1.1

Gene-based Medicines for Treatment of Neurological Disease

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The application of gene-based strategies for treating or alleviating the symptoms of neurological disease holds enormous potential but to date, only a small number of these have been trialled in human patients. Within the last decade, advances in the development of gene transfer agents that can mediate long-term and stable expression of foreign genes in neurons with no inherent toxicity and built-in safe guards within the design of the therapeutic strategy has led to the translation of this work from the bench to the clinic. Adeno-associated viral (AAV) vectors which are non-pathogenic viruses genetically modified to carry a therapeutic gene cassette are considered by many in the gene therapy research arena to be the vector of choice for human gene therapy. In this seminar, I will discuss the general principles and our experiences with the development of gene-based therapeutic strategies for Parkinson's disease and other neurological diseases.

1.2

Rat Model of Huntington's Disease Generated by rAAV Vector-Mediated Gene Transfer

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Advances in understanding the neuropathology of Huntington's Disease (HD) have been facilitated by the development of a variety of animal models. Several transgenic mouse models of HD have been reported, which recapitulate some of the features of HD in humans. However, transgenic mouse models exhibit deficiencies in replicating hallmark features of HD such as lack of substantial striatal neuronal degeneration. Also, transgenic models cannot currently be developed in higher organisms such as non-human primates, limiting translational therapeutics screening. We have generated a model of HD in the rat using recombinant adeno-associated virus vector-mediated gene transfer into the striatum of an expression cassette encoding exon 1 of the huntingtin gene with 70 CAG repeats (HD70). Expression of HD70 progressively and rapidly leads to neuropathological features associated with HD. These include the formation of intranuclear inclusions that are immunopositive for ubiquitin and molecular chaperones, substantial striatal neuronal loss, reactive astrogliosis, striatal atrophy, and body weight loss relative to controls over 8 weeks. Behavioural assessments revealed HD70 rats displayed hyperactivity in an open field. HD70 rats showed impaired freezing ability, as well as choreiform-like movements following shock administration and impaired contextual memory in the fear-conditioning test. These results support the use of this model as a tool for the further elucidation of the biology of HD and as a platform for testing therapeutic strategies.

Support: NZ HRC.

1.3

Puberty, Reproductive Endocrinology and Reproductive Performance in Sheep with Batten Disease (CLN6)

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Reproductive disturbances have been reported in Batten disease patients. However, the genetic heterogeneity of subjects, clinical variation and medications complicate assessment. We have systematically investigated aspects of reproductive physiology in a uniform group of CLN6 sheep. Onsets of puberty and pituitary responsiveness to gonadotrophin releasing hormone (GnRH) during the peri-pubertal period were similar. Onset of testis size increase was similar in affected and heterozygous rams, but the increase was slower in affected animals. Testosterone peri-pubertal profiles were similar.The first ovulation in affected ewes was delayed by 4 weeks. Basal lutienising hormone concentrations were similar in all animals. Responsiveness to GnRH was similar in peri-pubertal rams and ewes (23 to 40 weeks). There was a clinically insignificant increase in pituitary response in affected animals after 31 weeks. The other differences could be attributed to slower growth rate in the affected animals. Affected mature rams with clinical disease are fertile (69% lambing). Affected ewes show a lower response (6.7 corpus lutea/ewe) to superovulation than controls (9.8 corpus lutea/ewe) and yield fewer good embryos, which mature more slowly at first although their viability is not compromised. The hypothalamic, anterior pituitary and gonadal histology of animals with advanced disease is normal. We found no evidence of precocious puberty or any other endocrinal disturbance in the affected sheep. In fact their reproductive capacity remains remarkably intact despite severe brain atrophy and clinical disease.

1.4

Decreasing Endogenous Secreted Amyloid Precursor Protein Reduces Long-term Potentiation in Anaesthetised Rats

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The leading hypothesis for the cause of Alzheimer's disease is an intracellular accumulation of the neurotoxic peptide, amyloid-b (Ab). Concomitant with the rise of Ab is a decrease of secreted amyloid precursor protein (sAPPa), a neurotrophic fragment cleaved from the same parent protein as Ab. Exogenous sAPPa enhances behavioural memory and learning in rats, and hippocampal long-term potentiation *in vitro*. The present research investigates the role of endogenous sAPPa in the induction of LTP *in vivo*. Adult male Sprague-Dawley rats were anaesthetised with urethane and acutely implanted bilaterally with a recording electrode and cannula in the dentate gyrus, and stimulating electrode in the perforant path. Following 30 min of stable baseline recordings, saline, sAPPa- or non-sAPPa-binding antibodies were injected into the hippocampus. Thirty min after the injection, LTP was induced with 50 trains of HFS (400 Hz), and monitored for 2 h. The two groups injected with sAPPa-binding antibodies showed a sustained and significant reduction of LTP of the synaptic potentials (30 ± 2%, n=5, $p<0.015$; and 32 ± 8%, n=4, $p<0.035$) compared to the combined saline and IgG antibody injected group (57 ± 6%, n=8). Furthermore, the LTP induced in the two groups injected with non-sAPPa-binding antibodies (45 ± 4%, n=4, $p>0.45$; and 41 ± 8%, n=4, $p>0.71$) was not significantly different from a second saline injected group (43 ± 6%, n=4). These results suggest that endogenous sAPPa in the hippocampus may contribute to the induction of LTP. Therefore, the decrease of sAPPa during the pathogenesis of AD may contribute to the memory deficits observed in AD.

1.5

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

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This study used a physiologically relevant mode of ethanol delivery to investigate the acute effects of a single ethanol binge on the neonatal rat forebrain. Sprague Dawley rat pups 7 days of age were exposed to ethanol (E4.5 - 4.5g/kg/day or E6.6 - 6.6g/kg/day ethanol in two feeds via intubation) or sham intubated (control group) (n=6 pups per group). Ten hours following ethanol delivery pups were killed. The forebrain was frozen and serially sectioned at 10µm. Matched, coded sections were stained with Hoescht 33342 or Haematoxylin. Semi-quantitative methods were used to determine the number of apoptotic nuclei per unit area in specific subregions of the forebrain. ANOVA with posthoc analysis (SPSS) indicated that specific brain regions across treatment groups were significantly different ($p<0.05$). The density of apoptotic nuclei ($x10^{-6}$) per μm^2 for the entire neocortex was 16.20 ± 11.51 in the control group compared to 62.40 ± 30.87 in the E4.5 group and 144.96 ± 34.78 in the E6.6 group. Ethanol also induced significant acute apoptotic cell death in the frontal and cingulate cortices and the hippocampal subregions, CA1 and dentate gyrus. The acute cell death observed in this study suggests that a single binge of alcohol during human third trimester development may induce similar cell death in the fetus. Whether this cell death leads to permanent anatomical and functional deficits is yet to be determined.

2.1

Time to Remember: Foreperiod Duration Affects Motor Preparation

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Partial or complete information about an upcoming movement response provided via the parameter precuing technique has been shown to affect reaction time (RT). As uncertainty about the nature or number of parameters increases, RT becomes longer. In this study the duration (foreperiod) between precue and stimulus presentation was varied to minimise anticipatory errors. The effect of the nature and number of parameters, and foreperiod duration on motor preparation was investigated by measuring changes in cortical and muscle activity and RT. Twelve participants each performed 1280 trials. Five parameter precue conditions comprising simple, two- and four-choice RT tasks utilised hand (left or right) and direction (left or right) precues. The precue (500 ms) was followed by a foreperiod (1000, 1500 or 2000 ms) then the imperative visual stimulus. Precues provided no, partial or complete information about the response hand, response direction or muscle associated with one, two or four targets. The distribution of parameter, target and foreperiod was randomised in each block of 80 trials. Across all parameter/target conditions RT, premotor time (PMT) and response time were significantly ($p < .005$) slower for the 1000 ms foreperiod. Latencies for the 1500 ms and 2000 ms foreperiods were faster and not different from each other ($p > .05$). Foreperiod duration did not significantly affect motor time (MOT), movement time or the amplitude of the lateralised readiness potential (LRP). The amplitude of the contingent negative variation (CNV) potential measured as the average of 100 ms preceding stimulus onset at both C3 and C4 electrodes was significantly larger for the 2000 ms foreperiod than for the 1500 ms foreperiod that in turn was significantly larger than the 1000 ms foreperiod. The observations that longer foreperiod are associated with shorter RT, PMT, response time and larger CNV amplitude indicates a central effect on motor preparation. The null effect of foreperiod duration on MOT lends support to this interpretation.

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2.2

Failure Of Voluntary Drive To Muscle During Hyperthermia

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Fatigue is increased during sustained maximal voluntary contractions (MVCs) performed with hyperthermia. This is partly caused by a greater decline in voluntary activation of muscle. The present study aimed to localise the site of failure of voluntary drive during hyperthermia. Subjects (n=7) made brief and sustained MVCs of elbow flexors in two experiments. Core temperature was normal (~37°C) in the first and elevated (~38.5°C) in the second. During MVCs, motor cortex stimulation was delivered and the evoked torque (superimposed twitch) and EMG responses were measured. With hyperthermia, voluntary torque was reduced by ~12% during sustained MVCs ($p=0.01$) and the superimposed twitch was ~50% larger ($p=0.01$). Thus, the ability to drive the muscle maximally in a sustained fashion was decreased and some motor cortical output, which could have increased torque, remained untapped by voluntary drive. This additional 'central fatigue' was not associated with altered motor cortical excitability as EMG responses to stimulation were similar at the two temperatures ($p<0.05$). Furthermore, cardiovascular changes were an unlikely contributor because mean arterial pressure was similar in both conditions. However, the peak relaxation rate of muscle increased by ~20% ($p=0.005$) with hyperthermia. Hence, faster motor unit firing rates would be required to produce fusion of force. The increased central fatigue during hyperthermia may represent a failure of descending voluntary drive to compensate for changed muscle properties despite the availability of additional motor cortical output.

2.3

Coordination Modulates Excitability Within Motor Cortical Networks

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Human neurophysiological experiments undertaken within the context of rhythmic manual performance indicates that there is extensive modulation of excitability in motor pathways that occurs in phase with movement kinematics, even in the absence of voluntary activation. This modulation of excitability crosses the midline and extends to bimanual performance where interactions between the hands are twofold and paradoxical. On the one hand (no pun intended), unimanual movement is characterised by an increase in excitability, or facilitation, in the motor pathways that drive musculature in the contralateral hand. On the other hand, at certain times, the net change in excitability may also be inhibitory and functionally relevant e.g., to prevent the emergence of mirror movements. Results from a few recent studies using TMS during rhythmic manual performance will be presented to illustrate that excitability of motor cortex circuitry devoted to hand musculature is modulated according to the *stability* of movement within the context of coordination. Such coordination may occur with respect to the opposite hand, the ipsilateral foot, or quite remarkably, an auditory pacing stimulus. These findings reinforce the view that perceptual-kinematic parameters can be modified contextually to derive beneficial changes to promote functional recovery after injury or disease.

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2.4

Movement Relationships of Pedunculopontine Tegmental Nucleus Neurons in the Rat

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Recent evidence suggests that the pedunculopontine tegmental nucleus (PPTg) is involved in the pathological processes of Parkinson's disease and may be a useful location for deep brain stimulation therapy for this condition. Although it has close connections with the basal ganglia and brainstem motor systems and lies within the brainstem "locomotor area" it is not known if neurons in the nucleus are involved in discrete goal-directed movements of the forelimb. We recorded from 44 PPTg neurons in conscious rats performing a skilled reaching task, using chronically implanted microwire electrodes. Neural activity was analysed with peri-event time histograms centred on the end of the extension phase of the reach. A majority of the recorded cells (31/44, 70%) showed some movement related activity. These cells had a significantly higher firing rate (22.7 ± 24.6 Hz, mean ± SD) than cells that were not modulated during the task (6.7 ± 10.0 Hz, $p < 0.01$, t-test). Most movement-related cells (71%, 22/31) showed reductions in firing rate, beginning on average –211 ± 365 ms prior to the end of the extension phase. The duration of inhibitions (0.93 ± 0.56 s) was significantly longer than for excitations (0.55 ± 0.41 s, $p < 0.05$), but there was no difference in onset time. These data show for the first time that PPTg is actively engaged during skilled forelimb movements.

Supported by the Neurological Foundation of New Zealand.

2.5

Central Neuromuscular Fatigue Following Stroke

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Neuromuscular fatigue is an acute impairment in the ability to exert muscular force immediately following or during an activity. Studies of neuromuscular fatigue in Multiple Sclerosis and Amyotrophic Lateral Sclerosis, suggest that the CNS may be an important site in the development of neuromuscular fatigue, but there is limited research on fatigue following stroke. The CNS has been idenifited as the primary cause of muscle weakness in people with stroke via a reduction in voluntary activation of the muscle. The aims of this study were to; a) investigate whether people with stroke developed proportionally greater amounts of neuromuscular fatigue compared to unimpaired participants; b) to elucidate the primary site of neuromuscular fatigue, and c) to consider the relationship between the site of fatigue development and voluntary activation. Fifteen people with stroke and 15 neurologically unimpaired people were included in the study. Neuromuscular fatigue was assessed during a 90s sustained maximal isometric contraction of the quadriceps muscle. The contribution of central neuromuscular fatigue was evaluated using twitch interpolation. Preliminary data analysis suggests that the development of central neuromuscular fatigue may be related to the degree of voluntary activation deficit in stroke participants. Those who have lower levels of voluntary activation during maximal voluntary contraction demonstrate less central neuromuscular fatigue during sustained activity. This might suggest the central neuromuscular fatigue is mediated by peripheral feedback mechanisms.

2.6

Intracortical Inhibition During Volitional Inhibition of Prepared Action

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The ability to inhibit prepared action or 'volitional inhibition' is a necessary motoric function. Neurophysiological evidence suggests volitional inhibition is achieved via a pathway involving the prefrontal cortex and basal ganglia before converging on the primary motor cortex (M1). The output of M1 is determined by the net balance of excitatory and inhibitory inputs onto corticospinal tract neurons. The purpose of this study was to investigate the role of intracortical inhibitory circuits within M1 during the volitional inhibition of prepared action. A volitional inhibition paradigm was employed whereby the subject was required to make an anticipated response (lift their index finger off a depressed key) 800 ms into a 1s sweep dial revolution (Go condition). On some trials, the clock hand sweep would stop prior to the anticipated response and on these trials the subject was required to inhibit their response by keeping the key depressed (Stop condition). Single and paired pulse transcranial magnetic stimulation (TMS) was applied over contralateral M1 immediately prior to execution of the anticipated response to investigate corticomotor excitability and intracortical inhibition of hand muscle representations. Electromyography (EMG) was used to record motor evoked potentials (MEPs) from the right *first dorsal interosseus* (FDI), *abductor pollicis brevis* (APB), and *first volar interosseus* (FV) of 14 participants. Corticomotor excitability was significantly suppressed in the agonist FDI for Stop compared to Go while it was unchanged in APB. Intracortical inhibition was significantly enhanced in both FDI and APB for Stop relative to Go. These results provide evidence of modulation of GABAergic inhibitory circuits in M1 during volitional inhibition tasks.

3.1

Priming of One Hippocampal Input Pathway Inhibits LTP and Promotes LTD in a Separate Pathway

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It has been suggested that for LTP and LTD to underlie information storage, homeostatic regulation of synaptic plasticity is required to maintain synapse strength within a dynamic range. This homeostatic regulation has been implemented in the Bienstock, Cooper and Munro (BCM) model by $\grave{e}_M$, a sliding modification threshold for plasticity that is dependent on previous levels of postsynaptic activity. An important feature of the BCM model is that a shift in $\grave{e}_M$ would affect subsequent plasticity at all synapses on a cell rather than just those previously active. We examined whether a high-frequency priming protocol applied to one input pathway affected the subsequent plasticity induced in a second pathway. Following stimulation of the Schaffer collaterals, field excitatory postsynaptic potentials (fEPSPs) were recorded in area CA1 of acute hippocampal slices from 6-7 week male Sprague-Dawley rats. The priming protocol consisted of two sets of three 100 Hz 1s trains (20s intervals between trains), with 15 min between sets. The priming protocol itself caused LTP in one pathway but on the non-primed pathway significantly reduced the level of subsequent LTP in response to 50 Hz and 100 Hz stimulation protocols and increased LTD induced by 10 Hz conditioning. These results are similar to those of Wang and Wagner (1999) and suggest that homeostatic regulation of a cell's total synaptic input strength may play an important role in hippocampal plasticity and information storage.

3.2

Parameters of Human LTP

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Rapid presentation of a visual stimulus leads to a prolonged increase in the N1b component of the visual evoked potential. In earlier experiments, we have demonstrated that this effect lasts up to one hour post rapid stimulation. In order to further explore this effect, two parameter studies have been conducted. The goal of the first study was to determine the optimum rate of presentation of the visual stimulus during the testing phase (the pre and post blocks). We tested 4 rates of stimulus presentation (1Hz, 0.5 Hz, 0.25 Hz, and 0.0625Hz), and collected VEPs for two blocks at each rate. At all rates, VEPs were stable over the two blocks of testing, however the amplitude of the N1b component was largest for the two intermediate rates (0.5Hz and 0.25Hz), and the slowest rate (0.0625 Hz) contaminated the VEP with a P300 like response, probably due to temporal uncertainty. The second parameter examined was the frequency of tetanic stimulation. Currently, data has been collected at two frequencies (5 Hz and 9 Hz), with 9Hz demonstrating a significant post-tetanus increase in the N1b, while the 5Hz rate resulted in no significant increase, unless only a very limited set of electrodes are examined. Data from two additional tetanus rates are currently being collected (one slower and one faster than above) in order to explore any possible relationship between the size of the increase and the rate of stimulation.

3.3

Alterations in Glutamate Receptor Subunit Expression in the Rat Dentate Gyrus Associated with Long-term Potentiation

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Persistence of long-term potentiation (LTP) is dependent on *de novo* protein synthesis. However, the mechanism by which LTP is maintained over long periods is unknown. This study aimed to determine whether persistent LTP is also accompanied by increased a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) subunit expression. Total protein, cell surface, and synapse-enriched extracts were prepared from rat dentate gyri 48 h following *in vivo* unilateral tetanic stimulation of the perforant path, and compared against corresponding fractions obtained from the control non-tetanised hemisphere. Western Blot analysis revealed that both GluR1 and GluR2, which are components of activity-dependent membrane insertion and constitutive rapidly cycling AMPARs respectively, were elevated in total protein extracts (GluR1 45 ± 20%, n=11, $p<0.01$, Student's t-test; GluR2 36 ± 16%, n=11, $p<0.05$) but not in cell surface extracts (16 ± 15%, n-8; 29 ± 27%, n=6) or synaptic fractions (10 ± 10%, n=9; -8 ± 13%, n=7). As GluR3 levels showed no change in total protein (-3 ± 7%, n=12) or surface extracts (-2 ± 15%, n=4) these data suggest that LTP results in increased reserve pools of GluR1 and GluR2 which are not synapse-associated.

3.4

SAP97 Spliced Isoforms Dictate SAP97 Neuronal Localization, Activity-dependent Regulation, and Regulated Recruitment of GluR1 to Synapses

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SAP97 is a member of the MAGUK family of synaptic proteins that binds the glutamate receptor subunits GluR1 and NR2A. Alternative splicing of the SAP97 gene generates multiple neuronal SAP97 isoforms, resulting in the insertion of distinct sequences between the SH3 and GUK domain: I3, QI3, I2, I2I4, I2I4I5. We have investigated how SAP97 alternative splicing dictates the functional role of SAP97 in GluR1 synaptic trafficking. Transfection of GFP-tagged SAP97 isoforms into neurons showed that only some isoforms of SAP97 are localized to the synapse, indicating that these isoforms may direct GluR1 to the synapse. Co-transfection of GluR1 with SAP97 isoforms showed SAP97-I3 either directly or indirectly regulates GluR1 trafficking in a manner dependent on CaMKII activation. Interestingly, the diffusely expressed SAP97-I2 isoform is also key in GluR1 trafficking in an activity-dependent manner. These studies show that alternative splicing of SAP97 dictates its synaptic localization and activity-dependent regulation, and this has functional consequences for recruitment of GluR1 to synapses.

3.5

Is Sensory-Induced Long-Term Potentiation Spatial Frequency Specific?

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Prior research at this department has found that Long-Term Potentiation (LTP) -like changes can be induced using sensory stimuli, such as visually presented checkerboards. The aim of the current study was to investigate whether sensory-induced LTP is specific to the spatial frequency content of visually-presented stimuli. Sine gratings of two different horizontal spatial frequencies (3 and 10 cycles per degree (cpd)) were presented to subjects before and after a tetanus. The tetanus consisted of horizontal sine gratings, of one of the spatial frequencies (3 or 10 cpd), presented at a rate of ~8.6Hz. Early results indicate a modulation of ERP components occurring only for the grating that is the same spatial frequency as the tetanus. These findings indicate that LTP isolates spatial frequency channels in the visual cortex. Therefore, LTP can be used to investigate the contribution of spatial frequency information toward higher-order cognitive processes, such as local-global processing.

3.6

Recovery of Function Following Exposure to MDMA

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The 2004 World Drug report revealed that the use of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') and other synthetic amphetamine-derivatives is widespread and still increasing. Decreased serotonin transporter (SERT) binding and serotonin (5-HT) levels are two consistently observed neurological consequences of MDMA exposure in animals. Interestingly, many studies have suggested recovery to control levels following exposure. However, the functional relevance of the deficits and a parallel recovery has not been documented. In the present study, the potency and efficacy of MDMA in producing hyperactivity was explored in groups of rats that had been pretreated with MDMA either 2 or 12 weeks prior to the test. MDMA produced dose-dependent hyperactivity in control rats in the groups that had received prior treatment with MDMA. There was a downward shift in the dose-dependent magnitude of the MDMA-produced increase in activity for the group that received MDMA 2 weeks prior to the test. This decreased efficacy of MDMA was not observed in the rats treated 12 weeks prior to the test, suggesting recovery of function. These findings suggest that exposure to MDMA produces neuroadaptation, resulting in a temporary decrease in function.

Poster 4.1

Structural Determinants of BK Channel Inhibition by Lolitrems

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BK ion channels are expressed in many tissues, including the brain, where they regulate important physiological processes such as neuronal excitability. The channels are voltage and calcium regulated. BK channels are potently inhibited by lolitrem B the major toxin implicated in perennial ryegrass staggers a nervous disorder of livestock grazing ryegrass-dominant pastures. The lolitrems, dominated by lolitrem B, are neurotoxic indole-diterpenoid compounds that have been isolated from ryegrass seed infected with the endophyte fungus *Neotyphodium lolii*. To investigate what structural features of the lolitrem class of compounds are required for BK channel inhibition, structural variants of lolitrem B were tested. The effects of lolitrems on BK channel function were investigated using inside-out membrane patches from HEK293 cells stably expressing *hSlo* channels. BK channels were activated by depolarizing voltage pulses in the presence of 10ì M free calcium. Lolitrem E potently inhibited *hSlo* potassium currents at similar concentrations to lolitrem B (IC_{50} of 4 nM), while 31-*epi*lolitrem B and lolitriol were less inhibitory than lolitrem B by about 10-fold and 100-fold, respectively. These results suggested that the presence of an acetal-linked isoprene unit, such as present in lolitrem B, is important for high affinity lolitrem binding to BK channels.

Poster 4.2

Histamine H_3 Receptors Regulate Ionotropic GABAergic Transmission in Mouse Medial Prefrontal Cortex (mPFC)

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Histamine H_3 receptors represent a new class of G-protein coupled receptor (GPCR). The receptors have a predominately presynaptic distribution and the mPFC expresses one of the highest densities of H3 receptors in the entire brain yet the functional role of these is yet to be studied. 450 micron coronal slices were isolated from 6-8 week old C57/BL6 mice (euthanased by IP barbiturate administration). Experiments were conducted at room temperature (22-24^{0}C) using the blind whole-cell voltage-clamp technique. We isolated evoked inhibitory postsynaptic currents (eIPSCs) in layer V mPFC neurons by stimulating in layer V close to the recording site in aCSF containing kynurenic acid (2mM). eIPSCs were presumably GABAergic as they were outwardly rectifying (in asymmetric salines), had a predicted reversal potential for a chloride current and were picrotoxin (100µM) sensitive. The selective H3 receptor agonist R-a-methylhistamine (100nM) strongly reduced the amplitude of eIPSCs (70% ± SEM 12% block in 4 sensitive cells, 2 of the treated cells were refractory to modulation). This is the first electrophysiological study to confirm that H_3 receptor activation inhibits GABAergic transmission at ionotropic synapses in intact brain structures. $GABA_A$ receptors are acknowledge targets for anxiolytic, hypnotic and anticonvulsant allosteric modulators which have many side effects (including unwanted sedation, tolerance, habituation and amnesia). Subtle presynaptic modulation of the $GABA_A$ system via H_3 receptors holds much promise for drug design.

Poster 4.3

Molecular Approaches for Understanding Antidepressant Function

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Genetic variation in individuals may affect their ability to respond to antidepressant drug treatment. As a means of identifying genes that may be important in antidepressant response, we are exploring the molecular effects of antidepressants in the brain. For this purpose we have developed a mouse embryonic stem (ES) cell-derived neuronal culture model, and exposed it to the selective serotonin reuptake inhibitor paroxetine. Microarray and proteomic assays were developed to look at genes and proteins that show altered expression and a range of genes and proteins were identified as being differentially expressed between drug and control. These molecular changes are currently being validated by qPCR and immunoblotting analysis. One protein, creatine kinase-brain, downregulated in the drug-treated proteome, has been successfully validated. The ultimate goal of this project is to develop a model system to identify genes that may be relevant to clinical responses to antidepressant treatment. Genes identified in the model system may play a role in cellular and molecular responses to antidepressants, and therefore inherited variation in these genes may contribute to inter-individual variability in antidepressant response. As candidate genes are derived from the model system, polymorphic variants will be identified in the human equivalents. These will then be used in allelic association studies in a clinical research setting to test their validity and relevance to antidepressant drug response.

Poster 4.4

An Ontological Representation of Gene-brain Diseases

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This work applies an ontology engineering approach to build a biomedical informatics knowledge base that aims to support knowledge discovery in biomedicine. Ontology specifies at a higher level what classes of concepts are introduced for the application domain and what classes of relations exist between these concepts classes. In this biomedical ontology we are representing crucial neuronal parameters like AMPA, GABA, NMDA, SCN, KCN and CLC that play major role in most of the mental disorders. The ontology representation enables a better understanding of the relationships between genes/proteins involved in brain disorders and the representation of the gene regulatory networks. The ontology is further integrated with the Computational Neurogenetic Modelling (CNGM) approach in order to evaluate its results. CNGM integrates dynamic gene networks with an artificial neural network model, in order to bring new original insights into how genes influence the dynamics of brain neural networks. We represent graphically, gene-brain knowledge and biological properties like discovered conserved residues and motifs, protein length, molecular weight, location of gene on a chromosome, mutation etc. These interacting elements enhance the chances of correct tuning the gene interaction network and in assignment of initial gene/protein expression values through which different states of the neural network operation can be achieved and the desired behaviour of the neural network can simulate certain brain states like epilepsy of several types.

Poster 4.5

Sequence Analysis of Subunit Neuronal Information-processing Parameter Proteins AMPA, GABA and NMDA to Facilitate Neurogenetic Modelling

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A complex interaction between genes and proteins in neurons affect the dynamics of the neural networks in the brain and is a major challenge for Neurogenetic Modelling (NGM). Complete understanding through molecular sequence analysis will enhance the chances of correct tuning gene interaction matrix thus strongly enhances the biological plausibility of neurogenetic models. This study aimed to analyse 20 subunit proteins of AMPA, GABA and NMDA that play a major role in most of the mental disorders through the direct or indirect interactions with several other genes/proteins. Sequences were retrieved from NCBI and analysis was performed for these 20 proteins using bioinformatics methods like discovering the motifs (MEME, p-value < 0.0001) and multiple alignment approach (CLUSTALW). Our result indicates 3 conserved motifs among 11 proteins and we found many conserved residues among all 20 proteins. The most interesting observation is the consistent conservation of phenylalanine (F at position 274) and leucine (L at position 360) in all 20 proteins with no mutations. We expect these residues to play some role as a binding centre for interaction of these proteins. We also obtained phylogenetic trees that indicated that all 20 subunit proteins are evolutionary closely related. Based on these observations we hypothesize that all the subunits may be collectively required for proper functioning and should be assigned as a single weight in gene matrix for NGM.

Poster 4.6

Kinematic Analysis of Tremor In Niemann-Pick Type C (NPC) Using Accelerometry and a Novel Spiral Analysis Technique

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NPC is a lipid storage disease associated with motor dysfunction including ataxia, dystonia, choreoathetosis, and action tremor. A clinical study in NPC patients is ongoing to assess safety and efficacy of oral miglustat. Tremor assessments in this study use accelerometry and a novel spiral analysis technique. The first detailed kinematic description of 15 NPC patients, at entry into the study entry, is presented. Upper limb accelerometry measurements were taken during rest, arms extended, and finger-to-nose conditions. Computerized spiral analysis was performed, expanding the subjective neurological assessment of freely drawn spirals to a quantitative kinematic assessment kinematics. Accelerometry showed large amplitude, low frequency, erratic movements, absent at rest, present during postural measurements, and most severe with action. 53% patients had postural tremor in the upper limbs (1.0±1.0 mm, 2.9±1.2 Hz), which decreased significantly in amplitude with loading ($p<0.05$). 80% had action tremor induced by finger-to-nose movements (4.8±3.6 mm, 4.2±2.1 Hz) with significantly larger amplitudes than postural tremor - ($p=0.03$). Spiral analysis showed that NPC patients exhibited significantly greater spatial deviations, greater rate of change in deviation patterns, higher pressure, and lower speeds compared to age-matched controls ($p<0.05$). Findings are consistent with the clinical spectrum of NPC, with increased motion resulting in more prominent dysfunction. High amplitude variability and change rate in spiral analysis likely reflect choreoathetosis or dystonia.

Poster 4.7

Poster 4.8

'Using our Brains' An Australian Tissue Resource Centre

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The aim of the Tissue Resource Centre (TRC) is to provide researchers, high quality fixed and frozen human brain tissue. The TRC is currently focusing on schizophrenia and allied disorders, Alzheimer's disease, alcoholism, motor neurone disease and control cases. There are inclusion criteria including: post mortem interval less than 60 hours; optimal agonal state (e.g. no long term hypoxia or hypotension); no proven infectious diseases; no history of IVI drug abuse and no unexpected neurological disorders. All cases are examined neuropathologically and neuropsychiatric cases are characterised according to the DSM-1 V criteria. There are standard procedures for tissue processing. One hemisphere is fresh frozen and one fixed (randomised). Prior to freezing the hemisphere is sliced into 1.0cm coronal slices and a set of routine blocks are taken. All frozen tissues are kept at -80°C. The other hemisphere is fixed in 10% buffered formal-saline, embedded in agar and sliced coronally at 3mm intervals. Tissue blocks from these slices are used for neuropathological analysis and for research purposes. To date the brain bank has over 400 specimens including cases of schizophrenia, depression, alcoholism, Alzheimer's disease, motor neurone disease, and control cases. This material has already proven useful for a range of different histological, immunohistological, morphometric and molecular biological studies. Researchers can access the TRC material by contacting the authors and submitting research proposals which have ethics approval.

Poster 4.9

Stroke, Complex Regional Pain Syndrome and Phantom Limb Pain: Common findings, Implications and Future Directions

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Stroke, complex regional pain syndrome type 1 (CRPS1) and phantom limb pain (PLP), despite being conditions of variable origins, demonstrate certain similarities. Clinical findings common to these conditions include referred sensations to touch and synchiria (reporting bilaterally touch following unilateral stimulation). Neuroimaging studies have shown that these conditions demonstrate similar reorganisation of the primary somatosensory and motor cortices. Parallels in clinical and imaging findings in these conditions suggest that they may respond to similar therapeutic interventions. A more comprehensive understanding of the similarities and differences between these conditions has provided impetus for the development of innovative treatment regimes. One such intervention is mirror therapy. During mirror therapy patients view their symptom-free side and its mirror-image during exercises. Mirror therapy has been anecdotally demonstrated to be effective in both (1) the treatment of motor recovery six months post-stroke, and (2) in sensory and pain symptom-management in patients with acute and chronic CRPS1 or PLP. Based on the similar clinical and neuroimaging findings in stroke, CRPS1 and PLP we propose crossing treatments from one group to another to determine their treatment potential. Using the examples of mirror-therapy, imagined movements, constraint-induced movement therapy, sensory discrimination therapy and repetitive-learning regimes we proposed future clinical and research guidelines to determine the application of these intervention with patients post-stroke, with CRPS1 or with PLP.

Poster 4.10

Exposure to Enriched Environments Alters Spatial Representation in the Hippocampus

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Previous research has demonstrated that environmental enrichment has widespread effects on brain anatomy, physiology, and function. We investigated the possibility that the enhanced performance in spatial memory tasks observed in enriched-group rats is due to changes in the firing properties of neurons in the hippocampus, an area implicated in spatial memory processes. Rats were raised from P36 in enriched, social, or isolated conditions. At eight months of age they were chronically implanted with electrodes in hippocampal area CA1. Place cells (n=104) were recorded while rats foraged in a square arena. The animals were then transferred to a circular track in a different room for a second recording session. Although there were no significant differences between groups in any general spatial firing measures, fewer cells in enriched rats continued to fire in the second session compared to cells in isolated and group rats (p=0.05). A second experiment was run to rule out effects due to cell instability or apparatus preference. Preliminary results are consistent with those of the first experiment. These data suggest that there may be a greater overlap between the representations of environments in social and isolated animals compared to enriched animals. The reduced overlap of spatial representations in enriched animals might contribute to an enhanced capacity to discriminate between spatial contexts and allow for the representation of a larger number of different environments.

Supported by a grant from the Marsden Fund of New Zealand.

Poster 4.11

Polymorphism Analysis of Novel Serotonergic Candidate Genes in Depression

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The 5-HT neurotransmitter system influences a wide range of behavioural and physiological processes including cognition, circadian rhythms and mood. Accordingly, genetic polymorphisms of the serotonergic system have been widely examined for association with variations in these and other phenotypes. However, transcriptional mechanisms controlling these pathways have been unexplored with regards to their role as possible new gene candidates in affective disorders. Recently, genes encoding transcription factors (*Nkx2.2*, *Nkx6.1*, *Gata2*, *Lmx1B* and *Fev*) that are activated downstream of Sonic hedgehog (*Shh*), have been shown to be necessary and sufficient for development of the specific subset of 5-HT neurons that project to the forebrain. Furthermore, in knock-out mice lacking *Fev*, the resultant defective development of the serotonergic system leads to a heightened anxiety-like and aggressive behavioural phenotype in adults. This suggests an important role for this class of genes in behaviour. The first aim of our research was to establish the level of natural variability in these of genes, using denaturing high performance liquid chromatography (DHPLC) and DNA sequencing. So far several promoter polymorphisms have been found in the putative promoter regions of *GATA2* and *NKX2-2*. The possible relevance of these variants to onset, symptom patterns or treatment outcomes in patients with affective disorders will be determined via association studies. Functional relevance of these SNPs is also being determined using promoter expression assays.

Poster 4.12

Inflammation in Alzheimer's Disease - Proinflammatory Characteristics of Advanced Glycation Endproducts and Possible Therapeutic Interventions

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Alzheimer's disease (AD) is characterised by neurofibrillary tangles, senile plaques (SPs), neuroinflammation and neurodegeneration. Advanced glycation endproducts (AGEs), heterogenous sugar-derived protein modifications, are present in SPs and are known to induce and/or potentiate the amyloid-induced expression of pro-inflammatory cytokines and iNOS in macrophages and microglia via the AGE-receptor RAGE. Although identification of specific properties of the active pro-inflammatory AGE ("active" RAGE agonists) would help in designing defined RAGE-antagonists, they are as yet not identified. RAW 264.7 murine macrophages were activated with model-AGEs such as BSA-AGE and nitric oxide production was quantified as nitrite by the Griess reagent. Results and Conclusion: To identify the "active principle" of AGEs, biochemical characteristics of AGEs such as the degree of glycation (on lysine and arginine residues), beta sheet content, superoxide production and hydroperoxide modification were determined, and compared to nitric oxide production (as a marker of activation). To interfere with pro-inflammatory signalling of AGEs downstream of the receptor level, various drugs including non-steroidal anti-inflammatory drugs (NSAIDs) and antioxidants known to be both "anti-inflammatory" and beneficial for AD patients were also tested for their potential to decrease AGE-induced NO production. Selected drugs from these classes, including the NSAIDs piroxicam and ibuprofen, were particularly effective at down regulating macrophage activity, which might explain their ability to lower the risk of developing Alzheimer's disease in long-term users.

Poster 4.13

Renin-Angiotensin System in the Ageing Rat Brain

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In some neurodegenerative disease prevalent in ageing (eg.,Alzheimer's and Parkinson's disease), the expression of components of the Renin-angiotensin system (RAS) is altered. However, an understanding of these changes is being hindered by the limited information on RAS expression in the normal brain.. In this study, the progressive changes in expression of the classical components of the RAS (angiotensinogen; receptors AT1a, AT1b and AT2, converting enzyme and renin) was investigated in male rats at 6, 12, 18 and 24 months of age (n=6-12). Controversial components cathepsin D and AT4/IRAP were also included. The cerebral cortex, thalamus, hypothalamus, midbrain, pons-medulla and cerebellum were removed from age-matched rats and extracted mRNA quantified by Reverse Transcriptase–Polymerase Chain Reaction (RT-PCR) for RAS components. Angiotensinogen and AT1a were also quantified by Western blots. All RAS components showed significant changes ($p<0.05$) with ageing in all regions examined, with five patterns of temporal change being observed. The most common pattern of change was a gradual rise with ageing. A next common pattern, particularly in the cerebellum, was an increased expression to 12 months followed by a decrease. Cathepsin D and AT4/IRAP showed a pattern distinct from RAS components. They showed no change, except for a transient peak at 18 months. This study supports previous reports of changed RAS expression in the ageing brain and provides further detailed observations on area-specific differences. The data should facilitate the recognition of disease-related changes, distinct from those of normal ageing.

Poster 4.14

D1/D5 Receptor Activation Mediates the Induction and Reversal of NMDA-dependent LTD in Rat Hippocampus

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Recent findings in various laboratories have suggested that D1/D5R activation may influence synaptic plasticity through the PKA-mediated phosphorylation of the GluR1 subunit of the AMPA receptor. The present study examined this as a possible mechanism for the reversal of NMDA-induced LTD (chemical LTD). In addition, we extended our study to the role of D1/D5R activation in the induction of LTD. Initial experiments were conducted using CA1 mini-slices prepared from 6-7 wk male Sprague-Dawley rats and placed in a multi-well incubation chamber. Chemical LTD was induced by the addition of NMDA (20 μM, 2 min) twice, 40 min apart. Western blot analysis was then used to determine the phosphorylation state of the serine 845 and 831 residues of the GluR1 subunit. Where required, field excitatory postsynaptic potentials were recorded in area CA1 of intact hippocampal slices. Initial field recording experiments demonstrated that chemical LTD (-18.3 ± 6.3%, n=5) was reversed by the D1/D5R agonist SKF 38393 (20 min, 100 μM) applied immediately after the second NMDA application (1.8 ± 3.9%, n=6). Western blot analysis of NMDA-treated mini-slices showed that SKF 38393 caused a 2-fold increase in the phosphorylation level of serine 845, but had no effect on serine 831. This effect has been associated with LTD reversal. Finally, in field recordings, blocks of D1/D5R during induction of LTD by low frequency stimulation (LFS) prevented LTD consolidation. We suggest that D1/D5R activation during LFS is critical for establishment of late-phase LTD but that post-LFS activation can reverse the LTD.

Poster 4.15

Mechanism of mGluR-Induced Depression of the NMDA EPSC in CA1 Pyramidal Neurons of the Rat Hippocampus

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Previous studies in hippocampal CAl pyramidal neurons have shown that the Group I metabotropic glutamate receptor (mGluR) agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) can potentiate the depolarization or current induced by applied NMDA, via the mGluR5 subtype. However, little work has been done to examine the effects of mGluR-activation on the NMDA receptor-mediated excitatory postsynaptic current ($EPSC_{NMDA}$). Here we investigated the effect of activating Group I mGluRs on the $EPSC_{NMDA}$, and determined the underlying subtypes of mGluR. Whole-cell patch-clamp recordings were made from young adult rat CAl pyramidal neurons in acute hippocampal slices maintained in vitro at 32°C. DHPG (20μM) persistently depressed the isolated $EPSC_{NMDA}$ recorded at a holding potential of -30mV. Pre-incubation with either the specific mGluR1 inhibitor, LY367385, or the specific mGluR5 inhibitor, MPEP, did not prevent the depression of the $EPSC_{NMDA.}$ However pre-incubation with both antagonists together, or with the broad spectrum mGluR antagonist LY341495, prevented the persistent depression of the $EPSC_{NMDA}$ by DHPG. Since strong calcium buffering with intracellular BAPTA did not prevent the depression by either subtype of mGluR, it is unlikely to be due to inhibition of NMDA receptors by an mGluR-induced release of calcium from calcium stores. These data suggest that both mGluR1 and mGluR5 can independently induce persistent depression of the $EPSC_{NMDA}$ using a signal transduction mechanism that is not dependent on calcium.

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Poster 4.16

Fluoxetine, a Specific Serotonin Reuptake Inhibiting Antidepressant Shares Electrophysiological Properties with both Novel and Classical Anxiolytics

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Classical anxiolytics which interact with the gamma-amino butyric acid (GABA) receptor have previously been demonstrated to decrease the frequency of hippocampal rhythmical slow activity (RSA). The novel anxiolytic agent Buspirone does the same. Buspirone is an agonist at 5-HT_{1A} receptors, and is pharmacologically distinct from classical, GABA-agonistic anxiolytics. Non-anxiolytic agents do not affect hippocampal RSA, making reduction in RSA frequency a useful marker for anxiolytic efficacy. The present experiment investigates the effect of a specific serotonin reuptake inhibitor, Fluoxetine, on hippocampal RSA. Fluoxetine is an indirect 5-HT_{1A} agonist, and is clinically anxiolytic as well as antidepressant. Six rats were implanted with bipolar recording electrodes in the dorsomedial subiculum of the hippocampus, and stimulating electrodes in the midbrain reticular area. Fluoxetine was administered at doses of 0mg/kg (vehicle control) 10mg/kg and 20mg/kg. Hippocampal RSA was stimulated every 30 minutes for 255 minutes. Both the 20mg/kg and 10mg/kg dose reduced the frequency of hippocampal RSA compared to control, and the 20mg/kg dose produced a reduction twice that of the 10mg/kg dose. Peak reduction in RSA occurred approximately 75 minutes post-injection. These data further validate reduction in hippocampal RSA as a marker of clinical anxiolysis, and provide additional evidence that changes in RSA can be achieved by alterations in 5-HT.

Poster 4.17

Chronic Prenatal Opiate Treatment Down-regulates the Neural Migration Specific Marker Doublecortin (DCX), and Perturbs Development of the Mouse Neocortex

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The opioid system consists of cell surface receptors that bind peptides that have a wide range of functions, one of which is to regulate brain development. Exogenously administered ligands such as morphine can also interact with the opioid system. The primary receptor for morphine is the mu-opioid receptor (MOR). Activation of MOR by ligand binding has been implicated in the integrated control of neuronal division, differentiation, migration and death, however, the role of MOR in modulating these processes is, at best, unclear and often controversial. Administration of morphine and naltrexone from embryonic day 12 onwards has previously been shown to alter neuronal number in the neonatal rodent cerebral cortex. To investigate opiate induced aberrations in neocortical development, we have used real-time PCR and western blotting to analyse changes in gene expression. Chronic prenatal exposure to morphine decreases expression of the neuronal migration-specific microtubule associated protein doublecortin. In addition, morphine down-regulates MOR expression, however, the opioid antagonist naltrexone does not significantly change MOR expression. Opioid receptor like receptor (ORL1) mRNA is however up-regulated by naltrexone exposure, despite the fact that ORL1 has little affinity for naltrexone. ORL1 mRNA expression is moderately decreased by morphine treatment during embryonic development. We hypothesize that chronic prenatal morphine exposure causes abnormal neuronal migration and induces a lissencephaly type phenotype, as well as interacting with opioid system homeostasis.

5.1

Altered Cortical Pain Processing in Chronic Pain Patients

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Chronic pain is associated with neural plasticity at multiple levels in the nervous system. In this study we looked for evidence of altered cortical functioning through analysis of the EEG during repetitive sensory simulation of a finger. A group of patients with chronic pain was compared to a group of normal volunteers. The EEG of each subject was continuously recorded using a 28-channel montage. Brief repetitive (at least 60) electric shocks were given via an electrode on the dominant index finger. Two intensities of electric shock were tailored to each subject, one that was easily felt but not painful and one that was moderately painful. The shocks were given in three sequences: 1) non-painful shocks, 2) painful shocks, 3) a random sequence of non-painful and painful shocks (4:1 ratio). The raw EEG was cleaned and 0.5second post-stimulus epochs averaged for each sequence giving clear sensory evoked potentials (SEPs). The SEPs were then analysed in greater detail. The most striking feature was the negative/postive/negative wave starting at approximately 200ms over the vertex. An increased amplitude was seen with painful stimuli versus non-painful stimuli. The wave was delayed by 20msec in the chronic pain patients versus the normal volunteers ($p<0.05$). In conclusion, detailed analysis of SEPs from multi-channel EEG demonstrates differences between the painful and non-painful stimuli and provides evidence of altered cortical processing in patients with chronic pain compared to normal volunteers.

5.2

Nadir CD4 Count is Associated with Subtle Cognitive Impairment in HIV-1

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Severe immunosuppression poses a significant risk for the development of AIDS dementia complex in individuals who are infected with HIV-1. It has been assumed however, that patients who experience a transient lowering of their CD4 count and are then treated with antiretroviral therapy do not experience permanent cognitive deficits, provided that their CD4 counts are restored to normal levels (>350 cells/mm^3). In order to examine whether nadir CD4 levels do affect cognitive function, 59 HIV-1 seropositive individuals aged 28 to 65 years (M = 46.9, SD = 8.4) were subjected to a standard neuropsychological test battery plus the Subtle Cognitive Impairment Test (SCIT). As expected, performance on all tasks was significantly better in individuals with high current CD4 counts (above 350 cells/mm^3) compared to individuals with low current CD4 counts (below 350 cells/mm^3), regardless of disease stage. Contrary to expectations however, it was found that individuals with high current CD4 counts but low nadir levels, performed significantly worse on the SCIT than those with high current and high nadir counts ($N=38$; $p<0.05$, 2-tailed). This finding questions the efficacy of current antiretroviral regimens to fully protect the brain and raises the concern that even a transient high viral load may cause subtle, permanent, cognitive deficits.

5.3

Stereoselective Effects of the Novel Anticonvulsant Lacosamide Against 4-AP Induced Epileptform Activity in Rat Visual Cortex *In Vitro*

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We examined effects of the novel anticonvulsant lacosamide and its inactive isomer (SPM 6953) in an *in vitro* model for tonic-clonic epileptiform activity. Focal field potential recordings (34 ± 0.2°C) were obtained from rat brain slices prepared from 17-22 day old Sprague Dawley rats. fEPSP amplitude and duration were not significantly altered (P>0.05; n = 4) by lacosamide (1μM-1mM). Recording from visual cortex during application of 4-aminopyridine (4-AP; 100μM) revealed both spontaneous and evoked 'ictal like' discharges. Spontaneous ictal-like discharges in the visual cortex were blocked by 100μM carbamazepine (CBZ), 100μM pentobarbital and 200mM phenobarbital (PHB) but were insensitive to the anti absence drug ethosuximide (750μM; n = 4; P>0.05). Lacosamide reduced tonic duration and maximal firing frequency with EC_{50s} of 41 and 71μM, respectively. The S stereoisomer; (100μM-320μM) produced no significant effect on spontaneous ictal activity (n = 3-4, P > 0.05). Seizures induced by high frequency (100Hz, 1s) stimulation were selectively reduced in amplitude by PHB (200μM) and frequency by CBZ (100μM, n = 6) and lacosamide (100μM, n = 4). GABAergic negative going potentials were attenuated by CBZ (irreversible) and lacosamide (reversible) but not by PHB. Lacosamide appears to inhibit epileptogenesis (seizure spread) by interacting with a stereoselective, but as yet unidentified, target site in rodent neocortex in the mid-micromolar range.

5.4

Studies on the Mechanism of Action of the Novel Anticonvulsant Lacosamide

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Lacosamide (LCM) is anticonvulsant in animal models and is in phase III assessment for epilepsy and neuropathic pain. Here we seek a mechanism of action for the new drug. 10 μM LCM did not bind with high affinity to a plethora of rodent, guinea pig or human receptor sites including: AMPA; Kainate; NMDA (glycine/PCP/MK801); $GABA_A$ (muscimol/benzodiazepine); $GABA_B$; adenosine $A_{1,2,3}$; a_1, a_2; $_1$, $_2$; $M_{1,2,3,4,5}$; $H_{1,2,3}$; $CB_{1,2}$; $D_{1,2,3,4,5}$; $5HT_{1A, 1B, 2A, 2C, 3, 5A, 6, 7}$ and K_{ATP}. Weak displacement (25%) was evident at batrachotoxin site 2 on voltage gated Na^+ channels. In primary cultures from rat cortex LCM (100 μM) produced a significant reduction in the rate of spontaneously occurring EPSC's and IPSC's and blocked spontaneous action potentials (EC_{50} 61 μM). LCM did not alter resting membrane potential or passive membrane properties following application of voltage ramps between -70 to +20 mV. The voltage-gated sodium channel (VGSC) blocker phenytoin potently blocked sustained repetitive firing (SRF) but 100 μM LCM failed to block SRF. LCM did not modulate Ca^{2+} channels (T-, L-, N- or P-type). Delayed-rectifier or A-type potassium currents were also insensitive to modulation by LCM (100 μM). Evidently LCM perturbs excitability in primary cortical cultures but not via a high-affinity interaction with an acknowledged recognition site on a target for existing antiepileptic drugs.

5.5

Coherence of Hemispheric Function in Developmental Dyslexia: An EEG Study

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Reading requires the use of both phonological and orthographical (lexical) decoding strategies, which are thought to reflect two functionally and anatomically distinct, but cohesive neural processing routes. Functional imaging studies suggest that these routes correspond to posterior brain systems in the left hemisphere: A dorsal (temporo-parietal) circuit and a ventral (occipito-temporal) circuit respectively. In the case of dyslexia this posterior system has been hypothesised to be functionally disrupted. Our earlier fMRI research found little support for this idea – although we found minimal left posterior activation by a dyslexic during reading tasks, maximal activity was observed in right inferior frontal areas. In order to investigate this effect further we used visual-evoked potentials and EEG to determine patterns of cortical activity in 12 dyslexic adults during a lexical decision task (concrete nouns versus two types of nonwords). Comparison groups were comprised of 14 normal readers and 15 bilingual (English as a second language) readers. Analysis of the behavioural data revealed accuracy and response time differences between the three groups only when responding to nonwords. Preliminary analysis of the evoked potential topography however, showed that the response to *words* over the parieto-occipital regions was the most consistent discriminating feature between the dyslexic and control adults. EEG coherence values indicate that controls had significantly greater cooperation between hemispheres at symmetrical locations, whereas dyslexics demonstrated significantly greater sharing within hemispheres. These data support the idea of dyslexia as a functional hemispheric disconnection syndrome.

5.6

Fibre Tracking and Localising Brain Injury with MRI

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Random motion of water in the brain (diffusion) is constrained by the anatomical structure the water encounters. For example, diffusion is greater along the white matter fibres than across them, and diffusion is different in white matter from in grey matter. Diffusion is sensitive to changes in the local microstructure, including damage and white matter fibre orientation. Therefore, diffusion is an important marker of both the microstructure of the brain and of brain damage at a localised level. Diffusion Tensor Imaging (DTI) is a specialised MRI technique that quantitatively measures diffusion, including its directionality. Fibre tracking uses this directional information to trace white matter pathways through the brain. This shows connections, and is of particular interest in studying the effects of injury and disease. However, the technique is only qualitative, and can only identify major tracts. To get quantitative information at a more detailed scale, a voxel based analysis of the diffusion data is done. This enables the localisation of brain damage in a way that is not possible with standard MRI. DTI measures the diffusion at each voxel in the brain. By comparing the diffusion of 81 professional boxers with that of 12 control subjects, we have been able to show at a voxel level where the diffusion of the two groups is different. This is taken as an indicator of brain damage.

6.1

Inhibitory Effects of Lolitrems on Human BK Channels Expressed in the Brain

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Large conductance calcium-activated potassium (BK) channels modulate action potential waveform, repetitive firing, and neurotransmitter release in the brain. They are coexpressed with an accessory beta subunit (b4) that is highly expressed in the brain and combines with the pore-forming *hSlo* a subunit. The voltage- and calcium-activation properties of a+b4 channels differ from those composed of the a subunit alone. The sensitivity of a+b4 channels to the BK channel inhibitors, charybdotoxin and iberiotoxin, is greatly reduced compared with a subunit channels. We wanted to know whether the inhibitory effects of lolitrems on BK channels are altered by the presence of the b4 subunit. We investigated this using *hSlo* BK channels expressed in human embryonic kidney cells and patch-clamping. BK channel currents were activated by depolarising voltage pulses in the presence of 10 µM free calcium from inside-out membrane patches. Effects of lolitrems on *hSlo* channel potassium currents, with and without the b4 subunit, were determined. We found that the presence of the b4 subunit did not significantly alter the degree of inhibition by 31-*epi*lolitrem B, lolitriol, or lolitrem B.

6.2

Examination of the Tremorgenic Mycotoxin Lolitrem-B in Rat Hippocampal CA1 and CA3

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The diterpenoid mycotoxin, lolitrem B potently inhibits K^+ current through human BK channel subunits (*hSlo*) expressed in human embryonic kidney cells (Dalziel et al. 2005). Hippocampal CA1 and CA3 neurons express BK channels, which are blocked by iberiotoxin and the fungal diterpenoid paxilline (PAX; Hu et al. 2001). Here we examined the effects of lolitrem-B (Lol-B) and paxilline on evoked CA1/CA3 responses *in vitro*. Stimulating electrodes were positioned in the Schaffer collateral-commissural pathway (*stratum radiatum*) and wire recording electrodes in CA1 *stratum pyramidale* or *stratum radiatum*. Paired pulse or tetanic stimulation paradigms were used to assess drug effects on CA1 population spikes, field EPSP's and CA3 fibre spikes. Low micromolar paxilline suppressed paired CA1 evoked responses and significantly reduced the rate of CA3 fibre spike repolarization. In addition, PAX reduced fibre spike amplitude and dramatically reduced fibre spike repolarization during tetanus. In contrast, lolitrem-B was ineffective at concentrations up to 500 nM. Given that Lol-B inhibits human BK channels in transfected HEK cells and the BK blockers iberiotoxin and paxilline inhibit action potential repolarization in rat CA1, our failure to see activity with Lol-B in hippocampus goes without immediate explanation. It is possible that the expression of accessory subunits, which augment subunit function in rat hippocampus, selectively suppress Lol-B activity in this brain region.

6.3

Tracing Functional Circuits in the Brain Using c-*fos* Regulated Expression of Marker Genes Targeted to Neuronal Projections

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We have developed novel techniques to trace functionally activated circuits and synaptic plasticity within the brain. We have generated transgenic mice, *FTL*, which contain a *tau-lacZ* fusion gene regulated by the promoter for c-*fos*. Following particular nervous system stimulation in these mice, only neurons which are functionally activated, will express LacZ, which is targeted to neuronal processes by the tau protein. In the *FTL* mice, we found highly inducible expression of lacZ by a range of different stimuli, and successful targeting of expression to neuronal cell bodies, axons and dendrites. To test if a functionally activated circuit could be visualized, the mice were deprived of water, which activates nuclei involved in body fluid homeostasis. LacZ was induced in these nuclei and their projections, allowing the mapping of a neuroendocrine circuit. Further studies have employed these mice in the analysis of neurons and circuits activated in vision, and learning and memory. We have also developed methods to measure markers of synaptic plasticity in the brain, and found significant experience dependent changes in the levels of these markers in different parts of the brain. We believe these techniques will aid in the identification of circuits for many different brain functions, and within those circuits, the locations of synaptic plasticity.

6.4

Visual Responsiveness of Striatal Spiny Neurons in Anaesthetised Rats: An *In Vivo* Intracellular Study

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The spiny neurons of the striatum are a site of convergence of motor and sensory inputs from the cortex and thalamus. Sensorimotor convergence at this level may provide a means by which sensory inputs become associated with specific motor actions through learning. Visual stimuli, particularly, are known to trigger goal-directed actions, as is suggested by plasticity in the firing of spiny neurons preceding visually-cued movements. To determine if spiny neurons exhibit synaptic plasticity in response to visual stimuli, we made intracellular recordings in urethane-anaesthetised rats and tested the response to an LED flashed into the eye. Only 33% of neurons responded, exhibiting a significant reduction in latency to the next membrane potential 'Up' state. However, all neurons in another group exhibited short-latency responses to light (100ms nominal; amplitude 12.2 mV; n=6) after disinhibition of the superior colliculus (SC) by local injection of bicuculline (BIC). This visually-evoked response was apparent up to 15 minutes after BIC, parallelling the duration of drug action. These results suggest that spiny neurons receive visual information sufficient to initiate a membrane depolarisation and an Up state transition, but that this information is usually gated by the SC under anaesthesia. This information may be relayed to the striatum via the thalamus and therefore could be a source of input used in the formation of sensorimotor associations within striatal spiny neurons.

6.5

Adenosine A2A Receptor Stimulation Reduces Activity of Globus Pallidus (GP) Neurons in the Freely Moving Rat

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Adenosine plays a role opposite to dopamine in the brain. The adenosine A2A receptors are highly expressed in the striato-pallidal neurons where they are co-localized with dopamine D2 receptors. However, the effects of adenosine receptor manipulation on neural activity of basal ganglia are unknown. We recorded single neuron activity of the GP using chronically implanted microwire electrodes in the awake rat, during equivalent resting periods before and after systemic injection of adenosine A2A receptor agonist CGS21680 (dose= 5mg/kg, n= 43 cells) and compared this with the effect of the dopamine D2 receptor antagonist Raclopride (R) (1.5 mg/kg, n= 43), or vehicle (n= 75). Raclopride produced catalepsy defined by immobility in the grid test (average grid time before injection 1 s, and after injection 68 s). CGS21680 also produced catalepsy, but of different quality. Animals were not able to grasp the vertical grid, so immobility was quantified using the bar test (average bar time 1 s before and 32 s after CGS21680 injection). Mean firing rates and firing patterns of recorded cells were analyzed. Both drugs significantly reduced firing frequency (R: 28±12 Hz before, 15±7 Hz after injection, $p<0.004$; CGS21680: 28±8 Hz to 12±4 Hz, $p<0.001$) and percentage of spikes in bursts (R: 66±25% to 49±23%, $p<0.001$; CGS21680: 56±23 to 30±15%, $p<0.001$). These data show that A2A agonist and D2 antagonist drugs have similar effects on neural activity in GP.

6.6

The Effects of rAAV CDCrel-1-mediated Aggregate Formation and Cell Death in the Substantia Nigra and its Effect on Behaviour of Rodents

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Autosomal recessive forms of Parkinson's disease (AR-JP), the major form of juvenile PD, are linked to mutations in the parkin gene. Parkin, a E3 ubiquitin ligase, appears to play a pivotal role in maintaining dopamine cell function by preventing the toxic accumulation of its substrates such as the neuron specific septin 5 (CDCrel-1). We have generated a genetic model for PD mediated by recombinant adeno-associated viral (rAAV) vector-mediated gene transfer of CDCrel-1 to the substantia nigra pars compacta of rats. Robust expression of CDCrel-1 protein in dopaminergic neurons was detected as early as 2 weeks post-injection. However, significant loss of tyrosine hydroxylase-immunoreactive cells was observed by 8 weeks after administration of the vector and was confirmed by HuC/D and GFAP immunohistochemistry and also by fluoro-jade staining. Dopaminergic cell loss was associated with impaired motor function at 8 weeks as assessed by an increase in amphetamine-induced rotatation behaviour, head position bias towards the ipsilateral side and impaired movements in the contralateral paw in the forepaw adjusting steps test. Generation of this model of AR-JP will provide a valuable tool for testing potential therapeutic approaches such as heat shock protein expression on prevention of CDCrel-1-mediated aggregate formation and cell death.

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7.1

Lateralization of Unimanual and Bimanual Motor Imagery

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Most studies of motor imagery have examined motor cortex function during imagery of dominant hand movement. The aim of this study was to examine the modulation of excitability in the dominant and non-dominant corticomotor pathways during kinesthetic motor imagery of unimanual and bimanual movement. Transcranial magnetic stimulation (TMS) was applied over the contralateral motor cortex (M1) to elicit motor evoked potentials (MEPs) in the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles of each hand, in two separate sessions. Transcutaneous electrical stimuli were also delivered to the median nerve at each wrist, to elicit F-waves from APB. Fifteen right-handed volunteers imagined unimanual and bimanual phasic thumb movements, paced with a 1 Hz auditory metronome. Stimuli were delivered at rest, and either 50 ms before (ON phase), or 450 ms after (OFF phase), the metronome beeps. Significant MEP amplitude facilitation occurred only in right APB, during the ON phase of motor imagery of the right hand and both hands. Significant temporal modulation of right APB MEP amplitude was observed during motor imagery of right, left and bimanual performance. F-wave persistence and amplitude were unaffected by imagery. These results demonstrate that the motor imagery is lateralized to the left (dominant) hemisphere, which is engaged by imagery of each hand separately, and bimanual imagery. This finding has implications for the use of motor imagery in rehabilitation.

7.2

Dexterity is Unaffected by Experimental Pain in an Intrinsic Hand Muscle

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There are many clinical and anecdotal reports that pain, and muscle pain in particular, impairs skilled movements; however, experimental evidence for this is lacking. In this study, we induced muscle pain in an intrinsic hand muscle used for precision manipulations, and examined its effect in normal adult subjects using several well-characterised tests of dexterity. Both hands of 14 subjects were tested with a modified version of the Purdue pegboard, the Lafayette grooved pegboard and the precision grip-lift task. In the latter, subjects gripped and lifted a special-purpose manipulandum between the finger and thumb: grip force and load force were measured continuously. There was no significant correlation between the three tests of dexterity in the absence of pain. Performance was assessed before and after the induction of muscle pain by the injection of 0.2 ml hypertonic (5%) saline into the first dorsal interosseous muscle of the dominant hand. This induced a mean level of pain of 4.5 on a visual analogue scale in which “no pain” was scored as zero and “worst possible pain” was 10. Pain intensity was scored every minute. Muscle pain did not significantly affect the performance of either of the two pegboard tasks or the grip-lift task. We conclude that short-term experimental muscle pain does not adversely affect skilled motor performance.

7.3

The Effect of Different Conditioning Protocols on Human Motor Cortical Excitability

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Repetitive transcranial magnetic stimulation (rTMS) can be used to modify motor cortical excitability in human subjects and to examine the associated behavioural effects. Subthreshold 'priming' rTMS delivered at 6Hz can facilitate the effect of suprathreshold rTMS delivered at 1Hz (Iyer et al. J. Neurosci., 2003). Our study was designed to establish effective priming protocols for different rTMS paradigms by first examining the outcome of priming alone. We investigated the effects of 10 minutes of intermittent 2 or 6Hz priming stimulation on cortical excitability in normal subjects (n=8 for both frequencies) at two intensities (80% and 90% of active motor threshold (AT)). The number of stimuli was matched between conditions. Motor cortical excitability was investigated by recording motor evoked potential (MEP) amplitude in a hand muscle before and after priming. Both 2Hz and 6Hz stimulation at 80% AT produced MEP inhibition ($P<0.05$) that lasted for up to 30 minutes. At 90% AT, priming did not induce group MEP change. However, the response to priming at this intensity was variable, with some subjects showing significant facilitation (2Hz, n=3; 6Hz, n=1) and others inhibition (2Hz, n=3; 6Hz, n=5; $P<0.05$). Priming stimulation, by definition, should have no measurable effect, and therefore, neither protocol is suitable for priming. Additionally, these results suggest that the intensity of stimulation may be as important as frequency for determining the effect rTMS has on motor cortical excitability.

7.4

Increased Motor Related Desychronisation in Patients With Writer's Cramp During Writing Tasks

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The classic symptom of writer's cramp is a task-specific cramping during writing. The cramping can be limited to a finger or may extend to the entire arm including the shoulder muscles. This study examined sensorimotor integration and motor functioning as indexed by neuro-oscillation induction recorded by electroencephalography (EEG). Eight controls and four patients with writer's cramp performed three tasks: writing the days of the week with and without a pen, and holding a pen by itself. These three tasks were repeated twice and participants were then asked to repeat the same tasks wearing a latex glove. There were no significant differences between conditions with and without gloves suggesting that in these patients at least, gloves do not provide a beneficial sensory trick that other patients have reported. There were significant increases in desychronisation in the upper beta frequencies ($\beta 2$) over the sensorimotor regions for the patients compared to controls during writing, which induced cramping; during the act of simply holding the pen which did not induce cramping; and also when writing without a pen which did not always induce symptoms. The changes in oscillations occurred at frequencies related to task specific motor functioning during tasks that are involved in eliciting symptoms.

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7.5

Mild Head Injury – A Close Relationship Between Motor Function at One Week Post-injury and Overall Recovery during the First Six Months

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Based on earlier findings that instrumented motor assessment after mild closed head injury (CHI) can provide sensitive markers of cerebral dysfunction, this study examined if early motor assessment can provide an indication of outcome after mild CHI. At 1 week post-injury, we assessed oculomotor performance, upper-limb visuomotor function and psychometric status in 37 mild CHI patients. Re-examination at 3 and 6 months determined outcome (in terms of post-concussional symptoms and performance of everyday tasks). We then examined the relationship between early motor function and outcome using linear regression. Motor-based regression models were able to explain a considerable proportion of the variance in outcome, with motor function at 1 week relating much closer to outcome at 3 and 6 months than early psychometric assessment, symptom status, or clinical measures of trauma severity. Patients who reported high levels of persistent post-concussional symptoms and everyday-problems at 3 and 6 months could be identified prospectively based on early motor function. Conversely, such patients could not be distinguished from the remaining patients based on age, gender, education, clinical measures of trauma severity, or neuropsychological assessment. Our findings suggest that early assessment of eye and arm motor function may considerably improve outcome prediction after mild CHI. Such assessment may assist in the better targeting of early health care intervention and help decrease head-trauma-related morbidity and rehabilitation costs.

7.6

Functional Muscle Synergies in Reaching Tasks: The Effect of a Stroke

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The purpose of this study was to determine if muscle synergies for forward reaching could be identified in control participants and in people with stroke. Ten people with stroke and five controls participated. A between groups, within participants repeated measures design was utilised. Two movement tasks, Task A (flexion-abduction) and Task B (flexion-adduction) were performed 15 times by each participant with each arm. Surface electromyography was recorded from: trapezius, anterior deltoid, middle deltoid, posterior deltoid, pectoralis major, biceps, triceps and wrist extensors. Kinematic data were collected from a marker on the metacarpophalangeal joint to identify movement initiation and end-point. Hierarchical cluster analysis indicated clear clustering for anterior deltoid, biceps and wrist extensors in control participants, but not in stroke participants. There was no difference in the timing of onset of activity in anterior deltoid between the stroke participants (affected arm) and the controls ($p>.05$). The onset of activity in biceps and wrist extensors was delayed in the participants with stroke (affected arm) compared to the controls in Task A ($p<.05$) but not in Task B ($p>.05$). There was no consistent order of onset of activity in anterior deltoid, biceps and wrist extensors for Task A ($p>.05$). There were weak order effects for Task B for the control ($W=.067$, $p<.05$) and affected arm of participants with stroke ($W=.362$, $p<.05$). There appeared to be a 'loosely organised' synergy in the control participants; three muscles were consistently recruited prior to movement but in no strict order. Participants with stroke demonstrated disruption to the temporal aspects of this synergy. Although the capability to perform a reaching task was retained the neuromotor organisation was impaired as reflected in lengthened response time and altered activation patterns in muscle synergies.

8.1

Computational Neurogenetic Modelling: Methodology and Preliminary Results

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We present a novel computational approach to brain neural network modelling that integrates dynamic gene networks with a neural network model. Interaction of genes in neurons affects the dynamics of the whole model neural network through neuronal parameters, which are no longer constant, but change as a function of gene expression. Through optimization of the gene interaction network, initial gene/protein expression values and ANN parameters, particular target states of the neural network operation can be achieved, and statistics about gene interaction matrix can be extracted. The behaviour of a model neural network is evaluated by means of the local field potential (LFP), thus making it possible to attempt modelling the role of genes and their interactions in different brain states, where EEG data is available to test the model. Support for this approach comes from recent analyses that brain electrical oscillations are genetically determined and differ between individuals and families. In our computer experiments, we have observed that different initial gene conditions can lead to the same outcome in terms of LFP. Moreover, different types of gene interaction dynamics, be it constant, periodic, quasi-periodic or even chaotic, can lead to a similar LFP of an associated model, provided some statistical distribution of gene interactions is maintained. In future, our approach can aid the studies on how genes and their dynamic interactions influence activity of neural networks in normal and diseased states.

8.2

Bridging the Gap Between the Biophysics of Single Neurons and Mean-field Models of the Cortex

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There are two approaches to modelling networks of neurons:(1) neural networks - model the details of individual neurons and their interconnections but computational limits restrict them to small networks, (2) statistical approaches (mean-field theories) - model the average properties of groups of neurons (over regions of one cubic millimetre). They can model larger networks at the expense of detailed information about individual neurons and their interconnections. Our group has used the second approach to model electroencephalogram (EEG) changes during anaesthesia and we are applying this model to sleep states. This approach should be applicable to modelling state changes of the brain, where the EEG changes due to a widespread change in neuron function. This change could result from changes in neuromodulator concentration or neuroactive drugs or neural diseases which affect large sections of the brain depending on spatial localisation rather than neural circuitry. The difficulty with such models is ensuring consistency with known changes happening at the level of individual neurons when determining the functional form and parameter values to use in the mean-field model. I will discuss using the NEURON software package to model moderate sized (1000 to 100,000 neurons) networks of biologically detailed neurons and using the statistical properties of these networks to model spatially localised changes in neuron behaviour in a mean-field model.

8.3

The k-complex of the EEG and its Links with Cortical Phase Transitions and Learning

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We present a discussion of the k-complex of the electroencephalogram (EEG) in terms of the dynamics of a relatively simple mean-field cortical model (where individual neurons and discrete firing events are not modelled explicitly, but averaged over macrocolumns). The k-complex is considered to be a result of a momentary excursion to an unstable high-firing state, in the form of a single-cycle travelling wave. Significantly, we demonstrate that the necessary conditions for a k-complex develop spontaneously in the model as a result of a simple synapse-strengthening (learning) rule. The model also implies a strong connection between the k-complex and the cortical slow oscillation, complementing recent experiments and modelling efforts where each neuron is considered explicitly.

8.4

1D Haemodynamic Model Predictions of Blood Flow from Circle of Willis (CoW) Geometry Measured by Magnetic Resonance Angiography

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Blockage of arteries leading to the brain can cause devastating stroke, moderate stroke or no stroke at all, depending in part on CoW geometry. A model which could predict stroke risk using individual patient CoW measurements would help with patient treatment and risk management. This research aims to establish the feasibility and validity of a 1D haemodynamic model of the Circle of Willis. CoW geometries for 23 patients with cerebral vascular occlusion were entered into the model. Blood flow resistance was calculated using the lengths and diameters of 6 efferent, 3 afferent and 3 communicating CoW arteries measured from clinical magnetic resonance (MR) angiography. Blood flow reductions were greater among patients with infarcts than patients without brain infarction, for several efferent vessels modelled. However, the model produced severe predicted flow drops for some patients with no infarction. The accuracy of the model is reduced by the substitution of average values for immeasurable blood vessels. Further investigation will allow identification of the CoW anatomical variations and critical geometries which are most at risk of stroke. The 1D model of CoW haemodynamics is computationally efficient and fast, but is limited by the availability and accuracy of blood vessel measurements.

8.5

Non-invasive Measurement of Geometrical and Anatomical Variations of the Circle of Willis (CoW) Using Magnetic Resonance Imaging

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Blockage of arteries leading to the brain can cause devastating stroke, moderate stroke or no stroke at all, depending in part on CoW geometry. A model which could predict stroke risk using individual patient CoW measurements would help with patient treatment and risk management. This research aims to establish the feasibility and validity of measurements of CoW geometry from clinical magnetic resonance (MR) angiography. The lengths and diameters of 6 efferent, 3 afferent and 3 communicating CoW arteries were measured for 79 normal subjects and 23 patients with cerebral vascular occlusion using an in-house software package. Measurements were taken from non-invasive MR imaging protocols which are routinely performed on stroke patients. The technique was limited by image quality and difficulty resolving small anterior and posterior communicating arteries in some patients. Otherwise, the technique proved feasible and reliable with results consistent internally, with data from subjects who also had digital subtraction angiography and from cadaveric data. The arterial measurements will be used for the calculation of flow resistance in a 1D model of CoW haemodynamics. In addition, a surface reconstruction algorithm is being developed to create a three-dimensional representation of each subject's CoW which will be used in a 3D computational fluid dynamics model.

8.6

A Phase-Transition Model for the Cycles of Natural Sleep

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Understanding the purpose and structure of sleep remains one of the grand challenges of neurobiology. The major states of vigilance— wake, slow-wave sleep (SWS), rapid-eye-movement (REM) sleep— are not properties of individual neurons; rather, they emerge from the collective behaviour of large populations of interacting neurons. Accordingly we adopt a population-based picture of the cortex using as our modelling element the macrocolumn, a cubic-millimetre volume of cortex containing about 100,000 neurons. We incorporate within the model the two major sleep modulatory effects: slow changes in both synaptic efficiency and in neuron resting voltage caused by the 90-min cycling in acetylcholine, together with even slower changes in resting voltage caused by gradual elimination during sleep of somnogens (fatigue agents) such as adenosine. We argue that the abrupt change from SWS to REM sleep can be understood as a phase transition from a low-firing, coherent state to a high-firing, desynchronized cortical state. We make predictions for the changes in EEG power, spectral distribution and correlation properties at the SWS-to-REM sleep transition, and demonstrate that these predictions are broadly consistent with clinical recordings for a sleeping human and laboratory recordings reported recently for a sleeping cat.

9.1

Musicians and Non-musicians Differ with Respect to the Lateralisation of Music Processing

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Music processing in the brain may be lateralized differently given the musical expertise of the individual. Recent research has shown that musicians process music mostly in the left hemisphere, whereas non-musicians process music mostly in the right hemisphere. It is hypothesized that the leftward activation seen in musicians represents their tendency to process music as a language. The aim of this study was to determine whether musicians would be slowed when performing language tasks with music playing in the background compared to performing these tasks in silence. Thirty-six expert musicians and 36 non-musicians performed a language comprehension task and a visuospatial search task under the conditions of silence, piano music played correctly and piano music played incorrectly. Musicians performed significantly more poorly in the language task under the two music conditions than in silence, and performance in the incorrect music condition was significantly lower than performance in the correct music condition. In contrast to this, the performance of non-musicians was not affected by music. On the visuospatial search task neither musicians nor non-musicians showed any effect of music. These results suggest that musicians have difficulty processing music and language at the same time, possibly due to competition in the neural system processing language.

9.2

Semantic Categorisation and Mental Rotation of Misorientated Letters and Numbers

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Mirror-normal judgement of misoriented letters is known to elicit an increase in ERP negativity with increased angular departure from upright. These ERP effects, which occur between 400 and 700 ms after stimulus onset, have been related to the process of mental rotation which is thought to be necessary for mirror-normal discrimination. In the present study, we have compared mental rotation and letter-number categorisation in order to determine the sequence of events associated with recognition of misoriented objects. In both tasks, we have found effects of orientation as early as the P1 ERP component (100-120 ms), and they persist over the N1 and P2 components as well. However, the systematic change in amplitude over the later time period (400-700 ms) is only present for the mental-rotation task. These finding are consistent with the idea that mental rotation is not necessary for object recognition and that orientation-relevant information is extracted as early as 100 ms.

9.3

Investigation of the Stroop Effect in Bilinguals Using EEG

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The Stroop colour-word interference task has been traditionally used as a tool to assess frontal lobe function in neuropsychiatric disorders, and in cases of brain injury. With the increase in availability of neuroimaging tools, there have been many recent attempts to more precisely determine the neural substrates involved in the detection and resolution of conflicts in the Stroop task. The implication of bilingualism on the interference pattern has not been investigated to date. The classic Stroop paradigm with concurrent EEG recording was used to investigate the interference effect in 24 late fluent bilingual subjects compared to 16 English monolingual subjects. The Stroop task consisted of three conditions (congruent, control and incongruent) and was performed in first (L1) and second language (L2-English) for the bilingual group and in English only for the monolingual group. The electrophysiological data showed temporal shifts in the ERPs in the condition comparisons between the two groups. Bilinguals consistently showed delayed latencies in the ERP components of interest for *both* languages (i.e., components in the 300-450ms range). Thus, the temporal dynamics of the underlying neural activity appears to differ between the groups. Bilinguals also showed particular differences while processing their second language as illustrated by the lack of significant ERP amplitude differences in the incongruent versus congruent condition. Reaction time data did, however, clearly show the presence of the Stroop effect: a significant incongruent versus congruent condition difference in L1 and L2. Together, there is evidence of a difference in processing L2 versus L1, but possibly at a neural substrate level that is not observable behaviourally.

9.4

The Poffenberger Paradigm in Adults with ADHD-I and ADHD-C

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The Poffenberger paradigm is often used as a simple and reliable way to measure interhemispheric transfer time (IHTT) or the time required for information to be transferred from one cerebral hemisphere to the other. This transfer occurs via the corpus callosum, the main band of fibres connecting the two hemispheres. It has been shown previously that individuals with ADHD have a smaller corpus callosum, in terms of cross-sectional area in both the rostrum and splenium, when compared to neurotypical controls. This might be reflected in slower IHTTs. Here, visual evoked potentials were recorded during the Poffenberger task. Interhemispheric differences in N170 latency with left and right visual field stimuli provide a measure of IHTT. Data were collected from controls and individuals with two different subtypes of ADHD: ADHD-I (predominantly inattentive) and ADHD-C (inattention with hyperactivity). Researchers generally fail to differentiate subjects according to subtype (ADHD-I and ADHD-C) despite clinical observations and MRI reports that these subtypes are distinct in nature. Our preliminary analyses (N = 21) show that participants with ADHD-I have significantly slower left to right interhemispheric transfer times for the N170 component compared to controls and ADHD-C participants. Interestingly, the ADHD-C group had faster interhemispheric transfer times in both directions compared to both control and ADHD-I groups, possibly reflecting a neural correlate of the behavioural characteristics of the subtype. These data support the existence of two distinct subtypes of ADHD.

9.5

Steroid Modification of Interhemispheric Transfer Time During the Menstrual Cycle

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It is well established that some cognitive processes are lateralised (predominantly processed in either the left or right cerebral hemisphere). However, these functional asymmetries are generally more pronounced in men. Recent evidence suggests that women are not less lateralised per se, but due to changes in gonadal steroids during different stages of the menstrual cycle, their functional asymmetries are less static than those of men. The degree of lateralization may depend in part on interhemispheric transmission time (IHTT) that may be affected by steroid levels. Here we employed EEG to obtain a direct measure of IHTT during different phases of the menstrual cycle. The interhemispheric latency difference of the N170 component of the visual potential evoked from left or right visual field presentation. Eighteen right-handed women with regular menstrual cycles were tested twice, once during the menstrual phase, when progesterone and oestradiol levels are low, and once during the mid-luteal phase when progesterone and oestradiol levels are high. Plasma steroid levels were determined by blood-based immunoassay at each session. It was found that luteal phase IHTT was significantly longer than that during the menstrual phase. Differences in IHTT across the menstrual cycle as measured here may underlie the observed differences in degree of cerebral laterality observed between men and women.

9.6

The Effects of Spatial and Temporal Uncertainty on the Generation of Predictive Saccades

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When tracking a target moving rhythmically between fixed positions, subjects normally produce anticipatory (predictive) saccades which have a much shorter latency than visually-guided saccades. We examined the limiting conditions under which predictive saccades are generated in nine neurologically healthy subjects. In our control condition, two targets positioned 10 deg to the left and right of the mid-line were illuminated alternately for one of three fixed durations (750 ms, 1400 ms and 2050 ms). We then applied several levels of spatial (0-8 deg) or temporal (0-30%) uncertainty to the above task. Thus, the targets appeared 0-8 deg either side of the expected positions or lasted shorter or longer than the expected durations by 0-30 %. Longer target durations resulted in decreased anticipation of the target [$F(2,16) = 18.06$, $p < 0.0001$], as did increased spatial [$F(7,56) = 5.11$, $p < 0.0002$] or temporal [$F(5,30) = 7.51$, $p < 0.0002$] uncertainty. Small amounts of spatial (≤ 1 deg) or temporal ($\leq 10\%$) uncertainty had no effect on latency. Predictive saccades generated under the conditions of spatial uncertainty were characterised by hypometric primary saccades, more pronounced at higher levels of uncertainty. These results demonstrate that small amounts of spatial uncertainty do not impair subjects' ability to generate predictive saccades, but the oculomotor strategy is to undershoot the target to minimise total saccadic flight time.

9.7

Binocular Rivalry and the Role of Induced Gamma Synchrony in Perceptual Binding

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It is still uncertain what elements of neural activity might contribute to the conscious awareness of visual stimuli. During binocular rivalry, one image is presented to each eye. Subjectively, one image is completely suppressed while the other is perceived. Work on the Macaque visual cortex has shown that neurons in V1/V2 continue to discharge to their preferred stimulus at a constant rate, regardless of whether it is consciously perceived. Work in strabismic cats has suggested that, with the introduction of a competitive image to the non-dominant eye, there is an increase in neural synchrony across neurons responding to the dominant image. To investigate the role of synchrony in determining image dominance during ocular rivalry the present experiment measures occipital gamma range synchrony on the mesoscale. Such measures are believed to reflect object binding, which is thought to play a role in the conscious representation of stimuli. EEG was measured from a human during the transition from one dominant image to the other. A burst of gamma activity was observed 200-300ms after the initiation of transition, focussed over occipital recording sites. Despite the subjective experience of binding being extended to 600-1000ms the obtained results were similar in both latency and duration to studies that have investigated object closure under normal viewing conditions. A possible dissociation between object binding as indexed by gamma oscillations and the subjective experience of perceptual binding is suggested.

10.1

Is the Ventral Tegmental Area (VTA) Involved Exclusively in Reward? : Elucidating the Fear Arousing Properties of Intra-VTA Electrical Stimulation

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The VTA and its dopaminergic (DA) mesocorticolimbic projections are thought to be essential to the brain's reward neurocircuitry. In human and animal experimental subjects, mild electrical VTA stimulation appears to have euphorigenic effects on behaviour. Paradoxically, aversive stimuli are known to activate VTA neurons and forebrain DA activity. Additional evidence suggests that the VTA is critical to the acquisition and expression of Pavlovian conditioned fear. The primary purpose of the present study was to demonstrate that electrical activation of VTA neurons in a fear-arousing context enhances learned fear responding. Using fear-potentiated startle as a behavioural index of emotionality, we found that immediate and delayed VTA stimulation following nonreinforced presentations of a fearful conditioned stimulus impaired the extinction of fear responding. This effect was found to be specific to the VTA since normal extinction learning was apparent following electrical stimulation of substantia nigra neurons. Additional experiments indicated that the electrical stimulation parameters were not aversive since laboratory rats failed to show fear conditioning when electrical VTA stimulation was used as the unconditioned stimulus. Also, VTA stimulation did not alter conditioned fear expression in non-extinguished animals. Based on these results, we suggest that VTA activation promotes a disinhibition of fear arousal, and as a consequence, the VTA neuronal excitation by aversive stimuli may play a role in the maintenance of fear related anxiety disorders thought to reflect extinction learning deficits.

10.2

The Anatomical Locus of Amphetamine- Enhanced Fear

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Paranoia, phobias, and other disorders involving abnormal fear, share a common dysregulation of intrusive thought. These disruptive thoughts elicit defensive behavioural responses in the absence of a genuine threat. Thus, the responses can be interpreted as the individual's inability to extinguish a learned fear. To better understand the neural basis of the extinction deficit seen in abnormal fear, our study employed an animal paradigm of abnormal fear involving the chronic administration of d-amphetamine. D-amphetamine (2.5 ìg/side) was infused into the ventral tegmental area (VTA) – a region whose dopaminergic projections are critical to fear neurocircuitry – prior to each of three extinction sessions. As d–amphetamine is especially effective in potentiating the release of mid–brain dopamine, and the hyperactivity of dopaminergic transmission has been repeatedly implicated in the genesis of abnormal fear, we predicted an infusion of the drug prior to extinction would result in an extinction deficit. The chronic administration of amphetamine to the VTA prior to extinction sessions interfered with the subject's ability to extinguish a previously conditioned fear, as tested on a subsequent fear-potentiated startle test. This result was not due to chronic amphetamine administration enhancing the baseline levels of conditioned fear. Administration of amphetamine (2.5 ìg/side) to the terminal field of the VTA dopaminergic projections, the amygdala, did not produce the extinction deficits yielded from the VTA. This regional specificity raises interesting questions about the role of somatodendritic dopamine release in the maintenance of abnormal fear.

10.3

Sensory Gating in Pedunculopontine Tegmental Nucleus

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Previous studies have shown that that lesions of the pedunculopontine tegmental nucleus (PPTg) impair prepulse inhibition, a "sensorimotor gating" phenomenon. However it is not clear whether PPTg is relevant to the regulation of prepulse effects on perception or movement, since PPTg accepts information from both ascending sensory inputs and descending output of based ganglia movement control system. The present study tested sensory gating of evoked spikes of single units in PPTg in conscious rats using a paired stimulus paradigm. Thirty PPTg neurons were tested under double sound or double light stimuli with 1000ms interstimulus interval (ISI), and 6 also with light-sound pairing. The results showed that the sensory gating, expressed as the average ratio between the firing rates following test and conditioning stimuli (T/C ratio), was 0.70 (24.8 ± 35.1 Hz vs 35.5 ±37.8 Hz, n=30, T= 4.47, P<0.0001) for auditory (sound-sound) gating, and 0.02 (0.05 ± 0.4 Hz vs 2.14 ± 2.3Hz, n=6, T=2.26, P<0.05) for visual gating. Interestingly, there was very little sensory gating in cells tested with light-sound stimuli, suggesting little cross modality gating in PPTg cells. This contrasts with the cross modality sensorimotor gating previously reported at the behavioural level. In addition, decreasing ISI to 50ms resulted in little gating, which contrasts with previous data showing strongest sensorimotor gating with ISI of 40-150 ms. These results suggest a differential mechanism between "sensory gating" and "sensorimotor gating" at the level of PPTg single neuron activity.

10.4

Effects of Vestibular Deafferentation on Performance in a Rat Food Foraging Task

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It has been suggested that the vestibular system may contribute to the development of higher cognitive function, especially spatial learning and memory that uses idiothetic cues (e.g., dead reckoning). However, few studies have been done using behavioural tasks that could potentially separate the animals' ability for dead reckoning from piloting. The food foraging task requires the animal to continuously monitor and integrate self-movement cues and generate an accurate return path. It has been shown that bilateral vestibular lesioned rats were impaired on this task. The present study used the same task to further examine the contribution of vestibular information to spatial navigation by comparing unilateral and bilateral lesions and by testing the animals at different time points following the lesion. The results demonstrated, for the first time, that: 1) at 3 months following the vestibular lesion, UVD animals were impaired on the foraging task when egocentric cues were required and this impairment disappeared at 6 months after the lesion; 2) UVD and BVD had distinct effects on animals' behaviour for as long as six months after the lesion, with BVD animals showing significant hesitation in leaving their home cage. This supports the notion that vestibular information contributes to dead reckoning and suggests possible recovery of function over time after the lesion.

10.5

Genetic Analysis of Stress-responsiveness in a Mouse Model

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In order to look for genes which might be involved in anxiety related behaviours, we have undertaken a genetic analysis of a simple mouse model of stress-responsiveness. Two inbred mouse strains have been identified which show either high or low stress-responsiveness. These strains were crossed to generate F1 progeny which were then crossed to generate F2 progeny, and in which there is segregation of genotype within individual animals. We have isolated DNA from these animals and conducted a genome scan in order to find regions on the genome which correlate with the stress-responsiveness. Several regions on the mouse genome show significant linkage with the stress phenotype. One region in particular, on chromosome 12, was further characterized and the most significant linkage was found between 32.8 and 44.8 centimorgan. These chromosomal regions may contain genes encoding proteins that are involved in the underlying neural circuitry involved in stress-responsiveness.

10.6

Visual Perception of Apparent Motion in Depth Revealed by MEG

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Primates are sensitive to the approach of objects in order to prevent threats from other animals. This expansion of the image supplied as a motion-in-depth cue is important in our daily life. The main purpose of this study was to investigate the perception of motion-in-depth from either optic flow or scale-change information. We used three types of stimulation: (1) real motion, (2) apparent motion stimulation by change of scale (two frames with changed size of patterns presented alternating), and (3) apparent motion stimulation by optic flow (one white square appeared in altered position). Different motion perception was induced from these dynamic changes of visual scene. Component N170m detected by magnetoencephalography was analyzed. Several observations were derived. First, apparent motion appeared to stimulate similar neurons to real motion. Second, humans seem to have mechanisms more sensitive to changes in scale than changes in optic flow. Third, two types of asymmetries existed in the visual system response. There were bigger changes to expanding stimuli than contracting ones. Second, activity was more prominent in the right occipito-temporal area. Finally, this study indicated that motion in depth evoked responses occurs around the V3 area.

11.1

Differential Control of Memory and Behavioural Inhibition by Different Sub-regions Along the Hippocampal Septo-temporal Axis

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The participation of discrete chunks of the hippocampal formation in hippocampal-sensitive behaviours was investigated by delivering neurotoxic ibotenic acid to lesion specific hippocampal target sites within a three dimensional "patchwork" in fifty rats. Lesion size for each rat was estimated in CA3, CA2, CA1, subiculum and dentate gyrus at five dorso-ventral levels to obtain twenty-five predictor variables. Dependant variables were measures of averaged performance or change in performance over time from open field (OF), spontaneous alternation (SP), Morris water maze (WM) and fixed interval (FI) bar-pressing tasks. Stepwise multiple regressions were used to hierarchically order the predictors with explanatory power for each dependant variable. The pattern of hippocampal damage related to behaviour change was distinct for all measures, but generally cognitive measures (SP, WM) were affected by damage to specific cell fields in more dorsal (septal) levels of Ammon's horn, and behavioural inhibition (FI, OF rearing) by more ventral (temporal) damage to dentate gyrus, subiculum and CA1. Separate and sometimes even proximal chunks could influence behaviour in opposite directions. Overall it appears that the hippocampus controls diverse and dissociable functions via complex circuitry that is distributed on both the septo-temporal and transverse axes of the structure. These circuits may be more segregated between cell fields closer to its septal than temporal pole.

11.2

Rhythmic Electrical Activity in the Hippocampus and the Midline Cortices of the Rat

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Studies of theta rhythm in humans mostly focus on frontal midline recordings. This source of theta oscillation has been argued to arise from the anterior cingulate cortex, which is known to be a part of the limbic system. We implanted electrode arrays in rats in the midline cortices throughout the anterior-posterior axes. Also, bipolar electrodes were implanted in the hippocampus. Preliminary data show multiple sources of rhythmic oscillation in the frontal midline cortices (including the anterior cingulate). The data also suggest the oscillations in the posterior midline cortices (retrosplenial cortex) are not volume conducted from the hippocampus. The oscillations in the frontal cortices, posterior cortices entirely and the hippocampus were found to become coherent with each other under certain circumstances. The results suggest there are multiple sources of frontal midline theta rhythm in the rat, and these sources are in a network that can interact with the retrosplenial cortex and the hippocampus.

11.3

Fluoxetine Impairs Learning in the Morris Water Maze

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Classical anxiolytics are agonists at the $GABA_A$ receptor. They have been shown to produce deficits in spatial navigation in the Morris Water Maze, a sensitive test of hippocampal dysfunction. The novel anxiolytic agent Buspirone produces a similar deficit. It has no effect on GABA but acts via $5\text{-}HT_{1A}$ receptors. Specific serotonin reuptake inhibitors (SSRI) can also act, indirectly, at $5\text{-}HT_{1A}$ receptors and can also be anxiolytic. All three classes of drug have been shown to reduce the frequency of hippocampal theta rhythm. We tested an SSRI, fluoxetine, for its effects on acquisition of the Morris Water Maze. Experiment 1 and 2 each used 12 rats. These were divided equally into one of three drug conditions. Experiment 1 tested 20mg/kg fluoxetine, 6.6mg/kg buspirone (active control) or vehicle (passive control). Experiment 2 tested 10, 5 and 0 mg/kg of fluoxetine. The rats were tested for four trials a day for three days and then received a transfer test. Fluoxetine impaired learning particularly earlier in training and at lower doses. These effects of fluoxetine on spatial navigation are broadly similar to buspirone and classical anxiolytics. But, unlike them, its dose relation in the water maze is different from its effects on hippocampal theta rhythm.

11.4

Identification of Multiple Sites Generating Theta Activity in the Posterior Hypothalamus

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Theta rhythm is a prominent form of electrical activity in the hippocampus. It is thought to contribute to hippocampal involvement in processes such as emotion, attention, learning and memory. The subcortical control of hippocampal theta may involve several distinct hypothalamic sites. We implanted recording electrodes in the posterior hypothalamic region of Sprague-Dawley rats and recorded the EEG during freely moving behaviour and during learning. We also tested the effect on these recordings of blocking septal input and so hippocampal theta activity. The mammillary nuclei and supramammillary area showed very stable, strong theta wave production. The theta signal immediately above them in the posterior hypothalamic area was weaker. There were a range of sites showing moderate amounts of theta in the dorsomedial and posterior hypothalamus, as well as one site in nucleus reuniens of the thalamus. Inactivation of the medial septum with tetracaine blocked theta in the MM but not SUM. This suggests that SUM but not MM controls hippocampal theta and that MM theta depends on output from the hippocampus. Tetracaine-resistant theta was also observed in a site below MM that appeared to be in the arcuate nucleus. This is consistent with other data suggesting that SUM is not the only source of theta input to the hippocampus.

11.5

Regional Variations and Age-related Changes in Cyclooxygenase in Memory-associated Brain Structures

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Cyclooxygenase (COX) converts arachidonic acid to various prostaglandins. Increasing evidence suggests that COX and prostaglandins participate in various physiological and pathological processes, including the aging process. The present study investigated regional variations and age-related changes in COX activity and COX-1 and COX-2 protein expression in the hippocampus and its adjacent entorhinal, perirhinal, postrhinal and temporal cortices. In young adult (4-month-old) rats, total COX activity was expressed at low levels and COX-1 and COX-2 protein expression varied across the hippocampus and its adjacent cortices. Regional variations were also observed across hippocampal sub-regions CA1, CA2/3 and dentate gyrus. When a comparison was made between young and aged (24-month-old) rats, we did not find significant age-related changes in COX activity and protein expression in the dorsal and ventral portions of the hippocampus and four cortical regions. Within the hippocampus, there was a significant decrease in the aged CA1 and a significant increase in the aged DG in total COX activity, but not COX-1 and COX-2 protein expression. In conjunction with previous studies, these results support the involvement of COX in brain aging. An investigation of the relationships between COX and age-related behavioural impairments is currently underway.

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