyl-D-aspartate receptor (NMDAR) expression, synapse-localised changes were not observed. As this may be due to difficulties in restricting analyses to potentiated synapses, here we have used laser microdissection to isolate stimulated and non-stimulated zones of the dentate gyrus molecular layer 48 h following induction of perforant path LTP in awake animals. High-frequency stimulation to the medial perforant path induced LTP at middle molecular layer (MML) synapses (48 h extracellular field potential: 19 ± 3% of baseline, n=6), and heterosynaptic LTD at outer molecular layer (OML) synapses (-26 ± 6%, n=6). Expression of the core NMDAR subunit NR1 was elevated in the MML 48 post-LTP (15 ± 3%, n=5, p=0.005, Student's t-test), but not the OML, or inner molecular layer. The relative distribution of AMPAR subunit GluR1 was increased in the MML at 48 h (LTP: middle layer 161 ± 36 % of inner layer; control: middle layer 115 ± 16 of inner layer, n=5, p=0.005, two-way ANOVA), while expression of GluR2 was unchanged. The LTP-induced increase in NR1 suggests an increase in size of postsynaptic specialisations, which may be populated by increased levels of GluR1-containing AMPARs that underpin LTP.

2.2

Regulation of Spatial Memory Processing by Endogenous Secreted Amyloid Precursor Protein-α

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Alzheimer's disease is characterised in part by abnormally low levels of a neuroprotective protein, secreted amyloid precursor protein-alpha (sAPPα). Inhibiting the function of endogenous sAPPα reduces long-term potentiation in the dentate gyrus *in vivo*, and reduces NMDA receptor-mediated currents *in vitro*. From these findings we predicted that endogenous sAPPα also plays a role in hippocampus-dependent spatial learning. Adult male Sprague-Dawley rats were surgically implanted with a cannula in each hippocampus. After recovery, animals were trained on a watermaze task for four days to locate a fixed hidden platform. On the fifth day, animals were given 16 trials on a new platform location. On this day, 15 min before and after training, animals were given bilateral intra-hippocampal injections (1 µl, 5 min) of the following solutions: DMSO vehicle, TAPI-1 (an inhibitor of α-secretase which produces sAPPα, 1.5 mM), recombinant sAPPα (300 nM), or TAPI-1 plus sAPPα (to replace the loss of endogenous sAPPα caused by TAPI-1). On Day 6, the animals were given a probe trial with the platform removed. Results on Day 5 showed that none of the injections affected memory for the original platform position, nor acquisition of the new platform position. However 24 h retention of the new platform position was significantly inhibited by TAPI-1, and this effect was prevented by co-administration of sAPPα. Together these findings indicate that endogenous sAPPα is a key contributor to synaptic plasticity and spatial memory. Its reduced production in Alzheimer's disease may thus contribute to the clinical memory deficits.

2.3

Modulation of Intracortical Inhibition by Low Intensity Theta Burst Stimulation

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Continuous Theta Burst Stimulation (cTBS) reduces motor cortical excitability, evidenced by a reduction in the amplitude of motor evoked potentials (MEPs). This effect is thought to be due to a decrease in the efficacy of excitatory synapses. cTBS may have a similar effects on inhibitory synapses as, in parallel with the MEP amplitude decrease, there is a reduction in intracortical inhibition (SICI). Given that cortical inhibitory circuitry has a low threshold for activation, the present study sought to investigate, by using low intensity cTBS, if it was possible to preferentially modify the efficacy of inhibitory circuits. cTBS (3 stimuli at 50 Hz repeated every 200 ms for 40 s) was applied over the motor cortex in eleven subjects at 70% of active motor threshold. Measures of intracortical excitability including SICI, ICF (intracortical facilitation) and short latency intracortical facilitation (SICF) were investigated using paired pulse transcranial magnetic stimulation before and following cTBS. There was no significant change in MEP amplitude following cTBS. SICI was reduced from 44.3 ± 8.4 % at baseline to 67.3 ± 13.2 % following stimulation ($p=0.03$). There was also an increase in ICF from 142.4 ± 22.9 % to 183.4 % ± 24.9 % post-cTBS ($p=0.04$). There was no significant change in SICF following cTBS. These findings demonstrate that cTBS can reduce SICI when applied at an intensity which is sub-threshold for inducing a change in MEPs. It is thought that the effects of cTBS are due to long term depression (LTD-like mechanisms. Therefore, we suggest these results indicate that low intensity cTBS may selectively induce LTD-like effects in inhibitory synapses.

2.4

Complexin II Plays a Positive Role in Ca2⁺-triggered Exocytosis by Facilitating Vesicle Priming

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SNARE-mediated exocytosis is a multistage process central to synaptic transmission and hormone release. Complexins (CPXs) are small proteins that bind very rapidly and with a high affinity to the SNARE core complex, where they have been proposed recently to inhibit exocytosis by clamping the complex and inhibiting membrane fusion. However, several other studies also suggest that CPXs are positive regulators of neurotransmitter release. Thus, whether CPXs are positive or negative regulators of exocytosis is not known, much less the stage in the vesicle life cycle at which they function. Here, we systematically dissect the vesicle stages leading up to exocytosis using a knockout-rescue strategy in a mammalian model system. We show that adrenal chromaffin cells from CPX II knockout mice exhibit a markedly diminished readily releasable vesicle pool, while showing no change in the kinetics of fusion pore dilation or morphological vesicle docking. Overexpression of wildtype CPX II but not of SNARE-binding-deficient mutants -- restores the size of the readily releasable pool in knockout cells, and in wildtype cells it markedly enlarges the readily releasable pool. Our results show that CPXs increase the primed vesicle pools for exocytosis and, therefore, are positive regulators of Ca2⁺-triggered exocytosis.

2.5

Reduced Expression of Pre-Synaptic Plasma Membrane Ca^{2+} ATPase (PMCA2a) Accompanies Enhanced Glutamate Release in a Model of Homeostatic Plasticity

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Homeostatic plasticity promotes neuronal network stability by adapting synaptic strength and neuronal firing to within a set range. In order to better understand the contributory mechanisms we modelled homeostatic plasticity by subjecting neurons to a period of long term inactivity. Combined hippocampal entorhinal cortex slices, 250 µm thick, from young Wistar rats (in accordance with Home Office, UK and University of Otago ethical approval) were maintained in culture and treated with excitatory amino acid antagonists, CNQX (40 µM) and APV (50µM). PMCA expression was evaluated by Western blot and whole cell voltage clamp recordings from CA3 pyramidal cells measured spontaneous miniature excitatory post synaptic currents (mEPSCs). After as little as 2 days, PMCA2a expression was specifically and reversibly reduced in the treated slice cultures, 45.9±1.6%, n=4, $p<0.001$, one way ANOVA). mEPSC amplitude was also enhanced from 12.5±0.2 to 17.0±0.5 pA (n=10, $p<0.01$, t-test) and the inter-event interval (IEI) reduced from 734±76 ms to 189±16 ms (n=10, $p<0.05$, t-test). 10 µM carboxyeosin, an inhibitor of PMCA, reduced mEPSC IEI in untreated cells from 640±70 ms to 245±5 ms (n=7, $p<0.05$, t-test) but was ineffective in the treated cells (n=6, $p=0.3$, t-test). Our results indicate that loss of PMCA2a, a transporter protein that normally clears Ca2⁺ from the pre-synaptic terminal contributes to enhanced glutamate release during homeostatic plasticity.

2.6

Towards Gene Therapy in Ovine Batten Disease

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The neuronal ceroid lipofuscinoses, or Batten disease are a group of inherited fatal neurodegenerative disorders of childhood characterized by blindness, seizures, dementia and premature death. Current treatments are palliative, however there are several ongoing human clinical trials using either gene or cell-based therapy. We are in a unique position, with three large animal models of Batten disease, to develop new treatment strategies for Batten disease. Two ovine CLN6 flocks and one CLN5 flock have been established. The CLN6 gene encodes an ER resident membrane-associate protein; CLN5 is a soluble lysosomal protein. Our previous studies demonstrated prolonged neurogenesis in the subventricular zone of affected brains and the persistence of cells undergoing chain-migration to the neocortex. Staining with a marker of neuroblasts, polysialated nuclear cell adhesion molecule (PSA-NCAM) indicated that this stream retains neuroblast activity. We have also shown that these PSA-NCAM positive neurosblasts can be targeted with lentiviral-based gene transfer vectors *in vitro*. We have now begun to test the feasibility of targeting neuroblasts in the subventricular zone *in vivo* as a means of distributing the normal gene product to degenerating regions of the brain.

2.7

SIRT1 Overexpression Delays Neuropathology in a Rat Model of Huntington's Disease

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The NAD-dependent histone deacetylase SIRT1 plays a pivotal role in mediating stress resistance in mammalian cells by regulating the activity of target proteins involved in cell death and cell survival such as p53 and FOXO, and has been linked to neuroprotection in both cell and *in vivo* models. With an interest in the development of gene therapy strategies for neurodegenerative diseases, the aim of this study was to determine whether adeno-associated viral (AAV) vector-mediated overexpression of SIRT1 would have neuroprotective efficacy in a rapidly progressing rat model of Huntington's Disease (HD). Subgroups of male Sprague-Dawley rats received an intrastriatal infusion of AAV vector expressing SIRT1, the dominant-negative SIRT1-H363Y or dYFP reporter gene. Two weeks later, rats received an AAV vector expressing an N-terminal fragment of huntingtin containing 70 CAG repeats (HD70) and subgroups of animals were euthanased at 2 or 5 weeks and the brains were processed for immunohistochemical analysis. At 2 weeks, huntingtin immunoreactivity in the form of intracellular inclusions were detected in a large proportion of transduced striatal neurons in the SIRT-H363Y and dYFP control rats and development of a striatal lesion as visualised by loss of NeuN immunoreactivity was already evident. In contrast, no discernible lesion was observed in the SIRT1-overexpressing animals injected with HD70 vector, although huntingtin-immunoreactive aggregates were present in the majority of striatal neurons. However, by 5 weeks post-AAV/HD70 infusion, lesion sizes between the SIRT1 and controls SIRT1-H363Y and dYFP were comparable. Our results suggest that SIRT1 overexpression is capable of delaying striatal cell death in HD although it does not appear to affect aggregate formation.

3.1

Advanced Imaging Techniques in the Management and Study of Stroke

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Advanced magnetic resonance imaging techniques are revolutionising the clinical management of people with stroke and playing an increasingly important role in stroke research. Diffusion-weighted imaging (DWI) confirms the diagnosis of ischemic stroke at the hyperacute stage when other imaging modalities may be normal. DWI in combination with perfusion-weighted imaging (PWI) may allow the selection acute stroke therapies in individual patients based on underlying pathophysiology rather than rigid time windows. Diffusion tractography enables the visualisation of white matte fibre tracts within the brain. Functional MRI using blood oxygen level dependent contrast images can identify regions of brain activity in response to given tasks. An overview of the strengths and limitations of each of these techniques in clinical practice and stroke research will be given. The potential application of multimodal MRI and other techniques in the prediction and monitoring of recovery for individual patients will be discussed.

3.2

Predictive Saccades and Cognitive Impairment in Parkinson's Disease

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Cognitive impairment in Parkinson's disease (PD) affects the ability to make predictive fast eye movements (saccades) to targets that alternate consistently in duration and amplitude. We present results from an ongoing trial investigating eye movements and measures of cognitive impairment. MoCA (Montreal cognitive assessment) scores and MMSE scores of 25 PD and 10 control participants were compared with saccade latencies to assess the effects of cognition on predictive saccades at a range of target interstimulus intervals (ISI). In each block of 41 trials, target direction (left, right, left etc.), amplitude (10 deg) and ISI (750, 1400, 2050ms) were entirely predictable. Participants were instructed to look at the target as quickly and accurately as possible. Latency from target onset to saccade initiation was the primary outcome variable. For the PD group, the MMSE scores exhibited a strong ceiling effect while the MoCA produced a larger range of scores, and there was a negative linear correlation between MoCA scores and latency at the 750ms ISI ($r=-0.54$, $p=0.05$). The same trend was seen at 1400ms ($r=-0.37$, $p=0.069$) and 2050ms ($r=-0.38$, $p=0.065$). That is, patients with lower MoCA scores had longer mean latencies than patients with higher MoCA scores, who anticipated more. There was no evidence of a correlation in the control group where there was less spread in MoCA scores. PD subjects with higher MoCA scores produced a wider range of saccade latencies as they were able to employ either predictive or reactive strategies, while people with lower MoCA scores were less able to make use of prediction.

3.3

Effects of Repetitive Transcranial Magnetic Stimulation on Cortical Excitability in Parkinsonian Rats

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Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a potential therapeutic tool in Parkinson's disease (PD). Recent research has suggested that the cerebral cortex excitability can be modulated via theta burst stimulation (TBS) mode of rTMS. The aim of this study was to explore the effects of TBS on the excitability of the motor cortex in chronic PD rats induced by unilateral infusion of the neurotoxin 6-hydroxydopamine (6-OHDA) into substantia nigra pars compacta. We explored the immediate effects of continuous TBS (cTBS) in which 3 pulses of stimulation were given at 50 Hz repeatedly in every 200 ms for a total of 300 pulses. A custom-made miniature magnetic coil was used for stimulation and for further evaluation purpose. Conventional evaluations of cortical excitability via single-pulse TMS and the apomorphine-induced rotational behavior were firstly evaluated. Furthermore, the changes in muscle rigidity were evaluated by a miniature biomechanical stretching device, developed in our previous study, to manually stretch the hindlimb of awake PD rats. Our results exhibited that the elevated motor evoked potentials (MEP) was recorded from calf muscle and the rotational behavior was suppressed after application of cTBS in three consecutive daily sessions. These observations indicated rTMS can lead to potentiation in motor cortex excitability which resulted in cumulative effects on behavioral recovery for at least 30 min. However, the long lasting effect and cortical plasticity should be further evaluated for utilizing rTMS as a novel treatment scheme for PD rats.

3.4

Reflexive and Voluntary Saccades in Parkinson's Disease

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Studies of saccades (fast eye movements) in Parkinson's disease (PD) report disinhibition of reflexive saccades, including increased production of 'express' saccades (latencies 80 -140 ms) and prolonged latencies and hypometria of voluntary saccades. The *tonic inhibition model* (Sereno, 1995) attributes these characteristic changes to impairment of the voluntary saccadic system in PD. It is not clear, however, whether saccadic disinhibition and express saccade production in PD are indeed associated with impaired voluntary saccades. Recently it was also suggested that L-dopa may prolong saccadic latencies in PD. This study measured saccades of 11 PD patients and 11 control subjects in two sessions using a reflexive and a voluntary saccadic task. The PD group was tested 'off' and 'on' L-dopa. As expected, significant interactions between task and group were found. The PD group made reflexive saccades at shorter latencies (161 ms vs 172 ms) and voluntary saccades at longer latencies (416 ms vs 367 ms) than the control group ($p < 0.05$). Saccades in the PD group were hypometric in the voluntary task but not in the reflexive task ($p < 0.05$). Size and direction of the effect of L-dopa varied between tasks and subjects, and L-dopa did not affect mean latencies or hypometria in the PD group. In contrast to the prediction of the tonic inhibition model, latencies of reflexive and voluntary saccades were positively correlated in the PD group. Subjects with PD who made voluntary saccades at prolonged latencies did not make more express saccades than the control group. This suggests that abnormal disinhibition of the reflexive saccadic system in PD may not necessarily be associated with impairment of the voluntary saccadic system.

3.5

Subtle Cognitive Impairment in Elderly People With 'Normal' MMSE Scores

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The mini-mental state examination (MMSE) is widely used to assess the presence and severity of dementia, with a score below 24 being indicative of probable Alzheimer's disease. There is a lack of consensus concerning the sensitivity of the MMSE to milder forms of cognitive impairment, and whether the various subtests of the MMSE are able to detect impairments in specific cognitive domains. In the present study, 96 community dwelling elderly persons aged 62-89 years (mean = 75.2 years) were tested on both the MMSE and a computer-based visuospatial task, the Subtle Cognitive Impairment Test (SCIT). All participants had an MMSE score of 25 or more, which is within the range that is often regarded as being cognitively 'normal'. Participants with an MMSE of 25-27 (n=10) performed significantly worse on SCIT (ANOVA $F(2,94) = 11.40$, $p<0.001$) than those with an MMSE of 28-29 (n=47), while those with a perfect score of 30 (n=39) performed best on SCIT. Only those individuals who made errors on the language, attention and visual construction subtests of the MMSE displayed impaired SCIT performance. Furthermore, participants with deficits on these subtests displayed a pattern of impaired performance on SCIT which was characteristic for that particular subtest. The present results suggest that MMSE scores in the range of 25-29 may indicate the presence of 'subtle' cognitive impairment. Our data also indicate that several distinct subtypes of subtle cognitive impairment may be common within the elderly population. It would be of interest to determine whether any of these subtypes has an increased probability of progressing to mild cognitive impairment and/or to Alzheimer's disease.

3.6

Limbic System Structural Integrity and Global Cognitive Status in Parkinson's Disease: A DTI Analysis

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DTI is a non-invasive, *in vivo* magnetic resonance imaging technique which quantitatively measures the diffusion of water in the brain. This information allows the inference of microscopic structural integrity as well as the mapping of white matter tracts (tractography). In this study we correlate neuropsychological measures with structural brain changes in Parkinson's patients using diffusion tensor MRI. The first 24 of a planned 45 Parkinson's patients completed extensive neuropsychological examination and 3T MRI scans, producing both DTI and structural (3D anatomic T1-weighted) MR images. A diffusion-weighted spin echo EPI sequence was used, with diffusion weighting in 28 uniformly distributed directions and 4 acquisitions without diffusion weighting. We used region-of-interest based analysis to investigate the correlations between the neuropsychological exam scores and DTI data in key components of the limbic system, namely anterior thalamus, hippocampus, parahippocampus, amygdala, anterior cingulate and posterior cingulate. There were correlations in the anterior thalamus bilaterally between both the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) and the DTI measures of fractional anisotropy and mean diffusivity (corrected $p<0.05$). Fractional anisotropy measures from bilateral hippocampus, parahippocampus, and amygdala significantly correlated with both MMSE and MoCA ($0.38< r <.57$). The only other significant mean diffusivity measures correlated with MMSE in the anterior cingulate. The current study shows DTI MRI to be a promising method to evaluate and potentially track anatomical substrates of cognitive decline in Parkinson's disease.

Poster 4.0

Regulation of Synapse Function by SAP97 Isoforms

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The activity-dependent insertion and removal of ionotropic -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid - type glutamate receptors (AMPARs) at the postsynaptic plasma membrane is thought to underlie neuronal plasticity, providing a molecular basis for learning and memory. Members of the discs-large (DLG) family of membrane-associated guanylate kinases (MAGUKs), including PSD-95, PSD-93, SAP97 and SAP102, have been implicated in the forward trafficking, accumulation, and retention of AMPARs at synapses. The Synapse Associated Protein 97 (SAP97) is the only MAGUK protein reported to directly interact with AMPARs. The beta SAP97 isoform contains an N-terminal L27 domain that is important for hetero- and homo-multimerisation. A recent study reported the existence of another isofrom, alpha-SAP97, in which the prototypic N-terminal L27 domain is replaced with a short sequence containing a putative palmitoylation motif. Using dissociated hippocampal cultures expressing GFP-tagged alpha or beta -SAP97, our colleagues 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. Fluorescence recovery after photobleaching (FRAP) revealed alpha-SAP97 has a very rapid turnover at spines compared with beta-SAP97. Moreover, we have found that alpha-SAP97 increased the amplitude of AMPA receptor-mediated synaptic transmission, while beta-SAP97 decreased it. Using the transfection of shPSD95 + alphaSAP97 or shPSD95 + betaSAP97 to dissociated hippocampal cultures, we found that alpha-SAP97 rescued the decrease of AMPAR EPSCs due to PSD95 knockdown, while betaSAP97 does not rescue the decrease of AMPAR EPSCs due to PSD95 knockdown. Furthermore, using chemical inducing and pair-recordings, we could induce LTD but not LTP in SAP97 transfected neurons. Together these data indicate that alpha-SAP97 and beta-SAP97 have a different role in regulating synaptic function.

Poster 4.1

Synaptic Changes in Cerebellar Neurons of an Ataxic Mouse

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The spontaneous recessive mutant mouse *stargazer* exhibits ataxia that is potentially linked to a cerebellar deficit in the brain-derived neurotrophic factor (BDNF). BDNF levels in the cerebellum are reduced by 70% and undetectable in cerebellar granule cells. Ataxia occurs at a time-point in cerebellar development when the BDNF gene is normally activated. BDNF is involved in synapse formation and plasticity. The aim of this study was to investigate the effect of lack of BDNF on cerebellar synapses in stargazer mutants using electron-microscopy, immunogold-cytochemistry and Western blot analysis. There is a significant decrease in the levels of glutamate at excitatory synapses. The proportion of synaptic vesicles docked at the presynaptic active zone and the thickness of the postsynaptic density are also significantly reduced in the stargazer mutants. Changes in the distribution of synaptic vesicles at the active zone are accompanied by a selective reduction in the levels of specific synaptic proteins involved in vesicle trafficking and exocytosis. Expression levels of the calcium channel CaV1.2 are also significantly reduced at cerebellar synapses as shown by immunogold-cytochemistry. Semi-quantitative Western blot analysis using isolated synapses confirmed that the levels of CaV1.2. were significantly reduced when compared to non-ataxic littermates (-35 ± 10, n=9; $P \leq 0.01$). The reductions in the expression levels of vesicle associated proteins and the CaV1.2 calcium channels are restricted to cerebellar regions of the brain and do not occur in the hippocampus. Collectively these data show that the stargazin mutation has a significant impact on both pre- and post-synaptic proteins involved in synaptic transmission and that the stargazer mutation is likely to have a pronounced effect on glutamatergic synapses in the cerebellum.

Poster 4.2

Functional Expression of the Plasma Membrane Ca^{2+} ATPase, PMCA2, at Inhibitory Synapses

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The plasma membrane Ca^{2+} ATPase, PMCA2 is widely expressed in the brain and a major route for Ca^{2+} transport out of cells. Here we show evidence to support a role for PMCA2 during inhibitory synaptic transmission. Combined hippocampal entorhinal cortex slices, 250 µm thick, from post-natal day 5-7 Wistar rats were maintained in culture for 7 days in vitro (DIV). 270 µm thick acute saggital cerebellar slices from wild type and PMCA2-/- knockout mice (21-28 days old) were also prepared, all in accordance with Home Office, UK and University of Otago ethical approval. Whole cell voltage clamp recordings from CA3 and cerebellar Purkinje neurons measured the frequency and amplitude of spontaneous inhibitory post synaptic currents (spIPSCs). In CA3 neurons the frequency of spIPSCs increased when PMCA was pharmacologically inhibited by carboxyeosin (CE, 10µM). Mean median inter event intervals (IEI) reduced from 122.8±10.1 ms to 95.5±8.9 ms in the presence of CE, ($n=7$, $p<0.01$, paired t-test). CE also enhanced the frequency of spIPSCs in cerebellar Purkinje neurons, mean median IEI changed from 267±46 ms to 196±31 ms ($p<0.05$, t-test). In PMCA2 knockout mice the frequency and amplitude of spIPSCs was also enhanced ($n=10$, $p<0.05$, t-tests) compared with wild type; mean median IEIs were 224±45 ms and 95±15 ms and amplitudes were 122±6 pA and 171±22 pA respectively. These findings support a role for PMCA2 mediated Ca^{2+} extrusion during spontaneous GABA release within two distinct central nervous system networks.

We acknowledge the support of the New Zealand Neurological Foundation and Department of Physiology University of Otago.

Poster 4.3

Real-Time Spatially Resolved Analysis of Serotonin Transporter Activity Using the Fluorescent Substrate ASP^+

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The human serotonin transporter (hSERT) mediates clearance of serotonin (5-hydroxytryptamine, 5HT) from serotonergic synapses, thereby, regulating extracellular 5HT concentrations. Its dysregulation has been implicated in the pathogenesis of drug addiction and affective disorders. Radioligand uptake techniques are typically used to assess SERT function in native tissue and heterologous expression systems. The need for sufficient protein in samples, however, requires the use of homogenate preparations, potentially masking effects limited to a specific cell population. 4-(4-(dimethylamino)-styryl)-N-methylpyridinium (ASP^+) is a fluorescent high affinity monoamine transporter substrate that has recently been used to monitor dopamine and norepinephrine transporter function in single cells and in real time. The present live cell imaging studies examined the utility of ASP^+ for quantifying SERT function in heterologous expression systems. Herein, we show rapid membrane binding and intracellular accumulation of ASP^+ in HEK-293 and neuroblastoma 2A cells transiently transfected with hSERT. Consistent with a transporter-mediated process, ASP^+ accumulation is saturable, dependent on temperature, hSERT expression levels and the presence of sodium and chloride in the media. Acute or prolonged exposure of cells to 5HT re-uptake inhibitors produces a concentration-dependent decrease in ASP^+ accumulation and similar effects are observed in response to PKC activation. In contrast, activation of p38MAPK significantly increases ASP^+ accumulation. These data demonstrate that ASP^+ is a sensitive probe for monitoring SERT function in living cells. Drug-evoked alterations in SERT binding and uptake can be quantified in the same cell. Furthermore use of a within cell design permits analysis of time-related alterations in SERT function.

Poster 4.4

Neuromodulator Induced Ca^{2+} Signals in Identified Astrocytes of the Respiratory Network

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The respiratory rhythm is generated by specialized neurons in the medulla oblongata. Glial cells stabilize this rhythm. The neuropeptides substance P (SP), thyrotropin-releasing hormone (TRH) and the biogenic amine serotonin (5-HT) are potent stimulators of the respiratory network. However, the modulation of glial cells, in particular astrocytes by SP, TRH and 5-HT is unknown. To study, whether and how these neuromodulators evoke or modulate changes of astroglial calcium signalling, we bulk-loaded acutely isolated brainstem slices of early postnatal mice with the membrane-permeable fluorescent Ca^{2+} -indicator Oregon Green 488 BAPTA-1. We used a transgenic mouse line in which astrocytes express the monomeric red fluorescent protein mRFP1 (TgN (hGFAP-mRFP1)). In addition, astrocytes could be identified by Ca^{2+} influxes in response to application of a low extracellular K^+ concentration (0.2 mM). SP and TRH as well as 5-HT and the 5-HT_{2a}-R agonist α-methyl-5-HT induced astroglial calcium transients of different kinetics in the absence of neuronal activity (blocked by 500 nM TTX). Additionally we were able to demonstrate the expression of NK1, TRH-R, and 5-HT_{2a}-R in astrocytes of the VRG by immunohistochemistry. Since it is known that any rise of intracellular calcium in astrocytes leads to a vesicular release of glutamate, it is tempting to speculate that the neuromodulators SP, TRH and 5-HT constitute a modulatory mechanism of synaptic function in the respiratory network via a direct effect on astrocytes.

Poster 4.5

Synaptic Integration in Mitral Cells is Regulated by a Persistent Sodium Current (I_{NAP}-I_{NaP})

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Mitral cells (MCs) are the principal neurons of the olfactory bulb of the brain. They receive direct synaptic input from olfactory receptor neurons of the nose, integrate this odour information with synaptic input from local circuit neurons, and relay processed output to olfactory cortex. Intrinsic postsynaptic membrane properties determine how neurons integrate synaptic input: we are investigating active membrane properties of MCs that may influence their responses to synaptic input, using *in vitro* olfactory bulb slice preparations and whole-cell patch recording methods. Our voltage- and current-clamp studies show that that MCs generate a TTX-sensitive persistent Na^+ current (I_{NaP}-I_{NaP}). This voltage-dependent inward current is active in MCs at membrane potentials subthreshold for action potential generation. It contributes to the generation of MC resting potentials, influences their action potential firing patterns and rate, and may regulate olfactory processing by amplifying MC responses to synaptic input from the nose.

Supported by the Marsden Fund and the Department of Physiology, University of Otago.

Poster 4.6

What Does it Mean to Have a Permanent Deficit of Hippocampal CA1 Cells Following a Single Binge Exposure to Ethanol During Development? An Animal Model Study

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Alcohol consumption during pregnancy results in altered fetal development. Significant cell death occurs in numerous brain regions within 15 hours of the initiation of a single binge exposure to ethanol. This study investigated the long-term effect of a single ethanol binge on cell number and behaviour in the mature rat. On either PN4, PN6 or PN7 Long Evans rat pups were weight matched and randomly assigned to one of three treatment groups; alcohol-exposed, AE; (4.5g/kg/day ethanol in two feeds two hours apart), sham intubated, SI; (intubated only) or suckle control, SC; (handled only). Peak blood ethanol concentration, 1.5 hours after the second ethanol feeding was 351±56 (*mean ± st.dev.*). A single binge exposure on PN4 resulted in a significant difference in total CA1 neuron number between treatment groups (*p=0.003*) with post-hoc comparison indicating that AE animals had lower number of neurons than SC (p=0.002) and SI rats (p=0.05). PN6 and PN7 data will also be presented. Ethanol treatment on either PN4, PN6 or PN7 had no effect on activity in the open field. There was also no treatment effect on the reference memory or delayed matching to place versions of the MWM. Despite significant acute cell death and a permanent deficit in hippocampal CA1 cell number animals do not show deficits on selected behavioural tasks. This suggests that the developing brain is able to compensate for structural damage that occurs following exposure to a moderate ethanol binge in order to maintain normal brain output.

Poster 4.7

Evaluating Cannabinoid Receptor Agonist for the Treatment of Salicylate Induced Tinnitus in Rats

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Although the mechanisms underlying the development of tinnitus are still not clear, it has been suggested that it is related to neuronal hyperactivity in the central auditory system. Recently, medicinal cannabinoids have been reported to be effective in treating neuropathic pain by reducing the neuronal hyperactivity. Our previous results have also shown the existence of cannabinoid CB1 receptors in rat cochlear nucleus neurons and they were down regulated in the ventral cochlear nucleus in rats with salicylate-induced tinnitus. Therefore, we hypothesized that cannabinoids may be effective in the treatment of salicylate-induced tinnitus. In this study, we investigated the effects of 2 different cannabinoid receptor agonists, delta-9-tetrahydrocannabinol (delta-9-THC) and WIN55,212-2, on salicylate-induced tinnitus. Tinnitus was induced by an injection of sodium salicylate (350mg/kg i.p.) and detected using a conditioned lick suppression behavioural paradigm at 3h after the sodium salicylate injection. Delta-9-THC (3mg/kg, 6mg/kg), WIN (3mg/kg), or vehicle was given 30 min prior to the sodium salicylate injection. Neither delta-9-THC nor WIN55,212-2 significantly reduced the expression of tinnitus, although delta-9-THC did cause a small but non-significant decrease. Although there is a possibility that higher doses of delta-9-THC may reduce tinnitus, it may also produce severe adverse side effects. Therefore, endocannabinoid enhancing drugs, that have fewer effects on psychomotor functions, may be a more effective avenue of investigation for the investigation of novel drug treatments for tinnitus.

Poster 4.8

Lithium Treatment *in vitro* has Direct and Adaptive Effects on Neuronal Excitability

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For over fifty years the elemental cation lithium has been used in the treatment and prophylaxis of Bipolar Disorder; however its therapeutic mechanism of action remains unknown. We have investigated the effects of lithium on the activity of brain neurons, mitral cells of the mouse olfactory bulb *in vitro*, using whole cell and extracellular recording techniques. Lithium (0.5-10mM) caused a dose dependent increase in the excitability of mitral cells, depolarizing resting membrane potential, increasing action potential firing rate, and increasing the time constant of action potential repolarization. These effects are consistent with a reduction of outward membrane current. Lithium washout was associated with a significant decrease in action potential frequency below pre-treatment firing rates which persisted for at least twenty minutes. These results suggest that lithium treatment has direct and indirect, possibly adaptive, effects on neuronal membrane properties. We hypothesise that lithium treatment decreases activation of a sodium dependent potassium current (IK_{Na}), known to be abundant in mitral cells and regulates action potential firing. Decreased IK_{Na} during lithium treatment may lead to increased neuronal excitability, and be associated with persistent adaptive changes in membrane properties that lead to reduced excitability when lithium is removed. We are characterizing the membrane currents acutely affected by lithium treatment, and following lithium washout.

Poster 4.9

Afferent Axonal Pathfinding in Developing Chicken Rhomboencephalon

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The developing hindbrain of vertebrates i organized in a series of rhombomeres, each giving rise to specific nuclei. The role of this segmentation has been extensively studied with respect to the origin of motor nuclei. The development of afferent innervation, however, has received little attention. Afferent axons enter the brainstem prior to the migration of their central targets and must therefore navigate in the absence of target derived information. Since the target nuclei for each afferent component originates within discrete rhombomeric boundaries, it is possible that the same positional information that is used by neuronal progenitors to define their final fate, may be available to afferent axons to direct them through their initial growth. This study was aimed at determining the normal sequence that characterises the growth of afferent axons in the hindbrain within the context of the site of origin and of the organisation of second order sensory neurons within specific rhombomere boundaries. Afferent axons were labelled at different embryonic ages using fluorescent lipophilic dyes. Crystals of DiI and/or DiO were placed on specific exposed nerves or nerve branches of fixed embryos. Embryos were incubated at 30 C for 18 hrs, after which the hindbrains were dissected, cleared in glycerol and analysed as whole-mount preparations with confocal microscopy. Afferent axons formed a series of fascicles that extended longitudinally along the alar plate, beyond the rhombomeric boundaries that give rise to their target nuclei. At early stages, the degree of organization and segregation of afferent axons did not appear to reflect the adult patterns. Thus, it appears that the appropriate pathfinding and final segregation of the afferent components involves an initial profuse growth into the hindbrain, and that proper afferent patterning involves axon retraction and may require the initiation of migration if the central targets towards their final position.

Poster 4.10

Spine Elimination in the Hippocampus and a Novel Finding with MAP2

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Plasticity of the circuitry wiring our brains is a fundamental property of neurons thought to underlie behaviour, cognition, learning and memory. The development of new synapses, the activity-dependent changes in the strength of existing synapses and the elimination of synapses have all been proposed to form the basis of this plasticity. The NMDA-type glutamate receptor expressed at excitatory glutamatergic synapses is required for learning and memory and is critical for normal brain function. This receptor plays a pivotal role in triggering and controlling synaptic plasticity. Dendritic spines are small post-synaptic protrusions of which the majority of excitatory synapses form on. My research examines the sub-cellular mechanisms of how NMDAR-dependent long-term depression (LTD) induces dendritic spine and synapse elimination in dissociated hippocampal cultures. We found spine elimination to be accompanied by pre- and post-synaptic collapse, using the markers Synapsin and Bassoon, and Homer, respectively. The relationship between structural spine plasticity and functional synaptic plasticity remains to be clarified. Interestingly, we also observed a novel change in the microtubule-associated protein 2, MAP2, following LTD induction. The function of this change remains to be determined but could involve binding of actin – a highly concentrated spine protein involved in structural spine plasticity. This data and future research planned will provide key information on how changes in NMDAR activity can dictate changes in spine and synapse number in the remodelling of brain circuitry. Synapse elimination is not only a fundamental process during brain development and maturation, but also a major component of the induction of neuro-degeneration. Therefore research in this area will provide important cellular information on how degeneration occurs and may identify potential targets for brain repair.

Poster 4.11

A New Method to Detect DNA Synthesis in Proliferating Cells *In Vivo* Using 5-ethynyl-2'-deoxyuridine (EdU)

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At present the use of the nucleoside thymidine analog 5- bromo-2-deoxyuridine (BrdU) is the most common way to assess cell proliferation, cell cycle kinetics and cell viability both *in vitro* and *in vivo*. However protocols for BrdU visualisation involve intensive *in vivo* injection regimes and tissue denaturing conditions, often making it difficult to co-label with other antibody markers. In contrast, EdU (5-ethynyl-2'-deoxyuridine) is a fast easy method for detecting DNA synthesis by incorporation of EdU into replicating DNA of proliferating cells in S phase. EdU uses a novel "click it" chemistry method to identify cells in S phase. It uses small molecule fluorophores rather than antibodies which improves resolution and signal strength. EdU contains an alkyne group which reacts specifically and rapidly with the fluorescent azide molecule and lights up the newly synthesised DNA. In a copper catalysed reaction, the alkyne reacts with an azide, forming a very stable covalent bond- unlike the noncovalent bond between an antibody and an antigen. This is highly sensitive, does not require intensive tissue denaturing conditions and can be visualised in minutes. To date EdU has only been used for cell proliferation assays *in vitro*. In order to expand this technology we have been optimising techniques to utilise EdU for the first time *in vivo*. We have demonstrated the ability to inject adult rats with EdU and visualise proliferating cells in harvested brain tissue using the EdU "click it" reaction. This technology will provide a superior and exciting alternative to the current BrdU antibody based method for measuring cell proliferation *in vivo*.

Poster 4.12

Doublecortin Positive Cells in the Temporal Cortex of the Epileptic Adult Human Brain

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Doublecortin (Dcx) is a microtubule associated protein expressed in migrating new neurons during development (Gleeson et al., 1999). Recent studies have shown that Dcx is also a marker of new neurons in neurogenic regions of the adult animal (Brown et al 2003) and human brain (Jin et al., 2003; Fahrner et al., 2007). The expression of Dcx outside neurogenic regions has yet to be investigated in the adult human brain. The present study shows for the first time that Dcx positive cells are present in the temporal cortex of the normal and epileptic adult human brain. Quantitative studies reveal a significant increase in the number of Dcx positive cells in the middle temporal cortex of the epileptic brain compared to the normal brain. Interestingly, triple immunofluorescence labelling using the markers Dcx, proliferating cell nuclear antigen (PCNA) (a proliferative cell marker) and III-tubulin (an early neuronal marker) demonstrate that many cells immunopositive for Dcx in the epileptic temporal cortex also co-express PCNA and III-tubulin. Taken together, these results suggest that epilepsy may increase the expression of Dcx positive cells in the adult human brain and provide evidence suggestive of cortical neurogenesis in the adult human brain.

Poster 4.13

An Examination of the Extent of Adult Neurogenesis in the Carpet Shark *(Cephaloscyllium Isabellum)*

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Following Altman's and Kirsche's challenge to the dogma that no new neurons could be produced during adulthood in the 1960's, adult neurogenesis was shown in most vertebrate lineages. From a phylogenetic point of view, adult neurogenesis is not an uncommon event, having been demonstrated in reptiles and birds, amphibians, bony fishes and mammals. At present, however, adult neurogenesis has not been examined in cartilagineous fishes, the stem line of vertebrates. Sharks are an ideal group in which to study the extent of adult neurogenesis for several reasons: (i) they exhibit continuous body growth throughout life; (ii) in the stingray the number of peripheral axons and neurons continues to increase into adult life; and (iii) in adult gray reef sharks the number of inner ear hair cells also continues to increase. We have begun to evaluate the extent of adult neurogenesis in the carpet shark *(Cephaloscyllium isabellum)*. A specimen of *C isabellum* was injected i.p. with 230 mg/kg of BrdU, anaesthetised and perfused after 2 hrs. The brain was cryoprotected and cut at 40 µm, and processed following standard immunocytochemical techniques. BrdU was found in a small number of nuclei in close proximity to the ventricular surface, in a similar position than occasional cells labelled with an antibody aginst β-tubuline (III). Some BrdU labelled nuclei were also found throughout the brain that were not stained with our neuronal marker. These preliminary data suggest that adult neurogenesis occurs in sharks and that like in bony fishes, but unlike birds and mammals, it may also occur in non-telencephalic areas. If widespread adult neurogenesis can be unequivocally demonstrated in sharks, it would indicate that it represents the primitive condition. This therefore raises the question of what modifications in brain evolution of modern vertebrate lineages led to the restriction of this ability to specific forebrain areas.

Poster 4.14

Chemokines Direct Neural Repair in the Adult Rodent Brain

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A number of studies have observed the directed migration of resident adult neural progenitor cells to sites of brain injury. We recently demonstrated that directed migration of SVZ-derived progenitor cells in response to QA-induced striatal cell loss is acute and transient, with the majority of cells present in the damaged striatum generated from progenitor cells dividing within 2 days either prior to or following the QA lesion. The current study provides unique evidence demonstrating a role for the chemokines GROα, MCP-1 and MIP-1α in regulating adult SVZ progenitor cell migration following striatal cell death. Each of these chemokines was significantly upregulated within the first 2 days following QA-induced striatal lesioning. Furthermore, we established that SVZ progenitor cells in the adult brain express receptors for each of these chemokines, and demonstrated GROα, MCP-1 and MIP-1α to be potent chemoattractants for adult SVZ-derived neural progenitor cells *in vitro*. We therefore propose that induction of the chemokines GROα, MCP-1 and MIP-1α following QA lesioning leads to chemoattraction of SVZ progenitor cells into the lesioned striatum. Furthermore, the transient expression of chemokine migratory cues following cell death may be responsible for the reduction in progenitor cell recruitment previously observed in the damaged striatum.

Poster 4.15

Reflexive Orienting in Child, Adolescent, and Young Adult Males

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Inhibition of Return (IOR) refers to the phenomenon whereby spatial attention is slower to return to a recently attended location than to a novel location (Posner, Rafal, Choate, & Vaughn, 1985). While numerous studies have explored IOR in healthy and clinical adult populations, comparatively little is known about IOR in the context of child and adolescent cognitive development. IOR is typically investigated using covert orienting of attention tasks where participants are asked to fixate a central cross and then execute a speeded response to a target appearing in one of two peripheral boxes located to the left and right of the fixation cross. Targets are preceded by a peripheral cue (a brief luminance change) and the cue-target interval (SOA) is varied. Cues are non-informative in that the location of the cue does not predict the location of the subsequent target. In the present study, we examined the early facilitatory effects and later inhibition of return effects of exogenous cues in right-handed males between the ages of 5 and 25. Participants were grouped by developmental stage (5-10, 11-17, 18-25). Initial pilot data revealed no evidence of IOR, however this was due to errors in the experiment design. Subsequent data using a corrected low luminance double-cue procedure showed evidence of IOR in participants of all ages (N=15) at 650ms SOA. The results suggest that reflexive orienting is established early in development although younger participants aged 5-10 showed more variability in responses and slower reaction times compared to participants aged 11-17 and 18-25. This may indicate an improvement in the strategic control of attention in early childhood with adult-like abilities achieved just prior to adolescence.

Poster 4.16

What Causes a Neuron to Fire? A Theoretical Analysis Using Hamilton's Equations of Classical Mechanics

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We use a theoretical and computational approach to investigate the behaviour of a cortical neuron on the approach to an action potential. We use a two-component dynamic model of a single neuron, due to H. R. Wilson, modified with noise inputs. We derive a Lagrangian for the system, from which we construct Hamilton's equations using the recipe from classical mechanics. The conjugate momenta of Hamilton's equations are found to be linear combinations of the noise inputs to the system. We then use a theoretical analysis and computer simulation of the resulting equations to consider the most likely manner in which a neuron approaches a firing event. We find that the firing of a neuron is a result of a drop in inhibition, due to a temporary drop in the mean noise input to the inhibitory control equation. Moreover, we demonstrate that, on average, the mean noise input changes in an exponential manner on the approach to an action potential. Therefore, in the Hamiltonian description, an action potential can be considered a result of the exponential growth of the conjugate momenta pulling the system away from its equilibrium state, into a non-linear (firing) regime.

Poster 4.17

Binding of Visual Features in Short-Term Memory

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Different features of a visual scene (e.g. colour, motion, form etc.) are coded in different cortical areas. As a result of this, the visual system is required to bind these disparate sources of information to create veridical representations of objects in the visual environment. The mechanism by which this is achieved is thought to involve attentional processes: visual features that share a common location are bound together by attention when attention is allocated to that location. It is unclear, however, whether visual short-term memory maintains information in a bound state, as integrated representations, or if visual information is coded in the form of separate visual feature stores. In this study, I present results from a behavioural change detection experiments involving coloured letters. There were two types of possible change: *novel changes* which involved the addition of new letters or new colours and *binding changes* which involved letters swapping colours. In addition to the change detection task, an attentionally demanding visual search task was performed during the delay interval in some conditions. A repeated-measures ANOVA showed that the visual search task preferentially disrupted memory for binding information (*binding changes*) relative to memory for single visual features (*novel changes*). This suggests that attentional processes play an important role in maintaining binding information in visual short-term memory.

Poster 4.18

The Late Negativity For Binaural Pitches: Object Related Negativity or Pitch Onset Response?

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As with earlier studies, we wished to expand our research investigating the neural mechanisms underlying auditory segregation. Particularly, to elucidate the mechanisms underlying concurrent sound segregation, especially whether the late negativity evoked by dichotic pitch in previous experiments, indexes pitch processing mechanisms (POR) or concurrent sound segregation mechanisms (ORN). We employed a new stimulus that consists of either one or two narrow bands of noise that could have control and target lateralized to both the left and the right side of auditory space (called spatial pitch; SP). To 'bridge' the use of the SP stimulus, a dichotic pitch stimulus was developed with both control and targets lateralized. Auditory ERPs were measured from 15 participants in separate listening conditions where participants had to indicate whether one or two pitches were presented for DP (Experiment 1) or SP stimuli (Experiment 2). Both DP and SP stimuli evoked an object-related negativity (ORN) at a latency of 150-280 ms after stimulus onset. A P400 component was only evoked for the SP stimuli, with a latency of 400-500 ms. The results indicate that the late negativity observed in previous experiments using DP is related to concurrent sound segregation mechanisms (ORN) and not pitch specific processing (POR).

Poster 4.19

Brain Stimulation Reduces Terror Related Prejudice Post 911

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Stimulation of the brain via repetitive Transcranial Magnetic Stimulation (rTMS) is beginning to yield interesting results in many cognitive domains. Inhibiting the Left Anterior Temporal Lobe (LATL) appears to have dramatic effects on people's semantic conceptualisation. Some evidence exists to suggest that people with damage (or virtual lesion) to the LATL show signs of semantic dementia and appear to focus on component details of their surroundings rather than the concepts summarizing them. However, little research has been done on whether this bias towards 'details' induced by rTMS can produce cognitive benefits where overarching schemata are negative or debilitating. Here we show that neural inhibition via rTMS (1 Hz) is capable of reducing terror-related prejudice against people of Arabic descent. We used an Implicit Association Test and interview to demonstrate a discrepancy between participant's self-reported positive pre-disposition towards people of Arabic descent and their non-conscious association of Arab peoples with terrorism. More importantly, we demonstrate that this prejudice was significantly reduced by rTMS to the LATL (but not Sham) in post-stimulation IAT scores. This experimental reduction is important because racial prejudice is not only debilitating and de-stabilizing to multicultural societies, it also appears to be a necessary pre-condition for large-scale atrocious acts. Understanding what is necessary to the functioning of prejudice at a neural level may have profound applications.

Poster 4.20

Spatial and Non-Spatial Information in Dichotic Pitch

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Auditory scientists have proposed that the auditory system processes different auditory features (eg. pitch and location) in separate processing streams. Empirical data from various electrophysiological and neuroimaging studies have confirmed the temporal advantage of preattentive processing for spatial sound compared to non-spatial sound. To supplement the analysis on automatic or preattantive level, current study aimed to investigate the discrepancy between the neural processing of spatial and non-spatial information in dichotic pitches when listeners are actively attending to the sound features. Mismatch negativity (MMN), measured by surface electroencephalogram (EEG), was used as an indication of conscious processing of acoustical stimuli, in which conventional sounds can elicit a MMN for spatial and non-spatial changes but not for illusory changes in dichotic pitch. 128 channels EEG was recorded from 14 normal hearing adults with a sampling rate of 250 Hz. Average ERPs were digitally filtered with a band-pass of 0.1-30 Hz and referenced to the mean reference. The generation of dichotic pitch stimulus required one of the replications of the band-pass filtered noise to have an interneural time delay of 500 μs. The ERP results suggested the location MMN was significantly larger in amplitude compared to the pitch MMN. In addition, the pitch MMN was followed with a P300 but the location MMN was not. This conclusion has supported the auditory dual stream hypothesis.

Poster 4.21

Fast Clinical MRI Assessment of Amygdalar Size From a Single Slide Measurement

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Numerous MRI studies have shown significant volume loss of the amygdala in patients with Alzheimer's disease. MRI volumetry of the amygdala has proved to be a relevant marker of dementia severity. To evaluate the changes of amygdalar volume, there exist many manual tracing techniques, which are quite time-consuming for clinicians. On the basis of our previous studies, we developed an easy method which allows estimation of the total volume of the amygdala from a simple referential section (frontal section in the level of the anterior pole of the hippocampus). Boundaries of the amygdala in this level are clear and can be easily distinguished from neighboring structures. This protocol was elaborated on a sample of 70 healthy brains (anatomical preparations and MRI examinations of healthy volunteers). The average area of the section through the amygdala in the reference level was 1.64 cm^2 (SD=0.23). In normal brains, the area of the section through the amygdala correlated highly with the total volume (r=0.65). We tested this technique on a sample of 20 patients with the clinical diagnosis of Alzheimer's disease. Correlation of the reference plane and amygdalar volume showed to be even higher (r=0.82). Using our protocol, clinicians can be informed about amygdalar size within a few minutes without the requirements of lengthy measurement by simply adding the obtained data into the working diagram or a simple calculation of how many standard deviations an individual differs from the average value (z-score).

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Poster 4.22

The Effects of Normal Ageing on Visual Attention and Perception

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Reflexive visual orienting, in response to peripheral cues is an automatic process and is shown in neuroimaging studies to recruit ventral areas of the frontoparietal attention network. The effects of normal ageing on peripheral visual attention and perception were examined using a spatial cuing paradigm. In Experiment 1 a simple paradigm was used in 18 younger adults (mean age 23.9 yrs) and 17 older adults (mean age 65.6 yrs). In the Attention task, two letters ('X' and 'T') randomly alternated between the left and right peripheries and participants were asked to shift their attention appropriately in response to these letter cues, in order to aid their responding to a target asterisk. In contrast to earlier findings (Lambert and Holmes, 2004) both younger and older adults shifted their attention appropriately in response to letter cues. In the Perception task, the same two letters were again randomly switched between the left and right peripheries, but this time participants were instructed to respond to the specified target letter as quickly and accurately as possible. No effects of ageing were found, and both groups showed a similar decrease in accuracy when the target stimulus was masked. Older participants responded more slowly and all participants responded more slowly under masked conditions. Our findings suggest that when cue encoding demands are modest, normal ageing has no effect on attentional orienting in response to peripheral cues.

Poster 4.23

A Computational Model of the Neural Basis of the BOLD (Blood Oxygen Level Dependent) Signal

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The brain imaging method fMRI (functional Magnetic Resonance Imaging) does not detect neural activity directly, but rather changes in the blood flow and oxygenation in neighbouring blood vessels, this being the BOLD (Blood Oxygen Level Dependent) effect. It is still an open question as to how increased neural activity transmits a signal to nearby arterioles; however, there is an increasing consensus that astrocytes are vitally involved. We have constructed a computational model of the steps leading from increased glutamate release at neuronal synapses to vasodilation in nearby arterioles. The steps are: (1) neural activity releases glutamate at synapses; (2) glutamate overspill acts on metabotropic receptors on astrocyte processes surrounding these synapses, leading to the production and release of EETs (epoxyeicosatrienoic acids) from the astrocytes, particularly from their endfeet which are in close proximity to arterioles; (3) these EETs diffuse in the extracellular space and act to hyperpolarize the smooth muscle cells that form the walls of the arterioles; (4) this hyperpolarization propagates electrotonically along the smooth muscle cells of the arteriole; (5) this in turn causes the closure of calcium channels in the smooth muscle cell walls and the subsequent decrease in cytosolic calcium results in vasodilation and hence increased blood flow. The model successfully accounts for the main observed changes in blood flow in cat visual cortex following stimulation by high-contrast drifting grating and in rat cortex following single whisker stimulation. Using an extension of the balloon model to multiple compartments, we are also able to predict changes in the BOLD signal that are in agreement with experiment.

Poster 4.24

The Acute Subjective Effects of TFMPP in Healthy Volunteers in a Pharmacokinetic Trial

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Party pills containing benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) were legally and widely available in New Zealand until April 2008. The combination of BZP and TFMPP were marketed as safe alternatives to methamphetamine and methyldioxymethamphetamine (MDMA). TFMPP is a serotonergic agent and anecdotally is reported to produce similar subjective effects to MDMA and lysergic acid at low doses. This double-blind controlled study reports the acute subjective effects of TFMPP in healthy human volunteers. Participants (n=8) were given a single oral dose of TFMPP (60mg) and tested at 0, 30, 60, 120, 240, 350, 480, 1440 minutes. Subjective and mood effects were evaluated using the Visual Analog Scales (VAS) and the Brunel Mood Scale (BRUMS). The detection and quantification of TFMPP was carried out using liquid-chromatography with mass spectrometry (LCMS). TFMPP significantly increased Drug Effect, Good Drug Effect, Drug Liking, Stimulated, High, Friendly and Alert. VAS demonstrated that TFMPP exerted maximum effects between 90 and 120 minutes post administration with effects lasting for 350 minutes. BRUMS revealed maximum level of Vigour at 120 minutes. In contrast to the subjective effects LCMS data demonstrates that TFMPP reached a maximum plasma concentration at approximately 105 minutes (Tmax) demonstrating that peak plasma concentration correlates with subjective effects. Our pharmacokinetic data shows distinct redistribution and elimination phases. Further work on the pharmacokinetics of BZP and BZP/TFMPP is currently underway to define the relationship between plasma drug levels and subjective effects.

Poster 4.25

The Effects of Regular, Long-Term Benzylpiperazine (BZP) and Trifluoromethylphenylpiperazine (TFMPP) Based Party Pills on Cognition and Mood

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Party pills (PPs) containing BZP and TFMPP were widely available in NZ until 1 April 2008. Industry estimates suggest 26 million doses have been consumed in the past 7 years. The only human trials, published in 1973, found physiological and psychological similarities between BZP and dexamphetamine. BZP has dopaminergic activity and TFMPP serotonergic activity, hence the combination is used recreationally to mimic the effects of MDMA (Ecstasy). As prolonged use of MDMA is thought to result in cognitive and mood changes, this study sought to determine if frequent PP use resulted in similar changes. To date eleven regular PP users have been recruited. The IntegNeuro battery of cognitive tasks was used to determine the cognitive abilities of each participant. Data was sent to the Brain Resource Company (Sydney) who compared results to age, gender and education matched controls and provided reports on individual participants. The WHO-Composite International Diagnostic Interview was used to determine the presence of mental illnesses such as depression and dependence. Preliminary findings indicate potential deficits in attention and executive function. According to the WHO-CIDI diagnosis, no one exhibited PP dependence and one participant displayed moderate-major depressive illness. These results are preliminary. However, our findings of possible deficits in attention and executive function are in keeping with results from studies showing similar cognitive deficits in humans following regular MDMA use. The single diagnosis of depression showed an onset prior to PP use. Whether this conferred an increased susceptibility to PP use is unknown. The lack of PP dependence may reflect minimal abuse liability.

Poster 4.26

Separate Models for People with Dementia or Other Brain Disorders Increase the Accuracy of Classifying On-Road Pass or Fail Based on Sensory-Motor and Cognitive Tests

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Brain disorders can decrease a person's ability to perform the physical and cognitive functions necessary for safe driving. A computerized battery of sensory-motor and cognitive tests (*SMCTests*) has been developed comprising tests of visuoperception, visuomotor ability, complex attention, visual search, decision-making, impulse control, planning, and divided attention. A previous study with n=50 persons with brain disorders (primarily stroke) showed that *SMCTests* could correctly classify 94% and 90% of referrals respectively as on-road pass or fail using binary logistic regression (BLR) and nonlinear causal resource analysis (NCRA) models. The current study investigated the power of BLR and NCRA models to classify blinded on-road pass or fail with a larger group of people (n=200) with a wider range of brain disorders. BLR and NCRA models were both only 69.5% accurate in classifying on-road pass or fail. However, greater accuracy could be achieved when the referrals were split into two groups: (1) Dementia (suspected or diagnosed dementia or mild cognitive impairment) and (2) Non-dementia (stroke, traumatic brain injury, Parkinson's disease, etc). The BLR models classified on-road driving outcome as pass or fail with an accuracy of 76% (Dementia) and 75% (Non-dementia), while the NCRA model had an accuracy of 77% (Dementia) and 80% (Non-dementia). We conclude that while *SMCTests* provides useful data regarding areas of sensory-motor and cognitive dysfunction in people with brain disorders, an on-road assessment is still required to make a final decision regarding on-road driving safety. Further research is required to identify additional factors which underlie inability to drive safely (e.g., attitude, confidence, insight) in people with brain disorders.

Poster 4.27

Poor Response to Clozapine in Patients with Ultra Treatment Resistant Schizophrenia

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Clozapine is an atypical antipsychotic that is the drug of choice in treatment resistant schizophrenia. Clozapine offers unsurpassed efficacy in patients with schizophrenia unresponsive to other antipsychotics (<30% of patients), however, there remains a population of patients in which it fails to improve symptoms. This study aimed to review ultra treatment resistant patients' clozapine dosing regimen, plasma levels and their response to treatment in order to determine a relationship between dose and response. The patients included were inpatients at a twenty-bed, all male psychiatric long-term rehabilitation facility in Auckland. Patients are referred from throughout the greater Auckland region where they demonstrated a poor response to treatment. HoNOS (Health of the Nation Outcomes Scale) is a routinely used outcome measure that reflects the patient's progress over the preceding two week period and encompasses behaviour, impairment, symptoms (both psychiatric and somatic) and social functioning. The HoNOS score is out of forty-eight, with zero being symptom-free and higher scores being progressively more unwell. Clozapine dose regimens and plasma levels were obtained from the patients' current and archived medicine charts and compared to HoNOS scores over the corresponding period. Within the last year, 28% patients at this unit have been found to show no response to clozapine. All subjects included were male with a history of smoking. The mean of the HoNOS scores obtained for these patients three months after the initiation of clozapine up to one year was 11.8 (± 2.9) demonstrating non-responsiveness. The reasons for this are unknown. This research aims to further investigate these deficits using cognitive testing in combination with EEG (electroencephalography) and genetic testing.

Poster 4.28

Visuomotor Adaptation After-effects in Parkinson's Disease

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Parkinson's disease (PD) makes movements smaller (hypometria) and slower (bradykinesia). We used a virtual environment to distort visual feedback so that reaching movements appeared to be shorter than they actually were. This induces an adaptive increase in movement amplitude. We investigated the ability of 16 people with PD and 16 age- and sex-matched controls to adapt to such a manipulation, introduced either suddenly or gradually during a reaching task which was either visually- or memory-guided. A further 7 pairs provided a non-adaptation baseline. The PD participants adapted to the gain manipulation as quickly as the controls in all conditions except sudden+memory ($p < 0.01$). Over all manipulation conditions, there was no difference in the immediate after-effect between PD participants and controls (14 mm vs. 10 mm, $p = 0.28$), although the long-term after-effect was greater in the PD participants (10 mm vs. 3 mm, $p < 0.05$). There were no overall effects of task (visual 11 mm vs memory 13 mm, $p = 0.13$) or manipulation condition (gradual 14 mm vs. sudden 10 mm, $p = 0.45$). In the controls there was an increased after-effect in the gradual+memory condition (18 mm vs. 7-9 mm in other conditions, $p < 0.01$). In the PD participants there was a reduced after-effect in the sudden+memory condition (6 mm vs. 15-18 mm in other conditions, $p < 0.01$). This is the first experiment to show a larger after-effect in people with PD, with potential implications for rehabilitation. Additionally, although the basal ganglia are proposed to play a greater role in memory-guided tasks and sudden manipulations, only the combination of these caused a decreased learning rate and reduced after-effects for the PD participants.

Poster 4.29

Saccadic Function in Alzheimer's Disease: An fMRI Study

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Alzheimer's disease (AD) is associated with a number of eye movement deficits thought to result from an underlying reduced ability to shift or direct attention. These saccadic deficits include prolonged reaction times and a reduced ability to suppress saccades. fMRI has been used to map the cortical activation of saccadic paradigms in a healthy population however its application to AD is in its infancy. The sole study (Thulborn et al, 2000) applied just a simple visually guided test, and found reduced right hemisphere dominance in the activation of the parietal lobe, unlike controls, possibly reflecting dysfunctional spatial attention. This study aims to increase the knowledge of cognitive and behavioural aspects of the saccadic network in AD by applying a more comprehensive battery of neuropsychological tests and additional saccadic paradigms that probe the integration of cognitive and sensori-motor neural networks. In this ongoing study, up to 16 people with probable AD and 16 cognitively able controls will be selected. All subjects perform the same saccadic paradigms using two different experimental designs via fibre optic glasses in a high field 3T fMRI. The first two experiments are an array of saccadic tasks: reflexive, predictive, and gap alternated every 27s with fixation as the baseline in a block design. The anti-saccade task is an event-related design with random inter-stimulus intervals used to extract time courses of voxels and to differentiate erroneous trials. Eye movements are recorded during imaging to provide accurate gaze position and to ensure task compliance. Preliminary fMRI results show robust activations in areas known to be consistent with saccade performance.

Poster 4.30

Effects of Optical Flow on Gait Patterns in Parkinsonian Rats

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Parkinson's disease (PD) is a common age-related neurodegenerative disorder in which visuospatial cognitive functions including spatial navigation are impaired. The characteristic gait disturbances of Parkinson disease (PD) include shuffling gait, short steps and low walking velocity. Research has shown that gait improvement can be facilitated by the perception of motion from optical flow, i.e. moving visual cues. In this study we investigated the features of treadmill walking in a rat of partial akinesia obtained from PD caused by unilateral infusion of the neurotoxin 6-hydroxydopamine (6-OHDA) into substantia nigra pars compacta. The images of foot prints of rats walking on the transparent belt of a treadmill were captured using a digital camera. Image analysis was performed off-line to identify the foot contact time of bilateral hindlimbs as well as the body orientation of control and PD rats during treadmill walking. The parameters of swing and stance time were firstly evaluated. Compared with controls, the gait impairment in PD can be clearly observed from asymmetrical gait patterns from a decrease in swing time especially in the affected side but an increased in stance time of both hindlimbs. Our results suggested that the unilateral rat model of PD reflected compensatory changes in the sound side for motor deficits resembling the key features of human parkinsonian gait. The validation tests of animal behaviors were further observed from the changes of body orientation performed under the influence of optical flow.

Poster 4.31

Cell Loss in the Cerebral Cortex in Huntington's Disease

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Huntington's disease (HD) is an inherited neurodegenerative disorder with a variable motor/mood symptom profile. HD is characterised by the loss of neurons in both the striatum and the cerebral cortex. This study aimed to investigate the neuronal cell loss in the primary visual cortex (1°VC), secondary visual cortex (2°VC), middle temporal gyrus (MTG) and superior parietal cortex (SPC) in the human brain in HD and to compare these changes to the dominant symptomatology (motor or mood) and neuropathological striatal grade of each case. The overall pattern of neuronal loss was investigated on perfusion-fixed human cortical blocks using Neuronal N with standard immunohistochemical procedures and unbiased stereological cell counting techniques. The stereological cell counts demonstrated that in HD there is a significant cell loss in the SPC (36%), MTG (27%) and 2°VC (27%), but no significant cell loss in the 1°VC. The cell loss in these three regions increased with the grade of striatal pathology, with a 32-39% neuronal loss in advanced grade 3 cases. Comparison of the cell loss with the motor/mood symptom profile showed that there was a significant cell loss in the SPC across both motor and mood HD cases, while cell loss in the MTG and 2°VC was only found in cases with a significant mood component. These findings show that in HD there is a significant cell loss in the parietal, temporal, and visual association cortex, and that this loss varies according to symptom profile.

Poster 4.32

Molecular Characterisation of the Ovine CLN6 Gene Causing Neuronal Ceroid Lipofuscinosis in South Hampshire Sheep

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The neuronal ceroid lipofuscinoses (NCL) are a group of fatal inherited neurodegenerative diseases characterised by severe brain atrophy, blindness, seizure and premature death. Large animal models have proved to be invaluable for understanding these diseases in humans, notably a form identified in the South Hampshire sheep. NCL in South Hampshires has been linked to ovine CLN6 (*oCLN6*) but no disease causing mutation has been found within the coding sequence of this gene. However *oCLN6* mRNA levels are significantly reduced in affected sheep. This indicates that the disease is likely to be caused by a mutation in a non-coding region that regulates gene expression. As the ovine genomic sequence for this region is unknown, a bioinformatics approach was used to identify conserved non-coding sequences (CNCS) which potentially contain regulatory elements. CNCS have been identified in the 5'UTR, 3'UTR and intron 1 of *oCLN6*. Ovine BACs containing *oCLN6* and long-distance PCR products amplified from affected sheep DNA are sequenced to obtain the genomic *oCLN6* sequence as well as flanking sequence. Currently the pyrosequencing-based 454 sequencing platform is being used, followed by sequence analysis, to predict regulatory elements and identify potential disease causing mutations. There are a number of cases of a human variant late-infantile NCL (vLINCL) linked to the CLN6 gene in which no coding mutations have been found. Non coding regulatory elements identified for *oCLN6* are likely to indicate positions for these disease causing mutations.

Poster 4.33

Development of Testosterone-Sensitive Motor Neurons in the Absence of Müllerian Inhibiting Substance

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Müllerian Inhibiting Substance (MIS), which is also known as Anti-Müllerian Hormone, is a testicular hormone required for the early sexual development of male embryos. We have recently discovered that MIS is a neuronal survival factor *in vitro*, and that MIS generates a male bias in the number of lumbar lateral motor column neurons, which innervate the limbs. Testosterone and MIS dually control the development of the testes, which raises the possibility that MIS and testosterone dually regulate sexual motor neurons. Similarly, the abnormalities in *MIS* deficient mice could be secondary to disruption of the function of testosterone. If either possibility is occurring, then the number of sexual motor neurons in the Spinal Nucleus of the Bulbocavernosus (SNB) should be abnormal in $MIS^{-/-}$ mice. Therefore, we examined the number of SNB motor neurons in $MIS^{+/+}$ and $MIS^{-/-}$ male and female mice. Lumbar spinal cord sections were stained with cresyl violet and the number and size of the motor neurons from the SNB assessed. The MIS genotype had no effect on the number of motor neurons, with $MIS^{+/+}$ males having 85 ±7 motor neurons and $MIS^{-/-}$ males 95 ±6. Furthermore, the size of the motor neurons did not vary between the $MIS^{+/+}$ and $MIS^{-/-}$ mice. This indicates that MIS is not essential for the development of motor neurons involved in primary sexual function. It also suggests that MIS and testosterone regulate different populations of neurons.

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Poster 4.34

Changes in Hippocampal Cannabinoid CB2 Receptor Expression Following the Bilateral Vestibular Deafferentation

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The endocannabinoid system is recognised as one of the most important neuromodulatory systems in the brain and there is increasing interest in the therapeutic potential of manipulating it with cannabinoid drugs. In recent years, the established belief that the cannabinoid CB_2 receptors do not exist in the central nervous system (CNS) has been challenged by numerous scientists around the world and CB_2 receptors have been reported to regulate apoptosis and neurogenesis in the CNS. Previous studies have shown that, in addition to the vestibular nuclei and cerebellum, the hippocampus undergoes significant changes following damage to the peripheral vestibular system. Therefore, the aim of this study was to investigate whether there are changes in the expression of the CB_2 receptors in the CNS, and especially in the hippocampus, following bilateral vestibular deafferentation (BVD). Twelve Wistar male rats were sacrificed without anaesthesia at 72 hours after the BVD (n=6) or BVD-sham (n=6) surgery. Using immunohistochemistry and selective antibodies for the CB_2 receptor, we detected an increase in the level of CB_2 receptor expression in the hippocampus of BVD animals compared to sham animals. Double immunofluorescence labeling was also performed in order to determine on which cell type these CB_2 receptors were expressed. Surprisingly, CB_2 receptors were expressed on neurons, but not on astrocytes. Since the hippocampus has been reported to undergo atrophy following BVD, it is possible that changes in CB_2 receptor expression in the hippocampus are associated with hippocampal reorganization following the loss of vestibular input.

Poster 4.35

Secreted Amyloid Precursor Protein Alpha-dependent Upregulation of Synaptic Protein Synthesis is Dose and Protein Kinase G-Dependent

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Secreted amyloid precursor protein alpha (sAPPα) is a brain peptide with neuroprotective and neurotrophic effects. We have recently shown that sAPPα enhances long-term potentiation, a mammalian mechanism for information storage, *in vivo*. Furthermore, exogenously applied sAPPα enhances memory in rodents and chicks. This suggests that the reduction of sAPPα levels seen in Alzheimer's disease which occurs alongside increased toxic amyloid β protein levels, may be aetiologically significant. However, as yet the mechanism by which sAPPα brings about changes in plasticity at synapses remains unresolved. We hypothesised that sAPPα may stimulate changes in protein synthesis at synapses, an important mechanism for normal plasticity. To test this hypothesis we investigated the effect of sAPPα on protein synthesis in isolated synapses (synaptoneurosomes) prepared from the hippocampi of adult male Sprague-Dawley rats. Incubation of synapses with sAPP significantly increased the incorporation of [^{35}S]-methionine into acid insoluble proteins, a measure of protein synthesis (10 nM sAPPα: 64±7%, n=6, $p<0.001$). This effect was dose dependent and blocked by an inhibitor of cGMP-dependent protein kinase (KT5823: -15±9%, n=5, $p<0.001$) but not inhibition of calcium/calmodulin-dependent protein kinase II (KN62: 16±6%, n=10) or mitogen-activated protein kinase (PD98059: 13±5% n=5). These novel findings indicate that sAPPα regulates protein synthesis at synapses, which may underlie the long-lasting modulatory effects of sAPPα on synaptic plasticity.

Poster 4.36

Agmatine Suppresses Age-Related Increases in Nitric Oxide Synthase Activity in the Rat Hippocampus and Prefrontal Cortex

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Increasing evidence suggests that nitric oxide (NO), generated by nitric oxide synthase (NOS) from L-arginine, plays a significant role in the brain aging process. Agmatine, a metabolite of L-arginine by arginine decarboxylase, is a novel neurotransmitter and an endogenous regulator of NOS. The present study investigated age-related changes in NOS activity in the hippocampus and prefrontal cortex and the effect of agmatine treatment. The prefrontal cortex and the CA1, CA2/3 and dentate gyrus (DG) sub-regions of the hippocampus were harvested from 4 (young saline, n = 9) and 24 (aged saline, n = 8; aged agmatine, 40 mg/kg, i.p., n = 9) months old rats 30 min after the treatments. Aged rats with saline treatment had significantly increased NOS activity in the prefrontal cortex ($p < 0.001$) and the DG ($p < 0.05$), but not CA1 or CA2/3, sub-region of the hippocampus relative to the young adults. Agmatine treatment significantly suppressed age-related increases in NOS activity in the prefrontal cortex and hippocampal DG (all $p < 0.05$), with no effects on CA1 and CA2/3 NOS activity. The present study replicates our recent findings of age-related region-specific increases in NOS activity and provides further supports of the contribution of NO to the brain aging and the regulatory role of agmatine in NOS activity. An investigation of the functional significance of agmatine-induced suppression of NOS activity in aged rats is currently underway.

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5.1

Motion Correction in Magnetic Resonance Diffusion Tensor Imaging: Application to Neonates

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An important quantitative technique for studying brain development *in vivo* using MRI is diffusion tensor imaging (DTI). Research involving unsedated neonates is particularly challenging because of subject motion. While the total scan time DTI is quite long (typically several minutes), the data is acquired as many independent volumes, each of which is acquired over a much shorter time. This allows inter-volume motion to be corrected, while the intrinsic over-determination in DTI allows volumes that are corrupted by intra-volume motion to be discarded with only a moderate SNR penalty. A novel data processing scheme has been developed which iteratively corrects for inter-volume motion until a dataset that is optimally consistent with the signal model is achieved. This is applied to 10 consecutive scans of neonates, of which 4 were corrupted by motion (one severely). The motion correction produced improvement in all cases, yielding diagnostically useful information even in the most corrupted data. This shows that DTI of neonates is feasible for quantitative studies of brain maturation.

5.2

Neural Correlates of Simultaneous Interpreting: an fMRI Study

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Simultaneous interpreting is a uniquely professional cognitive skill that requires simultaneous comprehension of a language and verbal production of another; however, little has been done to explore the brain activation patterns of simultaneous interpreting. The study aimed to use fMRI to examine the functional neural correlates of simultaneous interpreting from the first (L1; Mandarin) language to the second (L2; English) language vs. from L2 to L1, using sparse paradigm (Hall et al., 1999). fMRI scanning results showed that the task of simultaneous interpreting into L1 elicited extensive activations in premotor cortex and dorsolateral prefrontal cortex, whereas activation in ventrolateral frontal cortex, inferior temporal cortex, premotor cortex, parietal cortex and cerebellum was observed for the task of interpreting into L2. The fMRI results in the study are different from those yielded from previous PET studies using single-word translation with different language pairs. The behavioral results in the study showed that interpreting into L1 was better than into L2. However, the all results are consistent with previous work in terms of suggesting that simultaneous interpreting into L2 is a cognitively more demanding task.

5.3

A Functional MRI Study of Recovery and Reorganization Following Unilateral Cerebellar Stroke

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While there has been considerable research on stroke to numerous areas of the human brain, little emphasis has been on exploring the neural areas which might become activated or deactivated following localized injury to the cerebellum. This is of great interest as lesions of the cerebellum are often followed by significant recovery. The present (ongoing) study applies functional magnetic resonance imaging to investigate brain activation during unilateral and bilateral tasks in people with unilateral cerebellar lesions. The task involves 3 conditions of pronation-supination movements of the upper limb (left alone, right alone, and bimanual), and two conditions of lower limb movement (tapping of the left or right foot). fMRI was carried out using a blocked design with alternating rest and active periods for each condition. Data on a patient with damage to the left cerebellar hemisphere due to stroke were collected at 5 time points following the trauma. She showed nearly full recovery in motor movements of the impaired side at approximately 2 months following stroke. fMRI findings reveal hyperactivation in the ipsilateral (left) sensorimotor cortex and the contralateral cerebellum (right) during left upper limb movements; this was reduced with recovery. Some hypoactivation of the damaged cerebellar hemisphere was also shown in the early tests of upper limb movements, particularly of the right (healthy) limb; more specific analyses are currently being undertaken to examine this curious issue further.

5.4

Investigation of Lapses of Responsiveness via Simultaneous fMRI and EEG

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Brief lapses of responsiveness ('lapses' of 0.5–15 s), including microsleeps and lapses of sustained attention, can be very serious, not only disrupting performance but sometimes leading to injury or death. We have commenced an investigation of the brain mechanisms underlying lapses in 20 non-sleep-deprived individuals. fMRI, EEG, video of the eyes, and visuomotor responsiveness data are being collected while participants perform a continuous 60-min visuomotor tracking task inside a 3T MRI scanner. Preliminary results have been obtained on the neural correlates of voluntary slow-eye-closure and voluntary non-responsiveness in 5 normal subjects during the first 10 min inside the scanner. During this phase, they were cued to simultaneously stop tracking and slowly close their eyes or stop tracking without eye-closure several times. Analysis of the fMRI data has revealed several regions involved in cued slow-eye-closure and cued task non-responsiveness, including occipito-parietal visual regions, midline default-mode regions, and fronto-parietal attention regions. These results will be of considerable value in the interpretation of changes in BOLD activation and EEG activity associated with behavioural microsleeps. While also provisional, preliminary analysis of fMRI data during extended tracking has revealed compelling BOLD changes in the brain corresponding to definitive behavioural microsleeps. When complete, our research promises an important advance in our knowledge of the characteristics of lapses and their spatiotemporal dynamics in the brain. Ultimately, this offers the potential to save many lives by helping in the development of lapse detection (and even prediction) technology to prevent serious accidents due to lapses.

5.5

The Neurobiology of Hysteria and Malingering: an fMRI study

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Hysteria (conversion syndrome) manifests as neurological symptoms unexplained by organic neurological disease and is thought to have a psychogenic basis. In malingering, symptoms and signs are deliberately feigned. Their neural mechanisms are controversial. To determine whether conversion syndrome and malingering could be distinguished by their patterns of neural activation, we carried out functional magnetic resonance imaging in 6 conversion syndrome patients (3 weak on right and 3 weak on the left side) and 10 control subjects. Functional MRI was performed during thumb tapping, visual imagery of thumb tapping and thumb tapping while feigning weakness (left, right and bilateral). A block design was used with six alternating periods of activity and rest in each series, and analysis was carried out using SPM5. In control subjects, tapping activated areas including the contralateral sensorimotor cortex and ipsilateral anterior cerebellum. Feigning and visual imagery (all sides combined) produced less activation than normal tapping in most of these, but greater activation of the left angular gyrus. Right tapping in patients with right-sided weakness produced less activation in the right cerebellum and posterior central gyri and a number of areas of reduced activation, compared to rest. There was activation of the left temporal lobe in conversion patients compared to feigners and in the left cerebellum and right precentral gyrus of feigners compared to patients. Patients with left-sided weakness activated the cingulate, right medial frontal and right middle frontal gyri during bilateral tapping more than controls. Control subjects activated the left putamen during bilateral tapping with feigned weakness more than patients. Thus normal thumb tapping, feigned weakness of thumb tapping and weak thumb tapping in conversion syndrome are associated with different patterns of neural activation which may be useful diagnostically and may contribute to an understanding of conversion syndrome and related phenomena.

5.6

High Resolution Cellular Localisation of $GABA_A$ and Glycine Receptor Subunits in the Human Basal Ganglia

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$GABA_A$ ($GABA_AR$) and glycine receptors (GLYRs) are multi-subunit ion channel inhibitory receptors found throughout the basal ganglia. In this study we have immunohistochemically investigated the precise localisation of $GABA_AR$ and GLYR subunits using antibodies to the $GABA_AR$ subunits and GLYR subunits. Fixed-frozen human basal ganglia sections were stained using immunoperoxidase and immunofluorescence multiple labeling techniques and viewed using light and confocal laser scanning microscopy. High resolution microscopic and laser scanning imaging of receptor immunoreactivity enable localisation of inhibitory receptor subunits at the cellular and subcellular levels and provide evidence for the subunit configuration of $GABA_A$ and Glycine receptors in the human brain. In the striatum, the projection neurons and interneurons show a differential pattern of GLYR and $GABA_AR$ staining. The neurons of the globus pallidus and substantia nigra pars reticulata (SNr) showed high levels of $GABA_A$ $\alpha1,\alpha3,\beta2,3,\gamma2$ (no $\alpha2$) whereas GLYRs were distributed on SNr neurons and a subpopulation of GP neurons. Neurons in the pars compacta (SNc) showed GLYR on cell bodies but had a specific $GABA_AR$ $\alpha3\gamma2$ subunit configuration. These results demonstrate that in the basal ganglia, neurons are generally associated with one of three different $GABA_A$ receptor configurations and suggests that throughout the basal ganglia GABA acts via $GABA_A$ receptors with variable subunit configurations and that glycine acts through GLYRs on cells scattered throughout the basal ganglia.

5.7

The Use of fMRI as a Clinical Tool for Planning of Surgical Intervention of Tumour Removal in the Brain: A Case Study

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fMRI is a useful adjunct to surgical planning for the removal of brain tumours. This patient presented with a history of new onset of seizures. MRI demonstrated a right frontal lobe mass Query oligodendroglioma. fMRI was requested to demonstrate the location of the sensory cortex in relation to the tumour. A GE 3T scanner with HDx platform was used. Motor and Visual fMRI paradigms were presented to the patient using the AVOTEC system. Good structural imaging was achieved initially. For the fMRI sequences the patient was able to co-operate well, and good visualisation of the motor and visual cortex areas were demonstrated, although as expected, anatomically displaced due to the compression effect of the tumour. This information was then used to guide the surgeon during the operation with minimal impact on the motor cortex. This patient has shown excellent improvement since the operation. The conclusion in this case was that fMRI, proved to play a major role in the clinical outcome, and surgical planning in the removal of this tumour.

5.8

Combined fMRI and DTI Study of Visual Awareness in Binocular Rivalry

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The neural basis of visual awareness can be investigated using binocular rivalry: When one image is presented to one eye and a different image to the other eye, only one image is seen at a time, which switches with the other image randomly every few seconds. The aims of our pilot study were (a) to detect the whole-brain activation pattern of changes in visual awareness during binocular rivalry, (b) to determine the anatomical links between these areas and (c) to test a new comparison condition for binocular rivalry. Three healthy human participants observed coloured gratings that either induced rivalry or fusion. We performed functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) of the whole brain using a 3T scanner. We analysed differences in brain activity with SPM5 and carried out probabilistic diffusion tractography with FSL4.0. (a) Our event-related fMRI results were consistent with the fronto-parietal activity reported in previous studies of binocular rivalry. (b) Probabilistic tractography showed that most areas associated with perceptual switches during binocular rivalry had direct white matter connections to other activated areas. (c) When we compared binocular rivalry to binocular fusion, activity in frontal and parietal areas was again present, most prominently in the precentral and inferior frontal gyri. Taken together, our findings support the association of changing conscious perception during binocular rivalry with fronto-parietal activity. They also indicate a high degree of structural connectivity between these simultaneously activated fronto-parietal areas.

6.1

Why Should Glia Excite Your Brain?

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Glial cells are critical for the homeostasis of glutamate, the key excitatory neurotransmitter in the mammalian CNS. We review the evidence from our laboratory and other laboratories, for the micro-anatomical localisation of specific splice variants of the glial glutamate transporters at sites close to and distant from synapses, and the anchoring mechanisms which control this localisation. In response to hypoxic insults and in models of stroke, we demonstrate that glial glutamate transporters are lost from astrocytes and these cells exhibit anatomical remodelling. This is accompanied by the compensatory up-regulation of a novel neuronal glutamate transporter in affected areas. We propose that this is an energetically efficient compensatory mechanism that has evolved to enable retention of some glutamate homeostasis when the brain has restricted energy reserves. The re-distribution of glutamate transporters and the changes in cellular morphology of glia as an early response to hypoxic insults has concomitant implications for the glial-derived amino acid D-serine which is assumed to be released at sites close to, and act upon NMDA receptors at the glycine binding site. Our data would suggest that glial retraction would, amongst other things reduce the likelihood that D-serine is released close to glutamatergic synapses, and could thus help minimise NMDA receptor over-activation in response to hypoxic insults or stroke.

6.2

Acute and Preconditioning Effects of Domoic Acid on Spatial Memory and LTP and LTD Induction in Rat Hippocampus

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For the past decade the focus on domoic acid (DA) has largely been on the effects of high dose exposure on seizures, neuronal degeneration and ionic conductance changes. Here we examined the effects of acute low dose DA and low dose DA preconditioning on LTP and LTD in hippocampal region CA1 *in vitro*, and on performance in the Morris water maze. Acute low dose DA (50 nM, 10 min) enhanced LTP but completely blocked LTD induction. In contrast, DA preconditioning (50 nM, 30 min wash-in + 30 min wash-out) markedly enhanced both LTP and LTD. The fact that preconditioning enhanced both, well after the toxin had been washed from the preparation, suggests that metabotropic KA receptors may be involved in metaplasticity processes. Acute low dose DA (0.25 mg/kg s.c., 30 minutes prior) resulted in significant impairment of performance in the Morris Water Maze but did not adversely affect new learning the following day, suggesting that low dose DA disrupts memory and learning by reversible shifts in neuronal excitability and plasticity. There were no differences between DA preconditioned (0.25 mg/kg s.c., 90 minutes prior) and saline treated animals in any of the trials on either Days 1 or 2. Taken together, our findings suggest that a disruption in the *balance* of net LTP and LTD impairs memory and learning, while enhancement of *both* LTP and LTD does not correspond to enhanced memory and learning.

6.3

Kainate Receptor Binding and Pharmacological Preconditioning by Domoic Acid and Isodomoic Acids A, B and C

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Pharmacological preconditioning and the induction of tolerance to excitotoxins is now well-established both *in vitro* and *in vivo* (Hesp et al., 2004; Hesp et al., 2007). Previously, we have shown that domoic acid (DA) and isodomoic acid-A (Iso-A) are functionally equipotent in acute seizure induction by intrahippocampal administration, while Iso-B and Iso-C are distinctly less potent (ED_{50}'s: 37 pmoles, 54 pmoles, 4,578 pmoles, and 1,102 pmoles respectively). Here we assessed therapeutic potential of DA, Iso-A, Iso-B and Iso-C as pharmacological preconditioning agents. Young male Sprague Dawley rats were implanted with a guide cannula into ventral hippocampus and behaviours recorded during preconditioning and seizure induction. Animals were administered a preconditioning dose of DA (15 pmoles), Iso-A (25 pmoles), Iso-B (6000 pmoles) or Iso-C (500 pmoles) one hour before a test dose of 100 pmoles of DA. Cerebral synaptosomal membranes were prepared and competitive radioligand binding employed to assess affinity of kainate receptors to DA and its isomers. Preconditioning with low-dose DA or Iso-A, 60 min before a high-dose of DA produced significant reductions in cumulative seizure scores. However, Iso-B and Iso-C each failed to induce tolerance to high-dose DA. Radioligand binding indicated a significant correlation between seizurogenic potency and kainate receptor affinity. Our results indicate that the neuroexcitatory effects of DA, Iso-A, and to a lesser extent Iso-C, involve kainate receptors. Like DA, Iso-A induces tolerance to the seizurogenic effects of DA, raising questions regarding inverse agonism of kainate-sensitive G-protein coupled receptors during preconditioning.

6.4

Adenosine-Based Experimental Strategies to Stem Oxidative Stress in the Cochlea

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In many tissues extracellular adenosine is a local modulator with cytoprotective function. The role of adenosine in cochlear protection from injury has been well established. We are investigating the role of adenosine in cochlear recovery from oxidative stress using acute and chronic loud sound exposure as a model stressor. In the cochlea, adenosine receptors (A_1, A_{2A} and A_3) are differentially distributed in sensory, neural and secretory tissues and blood vessels. Our gene expression studies in rats have shown that the transcript levels of adenosine receptors are altered during sustained noise exposure (4.5 kHz octave band for 24 hours) presented at 100 dB SPL (induces temporary hearing loss) or 110 dB SPL (causes permanent hearing loss). A_1 receptors were up-regulated at 100 dB SPL and A3 receptors at 110 dB SPL, whilst the expression of A_{2A} receptors remained unchanged. Our *in vivo* studies show that this stimulation of A_1 adenosine receptors promotes cochlear recovery after noise exposure, whilst the activation of A_3 receptors may produce an opposite effect potentially marking the onset of a 'destructive mode', likely mediated by the activation of JNK signalling pathways. This is also supported by the elevation of adenosine kinase (AdK) transcript levels in the cochlea at the sound level that induces permanent hearing loss (110 dB SPL). AdK is the principal regulator of adenosine metabolism, and this enzyme may have a pivotal role in cochlear response to injury, as the up-regulation of AdK is associated with increased cell death in the brain. Our experimental strategy to ameliorate cochlear injury induced by loud sound is thus based on selective activation of A_1 adenosine receptors or inhibition of A_3 receptors and adenosine kinase activity.

6.5

Is ROS-Generating NAD(P)H Oxidase Involved in Reperfusion-Induced Changes of Intrinsic Optical Properties and Mitochondrial Membrane Potential in Hippocampal Slices?

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Oxidative stress caused by excessive production of reactive oxygen species (ROS) contributes to neuronal damage during ischemia/reperfusion in many stroke models. We investigated the specific contribution of ROS generated by NAD(P)H oxidase to neuronal damage during reperfusion following 20 min of oxygen-glucose deprivation (OGD), while simultaneously monitoring light transmittance (a non-invasive method to estimate tissue swelling and damage) and mitochondrial membrane potential ($\Delta\psi_m$) in the stratum radiatum of the CA1 region in rat hippocampal slices (P35-42). $\Delta\psi_m$ was recorded using the fluorescent dye Rhodamine-123 (Rh-123). Two NAD(P)H oxidase inhibitors were examined. While aminoethyl-benzenesulfonylfluoride (AEBSF; 0.5 mM) had no significant effect on the light transmittance signal or $\Delta\psi_m$ during the reperfusion stage, diphenylene iodonium (DPI; 10 μM) reduced the rate of mitochondrial repolarisation and abolished tissue darkening, which normally indicates irreversible tissue damage. Tissue darkening and changes in $\Delta\psi_m$ were dissociated by application during OGD of a mitochondrial protonophore, carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP; 2 μM), which blocked mitochondrial repolarization but had no effect on tissue darkening. Inhibition of the mitochondrial NADH dehydrogenase (Complex I) with rotenone (1 μM) partially reduced mitochondrial repolarisation rate, but had no effect on reperfusion-induced tissue darkening. These results indicate a still unknown, yet potentially neuroprotective mechanism of DPI in reperfusion injury. Additional experiments will examine the possible inhibition of nitric oxide (NO) production by DPI.

6.6

Interaction Between 5-HT Pathways and the Endocannabinoid System in the Regulation of Anxiety

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The endocannabinoid system has been implicated in the modulation of anxiety and stress responses. Drugs that act on 5-HT pathways, such as selective serotonin reuptake inhibitors (SSRIs) also modulate certain types of anxiety. Anectdotal reports have suggested that SSRIs may interact with cannabinoids such as Δ9-THC in cannabis to generate panic attacks. We therefore tested for interactions between an SSRI (fluoxetine) and Δ9-THC using several behavioural paradigms in rats. We found that in the open field test, both fluoxetine and Δ9-THC reduced rearing behaviour (a measure of anxiety) and that rats receiving both treatments had even further reduced rearing behaviour. By contrast, in a social interaction test, fluoxetine reduced social inhibition whereas Δ9-THC increased it. Interestingly, fluoxetine reversed the effects of Δ9-THC in the social interaction test. Although we did not find any evidence for an interaction between Δ9-THC and fluoxetine in the generation of anxiety, we did find that rats treated with fluoxetine were resistant to Δ9-THC induced social inhibition. This may have implications for the use of cannabinoid medications by people using SSRIs.

6.7

Histamine and Neuronal Inhibition

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Histamine is a neurotransmitter released by neurons projecting from the tuberomamillary nucleus in the hypothalamus. Histamine has a clear role in modulating arousal, and for the last 20 years, investigation into the source of histamine's wake promoting action has focused on the H1 and H2 receptors. However we examined the effects of the newly discovered H3 and H4 receptors on synaptic and neuronal membrane properties in cortical slices and culture. We found that H3 receptors did not modulate the resting membrane potential of cortical neurons or effect the release of GABA from cortical interneurons onto pyramidal neurons however it did modulate autaptic connections on interneurons. We also found that activation of the H4 receptor hyperpolarized cortical neurons irrespective of type.

7.1

MDMA-Produced Drug-Seeking in Rats

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Rats (n=9) were trained to self-administer MDMA during daily 2 hr sessions. Initially, responding was reinforced according to an FR1 schedule by an infusion of 1.0 mg/kg/infusion MDMA. Once 90 infusions of this dose of MDMA were self-administered, the dose was decreased to 0.5 mg/kg/infusion and acquisition continued until an additional 150 infusions were self-administered. Once this criterion number of reinforcers was earned a series of tests aimed at measuring MDMA-produced drug-seeking were conducted. On Days 1 and 2, rats self-administered MDMA (0.5 mg/kg/infusion). On Days 3 and 4 the MDMA solution was replaced with vehicle and responding decreased substantially. On Day 5, the MDMA solution was still replaced with vehicle solution but the rats received an injection of MDMA (10.0 mg/kg, IP) and reinstatement of extinguished responding was measured. Additionally, locomotor activity during the reinstatement test was measured. Of the 9 rats, 6 met the criterion and the range to meet the criterion was 9-42 days. The other 3 rats failed to meet the criterion number of responses for 1.0 mg/kg/infusion MDMA self-administration and therefore reinstatement tests were conducted for these rats 21, 27 or 31 days following the first daily trial. The effect of MDMA was inversely related to days required to meet criterion; rats that met the criterion more rapidly showed the most pronounced reinstatement effect. Rats that failed to meet the criterion were not responsive to this effect of MDMA. Rats that acquired MDMA self-administration were also sensitised to the locomotor activating effects of MDMA. These data suggest an increased response to MDMA that might underlie its continued self-administration and propensity to relapse following withdrawal.

7.2

Effects of Chronic MDMA on Sensitivity to Reinforcement in a Behavioural Choice Task

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Long-term use of MDMA is associated with impairments in behavioural tasks such as decision making and self-control (see Kalant, 2001). However, the mechanism by which MDMA decreases performance in these tasks is not clear. One possibility is that MDMA diminishes the efficacy of reinforcement. Previous research has demonstrated that the efficacy or strength of reinforcement decreases with decreases in dopamine levels (e.g., Heyman, 1983). Chronic or long-term doses of 3,4-methylenedioxymethamphetamine (MDMA) have also been shown to affect the dopaminergic systems, with decreases in dopamine release and levels of dopamine metabolites (Green, Cross, & Goodwin, 1995). The present experiment directly assessed the effects of long-term MDMA exposure on sensitivity to reinforcement using an established operant paradigm (Davison & Baum, 2000). Seven hooded Norway rats completed a behavioural choice task where they could press two levers to receive occasional reinforcement (2.5 s access to condensed milk). The relative rates of reinforcement for pressing the two levers were varied across five conditions (15:1, 5:1, 1:1, 1:5, 1:15) within each session. Following extensive training, the effects of reinforcement on the subjects' behaviour were consistent with previous research with rats. Subsequent to this, rats were exposed to a chronic drug (MDMA) regime. This involved 0.5 mg/kg/injection administered post-session five days a week. Changes in sensitivity to reinforcement during this regime were examined. All rats showed a small but consistent increase in sensitivity to reinforcement. These results suggest that changes in reinforcer efficacy do not underlie the performance impairments found in other behavioural tasks with long-term use of MDMA.

7.3

Reference Memory Versus Working Memory Deficits Produced by MDMA ('ecstasy')

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Previous research has suggested that acute exposure to the recreational drug MDMA ('ecstasy') may impair memory-task performance because subjects confuse stable trial-independent elements of the memory task rather than via a disruption to working memory function. This possibility was examined using a version of the 8-arm radial maze task with rats that is designed to separate working memory function from reference memory function (Olton, 1983). In this task four arms are always baited with food and four arms are never baited. Visiting a 'never-baited' arm constitutes a reference memory error whereas re-visiting a previously baited arm within a trial is considered a working memory error. Using this task it was found that acute i.p. injections of MDMA dose-dependently caused a greater increase in reference memory errors versus working memory errors. In contrast, and as demonstrated previously, a cholinergic antagonist (scopolamine) produced a greater impairment to working memory versus reference memory. The pattern of deficit produced by MDMA was also seen following administration of the dopamine agonists GBR12909, quinpirole & A68930. However, citalopram (a 5-HT agonist) did not produce an increase in reference memory errors versus working memory errors. The overall indications are that MDMA produces memory task impairments that is best described as impairment with respect to the unchanging trial-independent elements of a task (as opposed to a specific problem in remembering 'what just happened'). This impairment may be related to the dopamine agonist actions of MDMA when administered acutely.

7.4

Role of D1 Receptor Mechanisms in Methamphetamine Self-Administration and Drug-Seeking

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Male Sprague-Dawley rats were trained to self-administer methamphetamine (0.1mg/kg/infusion) according to an FR1 schedule of reinforcement. The effects of the dopamine D1-like antagonist, SCH 23390 (0.0-0.02 mg/kg, SC) on methamphetamine self-administration (0.05; 0.1; or 0.2 mg/kg/infusion), and methamphetamine produced drug-seeking were then measured. SCH 23390 produced a dose-dependent decrease in self-administration of the lowest dose of methamphetamine, suggesting a rightward shift in the dose-effect curve. Methamphetamine (0.0 - 2.0 mg/kg, IP) dose-dependently increased drug-seeking as measured by reinstatement of extinguished responding and drug-seeking was dose-dependently decreased by prior administration of SCH23390. Taken together these results suggest the D1 receptor is involved in both methamphetamine abuse and relapse.

7.5

Serotonin Depletion and MDMA Self-Administration

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Although depletion of serotonin (5HT) is reported after administration of high doses of 3,4-methylenedioxymethamphetamine (MDMA), little is known about the neurochemical consequences of MDMA self-administration. In this study, we examined the effect of self-administration of MDMA or methamphetamine on brain 5HT content. Drug naïve rats were trained to self-administer 1.0 mg/kg/infusion of MDMA; after acquisition, MDMA self-administration was stabilised by reducing the dose to 0.5 mg/kg/infusion. Different rats were trained to self-administer methamphetamine (0.1 mg/kg/infusion). Control rats were not allowed to self-administer any drug. Five days following the last self-administration session, rats were killed, their brain removed and dissected. Analysis of 5HT was performed using HPLC with electrochemical detection. A decrease in 5HT tissue level was observed in the frontal cortex, striatum, amygdala and hypothalamus, but not in the nucleus accumbens or hippocampus of rats that self-administered MDMA. In addition, a negative correlation between the level of 5HT and the average amount of MDMA self-administered per day was observed in the frontal cortex, the striatum and the amygdala. Rats that self-administered methamphetamine did not exhibit 5HT depletion in any of the brain region studied. These results show that, like MDMA binge administration, MDMA self-administration induced 5HT depletion. This decrease in 5HT level after self-administration appears to be drug-specific since, unlike methamphetamine binge administration, methamphetamine self-administration did not induce 5HT depletion. It also indicates that 5HT depletion observed after MDMA self-administration is region-specific, which might account for rewarding and drug-seeking properties of MDMA.

7.6

Effects of Acute MDMA Administration on Temporal Discrimination in Rats

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Examination of the effects of acute MDMA on behaviours previously shown to be moderated by dopaminergic systems may allow a better understanding of the role of dopamine in cognitive deficits associated with MDMA use. The temporal bisection procedure is a behavioural approach to timing research designed to gauge the speed of the "internal clock". It has been shown that increases in dopamine release with methamphetamine result in a leftward shift of the obtained functions from temporal bisection procedures (e.g., Maricq & Church, 1982), and this is thought to indicate a speeding up of the internal clock. Like methamphetamine, acute administration of MDMA also increases dopamine (Colado, O'Shea, & Green, 2003), but the effects of MDMA on timing are unknown. Six Norway hooded rats were trained in a temporal bisection task where responses to the left lever were reinforced following a 3 s sample stimulus presentation, and responses on the right lever were reinforced following a 9 s sample stimulus presentation. Following training to criterion (90% accuracy), non-reinforced test trials of five intermediate durations were randomly interspersed throughout each session. Administration of MDMA three days a week for three separate doses of MDMA (1 to 3 mg/kg) resulted in a dose-dependent (leftward) shift of the sigmoidal function, perhaps indicating an increase in the speed of the internal clock.

8.1

Stem Cells, Neurogenesis and Diseases of the Basal Ganglia in the Human Brain

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In the normal adult rodent brain, stem/progenitor cells in the subventricular zone (SVZ) of the lateral ventricle proliferate and migrate forming a neurogenic pathway, the 'Rostral Migratory Stream' (RMS), which extends from the SVZ to the olfactory bulb. The RMS has long been thought absent from the human brain. In the rodent, when there is damage to the brain, the SVZ stem cells proliferate and migrate toward the damaged area to replace dying neurons. Our results from studies on post-mortem human brain reveal the presence of proliferating progenitor cells and migratory neuroblasts in the SVZ and in a structure resembling the rodent RMS in the human forebrain. The human RMS begins at the SVZ, is closely associated with the rostral aspect of the caudate nucleus until it reaches the anterior olfactory cortex where it enters the olfactory tract en-route to the olfactory bulb. Also, we examined the SVZ in Huntington's disease (HD) by the use of immunohistochemical techniques to co-label cell cycle proteins, neuronal markers and astrocytic markers. Our results show that progenitor cell proliferation increases with pathological severity and 'CAG' repeat length in the HD gene and that stem cells in the SVZ form new neurons and glial cells in response to striatal cell death in HD. These results provide evidence of increased stem cell proliferation and neurogenesis in response to cell death in the diseased basal ganglia in the human brain and further indicate the plasticity and regenerative potential of the human brain.

8.2

Adult Neurogenesis: Paving the Way for Cell Replacement Therapy

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The occurrence of neurogenesis has become well established in the adult brain and can be divided into 3 phases: (a) progenitor cell proliferation; (b) migration and; (c) region-specific differentiation. Adult progenitor cells hold the potential to reverse, rather than merely attenuating cell loss associated with brain injury and disease. To achieve this we must understand the process by which progenitor cells migrate to regions of cell loss, differentiate into specific cell types and integrate appropriately into a neuronal circuit. This requires a greater understanding of the role environmental cues present in the injured brain play in regulating the process of neurogenesis. Using an excitotoxic model of striatal cell loss we have demonstrated that SVZ-derived progenitor cells respond to cell loss by increased proliferation and directed migration to the site of damage. Progenitor cell recruitment to the injured striatum is mediated by the chemokines GROα, MCP-1 and MIP-1α. However, progenitor cell migration is acute and transient due to a downregulation in chemokine expression over time following cell death. Furthermore, only a small percentage of new neurons that migrate into the damaged striatum survive long-term. Using AAV-mediated gene transfer we therefore examined the potential for the growth factors BDNF and FGF2 to augmenting adult neurogenesis. Ectopic expression of FGF2 supported the survival and proliferation of progenitor cells while BDNF increased the recruitment, generation and survival of new neurons in both the normal and injured brain. Overall, these studies suggest that the development of novel therapeutics to augment environmental cues may allow endogenous progenitor cells to provide a substrate for repair in the adult brain.

8.3

Differential Expression of Synaptic Proteins by Newly Generated Hippocampal Neurons

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In the dentate gyrus of the hippocampus new neurons are born from precursor cells throughout development and into adulthood. Newborn neurons can be imaged in acute or cultured hippocampal slices however the density of neurons in these preparations makes quantification of synaptic proteins problematic. Using BrdU incorporation and immunocytochemistry we previously found that dissociated hippocampal cultures continue to produce new neurons at a high rate. We have quantified the expression of synaptic proteins at newborn neuron synapses versus mature neuron synapses. Newborn neurons have a lower density (puncta/micrometer) of synapsin-1 positive synapses than mature neurons with no differences in GABAergic synapses labelled with GAD-65. In addition, newborn neurons expressed fewer NMDA and AMPA receptors than mature neurons. No differences in GABAA receptor expression were observed. We also observed differences in the expression of Bassoon, Piccollo, alpha-actinin, PSD-95, PSD-93 and Homer between newborn neurons and mature neurons. This data provides anatomical evidence of the developmental profile of glutamatergic and GABAergic synapses of newly generated neurons and shows that GABAergic synapses mature faster than glutamatergic synapses. In addition, this data shows that dissociated hippocampal cultures are a useful model system in which to study the integration of newborn neurons into existing neuronal circuits.

8.4

Subventricular Zone Progenitor Cell Dynamics in the Injured Adult Rat Brain

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Subventricular zone (SVZ) - derived progenitor cells have been show to respond to cell loss and generate new brain cells, suggesting a potential for endogenous cell therapy. This study aimed to characterise the dynamics of SVZ progenitor cell proliferation after striatal cell loss by *in vivo* delivery of the proliferation markers, chlorodeoxyuridine (CldU) and iododeoxyuridine (IdU), and multi-label confocal analysis with the SVZ progenitor cell subtype lineage markers Mash1 (type C progenitor cells) and doublecortin (Dcx; type A neuroblasts). IdU was injected into normal adult rats or adult rats either immediately, 1 or 3 days following a unilateral intrastriatal injection of quinolinic acid (QA). This was followed 24h later by an injection of CldU, 2h prior to death (1, 2 or 4 days after QA injection). Compared to normal animals, ipsilateral SVZ proliferation (CldU+), and the total number of cells re-entering the cell cycle (IdU+/CldU+), was maintained out to 2 days following lesioning and significantly increased at 4 days post lesion. However the percentage of IdU+ cells which re-entered the cell cycle was significantly reduced at 2 days post lesion compared to normal. While no significant alterations in Dcx immunolabelling were observed, the total numbers of both Mash1+ and CldU+/Mash1+ cells, and the percentage of CldU+ cells expressing Mash1 was significantly decreased 1 day post lesion and increased at 4 days post lesion compared to normal. These results suggest striatal injury results in an acute and transient alteration in SVZ progenitor cell cycle length concomitant with alteration in type C cell division mode from asymmetric/symmetric terminal to symmetric amplification leading to type C progenitor population expansion and increased proliferation.

8.5

Neogenin is a Multifunctional Receptor Regulating Neurogenesis in the Embryonic and Adult Brain

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At the onset of neurogenesis, vigorous proliferation occurs within the ventricular zones of the embryonic forebrain. In the ventral forebrain, progenitors give rise to interneurons that migrate tangentially into the developing cortex in the dorsal brain. Abnormal neurogenesis and neuronal migration is the underlying cause of several human disorders, including lissencephaly and epilepsy, and are now being linked to other common disorders such as schizophrenia, dyslexia and autism. However, at present, little is understood about how extrinsic factors within the local environment influence progenitor division, cell fate determination and neuronal migration. We hypothesized that the multifunctional receptor, Neogenin, regulates both neurogenesis and and neuronal migration in the early forebrain. Neogenin has been identified as a receptor for members of the Repulsive Guidance Molecule (RGM) family and plays a pivotal role in the guidance of axonal projections during embryonic development. We have demonstrated that in the mouse forebrain, *Neogenin* is expressed on (i) neural progenitors within the ventricular zones of the cortex and ganglionic eminences, and (ii) young interneurons migrating from the ganglionic eminences into the cortical plate. Furthermore, our recent studies in wildtype embryos demonstrate that Neogenin is a guidance receptor for migrating interneurons within the ganglionic eminence. Further support for our hypothesis comes from our preliminary examination of *Neogenin* null embryos which exhibit a reduction in size of both the embryonic cortex and ganglionic eminence. In this presentation we will describe our recent studies in *Neogenin* null embryos and adult mice suggesting that Neogenin is an important receptor governing neurogenesis in both the embryonic and adult brain.

8.6

Involvement of Activating Transcription Factor-2 in the Process of Neurogenesis

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The discovery of functional adult human neural stem cells (ahNSCs) raises the exciting possibility of cell replacement therapy for neurodegenerative conditions by either transplantation of *in vitro* propagated cells, or via stimulation of *in vivo* neurogenesis. A crucial step in developing NSC therapy is elucidating the signalling molecules involved in induced neurogenesis. Of interest is the transcription factor, activating transcription factor-2 (ATF2); which has previously been found to be crucial in neuronal development and shown to be expressed only in the mature neurons and NSCs of the subventricular zone (SVZ) in the human brain. Although the outcomes of ATF2 dysfunction and expression have been observed, there is yet to be a direct study reporting the role of ATF2 in neurogenesis. This study aims to determine the role of ATF2 in the process of neurogenesis by using P19 murine teratocarcinoma cells as a model of induced neurogenesis, and verifying the results using primary human neural stem cell cultures. Current findings indicate a differential expression of ATF2 during the course of P19 neurogenesis with expression/activation peaking during the neuronal maturation phase. Furthermore, ATF2 was strongly expressed in most differentiated P19 neurons, and knock-down of the gene resulted in a decrease in proliferation of the un-differentiated P19 cells. Although further investigation is needed, this study demonstrates the involvement of ATF2 in the process of neurogenesis and its role in the proliferation of the multi-potent P19 precursor cells. The above findings might shed light on ATF2's role in the neurons and non-neuronal SVZ precursor cells in the human brain.

8.7

Time Course Changes in Hippocampal Cell Proliferation Following Bilateral Vestibular Damage in Rats

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Over the last decade, accumulating evidence has suggested that bilateral vestibular damage causes learning and memory impairments in both animals and humans. Neurochemical and electrophysiological changes in the hippocampus, part of the brain involved in learning and memory, were also reported following the vestibular damage. Moreover, hippocampal atrophy was observed in patients with vestibular damage. However, the underlying mechanisms remain to be elucidated. In the present study, we investigated cell proliferation in the hippocampus in rats following bilateral vestibular damage. The animals were injected with BrdU at 24h, 48h, 72 h or 1 week after the surgery and were sacrificed at 24 h after the BrdU injection. BrdU immunopositive cells in the hippocampus were counted using an optical disector method. Bilateral vestibular damage resulted in a marked increase in the number of BrdU positive cells 72h post-op and the numbers remained increased at 1 week post-op. This result demonstrates, for the first time, that bilateral vestibular damage increases cell proliferation in the hippocampus. Although further studies need to be done to characterize the survival and differentiation of these newborn cells, our results suggest that they may be an important part of the injury induced CNS process following vestibular damage and therefore, may provide a potential therapeutic target.

9.1

Medial Prefrontal Cortex and Memory for the Location of Events

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Patients with frontal cortical damage often experience source memory impairment in that they may recognise a previously experienced object or event, but will not be able to tell where or when it was previously experienced. We found a similar deficit in rats with excitotoxic damage to the medial prefrontal cortex. We first developed a one-trial preconditioning procedure in which rats explored an elevated square platform in a dim room and experienced an auditory cue presented from a speaker situated off one corner. The auditory stimulus had little effect on exploratory behaviour, i.e. during and after presentation rats spent as much time in the quadrant of the platform near the active speaker as in the far end. The auditory stimulus was then paired with an aversive unconditioned stimulus in a separate context, and at a subsequent test, sham lesioned subjects avoided the corner of the platform that had previously been associated with the auditory cue. Rats with medial prefrontal cortical lesions displayed no such place avoidance. When the auditory cue was then played at test, all subjects (lesioned and unlesioned) strongly preferred the end of the platform away from the active speaker. Following these procedures, the two groups of subjects both learned the location of a hidden platform at a similar rate in a one day water maze training protocol, indicating that the lesions had not caused generic deficits in spatial learning. Rather the lesioned rats were specifically impaired in memory for the location of a discrete cue within the environment.

9.2

Do Objects Code for Cognition?

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Many studies have demonstrated a relationship between environmental complexity and a suite of neural and cognitive changes in laboratory animals. These include increases in cortical mass, dendritic spine density and enhanced problem solving ability. Environmental complexity has also been isolated as a factor in the rising IQ scores seen globally. Possible explanations for this 'Flynn effect' abound. Similarly, richer human linguistic environments have been shown to enable numerical cognitive manipulations with large discrete numbers, a capacity not present in speakers of numerically impoverished languages or in highly trained primates. Finally, research in education connects certain human-constructed artefacts (ranging from symbolic representation systems to graphical calculus software) with enhanced conceptual appreciation of mathematical phenomena. This accumulated evidence suggests a strongly causal role for environmental objects (broadly construed) in cognitive development. As well as the brain being able to offload elements of cognitive tasks to the environment, some architecture of the brain may be effectively 'coded' for by cultural technologies or objects. This analysis explores these phenomena and the degree to which they may inform our conception of the coding of cognitive devices and the architecture of the mind/brain. Strong evolutionary psychology posits that the mind consists of a massively modular suite of genetically coded adaptations. However, recent extended Darwinian paradigms suggest that ontogenetic mechanisms, particularly cultural evolutionary processes and niche construction, are likely to carry developmentally important coding information. The data outlined here fits such models more so than it fits evolutionary psychology. It is argued that this evidence supports a less genetically innate model of the mind/brain. This does not mean that cognitive devices are not adaptations; merely that much of the coding information may not be genetic.

9.3

Semantic Influences on Overt and Covert Visual Attention

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Stolz (1996) found orienting of exogenous (involuntary) attention to be influenced by linguistic processing; evidence against a theory of attention-shifting represented as a set of processes uninfluenced by semantic information. The objective of the current study was to discover how the meaning of a stimulus influences the control of attention, by investigating whether the semantic information associated with an exogenously presented object influences its ability to capture and hold covert visual attention. This was achieved by combining aspects of Posner's (1980) spatial cuing paradigm with eye tracking techniques. One or two uninformative cues were briefly presented either to the left, right, or both visual fields while participants maintained fixation until the appearance of a target symbol, to which participants were to respond. The semantic value of the cue could be either biologically salient (i.e., a face) or neutral (e.g., clothing), and could either correctly (i.e., validly) or incorrectly (i.e., invalidly) predict the location of the upcoming target. Targets correctly predicted by faces rather than neutral cues were identified (using button-presses) faster, an effect apparent only when two cues were presented simultaneously. This trade-off between semantics and low-level perceptual features depending on whether the cues were in competition or not (i.e., two versus one cue), suggests semantic information has a larger influence in more complex visual environments where more objects compete for your attention. An unexpected cuing effect, since replicated, arose when participants were to make a speeded saccade to the appearance of the target. Validly cued targets received no facilitatory effects, contrary to previous research; a possible result of using eye tracking techniques to strictly monitor fixation maintenance, allowing measurement of purely covert visual attention shifts.

9.4

Effects of Emotional Valence on Memory Suppression in the Think – No Think Task: Behavioural and fMRI Findings

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In three experiments using the think – no think procedure of Anderson & Green, participants learned to associate word pairs in which the first item was either emotionally positive (e.g. joy) or emotionally negative (e.g. hatred). The second word was always emotionally neutral (e.g. socks). In Experiments 1 and 2 significant memory suppression was observed following 'no think' instructions for response words previously associated with emotionally negative material. No suppression was observed for memories associated with emotionally positive words. In Experiment 3 participants performed the think – no think task, while brain activity was monitored using fMRI. Both the degree of activation in anterior cingulate and prefrontal areas, and the degree of deactivation in insula, thalamus and fusiform gyrus was significantly greater when participants attempted to suppress awareness for words associated with negative cues, compared to positive cue words. Implications of these findings for the relationship between performance in the think – no think task and the notion of memory repression are considered.

9.5

Eye Movements – Functional Markers of Incomplete Recovery in Postconcussion Syndrome

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We examined eye movements in patients with postconcussion syndrome (PCS) at 3-4 months after mild closed head injury (CHI), including 20 PCS patients and 20 controls (i.e., CHI patients of similar injury severity but good recovery, matched for age, gender, education, and time post-injury). Our aim was to identify disparities in saccadic function and oculomotor smooth pursuit (OSP) between these groups, and compare these with neuropsychological function and self-perceived health condition. The groups differed markedly in postconcussive symptom levels and problems with activities of daily living. The PCS group had poorer performance on several oculomotor measures including more response errors in the antisaccade task, poorer visuospatial accuracy on anti- and memory-guided saccades, smaller number of self-paced saccades, longer saccade duration of self-paced saccades, higher number of eye movements in memory-guided sequences of saccades, with marginal deficits on fast sinusoidal and random OSP. Some neuropsychological group differences were present but smaller than anticipated. Neuropsychological functions more affected in the PCS group included executive function, sustained and divided attention, speed of information processing, and cognitive flexibility. The PCS group also had much poorer scores on measures of depression. Effect sizes of significant oculomotor and neuropsychological differences were equivalent. The oculomotor deficit profile of the PCS group was not consistent with that observed in non-trauma patients with major depression disorder. Eye movement assessment may provide additional information about brain function in patients with PCS, offering objective markers of ongoing cerebral impairment. These would be independent of patient self-report and neuropsychological assessment and might be useful in supplementing patient evaluation, providing external confirmation of incomplete recovery.

9.6

Enhanced Psychoacoustic Sensitivity and Auditory-Related Neural Processing is Related to Long-Term Musical Training

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The effect of long-term experience on auditory processing was assessed in musicians and non-musicians using a neuroelectric index of auditory processing, the mismatch negativity (MMN), and behavioral discrimination performance. Auditory stimuli were comprised of pairs of ascending pure-tone stimuli (standards). Occasionally, the frequency order reversed (deviants). Standards were presented on 90%, and deviants on 10% of the trials. Data were collected under three experimental conditions. Under one condition, the same two frequencies were used for each tone-pair (physical change condition). Under the other two conditions, ten different pairs of frequencies were varied across the tone-pairs. The deviant stimulus was drawn from the ten-frequency pairs with equiprobability. Thus deviance was based on reversal of frequency presentation (from lower to higher to higher to lower). This condition was called the 'rule-based change condition'. Under physical change conditions an MMN was elicited by the deviant stimuli for musicians and non-musicians and both groups could discriminate the deviants from the standards. Under rule-based change conditions, MMNs were elicited for the musicians and only the musicians were able to perform the discrimination task accurately. These results show that the psychoacoustic advantage, previously reported, for musicians extends to rule-based acoustic changes. In addition, neural modulation by long-term experience is apparent at a relatively automatic, pre-attentive level of auditory processing.

10.1

Two Hands, One Target: Time to React?

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Imagine standing in slips waiting for the 'nick' as the ball flies off the bat. Fast movement of both hands depends on fast motor preparation. Although movement of each hand is initiated via separate motor pathways from the left and right contralateral motor cortex, preparation requires integrated planning. It has been suggested that the left dorsal premotor area (dPMA) plays an overarching role in preparation. We have shown that when participants have to move two hands simultaneously to a single known target, simple reaction time (SRT) is slower for two than one-handed responses. And, in two-hand responses SRT was longer when hand movements were asymmetrical. Brain activity prior to stimulus onset was consistently greater in left dPMA. To determine whether increased dPMA activity was dependent on knowing the specific response to be prepared we used a choice reaction time task in which target location remains unknown until stimulus onset. We hypothesise that in the absence of target-specific information choice reaction time (CRT) will and dPMA activity will not increase. Here we present preliminary results (n=4) for reaction time. CRT increased when the number (2-3) of possible target locations increased. Within three two-choice conditions RT was longer for bimanual (300 ms) than unimanual (274 ms) and within bimanual RT was longer (308 ms) for asymmetric hand compared to symmetric hand movements (282 ms). Time to react (motor preparation) is affected by the number of hands, response symmetry and the number of alternatives. Given reaction time increased under "choice" conditions it is predicted that left dorsal premotor area activity will remain unchanged until stimulus onset.

10.2

Task-Dependant Modulation of Propriospinal Inputs to Human Shoulder

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In the human upper limb a proportion of the descending corticospinal command is relayed through cervical propriospinal neurons. This facilitates co-ordination of multiple joints of the arm, during tasks such as reaching. The present study was conducted to determine if a shoulder stabilising muscle, *infraspinatus* (INF), is functionally integrated into the cervical propriospinal network. Twelve healthy adults participated in this study. Transcranial magnetic stimulation (TMS) over the motor cortex was used to examine excitability of corticomotor projections to right INF. Motor evoked potentials were compared to responses conditioned by ulnar nerve stimulation. Conditioning was timed to summate with descending input from TMS at the level of premotoneurons. Participants performed a forearm and shoulder muscle co-contraction task or a grip-lift task that also co-activated forearm and shoulder muscles. Differential responses were evoked between the tasks in response to changes in TMS intensity. During co-contraction INF motor evoked potentials (MEPs) were facilitated by ulnar nerve stimulation at weak TMS intensities ($p = 0.001$) and suppressed at higher TMS intensities ($p < 0.001$). However, during the grip-lift task, conditioned INF MEPs were facilitated with weak intensity TMS ($p = 0.01$), but not suppressed with stronger intensities. To our knowledge this is the first demonstration that propriospinal networks mediate control between hand and shoulder in a task dependent manner.

10.3

Cortical Mechanisms Underlying Cross-Limb Transfer of Ballistic Motor Skill Revealed by Repetitive Transcranial Magnetic Stimulation

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Although it has long been known that practicing a motor task with one limb can improve performance with the opposite (untrained) limb, the mechanisms remain unknown. Hypotheses to explain this generalization of learning across limbs fall into two broad categories. Performance improvements in the untrained limb could be mediated either by neural adaptations in high-order cortical centers that are part of the control system for both limbs, or by crossed adaptations in both hemispheres due to a "spill-over" of motor activity during training. Here we tested whether "spill-over" mechanisms contribute to cross-limb transfer of ballistic motor skill, using a non-invasive method of inducing short-term reorganization in the human cortex. Twenty-one volunteers practiced a ballistic index finger abduction task with their right hand. Eight control subjects did not train. After training, repetitive transcranial magnetic stimulation (rTMS; 15 min at 1Hz, 1.1 x motor threshold) was applied to the left (trained) or right (untrained) primary motor cortex (M1) to induce a "virtual lesion". A third training group received sham rTMS, and control subjects received rTMS to the right M1. Performance and corticospinal excitability increased in both hands for training but not control subjects. Repetitive TMS of the left (trained) motor cortex specifically reduced training-induced gains in motor performance for the right-trained hand, and rTMS of the right (untrained) M1 specifically reduced left (untrained) hand performance. Thus, cortical adaptations within the hemisphere ipsilateral to the limb engaged in training contribute to cross-limb transfer of ballistic motor skill.

10.4

Influence of Muscle Contraction on Motor Evoked Potentials of the Submental Muscle Group

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Motor evoked potentials (MEPs) have been used to evaluate treatment effects on neural pathways underlying swallowing. These MEPs were recorded from pharyngeal and anterior hyo-mandibular (submental) muscles *at rest*. No studies have investigated MEPs measured during active contraction of this muscle group. Using a novel triggering method, we evaluated three conditions of muscle contraction on the amplitude of MEPs. Further, we examined test-retest reliability of MEPs. MEPs were recorded from 15 healthy volunteers during execution of three tasks: volitional submental muscle contraction (VC), volitional swallowing (VS) and reflexive swallowing (RS). Single pulse transcranial magnetic stimulation (Magstim 200, Magstim Company Limited, Whitland, Wales) was triggered when a pre-set EMG amplitude was reached. 15 MEPs were recorded for each subject in each condition. 10 subjects returned for an additional 3 sessions for repeated assessment. MEPs were measurable in all three tasks for 7/11 participants, during VC and VS in 2/15 participants and in VC only in 6/15 participants. Grouped repeated measures ANOVA on the 8 subjects that displayed MEPs in the two volitional conditions revealed that MEP amplitudes during VC were significantly greater than during VS [$F(1,7) = 7.88$, $p = .026$]. In the 7/11 subjects that displayed MEPs in all three tasks, no significant differences were found between amplitudes [$F = .074$, $p = .929$]. Test-retest reliability across 4 sessions was high with Cronbach's alpha coefficients of .899 for the VS task and .876 for the VC task. These data suggest differences in cortical drive between volitional contraction, volitional swallowing and reflexive swallowing. Therefore methods should be considered in future research investigating swallowing related MEPs.

10.5

Long Lasting Impairments in the Capacity of the Human Motor Cortex to Voluntarily Activate Knee Extensor Muscles Following Cycling Exercise

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Muscle fatigue is a reduction in the capacity to exert force and may involve a 'central' component originating in the brain and/or spinal cord. Here we examined whether supraspinal factors contribute to an impairment in central drive after a bout of locomotor cycling exercise. On two separate days, ten people (22.6 ± 1.4 years, 62.2 ± 2.8 kg, VO_2 max: 45.8 ± 1.8 $ml.kg^{-1}.min^{-1}$) completed locomotor cycling exercise session or a control session. Brief (2s) and sustained (30s) isometric knee extension contractions were completed before and after locomotor exercise consisting of eight, 5 min bouts of cycling at 80% of maximum workload. In the control session, subjects completed the isometric contractions in a rested state. Twitch responses to supramaximal motor nerve stimulation and transcranial magnetic stimulation (TMS) were obtained to assess peripheral force generating capacity and voluntary activation (VA). Maximum voluntary contraction (MVC) force during brief contractions decreased by 18% post exercise, and remained 10% below baseline 45 minutes later. Resting twitch amplitudes declined by ~45% ($P < 0.01$), and cortical VA declined by ~11% ($P < 0.001$) of pre-exercise values, and remained significantly reduced relative the control trials 30-45 minutes later. Sustained MVCs induced a greater reduction in maximal force after locomotor exercise than when the muscles were in a rested state. However, less (additional) *peripheral* fatigue was induced by sustained MVC, and more supraspinal fatigue was induced under the influence of locomotor muscle fatigue. Thus, locomotor exercise can cause long-lasting impairments in the capacity of the motor cortex to drive the knee extensors during maximal contractions.

10.6

Use of Bimanual Robotic Therapy as an Intervention For Upper Limb Movement Following Stroke

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In individuals with chronic stroke, training therapies that promote the performance of symmetric bimanual movements of the two limbs can benefit the restoration of movement control. Our study investigated the use of robot-assisted bimanual therapies for the upper limb. The main goal was to compare motor control and movement characteristics of the affected arm between unimanual robot-assisted movement and bimanual robot-assisted movement. A secondary goal was to compare movement characteristics during bimanual robot-assisted movement to bimanual voluntary movement, where both limbs moved independently without robotics. Subjects performed reaching tasks while attached to one (unimanual) or two (bimanual) HapticMASTER robots. Reaching movements were performed voluntarily or with robotic assistance, and with either one or both upper limbs simultaneously. A pre-defined movement trajectory was prescribed during unimanual robot-assisted movement; in bimanual robot-assisted movement the trajectory of the affected limb was replicated from that produced by the non-affected limb. We found that the onset of muscle activation and force generation was more appropriate during bimanual compared to unimanual robot-assisted movement. However, there were few significant differences in movement kinematics and kinetics between bimanual voluntary and bimanual robot-assisted movement. We suggest that bimanual robot-assisted training is suitable for lower functioning individuals who have a restricted range of active movement. Bimanual training without robotics may be more efficacious for moderate to higher functioning individuals who can generate suitable movement trajectories without robotic assistance.

11.1

High Field Magnetic Resonance Imaging of the Cochlea: Preliminary Studies

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The human inner ear in the temporal bone, with its soft sensory and neural tissues surrounded by dense bone is almost inaccessible to detailed study without destroying its structure. This imposes significant limitations to observations of normal and abnormal cochlear function and translation of animal research findings to humans. The continual evolution of MRI methodologies, however, offers considerable opportunities to examine cochlear structural features and measure its function, which may eventually be available for the intact human inner ear. We report here on preliminary functional studies of the guinea-pig cochlea using High Field MRI (HFMRI) to evaluate vascular permeability following loud sound exposure. Guinea-pigs were exposed to broad-band noise at 120dBSPL for up to 8 hours and then injected intravenously with a gadolinium-based contrast reagent (CR, 0.3 or 1.5mM/kg) or saline, Animals were euthanized and immediately examined using HFMRI (12T Biospec, Bruker). A 3D gradient-recalled echo MRI sequence was used to produce T_1-weighted images of the entire guinea-pig head with 90µm isotropic resolution. These preliminary studies showed an increase in T_1-weighted signal intensity in noise-exposed animals that received CR within discrete, highly vascularised regions of the cochlear lateral wall, compared with non-noise exposed control animals. Our interpretation, based on Dynamic Contrast Enhanced MRI principles (Li, X et al., (2005) Mag. Res. Med, 54:1351-59), is that this represents a noise-induced increase in local vascular permeability, which has been observed in guinea-pigs using other techniques. Further studies are being undertaken to quantify these changes and to assess use of a 7T MRI system to image the human inner ear. These preliminary studies are encouraging for the potential use of HFMRI to study aspects of inner ear function.

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11.2

Regulation of Cochlear Outer Hair Cells: Insights From Mathematical Modelling

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The outer hair cells (OHCs) of the cochlea are the source of much of our exquisite auditory sensitivity, providing sharp mechanical tuning and increasing the vibration of the basilar membrane by up to a factor of 1000. They accomplish this by a combination of mechanoelectrical and electromechanical transduction – providing positive feedback to enhance sound-induced vibration and cancel friction. Because the OHCs are sensitive to displacements of molecular dimensions, and yet are motile themselves, they must employ a number of negative-feedback (homeostatic) mechanisms to regulate their sensitivity in the face of daily disturbances. To understand some of these mechanisms, we have created a mathematical model of OHC, focusing on the links between ion transport, electrophysiology and OHC motility. The model we present offers insights into the regulation of OHC membrane potential and mechanoelectrical transduction, and provides a physiologically-plausible and internally-consistent explanation for the time-courses of the cochlear changes we have observed during different experimental perturbations performed in the guinea pig cochlea. We show how the known ionic mechanisms within OHCs act to regulate membrane potential and hair bundle angle over a very wide range of electrical and hydrostatic conditions, and

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11.3

Effects of Bilateral Vestibular Deafferentation on Attentional Performance in a Five-Choice Serial Reaction Time Task in Rats

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There is increasing evidence that vestibular damage leads to a variety of cognitive impairments in both animals and human patients. Aside from learning and memory deficits, it was reported that patients with vestibular damage have difficulty with concentration. However, attentional performance following bilateral vestibular deafferentation (BVD) has never been investigated in animals. In the present study, a five-choice serial reaction time task was used to compare attentional performance between sham (n = 10) and BVD (n = 10) rats at 7 months following the surgery. Rats were trained to discriminate a brief visual stimulus presented randomly in one of the five spatial locations and respond by poking their nose through the illuminated hole and collecting a food pellet from the magazine. It took the BVD rats longer to reach the criterion when compared with the sham rats. BVD rats also made fewer correct responses and more incorrect responses when performing the task, which indicates less accuracy in performance. A closer analysis further revealed that BVD rats made more premature and perserverative responses, which indicates a deficit in inhibitory control. However, there was no difference in the percentage omission between the sham and BVD rats. Our results suggest that the vestibular system may play a role in the attentional behaviours of rats.

11.4

Selective Reduction in Synaptic Proteins Involved in Vesicle Docking And Signalling at Synapses in the Ataxic Mutant Mouse *Stargazer*

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The ataxic mouse *Stargazer* has a specific and pronounced deficit in brain derived neurotrophic factor (BDNF) mRNA expression in the cerebellum. Cerebellar granule cells, in particular, show a selective and near total loss of BDNF. The mutation involves a defect in the calcium channel subunit Cacng2. This severely reduces expression of stargazin. A stargazin-induced failure in BDNF expression is thought to underlie the cerebellar ataxia with which the mutant presents. BDNF is known to regulate plasticity at cerebellar synapses. However, relatively little is known about the mechanism involved. We previously demonstrated that the *stargazer* mutation affects the phenotype of cerebellar glutamatergic neurons. *Stargazer* neurons have less glutamate and proportionally fewer docked vesicles at presynaptic sites than controls. The aim of the current study was to investigate whether changes in synaptic vesicle distribution at cerebellar synapses in the *stargazer* are associated with alterations in the levels of synaptic proteins essential for vesicle trafficking and exocytosis. Expression levels of synaptic-proteins were evaluated by measuring relative density of immunogold-label over parallel fibre terminals in ultrathin sections from ataxic *stargazer* mutants compared to matched non-ataxic littermates. We show that there is a selective and marked depletion in the levels of the vesicle-associated proteins synaptobrevin, synaptophysin, synaptotagmin and Rab3a but not of plasma membrane-associated protein SNAP-25, in the terminals of the BDNF-deficient granule cells. Changes are restricted to the cerebellum; levels in the hippocampus were unaltered. These data suggest that the BDNF deficits in the cerebellum of the *stargazer* affect synaptic vesicle docking by selectively altering synaptic-protein distribution and abundance.

11.5

C-Fos Expression is Increased During Ethanol Withdrawal in an Animal Model of Alcohol-Related Neurodevelopmental Disorder

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Prenatal alcohol exposure disrupts brain and behavioural development, leading to a range of fetal alcohol spectrum disorders. Although ethanol induces neuropathology via a number of mechanisms, some neuropathology may occur during periods of alcohol withdrawal. Ethanol withdrawal may lead to an increase in cell death within vulnerable regions in the brain, such as the hippocampus, which is important for learning and memory. This study examined the expression of c-Fos, an immediate early gene implicated in cell death, in a rat model of binge drinking during the third trimester. Rat pups were removed briefly from their mother on postnatal day 6, weighed and sexed before ethanol administration. One group of pups received ethanol via intubation (6.0 g/kg in milk solution (Intralipid); mean blood alcohol concentration of 440 mg/dl), and the control group received an intubation, but with no solution delivered. Pups received two ethanol feedings (3.0 g/kg each) and then two milk-only feedings at 2 hourly intervals. Animals were sacrificed 24 or 28 hours after the first ethanol dose, as these time points correspond to when pups show withdrawal symptoms. Brains were fixed, removed, cut with a vibratome (50μm) and processed for c-Fos immunoreactivity (1:16000 dilution overnight). Results revealed that animals exposed to a single ethanol binge on PN 6 showed an increase in c-Fos expression at 24 and 28 hours in all brain regions examined ($p<0.05$), including prefrontal, sensory and motor cortices, hippocampus and striatum. Thus, this study identifies c-Fos expression as a potential link between ethanol withdrawal and cell death as a mechanism for the development of ethanol-induced developmental brain damage.

11.6

MIS Deficiency Causes Alterations in Dendritic Spine Density

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Müllerian Inhibiting Substance (MIS) is a male-specific gonadal hormone during development, but is present in the blood and brains of adult males and females. Receptors for MIS are found on all neurons, with an apparent concentration in dendrites. Dendritic morphology is sexually dimorphic in some brain areas, but is also regulated in a non-dimorphic manner. We have therefore examined the role of MIS as a regulator of dendrites, by examining the abundance of spinophilin in MIS-deficient mice. Spinophilin is highly enriched in dendritic spines and is a semiquantitative indicator of spine density. Samples from different brain areas were micro punched and prepared for Western blotting, using anti-spinophilin and anti-beta-actin as an internal standard. The densities of the spinophilin and beta-actin bands were quantified with ImageJ (NIH) software and the spinophilin/beta-actin ratio calculated. The effect of MIS-deficiency varied between brain regions and the sexes, which may indicate that the action of MIS is influenced by neuronal sub-type and/or the presence of other regulators. The spinophilin content in the dorsal striatum of $MIS^{-/-}$ females was significantly increased ($p=0.0003$) relative to $MIS^{+/+}$ females, indicating that MIS directly or indirectly influences the structure of adult female brains. This effect on the striatum was not present in males. There was no detectable effect of MIS on spinophilin in the lateral septum and the medial preoptic area. These results are consistent with MIS regulating the abundance of dendritic spines, although further verification of this is needed by the direct visualisation of dendritic morphology in the affected regions.