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1.1

Human Parietal Lobe Contributions to Attention and Awareness

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Mechanisms of selective attention exert a profound influence on many aspects of visual perception. In the human brain, subregions of the parietal cortex provide an important source of attentional control signals, allowing visual information to be prioritized in the service of awareness and goal-directed action. I will discuss three recent studies from our laboratory which reveal some key properties of the human parietal cortex in selective attention. First, I show that acquired lesions of the parietal lobe result in a spatial gradient of perceptual impairment which is maximal at extreme contralesional locations. Crucially, the steepness of this pathological gradient increases with attentional load in a central task. Second, I show that stimulation of subregions of the inferior parietal lobule can selectively disrupt the ability to reorient attention in space, and that this effect follows a timecourse that implies distinct 'early' and 'late' parietal influences on selection. Third, I consider the potential effect of parietal control mechanisms on the representation of sensory information at the earliest stages of cortical processing. During a task requiring selection of rapidly sequential visual targets, we find that the widely reported 'attentional blink' is associated with attenuation of neural activity in the primary visual cortex. Taken together, our findings suggest a variety of roles for the human parietal lobe in modulating both spatial and non-spatial aspects of perception.

1.2

Time flies! Attentional Effects of Emotion on Time Perception for Visual Stimuli

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The temporal bisection task is a well-established and powerful tool in the study of time perception. Recent studies that used this task have shown that a stimulus' emotional content can influence its perceived duration and that effects are in line with activational theories of time perception. However, temporal bisection has only been used to study the impact of emotion on time perception for short durations (below 2 seconds). In the present study, a temporal bisection task was used to examine the independent effects of two emotional factors, arousal and valence, on time perception for a longer duration range. Forty-eight participants were assigned to one of four emotion categories created by combining arousal (high or low) and valence (positive or negative). Participants were shown a random mix of emotional and neutral images, displayed for 2000 to 6000ms, and decided whether the duration was closest to the short or long anchor duration. Point of subjective equality (PSE) analyses revealed that images from both high arousal conditions (positive and negative) and from the low arousal negative condition were underestimated to a similar degree, while durations for the low arousal positive group were relatively overestimated. These results are consistent with attentional theories of time perception and in marked contrast to the activational effects that have been reported for shorter duration ranges. Findings thus suggest that the effect of emotional factors on time perception can change over time. Moreover, the study revealed no differences between time estimates for emotional and neutral trials mixed within a block, suggesting that attentional effects of emotional stimuli carry over to influence time perception of neutral images.

1.3

Motor Plans Influence the Visual Processing of Observed Actions

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The perception and the execution of action appear to be linked by common neural mechanisms. Observed actions lead to increased activity in motor and premotor cortical areas and can interfere with the execution of opposite or incongruent actions. The "mirror" system has been suggested to mediate this link, directly matching observed actions onto equivalent motor representations in the motor system. While many studies have focussed on the influence of observed actions on the motor system, it is not known whether motor plans can similarly influence earlier visual processing associated with the perception of actions in a top-down manner. We tested this hypothesis specifically by examining visual evoked potentials (64-channel EEG) to images of hand gesture actions that were either congruent or incongruent with hand actions concurrently planned by participants in a Go-NoGo paradigm. The visual processing of observed actions was found to be significantly influenced by concurrent motor plans. Specifically, the N1/P1 component of the visual evoked potential to pictures of hand actions, occurring within approximately 100 ms of stimulus presentation, was significantly enhanced when the observed actions were incongruent with concurrently planned actions. Crucially, this effect was specific to the congruency of motor plans, and was not observed in a control condition involving similar stimulus incongruency but without motor planning. Our results provide further evidence for the association between the perception and execution of action, perhaps mediated by a mirror neuron system. Specifically, we have shown that motor plans or representations of intended actions in the motor system can influence the visual processing of observed actions.

1.4

The Role of Emotional Content in the Control of Eye Movements

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The pro/anti-saccade paradigm has been a favourite among researchers of attention and the control of eye movements. Most pro/anti-saccade studies have utilized meaningless stimuli, though stimulus meaning is known to have an impact on looking behaviour in free viewing conditions. Here, we explore the role of content in the control of pro/anti-saccades by contrasting two alternative views on the impact of emotional stimuli. One view supports an "informativeness" hypothesis, where visual processing is directed towards threatening stimuli, suggesting that RT should be particularly large for negative, high arousal pictures in an antisaccade task. An alternative view emphasizes approach and withdrawal behaviours. Here negative images are thought to encourage avoidance behaviours, causing faster RTs for antisaccades; whereas positive pictures encourage approach behaviours, causing faster RTs for prosaccades. Participants performed an antisaccade task in which they were presented with an image to the left or right visual field and instructed to look at or away from the picture. In Experiments 1a -b the instruction was given 200 ms before the picture was presented while in Experiments 2a -b the instruction will be given 200 ms after the picture is presented. The experimental design includes five groups of images, with a factorial combination of valence (positive or negative) and arousal (high or low), and a neutral condition. Results from experiments 1a -b suggested that while antisaccades have a longer RT, there was no difference as a function of the emotional content. It is expected that emotional content will have an effect in experiment 2a -b as the participant is able to process the picture (in their peripheral view) allowing attentional effects to be observed.

1.5

Tracking the Learning of Actions: Evaluation of the P3a Component

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The ability to correctly identify and evaluate actions that result in an unexpected and/or behaviourally significant sensory event is crucial to an organism's learning and survival. Recent theories propose that a phasic dopamine signal strengthens inputs into the striatum that are active just prior to a sensory event and that the anterior cingulate cortex (ACC) evaluates these various inputs. Typically, the event-related potential components, error-related and feedback-related negativities, are used to assess ACC activity. Our hypothesis is that the P3a, a neural signal typically associated with novelty, also captures increased ACC activity during the learning of actions that cause a sensory event. To test this hypothesis, we used a 'where task' to track the learning of actions that lead to a sensory event. Data from the where task were compared to control tasks, that did not require action discovery, to control for potential confounds. EEG activity, cursor movements and search times were recorded during all tasks. The P3a (maximal at FCz) was only elicited in the where task, supported by statistically significant differences between where and control tasks ($p < 0.0001$). Significant decreases in P3a amplitude were found when comparing block 1 to subsequent blocks across the task ($p < 0.05$). No differences were found across the control tasks ($p > 0.1$). Effects of learning were further supported by behavioural analysis. Results support our hypothesis that the P3a is a measure of ACC activity, potentially modulated by dopamine, as an organism learns to correctly identify and evaluate the actions that result in an unexpected and/or behaviorally significant sensory event.

1.6

Human Brains: A Moving Target

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Can we compare studies in psychology and the neurosciences? I present four brief arguments underscoring the role of context in shaping cognitive development and conclude that temporally separated data may not be directly comparable. First, there are many reasons to believe that Neanderthals possessed a cognitive capacity roughly equal to that of early humans. This includes a large cerebral cortex, the FOXP2 gene, and tool-making behaviour necessitating essentially modern cognition. Yet Neanderthals remained dumb nephews in comparison to the behavioural take-off of *Homo sapiens*, having never apparently mastered symbolic technologies. Second, we see that encultured primates can manipulate symbols representing concepts such as sameness and difference, whereas wild primates never do. Third, changes in pedagogy technologies in the last 300 years, such as the switch from oral to written exams at Cambridge, and the teaching of geometry and algebra to younger and younger school children, have dramatically enhanced general mathematical physical and scientific cognition. Finally, in the last 15 years, experience with virtual avatars is currently shaping the way humans experience themselves. All these drivers of cognitive development can cause a ratchet effect where the technologies that led to these cognitive innovations are reproduced and potentially modified further. This ever-changing technological/symbolic context means that human minds and, via a reasonable materialist assumption, human brains, are a target of investigation that is changing at an ever-increasing rate. Psychology and Neuroscience are young disciplines and are yet to be temporally tested. Comparison of temporally, and therefore contextually, disparate psychological and neuroscientific data in future years must be undertaken with caution.

1.7

The Role of Dopamine in Selective Attention in the 'Prefrontal Cortex' of Pigeons

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Selective attention is a crucial component of all sensory processing. Here we test the role of dopamine in attentional selection and in the maintenance of attention. Pigeons were trained on a moving-dot paradigm comparable to the shell game. In this paradigm, pigeons had to select a target among distractors and maintain attention to the target. Target and distractors consisted of white dots, moving at random about a touch-screen. The load on attention was modulated by varying the number of distractors and the duration of motion. Both manipulations affected performance equally. Intracranial injections of D1-antagonist (Sch23390) before testing led to decrements in performance that equally affected trials with different load on attention. This drop in performance cannot be attributed to altered motivation or motor performance. We conclude that dopamine has a critical role in attention. It is involved in the selection of targets for attention and in the stabilization of attention against interference. This is comparable to the role dopamine plays in working memory and argues for comparable mechanisms underlying selective attention and working memory.

2.1

Dynamic Regulation of the Endocochlear Potential of the Mammalian Cochlea

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Sound transduction in the cochlea relies upon precise regulation of the electrochemistry of fluids that bathe the sensory cells, particularly endolymph of scala media. This fluid has a high potassium concentration and positive electrical potential (endocochlear potential, EP, +100mV). We previously demonstrated that activation of ATP-gated ion channels lining the endolymphatic compartment causes a decline in compartment resistance. This suggests that humoral regulation of conductances in the compartment tissues is potential mechanism for controlling EP. To study this further we investigated the dynamic relationship between EP and the compartment resistance (CoPR) in mice. Mice were anaesthetized (Urethane, 1.6mg/g) and the cochlea surgically exposed. EP was measured from a micropipette in endolymph and resistance was measured by injecting current (1μA) and calculating the EP change. There was a positive correlation between baseline EP magnitude and CoPR. ATP injected into endolymph decreased resistance and EP in a dose-dependent manner. As ATP was metabolized, resistance and EP recovered equivalently further suggesting a strong relationship between EP and CoPR. However, as experiments proceeded baseline EP steadily declined which was accompanied by an increase in CoPR suggesting a reactive response of compartment tissues to the decline in EP. To test this we decreased EP by blocking the EP generator (Na-K-2Cl co-transporter in the stria vascularis) with furosemide. As EP declined, resistance increased but then returned to baseline as EP recovered. These data show a strong correlation between CoPR, possibly maintained by ion channels in tissues lining scala media, and EP suggesting a dynamic regulatory mechanism that maintains EP at its optimal level for transduction.

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2.2

Developmental Changes in Pre-synaptic Ribbons and Post-synaptic Glutamate Receptor Expression During Cochlear Neurite Remodelling

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The primary auditory neurones exhibit precisely timed neurite outgrowth, neurite refinement and neurite retraction to establish the mature innervation pattern in the mouse cochlea before the onset of hearing. Initially, type I fibres innervate inner and outer hair cells (IHCs, OHCs), and then the type I fibres specifically retract from the OHCs. However, the mechanisms driving this process of synapse remodelling remain elusive. Our hypothesis is that the fate of the neurite retraction might associate with synaptic strength, determined by the expression of the pre-synaptic ribbons and the post-synaptic glutamate receptors. Using immunohistochemistry and confocal microscopy, we found that type I neurites refine their innervation to IHCs by retracting their processes to where the ribbons were anchored in IHCs. Type I neurites retract from OHCs when the ribbons in OHCs disperse from the synaptic region. In addition, glutamate receptors (GluR2/3 and GluR4) were found to be stably expressed under IHCs, while a transient expression of these glutamate receptor subunits was found under OHCs. This transient expression of glutamate receptors coincide with the removal of the ribbons in the OHC synaptic region. These data show that a strong correlation exists between the changes in synaptic ribbons and the post-synaptic glutamate receptors and the type I neurite innervation during early cochlear development. These changes could correlate with functional decreases in synaptic strength leading to specific retraction of OHC-type I fibres synapses to establish the correct innervation pattern required for the onset of hearing.

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2.3

Survival and Neuritogenesis of Type I and Type II Spiral Ganglion Neurons are Differentially Regulated by BDNF and Peripherin

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Afferent innervation of sensory hair cells by spiral ganglion neurons (SGN) is refined during the first postnatal week so that Type I SGN (SGNI) exclusively innervate the inner hair cells, while Type II SGN (SGNII) innervate the outer hair cells. To gain a better understanding of the mechanisms that drive this refinement we used β-tubulin and peripherin immunofluorescence to distinguish SGNI and SGNII *in vitro* and investigated the effects that the neurotrophin BDNF had on survival and neuritogenesis of these neurons. Peripherin null mice were used to examine the potential role of this cytoskeletal protein in neuritogenesis. We show that SGNII are highly dependant on the presence of the organ of Corti (oC) for survival. Organtoypic culture, with intact oC, failed to protect SGNI, indicating the requirement for additional trophic support. Culture of the spiral ganglion, without the oC (explant) resulted in almost complete loss of SGNI and SGNII (standard media). Supplementation with BDNF (100ng/ml) rescues proportionately more SGNII compared with SGNI. BDNF promoted neuritogenesis in both SGNI and SGNII at P1, with signficantly greater efficacy for SGNII. Peripherin is exclusively expressed in SGNII and knockout of this intermediate filament protein resulted in enhanced neuritogenesis in the SGN explants (P1). These results suggest that BDNF is involved in survival of SGNII and the extension of their afferent dendrites during postnatal development. Peripherin expression by these neurons inhibits these processes.

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2.4

Early Interaction Between Bottom-up and Top-down Processes in the Beta-gamma Band During Ultra-rapid Visual Object Detection

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Selective attention is a universal mechanism underlying proper evaluation of the environment and goal-directed behavior. It has been a focus in numerous studies exploring processing of sensory information including visual target detection paradigms. Visual recognition even of complex objects is surprisingly fast (150-200 ms) and the majority of its research has been focused on the bottom-up analysis of information in the ventral visual stream processing increasingly complex object features. However, there is a question on possible involvement of top-down processes from the prefrontal cortex (PFC) presumably 'guiding' target feature selection and evaluation. Given the speed of visual processing, it is a challenging question on how fast the top-down process can be initiated. In this study, we used coherence/phase EEG analysis to study interaction of evoked oscillations during visual processing. EEG activity was recorded using 128-channel EEG instrument (Electrical Geodesic, Inc.) in 11 right-handed individuals detecting animals as targets in natural scenes by key pressing (Thorpe et al 1996). Images were presented for 26 ms every 0.8-1.6 s. Data preprocessing included Independent Component Analysis for artifact removal. ERP time-frequency analysis (power, coherence and phase of evoked activity at frequencies 6-60 Hz) was done using FieldTrip software. The task caused an increase in beta-gamma activity at 100-200 ms in the occipital (OC) and prefrontal (PFC) cortices which was larger for targets and appeared in the PFC as two distinct bursts at 110 and 150 ms. Coherence at beta-gamma frequencies measured in reference to the right PFC showed significant functional connectivity between OC and PFC at 110 and 150 ms. The corresponding phase showed an advance of the OC at 110 ms indicating a bottom-up process. However, the PFC was leading the OC at 150 ms presumably reflecting a top-down flow of information. Oscillatory processes in the beta-gamma band may play an important role in long distance synchronization between the ventral visual processing stream and the PFC. The data indicate a 'phase switch' from advance to lag between the OC and the PFC within 100-150 ms after the stimulus, which we interpret as a functional switch from bottom-up to top-down processing culminating in the 'act of recognition' of a visual object. Our data on the early involvement of the PFC provide support for the model, which suggests that the PFC receives partly processed information from the early visual system and generates initial 'guesses' about the stimulus, which are conveyed as top-down influences to the higher centers of the visual system (e.g., the inferior temporal cortex) and facilitate recognition of visual objects (Bar 2003).

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2.5

How the Brain Deciphers Complex Olfactory Information: Lessons from the Honeybee

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Olfaction is a crucial sensory modality for all animals, but the mechanisms underlying processing and learning of complex natural scents are not well understood. This study aimed to investigate how an animal with a sophisticated sense of smell, the honeybee, learns and recalls information from natural scent mixtures. Using an associative learning paradigm, the Proboscis-Extension-Reflex Assay (PER), we trained three groups of honeybees (in each group, n=30) to three complex scent mixtures, each composed of 14 common floral odorants. After the bees had learnt the mixtures, we tested them with the individual odorants, to examine which ones they had learnt and which ones they ignored. We also examined innate preferences for the individual odorants. Our study showed that honeybees learnt a selection of 2 to 8 key odorants as representative for a scent mixture. Neither physico-chemical properties of odorants, nor innate odour preferences seem to play a role in key odorant selection, but concentration of an odorant in a mixture does, with odorants of high concentration being more likely to become a key odorant. The number and type of key odorants learnt was not fixed but depended on the composition of the scent mixture. The neural mechanisms underlying this process are likely to be found in the wiring of the first olfactory neuropil, the antennal lobes. This study demonstrates how brains reduce complex information to an effective sparse code thus reducing noise and processing requirements.

2.6

The Neurexin/Neuroligin Complex: Role in Sensory Processing in the Insect Brain

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Neurexins and neuroligins are adhesive proteins found on synaptic membranes of neurons. These binding partners produce a trans-synaptic bridge that facilitates maturation and specification of synapses. It is believed that there exists an optimal spatio-temporal code of neurexin and neuroligin interactions that guide synapse formation in the postnatal developing brain. The combinatorial nature of neurexin/neuroligin interactions is believed to be key to neuronal plasticity mechanisms such as learning and memory, and also a likely mediator of mental disorders such as autism and schizophrenia. A mismatch of neurexin and neuroligin partners across synapses in the brain presumably leads to loss of synaptic plasticity and/or erroneous wiring, resulting in behavioural and cognitive deficiencies. This study aimed to investigate the function of the neurexin/neuroligin adhesion system in model organisms with simple and accessible brains, such as insects. We showed that honeybees and flies have one *neurexin* gene matched to four/five conserved *neuroligin* genes, and that this complex is highly conserved across species, even between vertebrates and invertebrates, although gene number and isoforms may vary. Quantitative expression analyses using three different behavioural paradigms (sensory deprivation, associative learning, and amputation of the antennae) showed that *neurexin* and *neuroligin* expression was highly correlated with sensory input in adult honeybees. Further experiments using conditional expression of *neuroligin* and *neurexin* in *Drosophila* showed these molecules play a significant role in higher order visual processing. This study is one of the first to investigate a role for these molecules at an organismal and behavioural level.

2.7

Auditory Processing of Conspecific Vocalizations in the Auditory Midbrain of the Zebra Finch

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The zebra finch is a songbird species of which the male needs to learn its vocalizations from a tutor that is usually the father. The song is biologically important for both reproduction and social interactions, making perception a key parameter in singing behaviour. It is not surprising, then, that brain nuclei involved in song production and perception have been intensively investigated in recent times. However, most of these studies have addressed the issues of song selectivity and auditory processing in the forebrain, while only a few studies have focused on earlier stages of the ascending auditory pathway. While it is known that some forebrain nuclei will respond specifically to either the bird's own song or to conspecific vocalizations, where in the auditory pathway the emergence of this specificity originates remains unknown. However, since most auditory information reaching forebrain structures passes through the midbrain nucleus mesencephalicus lateralis, pars dorsalis (MLd), this nucleus is a prime candidate for early tuning to complex sounds, including conspecific signals. We have investigated the tuning properties of MLd neurons to either simple sounds such as white-noise and pure tones, or complex sounds, namely conspecific and heterospecific songs. Preliminary data show that neurons in MLd can be classified into two main categories: units that responded to all types of stimuli and units that showed a higher level of selectivity. These selective neurons could represent a first stage in the processing of complex song.

3.1

Gene-environment Interactions Mediating Experience-dependent Plasticity in the Healthy and Diseased Brain

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Huntington's disease (HD) is caused by a CAG trinucleotide repeat expansion encoding a polyglutamine tract in the huntingtin protein. HD patients exhibit cognitive deficits (culminating in dementia), psychiatric symptoms (e.g. depression) and motor abnormalities (e.g. chorea). In a transgenic mouse model of HD we have correlated early deficits of synaptic plasticity and hippocampal neurogenesis with onset of cognitive and sexually dimorphic affective (depression-like) abnormalities, and identified potential molecular mechanisms mediating this 'pathological plasticity'. We have also demonstrated that altered sensory, cognitive and motor stimulation can dramatically modify the disease process in HD mice. These modulatory effects may be mediated by experience-dependent changes in transcription of specific genes, protein trafficking, synaptic plasticity and adult neurogenesis. These findings have been extended by our group, and others, to a variety of different mouse models of brain disorders. For example, we have identified behavioural changes in knockout mice suggesting that specific neuronal signaling pathways implicated in cortical maturation are crucial for development of various cognitive and sensorimotor functions, which are known to be disrupted in schizophrenia. We have identified behavioural deficits that can be rescued by increased levels of environmental stimulation, providing evidence for gene-environment interactions and experience-dependent plasticity of relevance to the pathogenesis of schizophrenia. These and other findings may inform molecular mechanisms mediating brain and cognitive reserve, and the development of novel therapeutic approaches for specific neurological and psychiatric disorders.

3.2

Environmental Enrichment and Cerebrolysin Promote Recovery of Function After Anterior Thalamic Lesions in Rats

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The extensive neural connections between the anterior thalamic nuclei (ATN) with the hippocampal system may explain the overlapping amnesic syndromes associated with diencephalic and medial temporal lobe brain injury. In rats, lesions to the ATN or hippocampus both produce spatial memory deficits. We have shown that postoperative enriched housing partially reduces these spatial memory deficits. Here we examined whether Cerebrolysin (2.5ml/kg per day for 30 days), a peripherally administered compound with CNS neurotrophic properties, has similar beneficial effects or can augment the effects of enrichment in this lesion model. Both treatments were comparable in their effectiveness in ameliorating the ATN induced spatial working memory deficits in a cross-maze task. The combination of enrichment and Cerebrolysin treatment was more effective in inducing recovery on a 40-second delayed version of the working memory task. As in previous studies, ATN lesions also produced marked c-*fos* hypoactivity in the retrosplenial cortex, but this change was not reversed by either treatment. Indeed, enrichment tended to produce further hypoactivation in this limbic cortex. The current study is the first to show that pharmacological intervention can improve memory deficits after ATN lesions and suggests that a combination of Cerebrolysin and enrichment may enhance recovery of function. This recovery appears to be independent of c-*fos* status in the retrosplenial cortex.

3.3

Molecular Therapy of Obesity and Diabetes by Hypothalamic Administration of an Autoregulatory BDNF-expressing Construct

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Obesity and metabolic syndrome are serious health concerns with substantial morbidity and mortality and socioeconomic burden. Hypothalamic brain-derived neurotrophic factor (BDNF) is a key element in the regulation of energy balance. The aim of this study was to evaluate the therapeutic efficacy of BDNF by gene transfer in mouse models of obesity and diabetes. Gene transfer of BDNF led to marked weight loss and alleviation of obesity-associated insulin resistance. To ensure that BDNF protein expression was appropriately decreased as weight loss progressed, thus preventing cachexia, we developed a molecular autoregulatory system involving a single recombinant adeno-associated virus vector harboring two expression cassettes, one constitutively driving BDNF and the other driving a specific microRNA targeting BDNF. The microRNA element was controlled by a promoter (that controlling the Agrp gene encoding agouti-related peptide) responsive to BDNF-induced physiological changes. Hence, as body weight decreased and agouti-related protein is induced, microRNA expression was activated, inhibiting transgene expression. In contrast to the progressive weight loss associated with a nonregulated approach, this microRNA-approach led to a sustainable plateau of body weight after notable weight loss was achieved. This strategy mimics the body's endogenous physiological feedback mechanisms, thereby resetting the hypothalamic set point to reverse obesity and metabolic syndrome. In an ongoing study, the same treatment improved metabolic profile and conferred anxiolytic-like effect (with increased center to total distance ratio in the open field test) in aged (15 month old) mice, thus further supports the potential health benefits of this treatment.

Poster 4.1

Enhanced Adenosine Levels in the Rat Cochlea Ameliorate Noise-induced Injury

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Adenosine is a constitutive cell metabolite which may have a pivotal role in cochlear protection from oxidative stress. Adenosine kinase (AdK) is the key enzyme for the regulation of adenosine levels on both sides of the cell membrane and also provides the primary route for purine recycling. Down-regulation of AdK increases extracellular adenosine levels and thus activates P1 receptor-mediated neuroprotective pathways. Our study investigated expression levels of AdK in the cochlea exposed to loud sound and the effect of elevated adenosine levels on cochlear recovery from noise injury. AdK transcript and protein expression levels were determined in the noise-exposed rat cochlea exposed to broadband noise at 90, 100 or 110dBSPL for 24 hours. AdK mRNA transcript levels were transiently increased in the cochlea exposed to 90dBSPL, but remained unchanged in the cochleae exposed to higher noise levels. Semi-quantitative analysis of AdK immunofluorescence demonstrated a transient increase of AdK in cochlear tissues, which returned to the basal level after 72 hours. Systemic administration of a selective AdK inhibitor ABT-702 in the post-noise period resulted in partial recovery of hearing thresholds. This study suggests that elevated endogenous adenosine levels can aid cochlear recovery from noise damage. Adenosine kinase inhibition thus represents a prospective treatment strategy for acute noise-induced cochlear injury.

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Poster 4.2

Adenosine and CCPA Mitigate Noise-induced Cochlear Injury

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Previous studies have demonstrated prophylactic action of *R*-PIA, a broadly selective A_1 adenosine receptor agonist, in cochlear injury induced by exposure to noise and the anti-cancer drug cisplatin. Here, we report that post-noise administration of selective A_1 adenosine receptor agonists can induce recovery of hearing thresholds. Selective adenosine receptor agonists were delivered onto the round window membrane (RWM) of the rat cochlea, and sound-evoked auditory potentials (compound action potential, summating potential, auditory brainstem responses) were assessed before and after exposure to broad band noise presented for 24 hours at 110 dB SPL. Adenosine and adenosine receptor agonists (CCPA, CGS-21680 and Cl-IB-MECA) were applied 5 hours after noise exposure to the RWM and auditory thresholds were measured 48 hours later. Our results show that sound-evoked cochlear potentials in control (non-exposed) rat cochlea were not affected by local administration of adenosine receptor agonists. In the noise-exposed cochlea, however, hearing loss was substantially reduced after administration of adenosine (non-selective adenosine receptor agonist) and CCPA (selective A_1 adenosine receptor agonist). In contrast, auditory threshold shifts in noise-exposed animals were not affected by selective A_{2A} receptor agonist CGS-21680 and A_3 receptor agonist Cl-IB-MECA. We have also observed an up-regulation of A_1 receptors in the noise-exposed cochlea, suggesting A_1 adenosine receptors as novel targets for pharmacological interventions aimed at restoring noise-induced cochlear injury.

All studies were approved by the University of Auckland Animal Ethics Committee.

Poster 4.3

Conversion Disorder and Motor Preparation: Preliminary Findings

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Conversion Disorder (CD) affects voluntary motor and sensory function and involves unexplained neurological symptoms without an organic cause, unlike Malingering, where symptoms are intentionally produced or feigned. This research examined impairments in the generation of volitional movement associated with CD. Brain and muscle activity was measured during motor preparation in two individuals with CD with unilateral (left) arm paresis, in two neurologically normal individuals instructed to deliberately feign weakness, and in five normal individuals behaving as usual (controls). The effects of uncertainty on reaction time (RT), movement time (MT), muscle and cortical activity were investigated using a parameter precuing paradigm in which participants made rapid finger flexions to an imperative visual stimulus. A precue provided information about the response hand (left or right) or finger (index or middle finger). Feigners were instructed to imagine they had difficulty moving their left upper limb under one of two instruction methods: "eliminate the effort to move", or "move against an imaginary resistance". Overall, the RTs of CD patients and feigners were slower than the RTs of controls. For all participants, RT increased as the number of precued parameters decreased (p<.001). For control participants there was no difference in RT between hands. In feigners, RTs were greater in the affected limb. In one CD patient RT in the affected limb was longer when hand was specified in advance. The other CD patient showed consistently faster RTs in the affected limb. Feigners and CD patients both exhibited consistently longer MTs for the affected limb. There was no between-hand difference in MT for controls. An overall increase in RT in CD patients indicates slower motor preparation even when uncertainty is minimal. The effect is replicated by feigning indicating that slowness is not necessarily due to damaged neural mechanisms. Inconsistent RT outcomes between CD patients will be further explored by examining electrophysiological measures during movement preparation and execution.

Poster 4.4

On Data Management and Interoperability Within the Cognitive Neurosciences

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The synthesis of neuroscience data sets is highly complex facing huge data volumes, heterogeneity, context dependency and terminology differences. Further more, experimental data are reported in various formats, impeding the comparison of data sets for e.g. species, experimental designs and recording methodologies. Consequentially data synthesis within the neurosciences suffers from neglected, unintegrated though relevant data reports. Here we studied four cognitive neuroscientific reviews for their data synthesis. Primary sources were annotated for their subjects, stimuli, sensory modus, task, brain area (if applicable), recording methodology and functional attribution. We found that these reviews are based on functional semantic similarity (cf. attention, decision, visual perception…) and exclude cross-species issues, neglect experimental design specifics (e.g. sensory modus) and have no clear protocol on how to integrate different recording methods. In other words: semantic descriptions of experimental designs replace the experimental design and the actual data, which should be the sole basis used in data synthesis. Within the field there are currently three major strategies: annotation, storage and data retrieval. Where annotation is related to ontology design and the semantic web, storage and data retrieval are primarily orientated towards database design. Here we present our workbench Metaneva (www/metaneva.org) which is orientated towards single unit recordings of monkey and rat data (storage and retrieval), which also integrates our contributions to the 'Ontology for Biomedical Investigations' (www.obiontology.org) (annotation). Our prototype DB (Metaneva) is the first of its kind to provide an improved data storage, retrieval and matching of cognitive neuroscience animal data sets. This presentation therefore is about the ontological hiatus for data synthesis in the cognitive neurosciences, the ontological reply and its application onto neuroinformatics workbenches.

Poster 4.5

Fitness to Drive in Dementia: Neuropsychological Predictors and Driver Self-report

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This paper presents data from a dementia driving clinic established as part of an ongoing clinical service (and believed to be the first private dementia driving clinic in Australia). Using a large dataset (n=150), the author considers not only neuropsychological predication of driver outcome, but also pass-fail rates relative to specific dementia subtypes. Data are also presented to investigate the proposition that elderly drivers with known or suspected dementia are able to nominate the appropriate time to retire from driving. Data indicate that failed drivers with dementia fail to endorse items referring to reduced driving skill on a driving status questionnaire (Driving and dementia toolkit, Dementia Network of Ottawa-Carlton, 2001), and in fact their driving self evaluation is not significantly different from drivers who passed their on road reviews (U=319.0, z= -0.689, *ns*, r= -0.09). On the other hand, a clinician administered insight questionnaire (CERAD insight questionnaire, after Mendez & Shapira, 2005) demonstrated highly significant differences in insight in failed vs passed drivers with dementia (U=32.5, z=-5.73 p<.0001, r= -.78). Furthermore, loss of insight appears to be unrelated to severity of dementia (as measured by MMSE) (U=84.00, z= -.40, *ns*, r= -0.05) and subtype of dementia (Alzheimer's disease vs frontotemporal dementia) (U=25.5, z= -.899, *ns*, r= -0.123).

Poster 4.6

Profiles of Developmental Dyslexia With and Without Comorbid Mathematical Learning Disabilities (Dyscalculia)

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Developmental dyslexia and dyscalculia (reading and mathematics learning disabilities respectively) both have an estimated prevalence of around 6%, and a high comorbidity rate (20-60%). While dyslexia has been extensively characterised, little is known about how this comorbidity with dyscalculia is related to the severity and nature of deficits in reading. We tested four groups of adults, dyslexia only (RD), comorbid dyslexia and dyscalculia (RDMD), dyscalculia only (MD) and control, on a battery of tasks targeting core cognitive processes involved in reading and mathematics. Tasks included reading of irregular, regular, and non words, phonemic manipulation (deletion and reversal), rapid naming of letters and digits, and short term memory (digits and letter span). Preliminary results show that on sub-lexical reading tasks (irregular and nonwords), RDMD participants show greater impairment (vs. controls) than RD participants, whereas on lexical reading tasks (regular words) both groups showed equal impairment. MD participants showed equivalent performance to controls on all reading tasks. However, participants with any learning disability (RD or MD) showed impairments both in pure phonological processing (phoneme deletion and reversal) and rapid naming, again those with RDMD showing even greater impairment. Interestingly, RDMD participants were the only group to show impairment in both digit and letter span. Overall these findings support the hypothesis that comorbid learning disabilities are associated with greater impairments in core cognitive components which contribute to reading, and in particular with greater phonological impairments.

Poster 4.7

Influence of Cognition in Parkinson's Disease on Eye Movements

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To assess the impact of cognitive decline in Parkinson's disease (PD) on the latency and execution rate of rapid eye movements (saccades), fifty PD patients with varying cognitive impairment as measured by the Montreal Cognitive Assessment (MoCA) instrument were compared with 18 controls on self-paced and reflexive eye movement tasks. In the self-paced task, two targets at ±10 deg (horizontal) were simultaneously and continuously illuminated for 30s and the total number of saccades between the two within 30s were counted. In the reflexive task, reactive saccades to targets with amplitudes of 5, 10, 15, and 20 degrees and inter-stimulus-intervals (ISI) of 750, 1000, and 1400ms were examined in 108 mixed randomised trials with either no gap, a 200ms gap, or 200ms overlap between successive stimuli. For each reflexive task (standard, gap and overlap), the latency between saccade initiation and target onset was measured. MoCA score was related to self-paced count ($r = 0.36$, $p<0.05$) and reflexive saccade latency (all tasks r between -0.53 and -0.64, $p<0.0001$) for PD subjects. Self-paced count and saccade latency were also negatively related in the PD group (r between -0.38 and -0.48, $p<0.05$). No correlations were observed in either task for Controls due to a higher (26.8, SD 1.69) and restricted range of MoCA scores than PD subjects (23.6, SD 5.3). Our results indicate that cognitive impairment in PD is associated with both a reduced self-paced rate and longer reflexive latencies. We conclude saccades may be a useful biomarker of cognitive status and progression in PD.

Poster 4.8

Using Neuroanatomical Imaging to Learn About New Zealand's Endemic Birds

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Isolated from the world, New Zealand became a place where birds, in the absence of terrestrial mammals, evolved a diverse assortment of shapes, sizes and behaviours. We know, however, very little about these birds. Our lack of knowledge stems from difficulties associated with the study of these animals. Many have behaviours that make them hard to study (nocturnal, live in harsh environments) or are protected or culturally significant, meaning that traditional scientific studies are difficult. The brain and sensory organs are optimised to process information from the environment and underlie all animal behaviour. I have used imaging technique to examine these organs in two endangered birds, the kakapo and kiwi and the extinct moa. By combining different anatomical imaging techniques and developing 3D modelling methods, I have uncovered the anatomical features of the brain of the kakapo, moa and kiwi as well as the hearing and visual organs in kiwi. I have shown that in order to cope with night time activities, kiwi have not developed an elaborate visual system, but instead have adopted mammalian-like anatomical strategies based on smell, touch, and hearing. The methods I have developed in this study can now be used to uncover previously unknown traits associated with the brain and sensory organs of other endangered species so that conclusions can be drawn regarding their behavioural, ecological and sensory specialisation.

Poster 4.9

PMCA2 Gene Deletion Profoundly Disrupts the Morphology of Cerebellar Cortex

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It is known that plasma membrane calcium ATPase 2 (PMCA2) is particularly important for normal cerebellar function as PMCA2-knockout (KO) animals exhibit severe gait ataxia, a well-characterised neurological disorder of cerebellar origin. Accordingly, our investigation aimed to determine specifically in what ways PMCA2 gene deletion affect the cerebellum at the histological level, so as to help elucidate the precise roles of PMCA2 within the cerebellum. We used immunofluorescence to visualise the key cell types within the mouse cerebellum. Various morphometric parameters were quantified with the image processing program, Image J. Remarkably, it was noted that whilst the cerebellum of the PMCA2-KO mouse was significantly smaller (p<0.001) than its wildtype (WT) counterpart, the size of the forebrain did not differ significantly between the two genotypes. The morphology of the cerebellar Purkinje neurons (PNs) was profoundly affected by PMCA2 gene deletion. The PMCA2-KO PNs were characterised by their smaller size, thinner dendrites and reduced spine density (p<0.001 in all cases). PN dendritic arborisation also showed a marked decrease in branching complexity, as quantified by Sholl analysis (p<0.001, two-way ANOVA). Interestingly, we also identified a large increase in the number of parvalbumin-positive molecular layer interneurons (MLI) in the PMCA2-KO cerebellum that far offset the observed small increase in PN density (p<0.001 in both cases). We reasoned that this disproportional increase in inhibitory MLIs could imply a net increase in synaptic inhibition of PNs. In conclusion, PN excitability is likely to be mitigated in the PMCA2-KO cerebellum due to severely altered PN dendritic morphology as well as increased MLI-mediated synaptic inhibition of PNs. Reduced PN excitability is known to be instrumental in the pathogenesis of cerebellar ataxia.

Supported by a University of Otago Research Grant.

Poster 4.10

A Single Ethanol Binge on PN6 Produces Neuronal Loss in the Anterior Cingulate Cortex

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Foetal Alcohol Spectrum Disorder (FASD) is used to encompass all abnormalities attributed to foetal exposure to ethanol including central nervous system damage which may result in behavioural abnormalities. During the third trimester of foetal development, the brain is particularly vulnerable to ethanol toxicity. Animal models indicate that apoptotic cell death occurs within 12 hours of a single ethanol binge exposure in many brain regions including the medial prefrontal cortex – important for executive and social functioning. On PN6, male and female Long-Evans rats were randomly assigned to either a 6.0, 5.25 or 4.5g/kg ethanol or a sham procedure via intragastric intubation or a suckle control group. For one cohort, beginning on PN30, play fighting in pairs was video recorded for 20 minutes a day on 3 consecutive days. For a second cohort animals were deeply anaesthetised (sodium pentobarbital 100mg/kg i.p.) and perfused (4% paraformaldehyde) on PN365. Brains were removed, cryoprotected, frozen and sectioned in the coronal plane at 60µm. A random systematic set of sections was stained with thionin and unbiased stereological methods used to determine the number of neurons in the anterior cingulate cortex (Acc).The 6.0 and 5.25g/kg ethanol treated animals showed a 39.6% and 30.8% (P<0.05) mean decrease in Acc cells relative to sham-intubated control animals. The 6.0g/kg group had significantly less Acc neurons than the 4.5g/kg group (P<0.05).We hypothesize that the two high dose alcohol groups will differ in the rates of both initiation and response to play fighting attacks. A single ethanol binge on PN6 results in a dose-dependent depletion in Acc neurons, and this may be a causative factor if abnormal play fighting is seen in the high-dose ethanol groups. This may have implications for playground behaviour of children that to date has not been considered to be due to in-utero induced neuropathology.

Poster 4.11

Alterations in Postsynaptic Density Proteins with Neurodegenerative Disease in the Human Brain

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Glutamate receptors such as the N-Methyl-D-Aspartate receptors (NMDARs) and their bound Synapse Associated proteins (SAPs) are critical for normal brain function, including learning and memory, synapse development and plasticity. SAPs act as scaffolding molecules and are responsible for maintaining the structure of synapses, trafficking of receptors and activating signalling molecules. We hypothesise that these proteins could play an important role in the changes in synapse function that occur in response to neurodegenerative diseases such as Parkinson's Disease or Huntington's Disease. We performed immunohistochemistry to visualise the expression of SAP97, SAP102, PSD95 and the NR1 subunit of the NMDAR in human brain tissue from control, Huntington's and Parkinson's disease patients. We have found significant changes in the protein levels of SAP97, PSD95 and SAP102 in the dentate gyrus, CA1 and CA3 regions of the human hippocampus in response to Parkinsons and Huntingtons Disease. In conjunction with changes in SAP expression levels, we have also shown an increase in NMDA receptor levels in diseased states. We predict that the observed changes in the expression and localisation of the SAP proteins within the hippocampus of the human brain may underlie the loss of normal brain function in these diseases. These results provide insight into the altered subcellular mechanisms that could manifest into neurodegenerative diseases, providing potential for the development of more effective therapeutic strategies.

Poster 4.12

Analysis of Chimeric Affected-normal Sheep to Determine Intercellular Communication in Ovine Batten Disease

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Some forms of Batten (neuronal ceroid lipofuscinoses, NCLs) disease arise from defects in soluble lysosomal proteins. Others arise from defects in membrane proteins. There are good theoretical reasons for assuming that intercellular correction can be an important part of therapies in diseases resulting from soluble protein deficits but is unlikely to be effective in deficits of membrane bound proteins. A naturally occurring CLN6 form in South Hampshire sheep resulting from a membrane bound protein defect is presumed to have entirely intracellular pathology. In order to test this we created fifteen chimeric sheep by mixing cells from affected and normal sheep16-32 cell embryos and re-implanting the hybrid embryos for development. Brain development and clinical signs were monitored for up to 40 months. The extent of chimerism was assessed by skin coat patterns, morphometric analysis and DNA analysis of tissue samples taken at post-mortem. CT scanning showed that brains of a number of chimeric animals recovered from sub-normal to normal mass, and three clearly chimeric animals showed no signs of disease. The extent of chimerism varied between different tissues but not within different regions of the brain. Storage body analysis also revealed chimerism by some cells containing storage bodies, whilst others did not. These storage bodies also had an unusual fuzzy appearance indicative of a cross cell influence. These results suggest that this membrane protein defect may involve the processing of some factor able to influence other cells, and thus transplant and gene therapy may be possible even in the membrane bound protein forms of Batten disease.

Poster 4.13

Human Astrocytes Secrete Neurotrophic Molecules

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Astrocytes have many varied functions within the brain, including regulation of the blood-brain barrier, production of components of the extracellular matrix, and providing nutrients for neurons. A number of studies have found that astrocyte conditioned medium has neuroprotective activity, suggesting that astrocytes are capable of secreting factors which promote neuronal survival. However, most studies investigating the neuroprotective effects of factors secreted by astrocytes have used mouse or rat cells and there is increasing evidence for significant species differences in brain cell biology. In the present study the effect of astrocyte conditioned medium on neuron growth and survival was examined using the human NT2A and hNT cell lines, which show characteristics of astrocytes and neurons respectively. Astrocyte conditioned medium was found to increase the percentage of neuronal cells surviving the first three days of cell culture by 40 to 60 percent, compared to fresh or control medium. Interestingly, this effect was only seen when astrocytes were grown in medium containing serum, not when grown in serum-free medium. Neurite outgrowth assays performed on images acquired from hNT neuronal cells grown in conditioned medium or fresh medium for seven days showed that astrocyte conditioned medium increases both total neurite outgrowth and dendritic branching. These studies show that human astrocytes when grown in serum conditions produce factors that enhance the survival and growth of human neurons. Future work will attempt to identify the neuroprotective factors produced by human astrocytes and their mechanisms of action. Ultimately, identifying neuroprotective factors may lead to new ways to combat neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

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Poster 4.14

Targeting Calcium Signalling at Synapses with a Cyclic Peptide

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Healthy synapse function depends on precise spatial and temporal control of intracellular Ca^{2+} levels via a network of interacting proteins. Disruption of this Ca^{2+} signalling at synapses has been observed in many disease states, including Alzheimer's and after cerebral stroke. Post Synaptic Density-95 protein is a neuronal scaffolding protein that couples specific proteins at the post-synapse. We have recently identified an interaction between PSD95, the plasma membrane Ca^{2+} transporter (PMCA2) and the NMDA receptor at synapses in mouse brain. Given that synaptic plasticity depends upon exquisite control of localized intracellular Ca^{2+} flux, we hypothesize that this linkage of a Ca^{2+} export pump to a Ca^{2+} import receptor is critical to normal synaptic function. We have designed and synthesised a small cyclic peptide (R2) targeting the interaction site of PSD95 with PMCA2 to investigate the consequences of decoupling this partnership *in vitro*. Results using immunoprecipitation and GST-pulldown experiments show R2 can diminish the amount of PMCA2 binding to PSD95 in synaptic preparations and cell lysates. Immunofluorescent analyses of cultured neuronal SHSY-5Y cells using confocal microscopy demonstrate cell permeability and colocalisation of R2 with PSD95. To further examine the specificity of the interaction we will use live mouse hippocampal slices followed by immunofluorescent visualisation of R2 and PSD95. Subsequently we will examine the functional effects of R2 in the mouse hippocampus by whole cell and extracellular recordings. These studies will help decipher the mechanisms involved in synaptic Ca^{2+} regulation and the importance of coupling localised influx to efflux.

Poster 4.15

Alteration in Calcium Channel Expression at Cerebellar Synapses in the Ataxic and Epileptic Stargazer Mutant Mouse

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The stargazer mouse is a spontaneous recessive mutant that displays cerebellar ataxia and absence epilepsy. The phenotype results from a single mutation which causes a defect in the expression of the voltage-dependent calcium channel (VDCC) subunit γ2, termed stargazin. Stargazin is the predominant γ2- subunit in the cerebellum and is essential for delivering α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPARs) to postsynaptic membranes. Consequently, stargazer mutants lack functional AMPA receptors at cerebellar synapses. Recently, a functional association between AMPARs and VDCCs has been reported. The aim of our study was to investigate whether the loss of stargazin might also alter the expression levels of calcium channels at cerebellar synapses. Electron-microscopy, immunogold-cytochemistry and quantitative Western blot analysis were used to investigate the expression levels of calcium channel proteins in ataxic stargazers compared to non-ataxic littermates. Our results indicate that there is a significant reduction in the expression of postsynaptic L-type $Ca_v1.2$ VDCCs at cerebellar synapses in stargazer mutants, whereas presynaptic P/Q-type $Ca_v2.1$ VDCCs are unaffected. This is in contrast to stargazer hippocampal synapses where no differences were detected in $Ca_v1.2$ and 2.1 levels compared to controls. This is likely due to the compensatory effects of the subunit-γ8, which predominates in the hippocampus. These results suggest that the stargazin mutation may contribute to the loss of L-type VDCCs at postsynaptic sites. It is therefore possible that stargazin is involved in the trafficking of both AMPARs and VDCCs to the postsynaptic membrane or in the formation of a functional AMPA receptor–calcium channel complex at postsynaptic sites.

Poster 4.16

Subcellular Distribution Of L-Type Calcium Channel Subtypes in Rodent Hippocampal Neurons

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L-type calcium channels play an essential role in synaptic activity dependent gene expression and are implicated in long-term alterations in synaptic efficacy underlying learning and memory in the hippocampus. The two principal pore-forming subunits of L-type Ca^{2+} channels expressed in neurons are the $Ca_v1.2$ (α1C) or $Ca_v1.3$ (α1D) subtypes. Experimental evidence suggests that calcium entry through $Ca_v1.2$ and $Ca_v1.3$ Ca^{2+} channels occurs in close proximity to key signalling molecules responsible for triggering signalling pathways leading to transcriptional responses. Determining the subcellular distribution of $Ca_v1.2$ and $Ca_v1.3$ L-type channels in neurons is clearly important for unravelling the molecular mechanisms underlying long-term alterations in neuronal function. In this study, we used immunogold-labelling techniques and electron-microscopy to analyse the subcellular distribution and density of both $Ca_v1.2$ and $Ca_v1.3$ Ca^{2+} channels in rat and mouse hippocampal CA1 pyramidal cells *in vivo*. We confirm that both $Ca_v1.2$ and $Ca_v1.3$ channel subtypes are predominantly but not exclusively located in postsynaptic dendritic processes and somata. Both $Ca_v1.2$ and $Ca_v1.3$ are distributed throughout the dendritic tree. However, the smallest (distal) dendritic processes and spines have proportionally more calcium channels inserted into their plasma membrane than located within cytoplasmic compartments indicating the potential targeting of calcium channels to microdomains within neurons. $Ca_v1.2$ and $Ca_v1.3$ Ca^{2+} channels are located at the postsynaptic density and also at extrasynaptic sites. The location of L-type $Ca_v1.2$ and $Ca_v1.3$ channels in distal dendrites and spines would thus place them at appropriate sites where they could initiate synapse to nucleus signalling.

Poster 4.17

Activation of Group I Metabotropic Receptors Reduces Intracellular Pools of the AMPA Receptor Subunit, GluA1

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Learning and memory are dependent on changes in synaptic efficacy, a process which itself depends on the localisation of ionotropic glutamate receptors to the postsynaptic density (PSD), as trafficked there from extrasynaptic or intracellular pools. Activation of Group I metabotropic glutamate receptors (mGluR) has been shown to both depress transmission and prime subsequent long-term potentiation. To determine whether the effects of mGluR activation are due to trafficking of GluA1 (aka GluR1)-containing glutamate receptors between cellular compartments, cell surface, intracellular and whole cell protein extracts were isolated from young adult male Sprague-Dawley rat hippocampal slices treated with either the mGluR agonist DHPG (100 µM, 10 min; 20 min washout) or ACSF vehicle. Cell surface proteins were separated from the intracellular fraction by using a membrane impermeable biotin-NHS ester tag and pull-down post-lysis using Neutravidin-agarose beads. Western blot analysis showed a small but non-significant increase in surface GluA1 (1.13±0.09, n=9, p=0.4901; paired t-test), a significant decrease in intracellular GluA1 (0.78±0.04, n=10, p=0.0058) and no change in total levels of GluA1(0.99±0.04, n=10, p=0.7894). No changes in total (0.99±0.04, n=9, p=0.8896) or intracellular (1.01±0.02, n=9, p=0.8668) GluA2 were detected, suggesting that DHPG treatment promotes specific trafficking of GluA1 receptors to the cell surface. As we were unable to detect an increase in GluA1 levels in PSDs isolated from DHPG-treated slices (0.91±0.07; p=0.4502; n=5), this study suggests that mGluR priming of LTP might be mediated by an increase in the extrasynaptic levels of GluA1.

Poster 4.18

Ultrastructural Analysis of Experience-dependent Changes in Vesicular Zinc in the Murine Barrel Cortex

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In the brain, a portion of the divalent cation zinc is housed within the synaptic vesicles of a subset of glutamatergic neurons. This 'vesicular zinc' is involved in a number of neuronal processes including cortical plasticity. In our laboratory, we have previously shown how manipulations of sensory input from the vibrissae, which results in robust plastic changes in the barrel cortex, is correspondingly accompanied by large alterations in vesicular zinc levels. Here, we employed electron microscopy in order to investigate the ultrastructural foundations for these changes in the levels of vesicular zinc. Namely, we were interested in establishing if these changes were driven by alterations in the number of zinc containing vesicles in a synapse and/or the total number of vesicular zinc containing synapses. To do this, male C57Bl/6 mice were lightly anesthetized and all mystacial vibrissae were removed unilaterally. Forty-eight hours later, the mice were perfused and the brains processed for ultrastructural analysis. We found that the number of synapses increased in the deprived barrels (non-deprived = 0.84 synapses/µm^3, deprived = 1.43 synapses/µm^3, p<.01). Additionally, we observed a trend towards an increase in the number of vesicles containing zinc in a synapse (non-deprived = 1.85 zinc containing vesicles/synapse, deprived = 3.86 zinc containing vesicles/synapse, p=.066). As zinc is able to modulate the activity of many receptors and secondary messenger systems, such changes in the complement of vesicular zinc would have large implications the neurotransmission in these neurons. Thus, these changes provide a mechanism for the modulation of experience-dependent plasticity by vesicular zinc.

Poster 4.19

Developing a Human Brain Tissue Microarray Platform

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Tissue Microarray (TMA) is a method for arraying large numbers (10-1000's) of small cylindrical cores of tissue (0.6mm to 2 mm in diameter), usually taken from paraffin embedded tissue blocks, by insertion into a blank paraffin block. We have recently established a human brain TMA facility at The University of Auckland. The Tissue Microarrayer (Advanced Tissue Arrayer, ATA100, Life Sciences), provides a way to precisely construct a TMA and compare up to a 1000 brain tissue samples at one time. Arrays are cut coronally and mounted onto microscope slides for histological, immunohistochemical and/or *in situ* hybridization analysis. Once processed in this standardized fashion images are acquired using the high-throughput automated Discovery-1 microscope system and analysed by High Content Analysis using automated Metamorph image analysis software. This new platform will allow for high throughput, standardized and objective studies to be performed to identify abnormalities in cell morphology and biochemistry (eg: changes in protein and/or mRNA expression) in a range of brain disorders as well as the expression and distribution of various proteins and genes in the normal human brain. The advantages of this TMA approach over traditional methods are standardization (eg: all brain spots are treated at the same time with the same reagents) and increased throughput of tissue processing, image acquisition and analysis and saving time, reagents and precious human brain tissue. This new platform will greatly advance New Zealand's capabilities in studying the normal and diseased human brain.

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Poster 4.20

Brain-Derived Neurotrophic Factor val^{66}met Polymorphism is Associated With Memory and LTP in Human Visual Evoked Potentials

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Long term potentiation (LTP) is a long lasting enhancement of synaptic communication and is the principal candidate for the mechanism of memory. LTP has been studied extensively at both the cellular and molecular level in animals. Only recently have models been developed that allow *in vivo* induction and measurement of LTP in humans. LTP involves a complex cascade of events, with brain derived neurotrophic factor (BDNF) identified as an important modulator of synaptic plasticity in humans. A single nucleotide polymorphism in the *BDNF* gene resulting in a valine-to-methionine substitution at codon 66 (val66met) has been shown to affect activity-dependent secretion of BDNF and is associated with lower performance in memory tasks. In the present study, we tested whether *BDNF* val66met polymorphism was associated with the induction of LTP-like changes in visual evoked potentials. We also tested whether LTP-like changes and *BDNF* val66met polymorphism was predictive of memory. Pilot results suggest individuals containing the polymorphism (Val/Met, Met/Met) had significantly lower LTP-like changes as indexed by amplitude changes of a late phase of the N1 component of visual-evoked potentials. Also, Val/Met and Met/Met individuals performed significantly worse than Val/Val individuals on measurements of visual memory as indexed by the Wechsler Memory Scale. These results add further weight to the suggestion from earlier studies that the LTP-like phenomena that is induced and measured by visual stimuli is indeed LTP, and provides further evidence for LTP being the mechanism underlying memory.

Poster 4.21

Alterations in Hippocampal Synaptic Plasticity in a Maternal Immune Activation Animal Model of Schizophrenia

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Changes in memory, due to functional alterations in neurotransmission and synaptic plasticity, could underlie the cognitive deficits in schizophrenia. We examined this hypothesis by recording hippocampal long-term potentiation (LTP) in an animal model. Epidemiological studies have shown that prenatal exposure to infection is associated with an increased risk of schizophrenia in adulthood. This effect is mimicked in the maternal immune activation (MIA) model by inducing an immune response in pregnant dams (gestational day 15) with the synthetic cytokine inducer polyinosinic-polycytidilic acid. Hippocampal plasticity was assessed in awake, freely-moving adult MIA and control male offspring by recording field potentials from the dentate gyrus while stimulating the perforant path. Input-output analysis of basal synaptic transmission revealed no differences between groups. The degree of paired-pulse depression of the field EPSP was also not affected by MIA treatment. However, there was a significant group x interpulse interval interaction for the population spike, with larger paired-pulse ratios at 60-80 ms interpulse intervals in MIA animals, suggestive of a decrease in the inhibition/excitation ratio. Five trains of high-frequency stimulation (400 Hz) induced mild LTP which did not differ between groups. With 20 trains of stimulation however, the MIA group showed significantly longer-lasting LTP than controls over a three week post-tetanus period. MIA animals also showed enhanced reversal memory in the Morris water maze at longer retention intervals. These data suggest that MIA causes changes to synaptic plasticity in the hippocampus, which is most likely underpinned by an imbalance in excitatory and inhibitory neurotransmission.

Supported by the New Zealand Health Research Council.

Poster 4.22

Regulation of Synaptic Plasticity by SAP97 Isoforms

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Accumulated evidence suggests a major role for postsynaptic scaffolding proteins from the membrane-associated guanylate kinase (MAGUK) protein family in regulating synaptic alpha amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA) receptor and N-methyl-D-aspartate (NMDA) receptor trafficking. Synapse Associated Protein 97 (SAP97), a member of the MAGUK family, has been involved in the correct targeting and clustering of glutamate receptors at postsynaptic sites. In the present study, we have used paired whole cell patch clamp electrophysiology to demonstrate that the effects of two postsynaptic, N-terminal isoforms of SAP97 on chemically-induced LTP and LTD in dissociated hippocampal neurons. We found that expression of α or β SAP97 prevented the induction of LTP. Moreover, LTD resulted from the LTP stimuli. The induction of LTD was not affected by either isoform. We identified that NMDA receptor excitatory postsynaptic currents were depressed in β SAP97 - expressing hippocampus neurons but not in α SAP97 - expressing hippocampus neurons. These results indicate that N-terminal splicing of SAP97 isoforms can control changes in synaptic strength by regulating the localisation of NMDA-type glutamate receptors at the postsynaptic density.

Poster 4.23

Inter-ocular Transfer of Long-term Potentiation

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Long-term potentiation (LTP), an integral mechanism that underlies learning and memory, has been investigated extensively at several biological levels in animals. Until recently, LTP was only successfully demonstrated in humans in isolated cortical tissue acquired from patients prior to surgery. LTP so studied exhibited properties that are identical to those found in animals. However, we have recently developed a paradigm for non-invasively inducing LTP in human visual cortex by using rapid visual stimulation. We have previously suggested that the locus of synaptic LTP is neocortical. In the study reported here we further test this assertion by testing whether inter-ocular transfer of LTP of evoked visual EEG potentials occurs. We evenly allocated participants to conditions in which either their left or right eye received an LTP-inducing stimulus. Participants received either a horizontal or vertical stimulus presented at a rate of 9Hz during the LTP-induction condition. Four pre-induction and four post-induction conditions, where participants were randomly presented with horizontal and vertical stimulus flashed at a rate of 1Hz, were employed. Visual evoked potential (VEP) recordings were taken separately for each eye. To help counter-balance potential confounding factors, participants were allocated such that half of them began VEP recording in the eye that received the LTP induction stimulus, and half that began VEP recording in the eye that did not. Results showed a significantly larger N1b response after the LTP induction, even in the VEP recordings obtained from the eye that did not receive an LTP-inducing stimulus ($p=0.03$). Hence, there is inter-ocular transfer of LTP of evoked visual EEG potentials. Therefore, this suggests that LTP is located in the visual neocortex rather than the ascending visual pathways.

Poster 4.24

Identification of Cholinergic Interneurons in Rat Striatum from the Extracellular Spike Waveform and Firing Pattern

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Tonically active neurons (TANs) in the mammalian striatum show a pause in their ongoing firing activity in response to reward related stimuli. This pause response develops through learning and becomes expressed synchronously by TANs located throughout the striatum. Intracellular recordings of this cell type are hard to obtain because of their rarity (≈1% of neurons) in the striatum. The aim of this study was to test the hypotheses that (i) extracellular recording techniques result in a higher yield of recordings from cholinergic interneurons than intracellular methods reported previously, and (ii) striatal cholinergic interneurons can be differentiated from other striatal neurons based on the average spike waveform and firing pattern. Male Long Evans rats, weighing between 250g and 380g were anaesthetised with urethane and neuronal activity in the striatum recorded with microelectrodes pulled from thick-walled borosilicate glass capillaries. Of 39 neurons recorded in total, all neurons recorded with low resistance electrodes (8-15MΩ, n=14) fired spontaneously. In contrast, the majority of neurons recorded with high resistance electrodes (16-33 MΩ, n=25) fired only in response to an oscillatory stimulus pulse delivered through the pipette. According to the average spike waveform and firing pattern of the spontaneously active neurons, three were considered to be cholinergic interneurons and another three were considered to be fast spiking interneurons. However, two separate models with parameters based on the average spike waveform and firing rate failed to clearly differentiate cholinergic interneurons from other neuronal cell types recorded in the striatum. Additional morphological evidence will be required to confirm neuronal cell types and to validate criteria used to differentiate cells based on extracellular recording characteristics.

Poster 4.25

A Microdialysis Study of Agmatine: Extracellular Pharmacokinetics in Rat Brain

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Agmatine, a metabolite of arginine, is a novel neurotransmitter. Our recent research has demonstrated the facilitating effects of exogenous agmatine on learning and memory in both young and aged rats in the task-dependent manner. It has been documented, however, that agmatine has limited permeability through the blood-brain barrier (BBB) and has a short half-life. The present study aimed to further address these issues by investigating the time course of extracellular agmatine level changes in the dorsal hippocampus in 3 (young; n = 4) and 24 (aged; n = 7) months old rats following intraperitoneal injection of agmatine (40 mg/kg) using the *in vivo* microdialysis technique. Five days after the surgical implantation of a guide cannula, a microdialysis probe was inserted to the dorsal hippocampus and equilibrated with dialysis buffer. Rats were dosed with saline (1 ml/kg) and then agmatine (40 mg/kg) in 60 min. The microdialysate samples were collected and the concentrations of agmatine were determined by liquid chromatoghraphy/mass spectrometry. The same experimental procedure was repeated after 4 days of agmatine treatment (40 mg/kg, once daily). There were significantly increased extracellular agmatine levels immediately after the administration of agmatine (but not saline), with the peak level at 10-25 min followed by a decline over time with an elimination half-life of approximately 12 h in both young and aged rats on both days. These preliminary results suggest that agmatine readily crosses the BBB in the rat. Since agmatine functions as a neurotransmitter, long-lasting elevation of extracellular agmatine may have significant impacts on neurotransmission and animal behaviour.

Supported by the Neurological Foundation of New Zealand and a University of Otago Postgraduate Scholarship.

Poster 4.26

The Cellular Effects of Smoking on Monoamine Transporters

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Cigarette smoke is the leading cause of preventable illness worldwide and results in 5000 deaths per year in New Zealand alone. Current smoking cessation therapies are largely ineffective with reported success rates as low as 7% for nicotine replacement therapies. The dopamine, serotonin and nor-epinephrine transporters (DAT, SERT and NET) have been shown to be regulated by many drugs of abuse. Despite this, little information is available on the regulation of these transporters by nicotine and cigarette smoke. This study has investigated the effects of nicotine (0.35 and 3 mg/kg, i.p.) and total particulate matter (TPM) from cigarette smoke on mRNA and protein expression of SERT, DAT and NET in key brain regions of the rat using real time RT-PCR and Western Blotting. Results show no change in the expression of SERT or DAT mRNA in the dorsal raphe nuclei, substantia nigra or ventral tegmental area in response to either nicotine or TPM (n=7-8). Interestingly, nicotine alone shows no change in NET expression in the locus coeruleus but TPM showed a significant decrease in NET mRNA expression in this area ($p<0.05$). No significant change in NET protein expression has been found in the hippocampus or prefrontal cortex in response to nicotine or TPM (n=6). This work has increased our understanding of the cellular effects of smoking and in future may lead to the development of better cessation therapies.

Poster 4.27

Modulation of Dopamine Transporter Function by Potential Anti-addiction Compounds

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Drug abuse is a major social and economic problem affecting 30% of New Zealanders and costing billions of dollars annually. The dopamine transporter (DAT) functions to remove dopamine from the synapse following drug taking, resulting in termination of the drug's rewarding effects. The kappa opioid receptor (KOPr) has been shown to modulate DAT function so is a potential target for the development of anti-addiction therapies. Traditional KOPr agonists cannot be used as therapeutics due to their undesirable side effects. Salvinorin A (SalA), a novel KOPr agonist, may provide better tolerated anti-addiction therapies, although further investigation into its cellular actions is needed. We have therefore investigated the effects of traditional and novel KOPr agonists on DAT function and show that activation of KOPr increases DAT function. Live cell confocal microscopy studies using cells transiently expressing KOPr and DAT proteins, showed that treatment with traditional KOPr agonist, U50,488H (10 µM) and Sal A (10 µM) increased uptake of the fluorescent substrate ASP^+ (23% and 45% respectively, One way ANOVA, Bonferroni post test). U50,488H also increased ASP+ binding by 50% ($p < 0.001$), whereas SalA had no significant effect. DAT function was also measured in striatal rat brain tissue. KOPr activation by U50,488H, or Sal A resulted in a 90% and 100% increase in DAT function respectively ($p < 0.01$, One way ANOVA, Bonferroni post test). Novel analogs of SalA are also being tested as they become available. These studies may help elucidate the cellular mechanism underlying the anti-addiction effects of these compounds, and will aid in developing better tolerated therapeutic compounds to treat addiction.

Poster 4.28

Acute Effects of Benzylpiperazine (BZP) on Cognition and Executive Functioning Using Functional Magnetic Resonance Imaging (fMRI) and the Stroop Paradigm: Results From the Pilot Study

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Party pills containing BZP have been marketed as safe and legal alternatives to illicit recreational drugs, such as 3,4-methlenedioxymethamphetamine or methamphetamine. BZP is a stimulant with similar effects to dexamphetamine (DEX). There is a paucity of information known about the effects of BZP in humans. This study is a randomised double blinded cross-over trial determining the effects of BZP on impulse control and executive function in comparison to DEX and Placebo using fMRI. 3 healthy right-handed participants aged 18-40, completed the Stroop Paradigm whilst being imaged by fMRI, 90minutes after an oral dose of BZP (200mg), DEX (20mg) or Placebo. The participants were tested with each condition on a separate occasion. Echo-planar images were collected on a 1.5T scanner (Siemens Magnetom Avanto 1.5 T, Germany).Data was pre-processed, analysed with SPM5 and then used to identify regional activation. Placebo caused changes in activation in the Cingulate Cortex for the Stroop effect (incongruent-congruent), and for incongruent versus control and congruent versus control ($p=0.05$). DEX caused activation change in the Dorsolateral Prefrontal Cortex (DLPFC) for all of these conditions, activation was accentuated in the Stroop Effect ($p=0.05$). BZP showed no significant activation. Reaction times (RT) and accuracy were compared by the condition and drug state. Accuracy was reduced by BZP and DEX compared to Placebo. There was no trend with RT. Results from this pilot study suggest BZP does not display characteristics typical of other psychostimulants such as DEX.

Poster 4.29

Distribution of 'Party Pill' Drugs BZP and TFMPP in the Brain and Other Tissue

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Benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are the active ingredients in the majority of piperazine-based 'Party Pill' drugs with measurable effects in the brain including stimulant effects similar to amphetamine and hallucinogenic effects similar to LSD, respectively. The plasma pharmacokinetic properties of these drugs have been described. However, little information is available on the distribution of these drugs in the brain and other tissues. Female Sprague-Dawley rats were chosen as a good animal model based on in vitro studies. The animals were given an intraperitoneal dose of BZP or TFMPP or BZP plus TFMPP (1 mg/kg in saline 1 mL/kg) and were sacrificed at either 30 minutes or 60 minutes (n = 4 for each treatment and time). Tissue including blood plasma, brain, liver, kidneys, lungs and heart were collected. The quantification of BZP, TFMPP and their metabolites in extracts of these tissues was carried out using liquid-chromatography with mass spectrometry (LCMS). Tissue concentrations of both drugs were greater than plasma concentrations with the kidneys and lungs displaying the highest concentrations of BZP and TFMPP respectively. Metabolite concentrations were highest in the liver. A similar pattern of distribution was seen in the single drug and combined drug treatments. These results demonstrate a great disparity between plasma and tissue concentrations of these drugs and highlight the need for in-depth tissue distribution studies if the pharmacology of these drugs is to be properly understood.

Poster 4.30

The Effects of Oral Benzylpiperazine on P300 Amplitude in Right-handed Males and Females

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"Party pills" containing Benzylpiperazine (BZP) used to be widely and legally available as recreational drugs in New Zealand. Early work (1973) on human subjects suggested that 100mg of BZP produced subjective and physiological effects similar to 10mg of dexamphetamine. More recently, we found a similarity between the subjective and physiological effects of BZP and those of other commonly known stimulants, such as amphetamine and MDMA. Here we report on the effect of BZP on the P300 potential, which is widely employed in the assessment of drugs. As Hoffman and Polich (1999) found that males have lower P300 amplitude than females, and there is evidence for sex differences in susceptibility to addiction and response to stimulants, we investigated whether there would also be a sex effect. In two double-blind, placebo-controlled trials the electrophysiological effects of BZP were investigated in healthy right-handed males and females aged between 18 and 40. Participants were tested before and 1.5-2 hours after administration of a single oral dose of BZP or placebo using a 128-channel electroencephalogram (EEG), which recorded event-related potentials (ERPs) during an auditory oddball task. Statistical analysis showed significantly lower P300 amplitude in the male BZP group compared to male controls ($p<0.01$) whereas there were no significant changes between the female BZP group compared to female controls ($p>0.05$). Thus, BZP administration caused a significant reduction in the amplitude of the P300 ERP in males but not in females. Sex differences in the response to stimulants are controversial; however these results suggest that it is possible that effects of BZP are sensitive to sex.

Poster 4.31

Effect of Δ-9-Tetrahydrocannabinol on Adolescent Learning and Memory

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Marijuana is the most widely used illicit drug in the world, the use of which commonly commences in the adolescent period. The main psychoactive constituent of marijuana, Δ9-Tetrahydrocannibinol (THC) has repeatedly been reported to affect spatial learning and memory tasks when assessed in the Radial Maze. Even though marijuana is commonly used by adolescents few studies have investigated the effects of THC on adolescent learning and memory. The effects of THC exposure in the adolescent period was investigated in male juvenile Sprague-Dawley rats (4 – 6 weeks old) using the radial maze. Animals were randomly assigned to either THC treated or sham-treated control groups and their performance followed over 26 days. At the end of the study period THC animals committed significantly more errors ($p=0.0092$) and made more reference memory errors ($p=0.0115$) than sham treated controls. Working memory errors after 26 days, as well as all error types at the end of the juvenile period (after 14 days of training) were not significantly different between THC and sham treated groups ($p>0.05$). Our data support the hypothesis animals treated with THC throughout the adolescent period exhibit delayed learning as reflected by more reference memory errors, but not working memory errors, after 26 days of training although this deficit was not observed at the end of the adolescent period (14 days).

Poster 4.32

Valproic Acid Enhances Microglial Phagocytosis of Amyloid-$\beta_{1\text{-}42}$

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Alzheimer's disease (AD) is a prevalent neurodegenerative disorder manifested by memory loss, confusion and changes in mood. A principal pathology of this debilitating disorder is extracellular deposits of amyloid-β (Aβ) protein. The 'amyloid hypothesis' postulates that a build-up of Aβ protein is responsible for neuronal loss and the ensuing symptoms of AD. One possible mechanism of Aβ clearance, and hence AD therapy, is phagocytosis of Aβ protein by microglial cells. Microglia are the brain's resident immune cells and phagocytosis is one of their innate functions. We are interested in identifying molecules that augment microglial-mediated phagocytosis of Aβ protein. We used the rodent BV-2 microglial cell line which readily phagocytose fluorescent latex beads and synthetic $A\beta_{1\text{-}42}$ peptide. BV-2 cells treated with the neuroactive drug valproic acid (VPA) showed greatly enhanced phagocytic activity for both latex beads and Aβ. VPA also reduced microglial viability by inducing apoptosis, as previously reported. Furthermore, we developed an automated method to quantify microglial phagocytosis. The relevance of these *in vitro* results to the treatment of AD is unclear but further investigation into the effects of VPA on the clearance of Aβ through enhanced microglial phagocytosis is warranted.

Poster 4.33

Does MIS Regulate the Bed Nucleus of Stria Terminalis?

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The bed nucleus of stria terminalis (BST) is a sexually dimorphic nucleus, which in humans is involved in gender identity. The principal nucleus of the BST (BSTp) is also dimorphic in rodents and is regulated by testosterone: dihydrotestosterone virilises females, whereas males which lack the androgen receptor have a feminised nucleus. Paradoxically, the sex difference in the BST of humans and rodents emerges when developing males have little or no testosterone. This could indicate that the BST is regulated by more than one male signal, with the testicular hormone Müllerian Inhibiting Substance (MIS) being a potential regulator as plasma MIS is high when testosterone is low. This possibility has been examined by using stereological techniques to determine the size and number of calbindin-D28k-positive (CB^{+ve}) neurons in the BSTp of 20-week-old $Mis^{-/-}$ and $Mis^{+/+}$ mice. The hypothalami were serially sectioned at 20 µm, and every third section stained with anti-CB using a free-floated procedure. The data were analysed by two-way ANOVA for sex and genotype differences, followed by *Student-t* tests. The initial data suggests that BSTp is incompletely virilised in male $Mis^{-/-}$ mice. Both the size and number of CB^{+ve} neurons were highly dimorphic, with a male bias ($p=0.0006$ & $p=0.0001$, respectively, $n=3$). The extent of the male bias in cell number was less in the $Mis^{-/-}$ male than their wild-type littermates ($p=0.031$), whereas MIS genotype had no effect on the size of the CB^{+ve} cells. This suggests that the BSTp consists of a mixture of MIS-dependent and androgen-dependent neurons and/or that MIS and androgens regulate BSTp neurons at different stages of development.

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Poster 4.34

MRI Volumetric Analysis of the Putamen and Caudate Nucleus in Parkinson's Disease

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Parkinson's disease (PD) is characterized by the loss of nigrostriatal dopaminergic projections. It is, however, unclear if this loss leads to volumetric changes in the striatum (putamen and caudate nucleus) *in vivo*. Previous studies have reported both significantly reduced and unchanged putamen and caudate nucleus volumes in PD. The aim of the current research was to investigate the striatal volumes in our local PD population. Total brain volume and the volumes of the putamen and caudate nucleus (head and body measured separately) were measured from high-resolution 3D T1-weighted magnetic resonance images taken from 60 PD patients and 28 controls. Volumes were defined using manual tracing methods in MRIcroN software. Both total putamen and caudate nucleus volumes (left and right combined) were significantly different between PD and controls when corrected for total brain volume, age, years of education and mini mental state examine scores (putamen; $p=0.03$, caudate nucleus; $p=0.01$). Further investigation of the volumes in relation to disease and cognitive status will be undertaken.

Poster 4.35

Characterizing Mild Cognitive Impairment in Parkinson's Disease

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The cumulative prevalence of formal dementia in patients with Parkinson's disease (PD-D) is 80%. There is growing interest in "mild cognitive impairment" (PD-MCI) to predict patients at greatest risk and to test novel treatment strategies. We assessed cognition in a 58 non-dementing PD patients and a comparison group of 34 age and education-matched controls. Seventeen of these patients (29%), met our criteria for PD-MCI, which required two sources of evidence of impairment at 1.5SD or more below age-corrected norms within at least one of four neuropsychological domains (executive function, attention and working memory, memory and visuoperceptual/visuospatial). PD-MCI assessments have, however, varied markedly across studies. When a more lax criterion for MCI was used, a significant number of our 41 "unimpaired" PD patients were categorized as MCI (78% and 49% if one measure at 1SD or at 1.5SD, respectively; 27% if two measures at 1SD; McNemar test, p values <0.0001). With more stringent criteria, a significant number of our 17 PD-MCI patients were categorized as unimpaired (35%, one or two measures at 2SD, p <0.031). Our criteria found 3/34 controls who were "MCI" (9%), but more lax criteria produced an unrealistic number of "MCI" cases for one measure at 1SD or at 1.5SD (68% and 39%, respectively, p <0.0001); the increase for two measures at 1SD was 13% (p <0.13). We propose that two measures within a cognitive domain, preferably at the standard criterion of 1.5SD below norms, provide a more realistic classification of MCI in PD.

Poster 4.36

Short-term Music Training Effects on Sensorimotor Integration

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Musicians undergo extensive training which enhances established links between auditory and motor areas of the brain. Previous research has indicated that auditory-motor associations form not only as a result of long-term training, but also after a very brief training period. After short-term training, it has been demonstrated that premotor areas are active during passive listening of trained music, suggesting that these mappings can rapidly become automatic. It has been suggested that these associations rely on activity in mirror neuron systems which are heavily dependent on actual sensorimotor experience. However some propose that sensorimotor experience is not required to activate this system, as listening to rhythm may be enough to demonstrate involuntary motor coactivation during listening. We aim to investigate the effects of short-term auditory-motor training on sensorimotor networks. We ask whether motor coactivation during passive listening after training occurs specifically for acquired sound-action mappings. Subjects participated in short-term adaptive training in which they were trained to play back randomly-generated basic piano melodies. Action-observation studies in this field have associated changes in *mu*-rhythm activity with the mirror neuron system. We utilised this technique in our action-listening study, and investigated the *mu*-rhythm, using electroencephalography, in order to detect involuntary motor coactivation during passive listening to melodies and rhythms. Pilot results showed that short-term auditory-motor training effects can be observed as changes in *mu*-rhythm activity, and these effects are found only for piano tones that had been used during training. When participants listened to rhythms there was no observable change in *mu*-rhythm activity from rest. These initial findings support the hypothesis that specific sensorimotor experience is important for the mirror neuron system.

Poster 4.37

Language Lateralisation in Late Proficient Bilinguals: A Lexical-decision fMRI Study

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With the development of neuroimaging techniques, it has become possible to investigate the role of each hemisphere and the cortical networks involved during language processing in bilinguals who possess the ability to speak and use more than one language. This has become an important area of research as it has been shown that more than half the world's population is now bilingual. In this study, functional magnetic resonance imaging (fMRI) was used to explore the hemispheric activations of eight late proficient bilinguals when using their first language, Macedonian (L1), and their second language, English (L2). Nine English-speaking monolinguals were also recruited as controls. A lexical decision task with five conditions (nonverbal task, letter case decision task in L1 and L2, regular word decision task in L1 and L2) was used to assess the degree of language lateralization in the bilingual subjects. Preliminary analyses suggest that there is a greater bilateral hemispheric activation in bilinguals when L2 is used as opposed to the typical left hemisphere pattern that occurs with L1. Greater activation was observed in areas such as the right inferior frontal gyrus, right fusiform gyrus, and right superior temporal gyrus. Overall, bilinguals also showed greater activation when compared to monolinguals in both L1 and L2. These results agree with earlier studies suggesting that bilinguals are less latereralised in their L2 compared to their L1, and also compared to monolinguals.

Poster 4.38

Theta in the Perception of Space and Time

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The relationship between time and space in the human mind has generated interesting but inconsistent research. Initial investigations suggested that perceptions of space were based on those of time (Clayton & Habibi, *Journal of Experimental Psychology: Learning, Memory, and Cognition* 17:263-271 (1991)) while a recent behavioural article using working memory (WM) tasks argues that the perception of time relies on the perception of space (Casasanto & Boroditsky, *Cognition* 106:579-593, (2008)). In either case the two perceptions should use a common brain region. Existing literature and the common finding of theta gating during WM tasks (Raghavachari et al., *The Journal of Neuroscience* 21:3175-3183, (2001)) suggest that the hippocampus is a likely candidate. As such EEG analysis focussing on theta activity was conducted during exposure to WM tasks separating time and space in stimulus displays. Three different conditions using displays of five coloured circles were used. In the first condition each circle was presented sequentially in a single location, this was the time only condition. In the second condition, the space only condition, the circles were presented simultaneously in different positions. In the final condition, the combined condition, the circles were presented sequentially in different positions. After a brief retention interval subjects were required to indicate which of two circles had appeared first/second in the time condition and which had been left/right most in the space condition. Either question could be asked in the combined condition. In pilot data theta activity during this task has not differed as a result of condition supporting the notion of a common neural representation, potentially involving the hippocampus (Kirk & Mackay, *Cortex* 39:993-1008, (2003)), for time and space.

Poster 4.39

Wernicke-Korsakoff Syndrome: With or Without Alcohol

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Wernicke-Korsakoff syndrome (WKS) is most commonly reported in association with alcohol abuse or dependence. Although there is general acceptance that the acute phase of WKS is due to thiamin deficiency, there has been controversy about the aetiology of the chronic phase, also known as Korsakoff's amnesia. It has been argued that thiamin deficiency alone cannot account for Korsakoff's amnesia. This hypothesis arises from the observation that when the condition is associated with alcohol, symptoms appear more severe then when the condition is not associated with alcohol. This view may be based on incomplete review of published studies. In this paper, we report a systematic review of published cases of WKS not obviously related to alcohol dependence or abuse published over the last century. The findings suggests that, contrary to commonly held views, WKS is relatively uniform in clinical presentation, irrespective of whether the condition is associated with alcohol. In addition we note several less well understood features of WKS including the frequency of multiple severe cognitive impairments, potential for recovery and the importance of effective treatment.

Poster 4.40

Remembering the Reward: Neural Correlates of Memory and Reward Anticipation in the Avian Prefrontal Cortex

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Delay activity refers to a change in cell activity during the period between stimulus presentation and a memory test. Because delay activity is typically found when an animal is under memory demand, delay activity is considered to be a neural correlate of memory for a stimulus. However, in animal experiments where there is memory demand, there is also an opportunity to gain a food reward. Therefore, delay activity could in fact code for reward anticipation. We recorded single unit activity in the nidopallium caudolaterale (NCL) of three pigeons. The pigeons were trained on a directed forgetting version of a delayed matching-to-sample (DMS) task. Red and white coloured discs were used as stimuli. In order to untangle memory demand from reward anticipation, we used a differential outcome procedure so that a correct response on the memory test following a red sample was rewarded with food, but a correct response on the memory test following the white sample was not rewarded. If delay activity is a neural correlate of memory, then we should observe significant delay activity on both red and white trials. On the other hand, if delay activity represents reward anticipation, then we should observe significant delay activity on red trials, but not on white trials. Our findings support the view that delay activity represents a code of the upcoming reward.

Poster 4.41

The Effects of Ageing on Visual Attention and Perception

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The effects of normal ageing on visual attention and perception were examined in two experiments. The Attention task of both experiments used a derived peripheral cueing task and participants were asked to shift their attention appropriately in response to peripheral letter cues, to aid responding to a target asterisk. The Perception task was similar except that participants were instructed to respond directly to the specified target letter as quickly and accurately as possible. In Experiment 1, in contrast to earlier findings visual attention and perception both remained intact with ageing. In Experiment 2, the same tasks were used but there were four valid and four invalid letters to increase the task complexity. Whilst visual perception appeared to be intact in the older adults, they were unable to successfully orient their attention. When cue-encoding demands were modest, normal ageing had no effect on attentional orienting in response to peripheral cues or on perceptual cue discrimination. However, in a more complex environment, with a larger set of novel attentional cues, older adults were unable to successfully orient their attention.

Poster 4.42

Perceptual Asymmetries in the Processing of Emotional Information in Previously Depressed and Never Depressed Individuals

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The diathesis-stress hypothesis of depression proposes that some individuals have a negative affective style which interacts with stressful life events to produce depression. This affective style is linked to a relative right frontal asymmetry as measured with EEG. This asymmetry is state-independent; it is present in people who are no longer depressed, and predicts future depression. The present study examined whether the rightward asymmetry associated with past depression is also observed in cognitive tasks. Participants completed a chimeric faces task; a divided visual field affective judgement task with emotional words; and two dichotic listening tasks, one identifying emotional tones of voice, and one identifying words. Compared to never depressed controls, previously depressed participants showed greater relative rightward asymmetry on the chimeric faces and emotional tone of voice task; and less leftward asymmetry on the divided visual field and word identification tasks. These results suggest a relationship between neurological and cognitive factors that contribute to a vulnerability to depression. Follow up analyses examined the relationship between perceptual asymmetries and therapeutic outcome in previously depressed participants, as EEG studies have demonstrated asymmetry differences between depressed individuals who respond to SSRI medication and those who do not. The potential for perceptual asymmetry tasks to predict treatment response in depression will be discussed.

Poster 4.43

Effects of Posterior Hypothalamic Lesions on Formalin-induced Pain Behaviours

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The posterior hypothalamus (PH)-supramammillary (SuM) region connects to variety of regions in the CNS, some of which influence affective-motivational behaviours. For example, the region is reciprocally connected to the hippocampal formation. The hippocampal formation is crucial for adaptive behaviours and, importantly, contributes to the negative affective-motivational state during pain. In the present study we explored whether PH-SuM as well modulate animal pain behaviours in the formalin model of persistent inflammatory pain. Formalin (1.25%, 0.1ml) was injected subcutaneously into the plantar surface of the right hind paw of PH-SuM lesioned or control non-lesioned animals. The lesion was induced by microinjection of the glutamate receptor ligand, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA, 0.99ng in 0.3µl). The lesioned animals were subdivided into a 'dorsal lesion group' and a ventral lesion group based on the affected area visualized using OX42 immunocytochemistry as a marker for microglia activation. The damaged area in the dorsal lesion group included the PH and adjacent areas, whereas the ventral lesion extended into the lateral SuM. The lesioned area was bilateral or either ipsilateral or contralateral to the injected paw. The lesion of SuM was incomplete. Neither dorsal nor ventral lesion affected animal behaviour in open field. Rather, ventral lesions that covered medial SuM enhanced exploratory behaviour. Interestingly, ventral lesion encompassing the lateral SuM attenuated animal behaviour to formalin. The effect was more marked during the later part of the formalin response leading to truncated duration of formalin pain-induced behaviours. An effect was also seen with dorsal lesion but was not as marked. These trends raise the possibility that PH-SuM region, especially ventrally influence the affective-motivational drive to pain.

Poster 4.44

The Use of fMRI to Assess Working Memory in Children Born Very Preterm

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Working memory deficits have been demonstrated in children born very preterm (<33 weeks of gestation) throughout childhood. However, the neurpathological processes that underlie these impairments during the school years remain uncertain. Our previous work with preterm infants has clearly shown that white matter injury during the neonatal period is a major contributing factor for impaired working memory at ages two, four and six years. Working longitudinally with the same cohort, we seek to understand the neuroanatomical correlates and compensatory alterations that may have occurred over childhood in response to early disturbances in cerebral development, in relation to working memory function. This paper discusses the development of two fMRI paradigms suitable for the assessment of verbal and visuo-spatial working memory in these developmentally atypical children. These paradigms were adapted from the classic Sternberg working memory task. Previously used fMRI paradigms will be reviewed and methodological issues unique to paediatric imaging research will be addressed. Preliminary analyses of the two current paradigms reveal behavioural results similar to those found in other Sternberg tasks with mean response time increasing linearly with memory set size. In general, the paradigm has been developed to understand the developmental consequences of early brain injury on working memory in children born very preterm.

Abstracts

5.1

Neuropsychological Correlates of Semantic Inhibition in Schizotypy

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The term schizotypy refers to a constellation of cognitive and personality traits that lead an individual to be seen as odd or eccentric, and reflect a vulnerability to psychosis. In our previous research, we demonstrated that high schizotypal individuals process ambiguous words differently than low schizotypal individuals; although both groups activate the most common meaning of the word, low schizotypes also inhibit the less common meaning, but high schizotypes do not. This pattern of reduced semantic inhibition has been associated with the right hemisphere, which has also been shown to be more active in high schizotypes than low schizotypes. The present experiment tested the hypothesis that semantic activation and inhibition are related to hemispheric differences in language processing. Sixty undergraduate students (30 high schizotypy, 30 low schizotypy) completed a semantic priming task and a visual half field task to measure hemispheric asymmetry for reading. On the priming task, participants saw an ambiguous word (e.g., *ball*) followed by a target related to either its common, dominant meaning (e.g., *round*) or its less common, subordinate meaning (e.g., *dancing*), and indicated whether the two words were related or unrelated. As expected, high and low schioztypes did not differ in their processing of dominant word meanings, but only the high schizotypes failed to inhibit the subordinate word meaning. This failure of inhibition was unrelated to hemispheric asymmetry for reading. The two groups did not differ in hemispheric asymmetry, and asymmetry was unrelated to either activation or inhibition of word meaning. These findings suggest that the failure of semantic inhibition that is consistently observed in high schizotypal individuals does not reflect an increased reliance on right hemisphere language processing.

5.2

Theta-Gating During a Modified Sternberg Working Memory Task

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Sternberg (*Science,* 153: 652-654 (1966)) found that the time taken (RT) to decide whether a given "probe" item was, or was not, in a memorized set was a linear function of the number of items in the set. This function was not influenced by whether the probe was in the set, or the position of the "probe" in the set. Sternberg concluded therefore that subjects scan the set serially and exhaustively in order to find a match for the probe. It has been shown that theta activity recorded from the cortical surface is gated during a working memory task (Raghavachari, et al., *J. Neuroscience* 21:3175–3183 (2001)), raising the possibility that scanning time may be indexed by the duration of increases in theta activity. In the present study, therefore, wavelet analysis was performed on scalp-recorded EEG data collected during the performance of a modified Sternberg task. The duration of theta gating over frontal electrodes was measured as subjects decided whether a probe letter was a member of a set of previously learnt letters (2, 4 and 6 letter sets were employed). Contrary to the predictions of the Sternberg hypothesis, the position of the probe in a set was found to be linearly related to the duration of the gated theta activity. These data are consistent with a serial self-terminating rather than a serial exhaustive search.

5.3

A Conceptual Model Of Hippocampal Single Unit Activity that Integrates Spatial and Goal Inhibition Views

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Hippocampal cells are often described as having spatial fields and, indeed, are often called "place cells". However, the same cells can also code time and the "places" they code under different circumstances do not fit any simple geometric rules. An alternative view of hippocampal function is that it is involved in the inhibition of conflicting goals. The only account this theory gives of "place" cells is that they only appear to code place and do so when a goal happens to be spatially located. I describe an analysis of goals in relation to approach, avoidance and approach-avoidance conflict that leads to a model where goals can be either positive or negative (point attractors or point repulsors); where, as in the earlier inhibitory view, the hippocampus receives efference copies of goal activities (that may be located in space or time or within some other cognitive matrix); and where, as in the earlier spatial view of the hippocampus, the spatial location of goals is an important factor in hippocampal processing. Critically, this analysis suggests that goals with different valences (attract/repel), which are located in the same place, and goals with similar valences (attract/attract, repel/repel), which are located in different places, will be coded by cells with firing patterns that appear similar; but the downstream processing of their outputs must be processed by different types of circuit within the hippocampus.

5.4

Brain Activity in Bilingual Developmental Dyslexia

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Reading requires the use of at least two anatomically distinct, but cohesive, left hemisphere processing systems. In the case of dyslexia, this network has been hypothesised to be functionally disrupted. We have previously reported that adult dyslexics show predominantly right frontal activation during various lexical decision tasks, likely as a compensatory reaction to left temporoparietal dysfunction. We have also shown that *bilingual* adults who have acquired their second language late appear to utilize right hemisphere resources during reading to a greater extent than their monolingual peers. It is generally agreed that, although essentially the same neural mechanisms are used for first and second languages, factors such as proficiency, age of acquisition and amount of exposure affects cerebral laterality. Little is known, however, about bilingual developmental dyslexia (BDD), particularly with early acquisition of both languages. Here we present an fMRI study of a German (L1)- and English (L2)-speaking dyslexic adult. Comparisons on five tasks in English were made with bilingual normal readers, monolingual normal readers, and monolingual dyslexics. A lettercase judgement task resulted in predominantly left angular gyrus activation across groups. In contrast, the amount of activation differed during irregular word reading between the BDD and monolingual dyslexics. Differences in the location of activity were observed between the BDD and all other groups during sublexical decision-making, with maximal activity in the left inferior frontal gyrus. Overall, the BDD showed some right hemisphere compensatory activity, but not to the same extent as monolingual dyslexics. Further, the extent and location of activation in the BDD during phonological processing was different from other groups, more closely resembling fMRI results from other labs with monolingual dyslexic children.

5.5

Hemispheric Asymmetries in White Matter Architecture

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Hemispheric specialisation is now well established in the human brain. In the majority of the healthy population, language functions are lateralised to the left hemisphere, while the right hemisphere specialises in visuospatial functions. While such functional asymmetries are well-documented, there is little evidence for any underlying structural hemispheric asymmetries. With the use of diffusion tensor imaging (DTI) we investigated interhemispheric asymmetries in the white matter architecture of various brain regions. Twenty-nine right-handed males underwent DTI, and fractional anisotropy (FA) was calculated for four brain regions within each hemisphere: the frontal, temporal, parietal and occipital. A significant rightward asymmetry in FA was observed across the parietal lobes, areas primarily involved in spatial and attentional processes. In addition, the parietal lobe FA was significantly higher than that in the other lobes in both hemispheres. In only the left hemisphere was the temporal lobe FA significantly higher than the occipital. These findings may provide structural evidence to support Robert Miller's hypothesis of the existence of asymmetrical repertoires of conduction velocities in the cerebral hemispheres. We speculate that increased FA in parietal regions may reflect the need for efficient conduction during attentional and spatial processes, while the greater FA of the left temporal lobe compared to occipital may signify linguistic processes given that it is a function typically lateralised to the left hemisphere.

5.6

Actions Speak Louder Than Words: Modulation of Actions by Concurrent Utterance of Action Words

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According to the Motor Theory of speech perception, speech sounds are akin to phonetic gestures (Liberman and Mattingly, 1981; Lotto et al, 2009). This idea has received some support from the fact that activation of Broca's area occurs both during speech, and during observation and execution of goal-directed actions. Simultaneous production of words and actions, moreover, disrupts action parameters. To support MT, however, the impact of uttering words on action execution should be systematic: action-congruent words should facilitate action execution, while incongruent words should disrupt. We tested this idea by having participants reach and grasp the top or bottom of a vertical bar, while uttering top- or bottom-congruent or incongruent verbs, nouns or adjectives, or nonsense words. We recorded action with a motion capture system, and analysed movement time, velocity and trajectory deviation. Preliminary results indicate that concurrent articulation of action-congruent verbs and nouns systematically facilitates action execution, consistent with MT theory of speech perception.

5.7

Complex Associations in Pigeons: The Ability to Combine Two Visual Dimensions

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Most research on the avian brain is related to the visual system, its asymmetrical organization and its high visual skills. Recent studies indicate that pigeons not only possess the ability to discriminate visual stimuli on the basis of one feature but are also able to differentiate complex stimuli on the basis of more than one dimension. However, it is less clear in how far pigeons are able to combine different stimulus dimensions. The aim of the present study was to explore if pigeons are capable of integrating multiple dimensions of artificial stimuli to find a combination of positive visual features. Pigeons were trained in a forced choice paradigm to discriminate pairs of visual stimuli that differed either in colour or form. Each pair consisted of one rewarded and one non rewarded stimulus. After reaching learning criterion, the form and colour stimuli were combined with each other to generate four new two-dimensional stimuli. Two of them were composed of the rewarded form and the non rewarded colour and vice versa. One stimulus consisted of a combination of the rewarded features and the last one just out of the non rewarded features. Hence there was only one combination with all correct features learned in the discrimination task, two that contained one correct feature and one that only combined incorrect features. These four stimuli were simultaneously presented on four pecking keys and the pigeons had to decide for one of them. Pigeons decided significantly more often for the stimulus which integrated all rewarded features. These data suggest that the animals had learned to combine different dimensions of previously learnt stimuli. This result confirms the ability of pigeons to learn complex associations and demonstrates this skill via the combination paradigm.

5.8

Pigeons Being Spoilt for Choice: A Study on Hemispheric Dominance

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The avian visual system is asymmetrically organized. Work on functional asymmetries commonly focuses on comparing performance measures between the hemispheres; hemispheric dominance, however, is rarely investigated in animal models. The aim of the present study was to investigate hemispheric dominance in pigeons. Animals were trained monocularly on a color discrimination task. They learned two stimulus pairs consisting of an S+ and an S- each. One stimulus-pair was trained with the right eye occluded, the other pair with the left eye occluded. After reaching learning criterion the animals were tested binocularly with compound stimuli. They had to choose either the S+ of the right eye combined with the S- of the left eye or the S+ of the left eye combined with the S- of the right eye. In these tests the pigeons chose significantly more often the S+ they had learned with the right eye. Since the optic nerve of avians is almost completely crossed, we conclude that the left hemisphere dominates the right hemisphere during visual discrimination. To investigate the underling mechanisms of this dominance the role of the visual wulst was examined in a second part of the experiment. Test trials were conducted with Tetrodotoxin or Saline injections into the left or right visual wulst. While blocking of the right visual wulst had no influence on performance, blocking of the left visual wulst resulted in an increased pecking on the S+ the animals had previous learned with the left eye. Blocking of both wulst resulted in a decreased pecking on the S+ the animals had previous learned with the right eye and therefore to a loss of dominance of one hemisphere. The visual wulst therefore plays a key role in shifting the dominance to the left hemisphere.

6.1

Using an Interval Bisection Task to Assess the Effects of MDMA on Temporal Discrimination

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This talk will present data concerning the effect of acute MDMA ('ecstasy') exposure on temporal discrimination performance in rats. In particular we were interested in comparing the effects of MDMA to amphetamine on performance in an interval bisection task. Some previous studies have shown that amphetamine produces left-ward shifts in the temporal bisection function (e.g. Maricq et al., 1981; Meck, 1986). This result has been attributed to amphetamine's ability to act as a dopamine agonist and has been interpreted in terms of a 'speeding up' of an internal pacemaker or clock process that an organism might use to measure the passage of time (as per Scalar Expectancy Theory). Given that acute MDMA acts as a dopamine agonist (amongst other things) then MDMA may also produce a similar effect on temporal discrimination task performance. However, contrary to this expectation we found that, in addition to the predicted left-ward shift, there was a flattening of the psychophysical function, more akin to an overall impairment in attention / discrimination. This particular result may have arisen because of MDMA's concurrent action as a serotonin agonist. The current findings also potentially aid our understanding of the behavioural mechanism by which MDMA effects performance in other conditional discrimination tasks (e.g. delayed matching-to sample).

6.2

MDMA Administration and the Subsequent Effects on Activity Rhythms in Male Rats

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MDMA (ecstasy) is a psychoactive compound that has been associated with rave and dance parties where it has been popular because of its entactogenic properties, its ability to cause heightened sensory awareness and because it increases alertness allowing users to stay up all night. Despite this, MDMA has also been associated with behavioural disturbances in systems modulated by 5-HT including mood and the sleep/wake cycle. Questionnaire studies in MDMA users have revealed that they commonly report both acute insomnia and long term trouble sleeping and animal studies have found that MDMA may disrupt the normal function of 5-HT as a regulator of the activity/wake cycle. In the present study, we examined the activity rhythms of 94 individually housed outbred male rats using Clocklab® software. Rats were housed under a 12-12 h light-dark (LD) cycle prior to treatment with MDMA (5 or 10 mg/kg) or saline which was administered via a single i.p. injection. Following treatment, animals were held under either the same 12-12 h LD cycle (1st experiment), or under constant darkness (2nd experiment). In experiment 1, MDMA treatment disrupted activity, causing increases in the amount of activity post-injection and a change in the distribution of activity throughout the day. To further examine whether the circadian system was affected, actograms of animals held under constant darkness post-treatment were examined to determine if these changes were the result of disruption to central circadian mechanisms. Results to date suggest that MDMA can affect the sleep/wake cycle, and this has implications for human users of MDMA as poor sleep and altered rhythms have been associated with adverse health outcomes.

6.3

Behavioural Economic Analysis of the Oral Self-Administration of MDMA ('Ecstasy') in Rats

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Recent studies have produced reliable self-administration of the so-called "party drug" 3,4-Methylenedioxymethamphetamine (MDMA, or ecstasy) in rats. This finding suggests that MDMA may share many of the addictive properties common to other prominent CNS stimulants (such as cocaine and amphetamine). Experimental evidence for the reinforcing properties of MDMA can be derived from manipulations of the self-administration procedure. Reinforcing efficacy can be studied by utilising an economic framework and examining changes in consumption (reinforcers consumed) as function of changes in the price (response requirement). In humans MDMA is primarily consumed in one or more oral doses, however animal studies have relied upon the IV route of administration in the study of its effects. This study sought to characterise animals' response to oral reinforcement using MDMA and to measure MDMA's reinforcing efficacy when delivered orally. The results of experiment 1 showed that animals in this study produced dose dependent responding for oral doses of MDMA using both water and saccharin as vehicle solutions. In experiment 2 an economic analysis was conducted by manipulating the Fixed Ratio (Price) requirement across sessions and doses (0.2, 0.4, 0.8mg/kg and vehicle). Demand curves were analysed and indicated increased demand for MDMA-containing solutions than for vehicle alone. The results of these studies provide evidence for the positive reinforcing effects of MDMA when it is delivered via the oral route of administration.

6.4

Oxytocin Mediates Some Subjective Effects of MDMA ('Ecstasy') but not Amphetamine – A Drug Discrimination Study in the Rat

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MDMA use results in distinctive mood changes, some of which are thought to be due to its enhancement of serotonin (5HT) release. Serotonin positively regulates the release of oxytocin in the central nervous system via the 5HT-1A postsynaptic receptor subtype, producing changes in mood and behavior. Using a drug discrimination paradigm, we examined how alterations in oxytocin levels affect conditioned behavioural responses to MDMA and a related stimulant with a primarily dopaminergic mechanism of action, amphetamine (AMP). Male and female Sprague Dawley rats (n=24) were trained to respond to MDMA (1.5 mg/kg) and AMP (1.0 mg/kg), and saline using a three lever drug discrimination paradigm. First we examined whether the oxytocin analogue, carbetocin, would generalize to either of the training drugs, and if so, whether pre-treatment with the oxytocin receptor antagonist, atosiban, would affect the discrimination. The results supported the hypotheses that the addition of an oxytocin analogue (carbetocin) would partially substitute for MDMA but not for amphetamine, and that both MDMA-appropriate responding could be attenuated by first blocking oxytocin receptors with atosiban. The selectivity of these effects was further examined using a tricylic antidepressant, imipramine, at a behaviourally active dose. Imipramine neither generalized to the training drugs nor altered their discriminability when it was given in combination with MDMA or AMP. It was concluded that oxytocin receptor activation is involved in some MDMA-specific interoceptive cues, and that the facilitation of oxytocin release is one of the features of MDMA that distinguishes it from AMP.

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6.5

Regulation of Serotonin Transporter Expression and Function Following MDMA ('ecstasy') Exposure

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MDMA (ecstasy) is a popular recreational drug that produces feelings of euphoria and well-being as a result of an acute, rapid release of dopamine and serotonin (5-HT) from nerve terminals. The adverse effects of MDMA abuse may include psychiatric disorders, memory and learning deficits, and neurotoxic injury to 5-HT neurons. Previous studies have shown that MDMA use results in depletion of 5-HT and serotonin transporter function (SERT). Using quantitative Western Blotting and real-time PCR techniques we have shown that total SERT protein in the dorsal raphe nucleus (n=3-4 animals; p> 0.45), striatum (n=3-4; p> 0.8), and nucleus accumbens (n=3-4; p> 0.8) and mRNA levels in the dorsal raphe nucleus (n= 8-9; p> 0.16) were not significantly changed following exposures to MDMA in rats (4 x 2 hr IP injection, 10 mg/kg). In neuroblastoma (N2A) cells transiently expressing green fluorescent protein-tagged human SERT (GFP-hSERT), we have shown redistribution of SERT from the cell surface to intracellular vessicles on exposure to MDMA using both cell-surface biotinylation and live-cell confocal microscopy techniques. To investigate the mechanism responsible for SERT redistribution we used specific antibodies to phospho-P38 MAP kinase, a known signalling pathway involved in SERT membrane expression. Results show that the MDMA induced redistribution of SERT from the cell-surface to intracellular vesicles occurs via a p38 MAP-kinase independent mechanism. Redistribution of SERT from the cell surface to intracellular vesicles on exposure to MDMA may contribute to the decreased SERT function seen in rats exposed to MDMA.

6.6

Salvinorin A and its Structural Derivatives Attenuate Drug-Seeking Behaviour in Rats

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Traditional kappa-opioid receptor (KOPr) agonists (U69593 and U50488H) have previously been shown to attenuate drug seeking behaviour in pre-clinical models of addiction. However, they are not used clinically due to undesirable side effects such as sedation, dysphoria and depression. Recently, a new KOPr activating compound called Salvinorin A (Sal A) has been discovered. Sal A has a unique structure compared to traditional KOPr agonists. We hypothesise that this novel structure may hold the key for developing anti-addiction pharmacotherapy without the unwanted side-effects. The aim of our study was to determine if Sal A and its structural derivatives (DS 1-240 and DS 3-216) have anti-addiction properties using an animal model of cocaine-seeking behaviour. Following acquisition and stabilization of cocaine self-administration, cocaine-produced cocaine-seeking was measured in rats. This test was conducted in a single day and comprised an initial phase of self-administration, followed by a phase of extinguished responding. The final phase examined reinstatement of extinguished cocaine self-administration followed by a priming injection of cocaine (20.0 mg/kg, intraperitoneal (I.P.)) in combination with traditional or novel KOPr agonists. Cocaine-induced drug-seeking was attenuated by pre-treatment with Sal A (0.3 and 1.0 mg/kg, I.P.), DS 1-240 (0.3 and 1.0 mg/kg I.P.) and DS 3-216 (0.3 mg/kg, I.P.) ($p < 0.05$). This study shows that Sal A and novel analogues attenuate cocaine seeking behaviour.

6.7

Methamphetamine Exposure: Effect of Contingency and Time Course of Recovery of Monoaminergic Tissue Levels

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Methamphetamine (MA) exposure has been purported to produce dopaminergic neurotoxicity and persistent monoamine tissue level depletions. However, most animal models employed to study these effects involve the administration of non-contingent MA that might not be representative of human drug users. The present study sought to determine whether there was an effect of contingency on monoamine tissue levels and whether any changes were persistent. Experiment 1 involved administration of MA at a dose of 10 mg/kg every 2 hours for a total of 4 injections within one day to male Sprague-Dawley rats (40 mg/kg MA in total), a regimen that has produced long-lasting monoaminergic deficits and neurotoxicity. This group was intended as a positive control for comparison with the self-administration experiments. Experiment 2 utilized a yoked MA self-administration model, where the purpose of this experiment was to determine the effect of contingency on monoamine levels during a 20-day period of self-administration. For both Experiment 1 and 2, rats were sacrificed at either 24 hrs or 7 days after the final drug exposure to determine whether monoaminergic depletions were enduring using HPLC analyses. Greater and longer lasting monoamine depletions were observed in the positive control group when compared to the actively self-administering group, and rats receiving 'yoked' or non-contingent MA infusions showed greater/more persistent deficits when compared to the contingent group. These differences likely represent a motivational state dependent on active/contingent drug self-administration demonstrating the importance of contingency in animal models of drug abuse.

6.8

Behavioural Sensitisation Following Repeated Exposure to MDMA ("Ecstasy") and Amphetamine

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Repeated exposure to a number of psychostimulant drugs results in sensitised responses to the behavioural and neurochemical effects. The present study was designed to compare the profile of the sensitised locomotor activating response to MDMA and amphetamine. Rats were pre-treated for 5 days with amphetamine (2.0 mg/kg, IP), MDMA (10.0 mg/kg, IP) or the saline vehicle. After a 2 day withdrawal period, the locomotor activating effect of each drug was measured. The acute activating effects of MDMA were restricted primarily to the periphery of the open field chamber. In contrast, acute amphetamine increased activity in both the periphery and the centre. Following repeated administrations, the sensitised response to MDMA reflected an increase in activity in the centre but not in the periphery of the chamber. Repeated exposure to amphetamine, however, increased activity in the periphery but not in the centre. These findings suggest different neuroadaptations reflected in different behavioural responses to these two amphetamine-type stimulants following repeated exposure.

7.1

Adrenergic Regulation of Sensory Long-term Potentiation in Rat Visual Cortex

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Previously we reported the induction of long-term potentiation in adult rat visual cortex using only sensory stimulation, a phenomenon we termed sLTP. We found that rapid presentation of a visual stimulus (9 Hz for 2 minutes) caused a lasting potentiation of the visual evoked potential (VEP), an effect that was blocked by the NMDA receptor antagonist CPP. While trying to explore the properties of this novel form of LTP, we discovered that its induction does not in fact occur as readily as we first observed. Varying a number of experimental parameters, such as stimulus properties and levels of inhibition in the visual cortex, failed to increase the reliability of sLTP. A recent *in vitro* study of plasticity in slices of visual cortex suggests that modulation of the adrenergic system can facilitate the induction of LTP. We administered the alpha-adrenergic agonist methoxamine (20 mg/kg, i.p.) and found a small but reliable potentiation of the VEP following a longer, slower photic tetanus (1 Hz for 1 hour) that did not occur in saline-treated animals. This LTP was similar to that previously observed in that it required a single tetanus and it was very persistent, exhibiting little decay during a 2-hour follow-up period. Activation of the adrenergic system, which mediates arousal, can improve memory performance as well as modulate the induction of electrical LTP. Thus, this result may provide an explanation as to why sLTP is difficult to induce in the anesthetized rat. We are currently exploring the use of other adrenergic agonists and planning to try sLTP in awake animals.

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7.2

Role of NR2B Subunit-Containing NMDA Receptors in Different Forms of LTP

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Long-term potentiation (LTP) is a diversified phenomenon. In area CA1 of the hippocampus, varied forms of LTP have been shown to coexist, each involving different intracellular signalling and effector cascades. Most forms of LTP are dependent on activation of postsynaptic NMDA receptors, however controversy exists over the relative roles of receptors containing different NR2 subunits. We have investigated the involvement of NR2B-type NMDA receptors in different forms of LTP at CA3-CA1 synapses in hippocampal slices from male Wistar rats (8-9wks). The selective NR2B antagonist RO 25-6981 (1 μM) had no effect on short-lasting LTP induced by 1 train of theta-burst stimulation (1 TBS, n=6), but reduced the magnitude and persistence of LTP induced by 4 TBS (n=7, $p<0.05$). Since NR2B-containing receptors might constitute a significant extrasynaptic NMDA receptor population, we asked whether extrasynaptic NMDA receptors alone could induce LTP induced by 4 TBS. Synaptic NMDA receptors were inhibited with the use-dependent channel blocker MK-801 (10 μM) during baseline stimulation. Following a 20 min washout of MK-801 in the absence of stimulation during which time synaptic NMDA receptors remain blocked, LTP induced by both 1 TBS (n=6) and 4 TBS was inhibited (n=4). Together these data show that long-lasting but not short-lasting LTP requires NR2B receptor activation and that synaptic NMDA receptors are necessary. It remains possible that the requisite NR2B receptors are located extrasynaptically but that they must work in concert with synaptic NMDA receptors. Future experiments will investigate the relative requirements of synaptic and extrasynaptic NMDA receptors and the role of other NR2 subunits in different forms of LTP.

7.3

Dendritic Spine Elimination and Synaptic Protein Removal in the Hippocampus with LTD

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Synaptic plasticity is a fundamental property of neurons thought to underlie behaviour, cognition, learning and memory. The development of new synapses, activity-dependent changes in the strength of existing synapses and elimination of synapses have all been proposed to form the basis of this plasticity. The N-methyl-D-aspartate (NMDA)-type glutamate receptor (NMDAR) expressed at excitatory glutamatergic synapses is required for learning and memory and plays a pivotal role in triggering and controlling synaptic plasticity. Therefore, changes in the expression level of this receptor will have significant consequences on the future ability of synapses to undergo NMDAR-dependent plasticity. Few studies have addressed how spine and/or synapse elimination are induced or what the mechanistic underpinnings for them are. Our data show that NMDAR stimulation used to induce chemical long-term depression (LTD) also induces a rapid-occurring long-lasting NMDAR-dependent spine elimination. Dendritic spine density decreases as early as fifteen minutes post-LTD induction and is still significant one week post-induction. The early spine elimination correlates with rapid elimination of the postsynaptic protein PSD-95 and of the NMDAR itself, suggesting that the post-synaptic terminal may be collapsing. These data will provide key information on how changes in NMDAR expression, occurring with neural activity, can dictate changes in synapse number.

7.4

Alterations to Vesicle Turnover Rates Associated with Three Different Forms of Long-Term Potentiation in the Hippocampus

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Long-term potentiation (LTP) of hippocampal synaptic transmission is an important process underlying learning and memory in the brain. At CA3-CA1 synapses in the hippocampus, three discrete forms of LTP (LTP1, 2 and 3) can be differentiated on the basis of persistence and induction mechanisms. However the relative roles of pre- and postsynaptic mechanisms in the expression of LTP1, 2 and 3 are unknown. In this study, the potential role of a presynaptic enhancement of neurotransmitter release in the expression of LTP1, 2 and 3 was investigated by measuring the electrically-evoked destaining of the styryl dye FM1-43 from potentiated CA3 terminals in 400μm thick brain slices taken from male Wistar rats (7-8 weeks). No difference in vesicle turnover rate was observed for LTP1 at one hour or two hours following induction by 1 train of theta-burst stimulation (1TBS) ($P>0.05$). A significant increase in release rate was found for LTP2 only at two hours after induction by 4TBS ($P<0.05$), and for LTP3 at both one hour and two hours after induction by 8TBS ($P<0.05$). A significant increase in the percentage of 'non-destaining' terminals was associated with LTP3 at both time points post-TBS, which correlated with an increase in the loading of FM1-43 at these terminals. We hypothesise that this 'non-destaining' population results from the loading of dye into alternative vesicle pools, since application of a high [K^+] solution eventually leads to destaining. This study suggests that more durable forms of LTP involve an enhancement of presynaptic vesicle cycling, perhaps involving recruitment of a reserve pool of vesicles in extreme cases.

7.5

Augmentation of Post-synaptic Potentials Following Dopamine-Dependent Potentiation of Cortical Synapses is Associated with Afterhyperpolarisations in Striatal Cholinergic Interneurons

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Pauses in the tonic firing of striatal cholinergic interneurons (CINs) emerge during reward-related learning and are triggered by conditioned cues. We hypothesised that dopamine-induced potentiation of cortical afferent synapses onto CINs triggers an afterhyperpolarisation (AHP) that delays the subsequent action potential. We stimulated corticostriatal fibres in rat brain slices and recorded excitatory postsynaptic potentials (EPSPs) in CINs using the visualised whole-cell patch-clamp technique. Test stimuli were applied every 5 s for a baseline period of 10-15 min and changes to the maximal slope of the EPSP assessed at 20 min following a high frequency stimulus (HFS, 100 Hz, 6 x 500 ms, every 10 seconds). A small depression was seen in response to stimulation within the ipsilateral hemisphere (-9 ± 8%, mean ± SEM, n=12). The same plasticity protocol resulted in a robust depression when crossed corticostriatal fibres were stimulated selectively in the contralateral hemisphere (-34 ± 4%, n = 7). Ipsilateral HFS in Mg^{2+}-free solution potentiated the EPSP slope (21 ± 8%, n = 7), and this effect was blocked by antagonism of either NMDA receptors (50 µM AP5, -14 ± 7%, n = 8), D1 dopamine receptors (10 µM SCH23390, 9 ± 5%, n = 10), or D2 dopamine receptors (10 µM sulpiride, -4 ± 4%, n = 11). The plasticity-induced changes in EPSP magnitude were positively correlated with the change in AHP magnitude in all conditions. Thus the induction of long term potentiation of afferent synapses is dependent on dopamine receptor signalling and this may contribute to the appearance of cue-induced pauses in tonic firing of CINs during learning.

7.6

Visually-Reinforced Spike-Timing-Dependent Plasticity in the Striatum

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Spike-timing-dependent plasticity (STDP) in the corticostriatal synapse depends on the presence of dopamine (DA). Phasic DA release is thought to be a crucial reinforcement signal during the acquisition of new behavioural strategies. One proposed mechanism of reinforcement learning involves the tagging of recently active synapses by a STDP-based mechanism and the induction of synaptic changes by a subsequent DA signal. We attempted to test this hypothesis *in vivo*. Intracellular recordings of striatal spiny neurons (n=12) were obtained from urethane-anaesthetised rats. Postsynaptic potentials (PSP) were evoked by electrical stimulation of the contralateral motor cortex. Postsynaptic potentials often consisted of up to three distinct components probably representing distinct corticostriatal pathways. After a 15 min baseline, cortical stimulation was paired with a postsynaptic AP evoked by intracellular current injection at a delay of ~10 ms. Each of the 60 pre-post pairings was followed by a light flash on the contralateral eye at 250 ms delay. Local disinhibition of the superior colliculus induced by an injection of bicuculline was used to enable the visual activation of the dopaminergic tecto-nigrostriatal projection (n=9). Induced changes were measured as the percentage change of the maximal slope of the PSP from baseline (5 min pre). Ten to twenty minutes post, potentiation was observed in two neurons (16% and 32%) and depression in two others (-24% and -17%). In three neurons, single PSP components were significantly increased. Synaptic changes induced without collicular disinhibition tended to be smaller (-18% to +6%, n=3). These results support a DA-reinforced STDP-based mechanism in the striatum. Because of the large variability of *in vivo* results, further data is needed for a definitive characterisation of the underlying mechanism.

8.1

The Segmental Myotomal Muscles of the Mammalian Embryo are Never Innervated

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The myotomal muscles are the first muscles formed in all vertebrate embryos, and in fish and tadpoles, are innervated almost immediately and used for swimming. An interesting question is whether in mammals, where the embryo does not need to swim, the myotome is still innervated. We examined this using immunohistochemistry to detect nerve (neurofilament and synaptophysin antibodies), muscle (myosin antibodies) and acetylcholine receptors (labelled alpha-bungarotoxin) in a staged series of rat embryos. The results show that after the myotome first forms, the dorsal rami of the spinal nerves grow out towards the myotome within each segment. However, the nerve growth then arrests just outside the medial boundary of the myotome for about 2 days, during which time only rudimentary growth cones are seen at the nerve tips. Later, the myotomes begin to lose their segmental character and transform into the complex deep back muscles (the epaxial muscles), which are the evolutionarily recent derivative of the dorsal myotome. At this time, the nerve rapidly enters the muscles and branches exuberantly within them. Clusters of acetylcholine receptors form within the developing epaxial muscles soon after. In contrast to the myotome, the pre-muscle masses of the limb muscles are densely invaded by nerve even before there is significant myogenic differentiation. From these results, we conclude that the embryonic myotomal muscles of mammals have lost some essential element that normally makes muscle an 'attractive' target for innervation; as a result, the myotome has lost its function as a neurally controlled contractile organ, and functions only as a scaffold on which the later epaxial muscles of the back will be assembled.

8.2

Telencephalon Expansion by the Convergent Evolution of Developmental Mechanisms

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Primates and some birds (parrots and songbirds) independently evolved an expanded telencephalon. Primates appear to have done so by selectively delaying neurogenesis and expanding their subventricular zone in the cortex. To determine how evolution altered brain development to endow parrots and songbirds with enlarged telencephalons, we examined brain development in two highly telencephalized vocal learners (zebra finches and parakeets) and a poorly telencephalized non-vocal learner (bobwhite quail). We estimated brain region volume as well as neurogenesis timing and examined telencephalic abventricular mitoses with a mitotic marker (pH3) in developing zebra finches, parakeets and quail. We found that zebra finches and parakeets delay and prolong telencephalic neurogenesis relative to quail. We also found that zebra finches and parakeets exhibit an expanded subventricular zone compared with quail. Collectively, our findings suggest that parrots and songbirds expanded their telencephalon using developmental strategies that are similar to those employed by primates.

8.3

Characterising Endogenous Neurogenesis Following Experimental Focal Traumatic Brain Injury (TBI)

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Neurogenesis occurs in response to various types of brain injury. However, the induction of specific regulatory stages of neurogenesis has not been examined in experimental TBI models. This study aimed to characterise the neurogenic response in a closed head injury (CHI) model of focal TBI. Methods: Adult C57BL/6 mice were subjected to CHI or sham-operation. BrdU (200mg/kg i.p.) was administered twice-daily for 4d beginning 1d post-injury, to label proliferating cells. Brains were collected 1,2,4&8w post-trauma (n=4-5). BrdU-labelled cells were quantified in the dentate gyrus (DG) and the subventricular zone (SVZ), to assess cell proliferation and survival. Neuronal differentiation was assessed following labelling with DCX (differentiated/migrating neurons). Neuronal and glial maturation/survival was quantified as the %BrdU-labelled cells co-labelled with NeuN or GFAP. Results: CHI increased the number of new cells at all time-points up to 3-fold in the DG ($P<0.001$), and up to 2-fold in the SVZ ($P<0.05$). A reduction in new cells occurred at 4w post-CHI in the DG ($P<0.01$), and at 2w in CHI and controls in the SVZ ($P<0.05$). Enhanced neuronal differentiation was evident at 1w in the DG ($P<0.05$) and SVZ, with migrating cells observed in the corpus callosum and pericontusional-cortex. At 4,8w post-injury, the majority of new cells in the DG expressed GFAP (~60%), while less expressed NeuN (~10%); however, the number of new neurons was not changed following CHI ($P>0.05$). In the pericontusional cortex, ~60% of BrdU-labelled cells were astrocytes, and very few new neurons were detected. Conclusion: Focal TBI induces proliferation and neuronal differentiation in the DG and SVZ, however, this does not result in enhanced neuronal production. Future studies will investigate stimulating neurogenesis with specific factors to enhance neuronal differentiation and survival, potentially aiding recovery following TBI.

8.4

Transcriptional Alterations in Adult Neural Progenitor Cells after Excitotoxic Cell Death

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Adult neurogenesis is altered by the presence of cell death induced by brain injury or disease. Using an excitotoxic model of striatal cell loss we have previously demonstrated that neural progenitor cells (NPCs) located in the subventricular zone (SVZ) of the adult rat brain respond to injury by increased proliferation in the SVZ and rostral migratory stream (RMS), and migrating acutely and transiently into the lesioned striatum. Interestingly, cells found in the damaged striatum born 2 or more days after lesioning expressed glial markers NG2 and GFAP, not doublecortin. This suggests a cell fate switch occurs in SVZ NPCs from neurogenesis to gliogenesis over time. We propose this reflects a temporal change in expression of neurogenic genes Pax6 and Dlx2, and oligoglial gene Olig2. To examine this, adult rats were injected with quinolinic acid (QA) to induce excitotoxic striatal cell death, and killed at 1, 2, 3 and 7 days post lesion. Using immunohistochemistry and qPCR, the expression of Pax6, Dlx2 and Olig2 by Mash1+ transit amplifying precursors (TAPs) located in the SVZ and RMS was examined. In the first three days following injury, Pax6, Olig2, and Dlx2 mRNA increased in the lesioned SVZ compared to controls. Immunohistochemistry analysis showed numbers of Mash1+ TAPs dropped significantly 1 day post lesion, then returned to normal by day three; however Mash1+ TAPs co-expressing the neurogenic marker Dlx2 did not change. This indicates an acute recruitment of Mash1+ TAPs to undergoing symmetric proliferative division rather than neuroblast production. Determination of the proportion of Mash1+ TAPs co-expressing the gliogenic marker Olig2 will further elucidate whether excitotoxic cell death induces a switch in cell fate over time.

8.5

In vivo and *in vitro* Evidence For Adult Neurogenesis in CLN6 Sheep

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Emerging evidence suggests that the brain can respond to damage or disease by increasing endogenous neurogenesis (the production of neurons from neural progenitor cells, NPCs). Stimulating this endogenous repair mechanism could provide new opportunities to replace cells that are lost in neurodegeneration and may have particular advantages over stem cell grafts. We have recently found evidence for continued neurogenesis in the CNS of CLN6 deficient South Hampshire sheep, with newly generated doublecortin (DCX) and PSA-NCAM positive neurons migrating from the subventricular zone (SVZ) towards regions of the cortex that undergo the most pronounced neuronal loss. Whether this enhanced neurogenesis represents an attempted regenerative response of the NCL CNS remains unclear, but these findings raise the possible therapeutic use of endogenous NPCs. As a first step towards this goal we are optimizing methods for their harvest and propagation. To determine whether CLN6 embryonic neural progenitor cells (NPCs) differ in their division and differentiation from wild type cells we have isolated neural progenitor cells from wild type and CLN6 sheep and expanded them in culture. Preliminary data suggest that cultured CLN6 deficient NPCs exhibit an enhanced proliferative capacity, as defined by an increase in the number of Sox2 +ve NPCs in these cultures. The developmental potential of these progenitor cells is currently under study.

8.6

Role of α-Lipoic Acid (ALA) Supplementation on Arsenic Induced Toxicity in Developing Rat Brain

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A steady increase in the levels of environmental arsenic is a matter of global concern. Arsenic induced toxicity has been reported in a number of organ systems including the nervous system. The present study aimed at determining the role of α -lipoic acid (ALA) supplementation on behavioral, biochemical & morphological parameters in context to hippocampus of rats exposed to sodium arsenite during early postnatal period. Mother reared Wistar rat pups were randomly assigned to various subgroups (n=6/subgroups): normal control and sham control; experimental animals receiving sodium arsenite alone (1.5 & 2.0 mg/kg body weight) or along with ALA (70-mg/kg body wt.) intraperitonealy from PND 4 to PND 15. On PND 14 –16, the animals were subjected to memory retention test on elevated plus maze. On PND 16, half of the animals from each subgroup were sacrificed by cervical dislocation followed by removal of brain. The hippocampus was dissected out on ice and used for estimation of glutathione (GSH) and superoxide dismutase (SOD). The remaining half were perfusion fixed with 4% paraformaldehyde and the brains were postfixed. The tissue blocks containing hippocampus were processed for paraffin embedding & sectioning (7μm) followed by staining with cresyl violet. These were observed under the microscope fitted with Image Analysis System (NIS Element AR 2.30) for morphological and morphometric features. The compiled data revealed significant decrease in retention transfer latency and in levels of GSH and SOD together with altered cell density and nuclear area measurements in animals receiving sodium arsenite alone and an apparent reversal of these parameters in animals receiving sodium arsenite supplemented with ALA, thereby suggesting the ameliorative role of ALA in arsenic induced toxicity.

9.1

Recovery of Motor Deficits and Restoration of the Dopaminergic System in MPTP-lesioned Monkeys after Delivery of AAV2-GDNF into Putamen

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Potent neuroprotective properties have made Glial-Derived Neurotrophic Factor (GDNF) a promising biologic for Parkinson's disease (PD). Unfortunately neurotrophic factors have failed to meet primary efficacy outcomes in PD trials to-date; likely due to delivery issues. In contrast to neuroprotection, we demonstrate for the first time the neuroregenerative effect of GDNF gene transfer in a primate model representative of early- and late-stage PD. Fifteen rhesus macaques were MPTP-lesioned to induce stable parkinsonian motor deficits. Six months later AAV2-GDNF (n=8) or PBS (n=7) was infused into the putamen using convection-enhanced delivery (CED) to maximize vector distribution. Clinical rating scores of 21±1 prior to AAV2-GDNF treatment were reduced to 8±1 after one year, and as low as 1 after two years. Increased dopaminergic activity measured by PET scanning at 6 months was positively correlated with functional recovery. AAV2-GDNF progressively increased putamen dopamine levels while dopamine turnover returned to a normal rate by 14 months post-treatment. Enhanced tyrosine hydroxylase positive fibers were observed within the putamen and substantia nigra of AAV2-GDNF treated monkeys indicative of GDNF-induced regeneration of the nigrostriatal dopaminergic system. Sustained GDNF expression was present throughout the putamen (63±21 ng/mg protein) with additional transportation to the substantia nigra (1.7±0.3 ng/mg). This extensive biodistribution indicates that a similar CED infusion protocol in humans may result in substantial coverage of the putamen – an essential requirement for growth factor therapy in PD. No safety or toxicity issues related to the AAV2 delivery or GDNF expression were observed. These results support initiating a Phase 1 clinical trial with AAV2-GDNF infused into the putamen via CED.

9.2

A New Look at an Old Model: Anaylsing Predicting Factors of Infarct Size in a Rat Perinatal Ashpyxia Model

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Hypoxia-ischemia (HI) is popular model of perinatal asphyxia. It involves a unilateral ligation of an internal carotid artery, followed by a period of exposure to 8% oxygen 92% nitrogen. The model has proved to be sufficiently flexible for it to be applied to rats and mice across a range of age groups. The cerebral infarct caused by HI is very similar to that caused by rat stroke models that involve a middle cerebral artery occlusion (MCAO). Because of this, HI has also been used as a model of thrombolytic and embolic stroke (Northington, 2006). Advantages of the model include its simplicity, the brief period it takes to perform, a low requirement for specialized equipment and a low mortality rate. However, the model is also very highly variable with respect to the degree of cerebral damage induced (Saeed et al., 1993). A notable source of variation is large differences in the morphology of major arterial collateral blood vessels (Brown, 1966). Our study investigates predictive factors of infarct size and the variability of infarction caused by HI on P26 rats. HI was performed on P26 rats. 3 days post HI the rats were sacrificed and their brains sectioned and stained for active mitochondria with triphenyltetrazolium chloride (TTC). Infarct volumes were calculated and compared with factors observed during hypoxia and post HI, including weight change and seizure activity. These data were then used in a statistical model to predict infarct size. As the seizure behaviour during HI was shown to be correlative with infarct size, we proposed that the HI model should use seizure behaviour as the end point of the period of hypoxia, rather than using a set period of time for all animals. The adjusted model gave less variable infarct sizes, lower mortality, and fewer rats with no infarction. Also, the mean infarct size in rats subject to the adjusted model was smaller and more consistently located. Importantly, this smaller infarction is more similar to that observed following human perinatal asphyxia and stroke compared with the conventional model. From this study we have developed a simple, non-invasive way of predicting infarct size in the HI model and developed a variation in the model that produces infarctions in the cerebrum that have greater consistency in size than the original model, more closely model human pathology, and provide greater statistical power for the testing of neuroprotectant treatments.

9.3

Evidence that Comprehensive Neuropsychological Assessments of Traumatic Brain Injury Should Include Measures of Social and Emotional Processing

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Background: The neuropsychological assessment of patients with non-penetrating traumatic brain injuries (TBI) has focused mainly on the assessment of cognitive functions associated with dorsolateral prefrontal function, while the assessment of social and emotional functions associated with ventral prefrontal pathology has been less common. *Methods*: A small group of patients with TBI (N = 13), and age- gender- and education-matched controls (N = 15) underwent neuropsychological testing which included 3 standard neuropsychological measures of processing speed, complex attention and executive functions, and 3 novel measures of social and emotional functioning, including a video-based awareness of social context task, an interoceptive awareness task involving heartbeat detection, and an animation-based perspective-taking task, to determine whether the standard cognitive measures or the social and emotional measures were more sensitive to the presence of TBI. *Findings*: A significant logistic regression revealed that the social and emotional measures distinguished between patients and controls (β = 9.59, p = .014), whereas the standard cognitive neuropsychological tests did not (β = 0.006, p = .466). *Interpretation*: Given that neuropsychological assessments are designed to capture problems at the individual level, these data suggest that it is important to adequately assess social and emotional functioning for each individual who has potential dysfunction in these areas, in order to make appropriate recommendations for both care and rehabilitation. Omitting such measures from standard assessments risks failing to detect some of the most serious difficulties commonly affecting patients with TBI: deficits in social and emotional competence.

9.4

Instrumental Activities of Daily Living in Cognitively Impaired and Unimpaired Parkinson's Disease Patients

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Growing interest in mild cognitive impairment (MCI) and dementia in Parkinson's disease (PD) has increased the need to identify impairments in instrumental activities of daily living (IADL) in PD. The Movement Disorders Society Task Force recently (2007) specified criteria for PD with dementia (PD-D), but no guidelines exist for IADL impairments in cases of PD-D and PD-MCI. We used receiver operating characteristic (ROC) curve analyses to evaluate Reisberg's 40-question ADL scale (2001, Int. Psychogeriatrics, 13: 163) in a group of 15 PD-D patients who received a Clinical Dementia Rating Score >1.0 by comparison to 12 PD-MCI patients (based on neuropsychological test scores and CDR=0.5) and 16 PD patients with unimpaired cognition (PD-U). The ADL scale can identify problems in non-PD MCI (Schmitter-Edgecombe et al, 2009, Neuropsychology, 23: 168). The criterion score of 1.1 for total ADL (min-max score: 0-4; sensitivity, SE=100%; specificity, SP=94%) discriminated PD-D and PD-U cases (+ve Likelihood Ratio, LR=16.0; Odds Ratio, OR=8.0); a criterion score of >1.2 discriminated PD-D from both the PD-MCI group and the combined non-dementing patients (respectively: SE=100%, both; SP=83% and 89%; LR=6.0 and 9.3; ORs=3.0 and 4.6). The PD-U and PD-MCI groups did not differ significantly in their total ADL score. Difficulty touring an unfamiliar place discriminated all three groups (PD-U vs PD-MCI, p<0.0005; PD-MCI vs PD-D, p<0.0002); multitasking differentiated PD-U from both groups with cognitive impairment (PD-U vs PD-MCI, p<0.011; PD-U vs PD-D, p<0.0001), but not between PD-MCI and PD-D (p>0.20). Items from the Reisberg ADL scale may be useful as a brief screening tool to identify functional status and their decline in Parkinson's disease.

9.5

Multimodal Magnetic Resonance Imaging of the Posterior Cingulate in Parkinson's Disease

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There is evidence that cognitive impairment, including that found in Parkinson's disease (PD), is associated with changes to the posterior cingulate. This study used multimodal Magnetic Resonance Imaging (MRI) measures from the PC, defined as a 20 x20 x30mm^3 voxel across bilateral gyri, to characterize PD subjects with varying levels of cognition. The following values were assessed: MR metabolite ratios (N-Acetyl Asparate/Creatine (Cr); Choline (Ch)/Cr; Myo-inositol (mi)/Cr; H20/Cr), diffusion values (mean diffusivity (MD); fractional anisotropy (FA), and cerebral blood flow (CBF). PD participants were classified as cognitively unimpaired (PD-U, n = 21), mild cognitive impairment (PD-MCI, n = 13), and dementia (PD-D, n = 6). Twenty-six healthy age-matched controls were also assessed. There was a significant group effect for CBF ($p<0.02$), MD ($p=0.021$), and Ch/Cr ($p<0.01$), with PD-D and PD-MCI groups showing less perfusion (CBF), reduced microstructural integrity (MD) and membrane dysfunction (Ch/Cr) relative to Controls; differences were also apparent between PD-D and PD-U groups. MR modalities did not significantly correlate in the posterior cingulate; MD significantly correlated with cognitive status (Montreal Cognitive Assessment; $r = -0.35$, $p = 0.004$). This study identified the posterior cingulate as a potential indicator of brain changes associated with cognitive decline in PD, highlighting the value of multimodal MRI in PD.

9.6

Developmental Dyscalculia in Adults: Neuropsychological Bases, and Influence of Comorbid Dyslexia

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Developmental dyscalculia (mathematical learning disability) affects around 6% of the population, and has been characterized in adults in only a few studies. It is comorbid with dyslexia around 20-60% of the time, although it is not known whether this is due to common cognitive and neural impairments. It has been suggested that dyscalculia may be due to a 'core deficit' in number sense, caused by structural and/or functional impairment of the intra-parietal sulcus (IPS). This theory remains controversial, however. In the current study, we tested adults with dyscalculia who either did or did not have comorbid dyslexia, and compared their performance to that of control participants on a battery of neuropsychological tasks targeting core cognitive processes involved in mathematics and reading. This battery included mathematical tasks which focused on non-symbolic number processing (known to recruit the IPS), and symbolic processing (e.g. symbolic numerical comparison, multiplication). Preliminary behavioral results provide some support for number sense as a core deficit in dyscalculia, and suggest that the deficit is more marked when dyslexia is also present. We will discuss final results and their implications for our knowledge of a neural phenotype underlying dyscalculia and the reasons for its high comorbidity with dyslexia.

10.1

Direct Involvement of Agmatine in Learning and Memory Processing

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Agmatine is a metabolite of L-arginine by arginine decarboxylase. Recent evidence suggests that it is a novel neurotransmitter and exogenous agmatine can modulate behaviour functions including learning and memory. We have recently demonstrated water maze training-induced region-specific increases in agmatine, and raised a novel issue of the participation of agmatine in the processes of learning and memory. The present study further addressed this issue by measuring the levels of agmatine in the hippocampus, parahippocampal region and prefrontal cortex in rats that were trained in the delayed non-match to position task in the T-maze ($n = 7$) with their yoked controls ($n = 7$). Significantly increased agmatine levels were found in the prefrontal ($p < 0.05$), entorhinal ($p < 0.05$) and perirhinal ($p < 0.01$) cortices, but not the sub-regions of the hippocampus, in the T-maze training group relative to the control one. There were significant positive correlations between prefrontal and perirhinal agmatine levels and animals' performance in the T-maze. These results demonstrate T-maze training-induced region-specific increases in agmatine and further suggest the direct involvement of agmatine in learning and memory processing.

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10.2

Behavioural Effects of Agmatine in the Rat are Dose- and Task-dependent

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Accumulating evidence suggests that agmatine, a metabolite of L-arginine, is a novel neurotransmitter and modulates behaviour function, including learning and memory. The present study investigated the effects of repeated pre-test intracerebroventricular microinfusion (once daily) on the reference and working memory versions of the water maze task, as well as the elevated plus maze and open field. Rats with high (100 µg), but not low (10 µg), doses of agmatine displayed reduced exploratory and locomotor activity in the open field on day 1 (received 3 infusions), but not day 12 (received 14 infusions), relative to the saline controls. There was no significant difference between groups in animals' performance on both days in the elevated plus maze tested prior to the open field. In the reference memory version of the water maze task, all three groups performed similarly in the cued navigation (day 2), place navigation (days 3–7) and probe test (day 7). In the working memory version of the water maze task (days 8–11), by contrast, the two agmatine groups generated markedly shorter path lengths and took significantly less time to reach the platform at the 180 s (all $p<0.05$), but not 30 s, delay as compared to the saline group. The present study demonstrates that repeated agmatine treatment produces transient impairments in exploratory and locomotor activity in the open field in a dose-dependent manner. The results of the water maze experiment suggest that agmatine may have differential effects on spatial working and reference memory.

10.3

Chronic Putrescine Depletion Results in Spatial Learning and Memory Impairment in Rats

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Recent evidence suggests that polyamines putrescine, spermidine and spermine are essential in maintaining normal cellular function. The present study investigated the effects of difluoromethylornithine (DFMO), a potent inhibitor of putrescine synthesis, on animals' behaviour and the polyamine levels in the CA1, CA2/3 and dentate gyrus sub-regions of the hippocampus and the prefrontal cortex. Rats with DFMO (3%) in drinking water over 5 weeks were significantly impaired in the place navigation, but not the cued navigation, of the water maze task relative to the controls. When the probe tests were conducted 2 min (Probe 1) and 24 h (Probe 2) after the final training trial of the place navigation, the DMFO group was markedly impaired in probe 2, but not Probe 1. Putrescine supplementation (0.25% putrescine in drinking water) was unable to reverse DFMO-induced performance deficits in the water maze task, although there was improved performance in the task acquisition during the place navigation. DFMO treatment for 8 weeks resulted in approximately 90% and 20% of reduction in the putrescine and spermidine levels across the four brain regions, respectively, with no effect on spermine. DFMO rats with putrescine (0.25%) supplementation in drinking water had 10-30% higher levels of putrescine, but not spermidine and spermine, in the hippocampus and prefrontal cortex as compared to the DFMO only rats. These results demonstrate that chronic depletion of putrescine by DFMO impairs spatial learning and memory in the water maze. Further research needs to be carried out to understand the roles and mechanisms of endogenous putrescine in learning and memory.

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10.4

Excitatory Effects of Histamine on Mammalian Cortical Neurones in Primary Culture

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Histamine has acknowledged roles in the CNS as an agonist at G-protein coupled receptors and it has been associated with ionotropic receptors only in the invertebrate nervous system. Hypothesis: that histamine can modulate native $GABA_A$ receptors in cortical membranes and directly activate $GABA_A$ currents at higher concentrations (as reported for recombinant GABAa isoforms[1]). Cortical cells were cultured for 3-4 weeks prior to patch clamp recording. GABA, benzodiazepines and histamine were applied as pulses through a Y-tube. 1mM histamine and 1 µM diazepam significantly enhanced currents evoked by 3 µM GABA. At ≥3mM histamine a direct current was indeed evoked but it did not reflect gating of the $GABA_A$ chloride channel. At a holding potential of -45 mV, using gluconate filled pipettes, GABA currents and spontaneous IPSCs were outward and the concentration-dependent currents evoked by histamine were inwardly directed. The evoked currents did not appear to saturate even at 100 mM histamine and the apparent reversal potential was extrapolated to circa +100 mV. The excitatory currents were not blocked by glutamatergic receptor antagonists or channel blockers although the GABA antagonist picrotoxin significantly enhanced the inward currents. In conclusion, histamine at 1mM can weakly modulate $GABA_A$ currents but at higher concentrations it activates an excitatory current. The molecular mechanism, pharmacology and physiological relevance of this novel current are being explored in the Lees laboratory.

[1] Saras A et al, *J Biol Chem*, 283, 10470-10475.

10.5

Modulation and Function of the Autaptic Connections of Layer V Fast Spiking Interneurons in the Rat Neocortex

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Neocortical fast-spiking (FS) basket cells form dense autaptic connections that provide inhibitory GABAergic feedback after each action potential. It has been suggested that these autaptic connections are used, rather than voltage or calcium sensitive potassium channels, because of the plasticity afforded by synaptic communication. Furthermore, while the large number of autaptic release sites have been measured anatomically, these connections have not been subject to quantal analysis. Here we show that layer V FS interneurons form autaptic connections that are largely perisomatic, and without perturbing intracellular Cl^- homeostatsis, that perisomatic GABAergic currents have a reversal potential of -78 ± 4 mV. Using variance-mean analysis, we demonstrate that autaptic connections have a mean of 14 release sites (range 4-26) with a quantal amplitude of 101 ± 16 pA and a probability of release of 0.64. We found that autaptic GABA release is sensitive to $GABA_B$ and muscarinic acetylcholine receptors, but not dopamine, 5-HT, adenosine, noradrenaline, μ-opioid, histamine, metabotropic glutamate or cannabinoid receptors. Our results indicate that GABA transporters do not regulate the autaptic connections of FS interneurons. We show that GABA released from autaptic connections does not induce either pre- or post-synaptic effects via the $GABA_B$ receptor, but does act at extrasynaptic $GABA_A$ receptors. Finally, we found that the $GABA_A$ receptor positive modulator zolpidem slows the firing of autaptic basket cells. This research confirms that the autaptic connections of FS cells are indeed plastic, though only via specific GABAergic and cholinergic mechanisms.

10.6

Trafficking of NMDA Receptors by Granule Cells in the Hippocampus

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Recently it has been shown that pyramidal neurons in the hippocampus utilize a novel pathway to traffic NMDA receptors to synapses. In this unique pathway NMDA receptors bypass the somatic Golgi and are instead processed in "Golgi outposts" in the dendrites of pyramidal neurons. Synapse associated protein 97 (SAP97) has been identified as the key protein that directs NMDA receptors through this novel pathway. The current study aimed to identify whether newborn and mature granule cells of the hippocampus also traffic NMDA receptors to synapses via this novel pathway, and at which developmental stage in the life of a granule cell this pathway becomes functional. NMDA receptors are known to be critical for the survival and integration of newborn granule cells. We have found that mature granule cells do have dendritic Golgi outposts whereas newborn granule cells do not. However, immature granule cells do have similar amounts of ER to mature neurons. In addition, we have examined the colocalisation of NMDA receptors in Golgi outposts, ER, ER derived vesicles and with SAP97. Colocalisation of these proteins in mature granule cells was found to be very similar to that in pyramidal neurons of the hippocampus. In summary, mature granule cells, like pyramidal neurons, traffic NMDA receptors to synapses via a unique pathway that bypasses the somatic Golgi and utilizes dendritic Golgi outposts and SAP97. In contrast, immature granule cells appear to lack this pathway and this may contribute to their low integration into neuronal circuits.

11.1

Muscle Fatigue and Hand Function

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Muscle fatigue is defined as an exercise-induced reduction in the force generating capacity of muscle. Here, we investigated the effect of muscle fatigue on hand function and motor learning. Young healthy adults (n=17) performed an object grip and lift task (weight 342 g) five times before and after 2 mins of relaxation or a 2-min sustained maximal pinch grip (that reduced maximal pinch force by ~60%). Pinch grip force (GF), lift force (LF), and first dorsal interosseous electromyographic activity (EMG) were measured. The temporal relation between GF and LF was assessed by cross-correlation of the rate of change in GF (dGF/dt) with the rate of change in LF (dLF/dt). The lift and hold phase of the task were analysed separately. Each parameter was analysed with 3-way repeated measures ANOVA for comparison of condition (fatigue, relaxation), time (pre, post), and lift (1-5). Task performance differed between conditions. The maximum cross-correlation coefficient in the lift phase (P=0.013) and mean GF (P=0.027) and GF/LF (P=0.019) in the hold phase were significantly lower in the fatigue condition (coefficient: 0.75±0.08; mean GF: 5.6±1.5 N; GF/LF: 1.67±0.45) than in the control condition (coefficient: 0.78±0.05; mean GF: 6.3±2.0 N; GF/LF: 1.91±0.60). However, root mean square EMG (lift phase) was significantly greater in the fatigue condition (0.58±0.30 mV) than in the control condition (0.38±0.18 mV; P=0.024). Our results suggest that the pattern of motor learning within each set of five lifts is unaffected by fatigue. However, fatigued subjects require more EMG to perform the task but produce less force and are less able to match changes in LF with changes in GF.

11.2

The Impact of Age on the Voluntary Inhibition of Motor Overflow

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Motor overflow is involuntary movement or muscle activity that may coincide with voluntary movement. This study examined whether 16 young adults (18–30 years) and 16 older adults (50–80 years) were able to voluntarily inhibit motor overflow. Participants performed a finger pressing task by exerting 50% of their maximal force output using their dominant or non-dominant hand. Initially, participants were not informed regarding their involuntary movement in the non-task hand, but under proceeding conditions were informed and asked to ignore their overflow, and then to inhibit overflow with, and without, visual feedback. Older adults were categorized into "good" and "poor" performers based on their ability to maintain the target force. Results demonstrated that all participant groups were able to significantly reduce their overflow when requested, irrespective of the presence of visual feedback. "Good" performing older adults exhibited significantly less overflow when informed that their involuntary movement was being recorded, compared to when they were uninformed, despite not being asked to inhibit it. "Good" performing older adults also exhibited greater overflow when their left hand was task active. In contrast, "poor" performing older adults, like young adults, did not demonstrate a significant difference between overflow exhibited in the uninformed and the informed conditions, despite a significantly greater magnitude of overflow and worse task performance compared to young adults. These findings suggest the presence of motor overflow is dependant on both motor and cognitive processes. Despite age related brain deterioration, some older adults are able to adapt and effectively recruit cognitive and motor resources in a manner compensatory to such changes.

11.3

Motor Imagery Induces Changes in Corticospinal Excitability in the Limb not Exposed to an Imagined Task

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Neuroimaging studies have demonstrated that motor imagery and actual movements share at least in part common neural substrates. Motor imagery could therefore be a useful tool for promoting beneficial cortical plasticity post-stroke. Previous studies of single joint upper extremity motor imagery have demonstrated temporal modulation of cortical excitability similar to the performance of the actual task. Furthermore, studies have shown that both actual and imagined hand movements increase corticospinal excitability in both the contralateral and ipsilateral primary motor cortex. The purpose of the current study is to determine whether lower extremity motor imagery can induce temporal changes in corticospinal excitability that resemble the modulation observed during actual task performance. We also aim to identify whether imagined movements of one limb can reproduce the temporal pattern of corticospinal modulation associated with actual movements of the contralateral limb. Ten seated healthy individuals were instructed to perform active or imagined repetitive ankle dorsiflexion movements at 1 Hz which were coupled to an auditory cue. Electromyographs were recorded from the tibialis anterior (TA) of both legs, and the first dorsal interosseus (FDI) muscle of the dominant hand. Transcranial magnetic stimulation (TMS) was applied over the vertex of the skull 200, 400, 600, 800 and 1000ms prior to the auditory cue at 110% of resting threshold for the right and left TA muscles. The amplitude of TMS-induced motor evoked potentials (MEPs) at each stimulation latency was compared between the actual and imagined tasks. Results: Imagined dorsiflexion induced time-dependent changes in corticospinal excitability which mirrored those observed during active dorsiflexion. While the amplitude of MEPs was consistently smaller during imagined movements, the temporal pattern of MEP modulation was consistent with that observed during active movement. A task-appropriate pattern of MEP modulation was also observed when subjects imagined performing rhythmic dorsiflexion task with the foot contralateral to that used in the active movement condition. These data support the idea that motor imagery can have dynamic effects on the excitability of motor cortex similar to those seen during actual movement performance induce modulation of corticospinal excitability that is appropriate for performing the imagined task. Our observations also suggest that it is possible to induce task-appropriate modulation of corticospinal excitability in a limb that has not been exposed to the active task. The ability to transfer patterns of corticospinal modulation between limbs may make this technique a viable candidate adjuvant therapy for stroke survivors.

11.4

Task-dependent Modulation of Inputs to Proximal Upper Limb Following Transcranial Direct Current Stimulation of Primary Motor Cortex

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Cathodal transcranial direct current stimulation (cTDCS) suppresses excitability of primary motor cortex (M1) controlling contralateral hand muscles. The present study was conducted to assess whether cTDCS has similar effects on M1 contralateral pathways to proximal upper limb muscles. Transcranial magnetic stimulation (TMS) of left M1 was used to elicit motor evoked potentials (MEPs) in the right and left infraspinatus (INF) muscle immediately before cTDCS of left M1, immediately after, and at 20 and 40 minutes post-stimulation. TMS was delivered as participants pre-activated the INF in isolation (Left) or both INF bilaterally (Bilateral). MEPs in the distal hand muscle, right first dorsal interosseus (FDI), were suppressed following cTDCS ($P < 0.000$) in agreement with previous findings. In contrast, changes to right INF MEPs were variable with no strong trend for suppression ($P > 0.34$). The ipsilateral silent period duration in the left INF was reduced after cTDCS ($P < 0.05$), indicative of altered transcallosal inhibition. However, left INF MEPs were *suppressed* after cTDCS in the Left condition, but *facilitated* during the Bilateral condition ($P < 0.05$) after cTDCS indicative of task-dependent modulation. The after-effects of cTDCS on neural pathways to contralateral proximal upper limb muscles differ from those to distal muscles. Effects of cTDCS on ipsilateral proximal muscles are task-dependent. This may have implications for the use of TDCS as an adjuvant to therapy after stroke.

11.5

Treadmill Walking for Non-ambulatory Patients During Inpatient Stroke Rehabilitation: The MOBILISE Trial

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Treadmill walking as an intervention for stroke rehabilitation is often thought to be the result of stimulating central pattern generators. However, an alternative hypothesis is that it allows more practice of the whole task of walking, especially when used with body weight support. The main objective of this randomised trail, therefore, was to determine whether treadmill walking was effective at establishing independent walking more often and earlier, than overground walking for non-ambulatory stroke patients. A prospective, randomised trial of inpatient intervention with a 6 month follow-up with blinded assessment was conducted. 127 stroke patients who were unable to walk independently early after stroke were randomly allocated to an experimental group (treadmill walking with partial weight support) or a control group (overground walking) within 4 weeks of their stroke. Both groups were restricted to up to 30 minutes per day and the help of one therapist. The primary outcome was the proportion of participants achieving independent walking each week. At one month, 41% of the experimental group was walking independently compared with 29% of the control group, at 2 months 65% compared with 52% and at 6 months 71% compared with 59%. In addition, 50% of the experimental group were walking by 5 weeks whereas it took further 2 weeks until 7 weeks for 50% of the control group to be walking. There were few adverse events in either group. Treadmill walking with body weight support appears feasible, safe and results in more people walking independently after stroke and earlier.