1.1

Adventures with Synaptic Plasticity: Calcium and Quanta

S. J. REDMAN

Division of Neuroscience, John Curtin School of Medical Research, Australian National University, Canberra, ACT, Australia

The mechanisms underlying the induction and expression of long term potentiation (LTP) of transmission between Schaffer collaterals and CAI pyramidal cells in the hippocampus have remained unclear, despite intensive investigations and many controversies. While elevation of post–synaptic calcium is widely accepted as a necessary condition for LTP induction, there are sub-plots to this story. The calcium signals responsible for inducing different forms of LTP are spatially segregated and originate from different sources. Short lasting LTP requires activation of ryanodine receptors, which selectively increases calcium in synaptically activated spines. Long lasting LTP is exclusively associated with a somatic calcium influx via L-type voltage activated calcium channels. LTP of intermediate duration is induced by activating IP3 receptors and subsequent calcium release in those dendritic branches that carry the activated spines. Quantal analysis has been the traditional tool for evaluating the origin of changes in synaptic strength: pre or post-synaptic or both. This technique is problematic when applied to central synapses, because the quantal current for the activated synapses cannot be measured as it can at some peripheral synapses. Never the less, a body of evidence has accumulated using quantal, optical and biochemical measurements to support the case that the expression of LTP at mature CA1 synapses involves both pre- and post-synaptic components.

1.2

Hippocampal Structural and Functional Deficits that Result From Prenatal Ethanol Exposure Can be Rescued by Voluntary Exercise

A. K. OLSON[2] and B. R. CHRISTIE[1,2,3]

[1]Department of Psychology, [2]Neuroscience Program, [3]Brain Research Center, University of British Columbia, Vancouver BC, Canada

The ingestion of ethanol during pregnancy has a number of deleterious consequences for the unborn offspring, producing structural and functional deficits that affect the brain and many other organs into adulthood. The hippocampus is a brain structure that is particularly sensitive to insult from prenatal ethanol exposure. In the present study, we investigated the effects of prenatal ethanol exposure (PNEE) on hippocampal dependent behaviours, synaptic plasticity and neurogenesis, and also tested the hypothesis that voluntary exercise would ameliorate any deficits observed. Sprague-Dawley females were administered one of three diets throughout gestation: (i) Ethanol (E): a liquid diet containing 35.5% ethanol-derived calories; (ii) Pair-fed (PF): a liquid control diet, with maltose-dextrin isocalorically substituted for ethanol, in the amount consumed by an E partner (g/kg body wt/d of gestation); and (iii) Ad lib-fed control (C): normal laboratory chow and water, ad libitum. We found that PNEE impaired performance on the Morris water maze, decreased LTP in the dentate gyrus and decreased hippocampal cell proliferation and neurogenesis. However, all these deficits were rescued and restored to control levels in PNEE animals that exercised. Our latest experiments are determining the effects of PNEE and acute stress on the induction of LTD in the hippocampal CA1 region. Overall, voluntary exercise appears to be a robust tool for alleviating the functional and structural impairments that result from exposure to ethanol *in utero*.

1.3

Control of AMPA and NMDA Receptor Targeting to Excitatory Synapses by SAP97 Isoforms

D. GENOUX and J. M. MONTGOMERY

Department of Physiology, University of Auckland, Auckland, New Zealand

At excitatory glutamatergic synapses, N-methyl-D-aspartate (NMDA)-type and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-type glutamate receptors are essential for the induction and expression of synaptic plasticity respectively. During long-term potentiation (LTP) or depression (LTD), AMPA receptors are known to be inserted or removed at the membrane surface. This property seems to be tightly controlled by an anchoring protein SAP97 (Synapse Associated Protein-97). SAP97 is a member of the MAGUK family of synaptic proteins that binds both the GluR1 subunit of the AMPA receptor and NR2 subunits of the NMDA receptor. Alternative splicing of the SAP97 gene generates multiple neuronal SAP97 isoforms, resulting in the insertion of distinct sequences between the SH3 and GUK domain. We have investigated how SAP97 alternative splicing dictates synapse function and plasticity. Paired whole cell recordings were performed on dissociated hippocampal cultures expressing GFP-tagged SAP97 isoforms. Our data provide a novel role of the I2 SAP97 isoform in specific activity-dependent regulation of AMPA and NMDA receptors. In contrast the I3 SAP97 isoform appears to play a critical role in basal synaptic function. Our data show that the insertion of specific inserts into SAP97 can dictate activity-dependent regulation of glutamate receptors that are critical for the induction and expression of synapse plasticity.

1.4

A Novel Trafficking Pathway for NMDA Receptors to Synapses

J. M. MONTGOMERY[1], M. SCHUBERT[1], T. DE SILVA[1], O. JEYFROUS[2,3], C. C. GARNER[2] and W. N. GREEN[3]

[1]Department of Physiology, University of Auckland, Auckland, New Zealand
[2]Department of Psychiatry and Behavioural Sciences, Stanford University, CA, USA
[3]Department of Neurobiology, Pharmacology & Physiology, University of Chicago, IL, USA

Plasticity of the circuitry that wires the brain is a fundamental property of neurons that is thought to underlie learning and memory. We and others have shown that the development and elimination of synapses and changes in the strength of existing synapses in the hippocampus form the basis of this plasticity. The N-methyl-D-aspartate (NMDA)-type glutamate receptor expressed at synapses is required for learning and memory and is critical for normal brain function. At a cellular level, this receptor plays a pivotal role in triggering and controlling synapse plasticity. Our data show evidence for a unique trafficking pathway for the movement of NMDA receptors from the soma to synapses in rat hippocampal neurons. NMDA receptors, together with the synaptic scaffold protein SAP97, bud from somatic endoplasmic reticulum (ER) compartments and travel within dendrites in ER-derived vesicles. Live cell imaging of GFP-NR1 + DsRed-ER or GFP-NR1 + RFP-SAP97 shows these vesicles are highly mobile. NMDA receptors bypass somatic golgi as neither disruption of somatic golgi function with brefeldin A nor temperature shift to prevent protein exit from the golgi influence subcellular trafficking of NMDA receptors. These data provide evidence for a novel sorting mechanism for NMDA receptors resulting in a unique trafficking pathway to ensure specific, highly regulated synaptic NMDA receptor targeting.

1.5

Inhibition of Hippocampal Glutamate Transporter 3 (EAAC1) Using AAV Antisense Delivery: Effects of Working Memory

A. M. BABCOCK[1], K. COOMBS[1], M. KAVANAUGH[2] and D. POULSEN[2]

[1] Department of Psychology, Montana State University, Bozeman, MT, USA
[2] COBRE Center for Structural and Functional Neurosciences, University of Montana, Missoula, MT, USA

The neuronal glutamate transporter EAAC1 (EAAT3) is present in hippocampal neurons and functions to prevent excessive glutamate accumulation and provide a source of GABA precursor for interneurons. Glutamate receptor-dependent synaptic plasticity is important for learning and glutamate transporters may modulate this action. To begin addressing the importance of EAAC1 in learning, adeno-associated virus (AAV) vector encoding an EAAC1 antisense sequence or AAV empty cassette were microinfused bilateral into the dorsal hippocampus of rats (n=7/group). Twenty-one days following surgery, rats were evaluated in reference and working memory versions of a water maze (sequential testing). In the reference memory task, latency to locate the hidden platform did not differ between groups. However, EAAC1 AS rats exhibited impairment during the probe trial phase ($p < 0.05$). Rats were also tested in a water maze working memory task. On four consecutive days (2 blocks/day), subjects were placed on the pseudo-randomly located hidden platform and given four trials to locate the target following a delay. Rats treated with EAAC1 AS exhibited shorter latencies to locate the target relative to controls indicative of improved working memory ($p < 0.05$). These data indicate that microinfusion of AAV encoding EAAC1 AS significantly altered performance on tasks involving glutamate transmission and the hippocampus.

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2.1

Effects of Memorisation of Target Location on Reaction Time and Brain Event Related Potentials

J. G. ANSON[1], L. UEHARA[1], D. F. HIGHT[1], J. R. WICKENS[1], K. JORDAN[2], R. L. SCOTT[1], J. DALLIMORE[1] and B. I. HYLAND[1]

[1] University of Otago, Dunedin, New Zealand
[2] Pennsylvania State University, State College, Pennsylvania, USA

In monkeys, memorisation of target location in a precued reaction time (RT) task is associated with faster RT, together with more sustained magnitude of the directional neuronal population vector, compared to non-memorised conditions. In contrast, results from a series of experiments in our laboratory indicate that in humans RT is shorter when memorisation is not required and longer when the location of the target must be remembered (memorised) until the "GO" signal occurs. Here we report the results of a new experiment in which electroencephalography (EEG) was used to measure changes in brain electrical activity during performance of this task. Six participants performed 48 trials to each of four targets in three foreperiod and two memorisation conditions, (a total of 1152 trials). On each trial, participants moved their index finger in response to a visual GO signal from a central, illuminated switch to one of four targets on a hemisphere at a radius of 6 cm. RT was the time from the GO signal to release of the switch. A precue provided 750 - 1050 ms before the GO signal indicated the correct target. This either remained illuminated during the entire foreperiod (non-memorisation condition) or was extinguished after 300 ms (memorisation condition). EEG data were recorded from $Ag^{++}Cl^{-}$ electrodes on the scalp surface, amplified (Synamps DC – 70 Hz, Gain = 500) sampled at 1kHz (Scan 4.2) and later processed to correct for DC-drift, DC-offset and ocular artefact. Consistent with our previous results, RT was significantly faster ($p < .05$) for non-memorisation (M = 251 ms) than memorisation (M = 271 ms). Brain electrical activity, represented as a contingent negative variation (CNV) event related potential over the left motor cortex (C_3') was quantified as the average amplitude over 100 ms immediately preceding the imperative stimulus. CNV amplitude was greater in the memorisation condition, when RT was longer. This disjunction between amplitude of CNV and RT suggests that CNV amplitude cannot be used as a simple measure of central motor preparedness, or as a substitute for vector analysis of individual neuronal firing rates. Activation of specific cell assemblies and development of neuronal population vectors is associated with reduced activity in all neurons not involved in the task, which may dominate recordings using spatially averaged techniques such as EEG.

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2.2

Sensorimotor Adaptation to Visual and Mechanical Distortions is Based on a Common Mechanism

O. BOCK and M. THOMAS

Institute of Physiology and Anatomy, German Sport University, Köln, Germany

It is well established that our sensorimotor system adapts to a variety of visual and mechanical perturbations, but it still remains open whether this adaptation is achieved by one common, or by several distinct mechanisms. To find out, we asked 24 subjects to point at visual targets while successively adapting to a visual rotation (which depends on hand position), and to a force field (which depends on hand velocity); the order of exposures was counterbalanced across subjects. Thus, the two perturbations differed both with respect to their physical nature (visual, mechanical) and their kinematic coupling to the hand (position-, velocity-dependent). Subjects' performance was quantified as the difference between target and hand direction 150 ms after response onset. We found that at the onset of a given perturbation, subjects' performance remained as it was before, and then gradually changed until it became adequate for the new perturbation. No signs of competition between conflicting adaptive processes were observed, i.e., no discontinuous or erratic behavior. Our findings are therefore in accordance with the view that adaptation was based on a common neural mechanism, which is flexible enough to accommodate perturbations of different polarity, physical nature, and kinematic coupling. The location of such a mechanism within the sensorimotor system remains unclear.

2.3

Learning Joint Mobilization Skill: Effectiveness of Two Forms of Feedback

J. Y. CHANG[1], G. L. CHANG[1], K. C. CHUNG[1] and A. T. HSU[2]

[1]*Department of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan*
[2]*Department of Physical Therapy, National Cheng Kung University, Tainan, Taiwan*

Performing joint mobilization is a complicated task and is characterized by great inter-subject and inter-session variability. It poses as a difficult skill to learn and to teach. This study was designed to investigate whether quantitatively augmented feedback could enhance the learning of joint mobilization and, more specifically, to compare the effects of training with concurrent feedback or terminal feedback by using a custom-designed joint translation simulator (JTS). Thirty-six undergraduate physical therapy students without known impairment of musculoskeletal system were randomly assigned into control, concurrent feedback, and terminal feedback groups. The JTS was designed to simulate tissue responses based on load-displacement relationships recorded from mechanical testing of glenohumeral specimens. Subjects applied specific mobilization grades of force (along with the accompanied movement) on the JTS. Quantitative feedbacks wase provided to the subjects in feedback groups either concurrently during a trial or terminally after a trial via a monitor, while the control group received no quantitative feedback. Pretest, immediate and delayed retention tests were conducted and normalized absolute errors of applied force (NE) were calculated. During acquisition and retention, both feedback groups performed more accurately and consistently than did the no feedback group ($p < 0.05$ for any grade of any model). No obviously superior performance was showed in terminal feedback group compared to concurrent feedback group during retention and, thus, a guidance hypothesis was not supported. The results of the present study indicate that learning of mobilization skills can be enhanced either by quantitative concurrent feedback or by terminal feedback. The JTS appears to be a promising tool for training joint mobilization.

2.4

Motor Unit Synchronization Measured by Cross-Correlation is Not Increased With Strength Training of a Hand Muscle

J. G. SEMMLER[1], M. V. SALE[1] and D. J. KIDGELL[2]

[1]Discipline of Physiology, University of Adelaide, South Australia
[2]School of Exercise and Nutrition Sciences, Deakin University, Australia

It is commonly believed that motor unit synchronization in a hand muscle increases as a result of strength training, although this has never been assessed directly. The purpose of the study was to use cross-correlation to directly quantify the strength of motor unit synchronization before and after 4 weeks of strength training the first dorsal interosseous muscle. Four young subjects performed a training protocol 3 times/week consisting of 6 sets of 10 maximal isometric index finger abductions. Motor unit activity was recorded with pairs of intramuscular electrodes in the first dorsal interosseous muscle before (n=42 pairs) and after (n=41 pairs) the 4-week training protocol. The training intervention resulted in a 27% (51.0 ± 10.0 N to 64.9 ± 17.0 N, P = 0.007) increase in maximal index finger abduction force, whereas there was a 20% (common input strength index; 0.77 ± 0.41 pulses/s to 0.61 ± 0.38 pulses/s, P = 0.03) reduction in motor unit synchronization following 4 weeks of strength training. Furthermore, there was no association between the change in strength and the change in synchronization in individual subjects after training. These cross-correlation data suggest that increases in strength following 4 weeks of training a hand muscle are not accompanied by increases in motor unit synchronization.

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2.5

Reference Frames for Visuomotor Transformation: Evidence from Spontaneous Movements without Directional Feedback

C. J. WORRINGHAM[1], O. BOCK[2], S. DAWSON[1] and A. D. TOWNSHEND[1]

[1]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia
[2]Institute of Physiology, German Sports University, Cologne, Germany

Many studies using a range of paradigms have sought to clarify the principles underlying visuomotor transformation. In two experiments, we investigated the "rules" of this transformation with a joystick-controlled computer-based aiming task in which no vision of the limb or feedback concerning movement direction was provided. Several factors were varied, including the orientation of head, trunk and limb. Any stable relationship between the direction of each target relative to the start position, and that of the ensuing limb motion, should reveal something of the underlying rules of visuomotor transformation. In the first experiment, 36 subjects either faced the display with the controlling limb aligned in the sagittal plane, or viewed the display over the left shoulder with the controlling limb extended to the right. Analysis centred on directional error, using circular statistics. Initial spontaneous movements for all but one subject suggest the spontaneous use of an intrinsic reference frame corresponding to a "visuomotor compatibility" principle. A second experiment explored the small deviations from this principle by having right-handed subjects use a joystick in nine positions from extreme left (across the body) to extreme right (right arm fully extended), but in which the y axis was always parallel to the vertical on the display and the sagittal axis. Direction errors show a strong tendency for spontaneous motions to employ a reference frame based on the "virtual" line of sight to the unseen limb, independent of its location. Together, these experiments provide strong support for the operation of a visuomotor compatibility principle in which virtual line of sight is a critical reference.

2.6

Motor Constancy/Equivalence and the Relationship Between Tangential Velocity and Radius of Curvature

J. G. PHILLIPS

School of Psychology, Psychiatry and Psychological Medicine, Monash University, Australia

A movement such as a circle can be performed using a variety of effectors, and this is an instance of motor constancy/equivalence. To resolve the complexity of motor coordination over different effectors, constraints are invoked such as the lawful relationship between tangential velocity and radius of curvature (1/3 power law). Previous studies have suggested that this power law could arise from faster, more fluent motion occurring over fewer joints. Two experiments considered the strength of the power law over a variety of joints (elbow, finger, shoulder, wrist) or movement spaces (large, medium, small). Participants performed circling motions in a vertical plane upon a Smartboard that sampled finger tip position at 100Hz. Movement speed or fluency could not explain the strength of the power law, instead the power law was stronger for fewer joints or smaller movement spaces. As the strength of the power law varies with effector, it is debatable as to whether the power law alone can explain a constancy of motor output.

3.1

Assessing RNA Quality in Postmortem Human Brain

I. A. CHEVYREVA[1], R. L. M. FAULL[1], C. R. GREEN[2] and L. F. B. NICHOLSON[1]

[1]Department of Anatomy with Radiology, [2]Department of Ophthalmology, University of Auckland, Auckland, New Zealand

Obtaining high quality RNA form postmortem (PM) human tissue samples is essential for successful microarray studies. We assessed RNA quality in a range of human brain tissues obtained from the NZ Neurological Association Human Brain Bank at the University of Auckland Medical School. This has involved screening RNA extracted from a number of human brain samples from different brain regions taken from both the normal brains and brains from patients with neurological diseases (33 cases altogether). The aim of the study was to determine how various parameters, primarily the postmortem delay, affect the quality of the RNA extracted from the tissue samples. The initial screening was performed using samples from the cerebellum. The brain areas used in the second part of the study were those regions secondarily affected in a specific neurological disease: caudate nucleus for Parkinson's (n=4), motor cortex for Huntington's (n=5), medial temporal gyrus for Alzheimer's disease (n=5), hippocampus for epilepsy (n=3) (epilepsy samples were obtained following temporal lobectomy) and the corresponding areas taken from normal controls. Pearson correlation coefficients and linear regression were used to correlate PM delay with RNA quality for all samples and with and between disease groups, and also to compare different brain regions. The results showed that RNA quality is variable from brain region to region within the same case and that RNA quality is not dependent on PM delay.

3.2

Motor Phenotype in a Novel Mutant Tau Transgenic Mouse Model

N. A. DETERS, T. FATH, N. SCHONROCK, P. GUNNING, J. GÖTZ and L. M. ITTNER

Brain and Mind Research Institute, University of Sydney, Sydney, Australia

Aggregates of hyperphosphorylated forms of the microtubule-associated protein tau have been described in a number of common neurodegenerative diseases, including Alzheimer's disease, Pick's disease and fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Besides cognitive and memory impairment, motor control abnormalities and amyotrophy has been reported previously upon expression of human tau isoforms in transgenic mice. Here, we have developed a novel four repeat mutant human tau transgenic mouse model, Syd1, to study muscle abnormalities in tau pathology background. We report that Syd1 mice are indistinguishable from control littermates up to one month of age. During the second month of age however, Syd1 mice gain less weight and adopt a lean stature compared to age-matched controls. At four months of age, Syd1 mice have a 50% reduction in body weight compared to wild-type littermates, due to a markedly reduced muscle mass. Organ weight, reproductivity and overall survival were not affected, however. Syd1 mice showed expression of transgenic hyperphosphorylated tau in motor neurons of the spinal cord with neuronal loss. Analysis of muscle tissue from two month old Syd1 mice revealed fibers with swollen and centralized nuclei, a sign of early degeneration. In older animals the musculature showed fielded degeneration, typical of denervation. In motor tests, the Syd1 mice showed an impaired performance. Taken together, our findings demonstrate that expression of pathogenic human four repeat tau in mice leads to peripheral neuropathy resulting in nerve cell loss, amyotrophy and subsequent motor control dysfunction.

3.3

Protection Against Huntington's Disease Progression: AAV-Mediated Delivery of Biotherapeutics

A. P. KELLS and B. CONNOR

Department of Pharmacology, University of Auckland, Auckland, New Zealand

Neurodegeneration within the caudate-putamen of Huntington's disease (HD) patients is a relentless progression that needs to be stalled for effective long-term clinical treatment. Numerous neuroprotective agents have proved capable of supporting striatal neurons however delivery challenges to the CNS have hindered their *in vivo* efficacy. Advances in adeno-associated viral (AAV) vectors for gene therapy have demonstrated safe production of biotherapeutics within the CNS. We investigated whether AAV-mediated gene delivery could direct biotherapeutic production and support vulnerable striatal neurons. Our focus is on brain-derived neurotrophic factor (BDNF), important for maintenance and functional plasticity of the striatum, and reduced in HD patients. We increased BDNF expression in Wistar rats by striatal injection of AAV-BDNF three-weeks prior to unilateral striatal injection of the neurotoxin quinolinic acid (QA), a model of HD. AAV vectors were shown to spread anterogradely from the striatum to the globus pallidus and substantia nigra with AAV-mediated transgene expression in both striatal neurons and neurons within the projection nuclei. Behavioural assessment revealed that AAV-BDNF significantly restricted the development of forelimb use imbalance ($P < 0.05$) and of sensorimotor neglect ($P < 0.01$). DARPP-32 stereology to quantify the survival of striatal neurons eight-weeks after lesion did not find any significant difference between AAV-BDNF treatment and controls. These results show that while AAV-BDNF can alleviate the development of behavioural impairments, increased BDNF expression alone appears insufficient to protect against QA-induced cell death but may still hold therapeutic value for HD.

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3.4

Investigating Pick's Disease: A Novel Tau Transgenic Mouse Model

Y.-A. LIM, N. SCHONROCK, L. M. ITTNER and J. GÖTZ

Brain and Mind Research Institute, University of Sydney, Sydney, Australia

Tauopathies are conformational diseases of the brain characterised by tau deposition in filaments which eventually forms neurofibrillary tangles (NFTs). Previously, a K369I missense tau mutation was observed in a patient with Pick's Disease, which led to fibrillar aggregation of hyperphosphorylated tau in intra-neuronal Pick bodies. To investigate the mechanisms underlying Pick's disease, mutant K369I tau was expressed in mice under the control of a neuron-specific mThy1.2 promotor. The transgenic mice express mutant tau in cortex, hippocampus and basal nuclei with expression levels significantly higher in wild type controls and in the well established P301L mutant tau transgenic mice. Tau phosphorylation and aggregation was confirmed by using a set of phospho-tau specific antibodies and Bielschowsky silver impregnation. As found in patients with the K369I mutation, tau aggregation in our samples showed negative Gallyas staining. Together, K369I mutant tau expression in transgenic mice was shown to cause hyperphosphorylation and subsequent aggregation of tau, recapitulating the histopathological findings observed in patients.

3.5

Hyperactivity and Memory Deficits after Repeated Hypoxia During Development: A Novel Rat Model of Extreme Prematurity

S. E. SAUNDERS[1], M. COVEY[1], D. BILKEY[2] and D. OORSCHOT[1]

[1]Department of Anatomy and Structural Biology, [2]Department of Psychology, University of Otago, Dunedin, New Zealand

Extremely premature infants born at 22-28 weeks-of-gestation often have memory and behavioural deficits such as attention deficit hyperactivity disorder (ADHD) later in life. These deficits may be caused by exposure to repeated bouts of sublethal hypoxia. We are currently developing a rat model of this brain injury. This model consists of exposure to repeated bouts of hypoxia during postnatal days 1-3. The neuropathology seen in extremely premature infants is replicated in this model. The aim of this study was to investigate whether memory deficits and hyperactivity are present in adult rats exposed to repeated hypoxia during development. The radial arm maze was used to test for deficits in spatial memory. Compared to control rats, repeated hypoxic rats achieved significantly fewer days of 100% success in this maze. A fixed interval-extinction multiple component lever-pressing task was used to investigate ADHD-like behaviour. This task is used to detect attention deficits, impulsivity and hyperactivity in response to delayed reward. We found that repeated hypoxic rats are hyperactive in response to delayed reward, but do not have attention deficits. This is the first study to show that repeated hypoxic rats have memory deficits and display ADHD-like hyperactivity. This mimics what is seen in some children born extremely prematurely and provides a new animal model to investigate biological mechanisms and treatments of extreme prematurity.

3.6

Initial Studies Towards Gene Therapy in Ovine Batten Disease

D. N. PALMER[1], G. W. KAY[1], M. J. OSWALD[1], S. M. HUGHES[2] and J. D. COOPER[3]

[1]Agriculture and Life Sciences Division, Lincoln University, Canterbury, New Zealand
[2]Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand
[3]Institute of Psychiatry, London, England

It is usually taken as axiomatic that the storage material in lysosomal storage diseases is the primary cause of the pathology, but there is little evidence for this proposition. Studies in an ovine form of the group of neurodegenerative diseases collectively known as Batten disease (neuronal ceroid lipofuscinoses, NCLs) indicate that this is not the case. A series of 11 age matched control and affected brains aged from 50 days prenatal until advanced clinical disease were studied. While there was no association between storage and the first affected regions of the brain, a close association was noted with glial activation, indicated by glial fibrillary protein immunohistochemistry for astrocytosis and with a lectin and MHC II immunohistochemistry to detect activated microglia and perivascular macrophages. This glial activation begins prenatally indicating that it is primarily involved in the pathogenesis. Immunohistochemsitry with calretinin and calbindin antibodies suggested prolonged neurogenesis in the subventricular zone of affected brains and the persistence of cells undergoing chain-migration to the neocortex. Staining with a marker of neuroblasts, polysialated nuclear cell adhesion molecule (PSA-NCAM) indicated that this stream retains neuroblast activity. Lentivirus derived vectors have been used to transduce and express green fluorescent protein in PSA-NCAM positive neuroblasts and MAP2-positive neurons in culture. These studies open the way to consider therapy based on a combination of suppression of glial activation and gene therapy targeted into the subventricular zone.

Poster 4.1

Modafinil Fails to Attenuate Working Memory Decline of Rats in a Swim Task

S. CHADHA, J. HARSH and J. MCCOY

Department of Psychology and Behavioural Neuroscience, The University of Southern Mississippi, USA

Recent evidence attributes learning and memory improvements to modafinil, an FDA-approved drug for treating hypersomnia. Despite supporting evidence for a cognitive-enhancing effect of modafinil, its influence over memory processes are poorly understood. The current investigation addressed the possibility that modafinil enhances working memory. This effect was explored through manipulation of the intra-trial delay (DI) between an 'information' and a 'choice' swim within a delayed-non-matching-to-position (DNMTP) swim-task using young-adult, male Wistars. Rats were trained to search for a hidden platform to escape from the water maze. Acquisition proceeded until a 90% performance criterion was met. Next, working memory was tested by manipulating the DI (10 - 190 sec) during two, within-subjects testing phases using intraperitoneal injections of 100 mg/kg of modafinil or vehicle, respectively. The intervals used were established in a prior pilot study. Contrary to the findings of Berachocea et al. (2001), who were first in reporting a modafinil working memory-enhancement effect in mice, we showed that modafinil affected neither working memory task performance nor locomotor activity. Additionally our data showed a significant linear decrement in task performance when intra-trial delays were extended from 10 sec to shortly over three minutes; this decline was independent of drug treatment. Therefore, any performance-related improvements due to modafinil within the DNMTP swim task are likely to derive from other aspects of learning, such as memory consolidation/recall, and attention, etc.

Poster 4.2

Plasticity-Induced Regulation of Group I Metabotropic Glutamate Receptors in Cultured Hippocampal Neurons

J. E. CHEYNE, K. R. HOFSTRA and J. M. MONTGOMERY

Department of Physiology, University of Auckland, Auckland, New Zealand

Synapse plasticity involves the processes of synapse formation, synapse elimination and alterations in synapse strength. Group I metabotropic glutamate receptors (mGluR1 and mGluR5) are known to modulate synapse plasticity and synaptic transmission. Here we show that most silent synapses do not contain Group I mGluRs and that mGluR5 is expressed at more silent synapses than mGluR1. In addition we show that the synaptic expression of mGluR1 but not mGluR5 is increased by chemical induction of long term potentiation and decreased by chemical induction of long term depression. The regulation of Group I mGluRs by synapse plasticity will have important effects on the ability of synapses to undergo further plastic changes.

Poster 4.3

Environmental Enrichment Alters Hippocampal Representation of Context and Behavioural Response to Context Change

K. R. CHEYNE, D. D. DICKERSON, X. LU, W. C. ABRAHAM and D. K. BILKEY

Department of Psychology, University of Otago, Dunedin, New Zealand

Previous research has demonstrated that environmental enrichment has widespread effects on brain anatomy, physiology, and function. We have previously 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. Our data indicated significantly greater changes in the firing rates of place cells of enriched rats compared to social control rats when cells were recorded in two relatively similar contexts. To further investigate this finding, rats were chronically implanted with electrodes in hippocampal area CA1 after being raised for at least three months in enriched or social conditions. When rats were moved between two dissimilar recording arenas it became apparent that many place cells recorded from enriched rats were involved in the representation of only one of the arenas, whereas most cells of social-group rats had place fields in both (30 of 32 cells, compared with 22 of 31 enriched-animal cells; $p < 0.05$). A subsequent behavioural study suggested that enriched rats were better able to discriminate between a familiar and a novel context than were social rats. These data are consistent with our hypothesis that enriched animals are more sensitive than social animals to contextual changes, and that this difference is a result of more orthogonal representations of space in the enriched-group animals.

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Poster 4.4

Selective Volitional Inhibition of Prepared Action

J. P. COXON, C. M. STINEAR and W. D. BYBLOW

Human Motor Control Laboratory, Department of Sport and Exercise Science, University of Auckland, Auckland, New Zealand

Research to date investigating the ability to exert volitional inhibition over a frequently presented motor response has been conducted using paradigms requiring non-selective inhibition. In this context, inhibition of the response is achieved by preventing all intended movement. Here we examine our ability to inhibit one response while concurrently executing another. The purpose of this study was to investigate the ability to exert volitional inhibition in a selective context. Subjects were required to observe two bars filling at an equal rate. Their task was to lift their index and middle fingers from depressed keys to intercept the left and right filling bars respectively as close as possible to a target positioned 800 ms from trial onset (Go trials). On an infrequent number of trials, either one or both bars would stop prior to the anticipated response signalling for the subject to inhibit lifting their finger on the side the bar stopped (Stop trials). Stop All, Stop Index, and Stop Middle trials were presented 300, 240, 180, and 120 ms prior to the target. On Stop trials, the probability of responding was significantly greater for Stop Index and Stop Middle relative to Stop All. In addition, selective Stop trials significantly delayed the response of the other finger relative to the Go trial delay. These results will be discussed in the context of inhibitory function within primary motor cortex.

Poster 4.5

Neuronal Migration From the Ganglionic Eminence to the Cerebral Cortex in Dopamine Receptor Knockout Mice

J. E. CRANDALL, D. M. MCCARTHY and P. G. BHIDE

Shriver Center, University of Massachusetts Medical School, Department of Neurology, Harvard Medical School, Boston, Massachusetts, USA

Dopamine receptor subtypes D1 and D2 as well as dopaminergic axons appear by embryonic day 13 (E13) in the mouse forebrain, while large-scale tangential migration of neurons from the ganglionic eminence (GE) to the cerebral cortex is ongoing robustly. We have previously shown that pharmacologically altering the balance between dopamine receptor subtypes alters tangential migration: D1-receptor stimulation increases tangential migration, and D2-receptor stimulation decreases it. We sought to extend these studies by using dopamine receptor knockout mice. In homozygous D1-receptor knockout mice, dopamine can only activate D2-receptors and conversely, in homozygous D2-receptor knockouts, it can activate only D1-receptors (assuming minimal contributions from D3-, D4- and D5-receptors). Coronal slices of E15 mouse forebrain were cultured on membranes in defined medium, and DiI crystals placed in the GE. Slices were exposed to dopamine (10μM) for 48 hours, and the percentage of DiI-labeled cells entering the cerebral wall was assayed. For the D1-receptor knockout mice, there was a 52% decrease in the percentage DiI-labeled cells migrating to the cerebral wall compared to heterozygous or wildtype littermates. In D2-receptor knockout mice there was a 23% increase in tangential migration compared to heterozygous or wildtype littermates. These results confirm our earlier data that the balance between dopamine receptor subtypes is critical to successful tangential migration from the GE to the developing cerebral cortex.

Poster 4.6

AT_4 Ligands Potentiate Neuronal Glucose Uptake: A Potential Mechanism Underlying Memory Enhancing Effects

R. N. FERNANDO, A. ALBERTSON and S. Y. CHAI

Howard Florey Institute, University of Melbourne, Parkville, Australia

AT_4 ligands enhance spatial learning, memory acquisition, retention and retrieval and reverse memory deficits caused by experimental models of amnesia. At a cellular level AT_4 ligands enhance evoked acetylcholine release and facilitate LTP *in vitro* and *in vivo*. The central binding target of these ligands is the insulin regulated aminopeptidase (IRAP). IRAP is involved in regulated glucose uptake in peripheral tissues via an association with the insulin regulated glucose transporter, GLUT4. In adipocytes, specialised vesicles containing IRAP and GLUT4 translocate to the cell surface in response to insulin stimulation, facilitating regulated glucose uptake. We propose IRAP is associated with GLUT4 in the brain in a regulatable glucose uptake system analogous to that present in adipocytes. Using an in-house antibody IRAP immunohistochemistry was demonstrated in high concentrations in neurones in the brain. Additionally in some regions including the pyramidal cells of the hippocampus IRAP is found highly co-localised with GLUT4 in vesicular populations. Using a hippocampal slice glucose uptake assay we have demonstrated that 30mM KCl induced ^{3}H-2-deoxyglucose uptake, is potentiated by the AT_4 ligand LVV-H7. We have further demonstrated that the uptake of glucose occurs specifically in cells expressing IRAP and GLUT4 as visualised with a fluorescent 2-deoxyglucose analogue. We propose that an inducible glucose uptake system responsive to depolarisation exists in hippocampal neurones. The presence of vesicular IRAP and GLUT4 in these cells suggests the involvement of a system analogous to that present in insulin responsive cells. Enhanced glucose uptake in selected neurones may therefore underlie the cognition enhancing effects of AT_4 ligands.

Poster 4.7

The Menacing Phantom: What Triggers Phantom Limb Pain and Why?

M. J. GIUMMARRA[1,3], N. GEORGIOU-KARISTIANIS[1], S. J. GIBSON[2,3], M. CHOU[2] and J. L. BRADSHAW[1]

[1]Experimental Neuropsychology Research Uni, School of Psychology, Psychiatry and Psychological Medicine, Monash University, Clayton, Australia
[2]Caulfield General Medical Centre, Caulfield, Australia
[3]National Ageing Research Institute, Parkville, Australia

Little is known about the triggers of phantom limb pain. Amputees generally experience phantom limb pain when internal representations of the body are triggered by motivational factors (e.g., intention to act) or from afferent feedback from the amputated limb, the contralateral limb, or other parts of the body. This study explored triggers of phantom limb sensations in order to understand the mechanisms underlying phantom limb pain (PLP). 36 upper limb, 216 lower limb, and 6 combined upper/lower limb amputees described their circumstances of limb loss, phantom limb sensations (PLS) and factors that trigger or alter phantom sensations. Phantom sensations were perceived by 247 participants (70.2%), and 83 per cent of these amputees reported at least one trigger of their sensations. Ten types of trigger were identified: (1) Behavioural "motor act"; (2) Psychological, autonomic or emotional arousal; (3) Empathy for another's pain; (4) Diurnal patterns; (5) Change in weather; (6) Changes in body posture; (7) Vestibular stimulation; and referral of perceptual event to phantom from (8) the amputated limb and/or stump; (9) the contralateral limb; or (10) another part of the body. Phantom limb pain appears to be associated with complex patterns of activity in the central and autonomic nervous systems and activation of central representations of the body.

Poster 4.8

Orosomucoid Influences Both Antidepressant Tolerance and Response

J. A. HARLEY[1], R. L. ROBERTS[2], P. R. JOYCE[1], R. T. MULDER[1], S. E. LUTY[1], C. M. FRAMPTON[1] and M. A. KENNEDY[2]

[1]Department of Psychological Medicine, [2]Department of Pathology, Christchurch School of Medicine and Health Sciences, University of Otago, Christchurch, New Zealand

Orosomucoid, an acute phase reactant (APR), carries basic drugs including antidepressants. Elevated levels have been reported in depressed patients. It has yet to be established whether concentration influences antidepressant response. Its gene, *ORM1,* is polymorphic and has three common co-dominant alleles ORM*F1, *F2 and *S. The variants have differing pharmacokinetic properties which potentially alter plasma profile and blood brain barrier transport of antidepressants influencing tolerance and efficacy. One hundred and fifty-seven outpatients in a trial of fluoxetine versus nortriptyline were genotyped for the *ORM1* variants. Plasma concentrations of APRs were also measured. Outcomes were tolerance and response. Tolerance was defined as the completion of a six week trial and response as an improvement of greater than 60% on the Montgomery-Asperg Depression Rating Scale at 6 weeks. Groups were compared using one-way ANOVA and Chi-squared tests. Outcome predictions were performed using binomial logistic regression. Individuals with an ORM1*F allele were more likely to tolerate antidepressants (OR=4.707, 95% CI 1.769-12.527, P=0.002). Higher orosomucoid concentrations were found in antidepressant non-responders (91.4% vs 79.1%, F-stat 6.071, P=0.015). For every 1% increase in orosomucoid the odds of response were decreased (OR=0.984, 95% CI 0.971-0.997, P=0.018). The two effects of orosomucoid - polymorphism affecting tolerability and concentration affecting efficacy - emphasise its importance in the handling of antidepressants.

Poster 4.9

Brain-Gene Ontology (BGO)

V. JAIN, L. BENUSKOVA, P. GOTTGTROY and N. KASABOV

Knowledge Engineering and Discovery Research Institute, Auckland University of Technology, Auckland, New Zealand

This article summarizes the ongoing research on brain-gene ontology (BGO) project that we intend to use as a tool for educational purpose and research. It covers the concept from brain organization (structure, neuronal bundles, and synapses) through dogma (gene regulation, ion channel proteins and mutations) to modelling and simulation of brain diseases. Behind our goal is Computational Neural Genetic Model (CNGM), a novel methodology to simulate brain functions or a brain disease manifestation and ontology maps (linked to diseases) which provides a conceptual framework to store and access factual knowledge. We demonstrate that tuning the interaction between genes and their initial expression levels, different states of the neural network operation can be achieved. Users are able to simulate the activity of certain parts of brain using biologically plausible neural networks (spiking neural network, SNN) and the link to the genetic level, in an attempt to enable discoveries of yet unknown dynamic relationship between genes and states of the brain activity. The system is incorporated into Protégé and also we are incorporating novel animations on signal propagation etc. Using ontology modules, a user can gain the knowledge not only on understanding brain functions but also on genes/proteins and other biological properties like sequence length, molecular weight, locus link, mutation etc. Related projects are brain-map (at Allen institute) and brain models on the web (Arbib, 1999). For earlier publications on CNGM and recently accepted IJNS paper, kindly visit: www.kedri.info

Poster 4.10

The Neural Basis of Dyslexia: An fMRI Study

Y. JI, S. L. HORROBIN, I. J. KIRK and K. E. WALDIE

Department of Psychology, Research Centre for Cognitive Neuroscience, University of Auckland, Auckland, New Zealand

Dyslexia is a developmental neurological disorder characterized by poor reading ability regardless of intelligence, attention and motivation. Proficient readers show asymmetric hemispheric lateralization during language tasks, with the left side being predominant. Earlier studies with dyslexic individuals have reported less activity in left temporoparietal cortex and left inferior frontal areas during phonological and auditory processing tasks, respectively. An earlier fMRI study in our lab provided new evidence that dyslexics show maximal activation in right inferior frontal area during lexical decision, making suggesting that a shift to the right hemisphere may compensate for left hemisphere deficits. In the current study, we recruited 8 dyslexic adults (M = 31 years, SD = 9.97, all right-handed, 3 female), and the areas in the whole brain that were activated while subjects performed five different go/no-go tasks were monitored: two baseline tasks (shapes, letters), two lexical decision tasks (regular and irregular words) and a sublexical decision task. The findings (SPM5) revealed that dyslexic readers process nonverbal stimuli in the same area as normal readers (right parietal). During irregular word reading, however, dyslexic subjects showed maximal activation in their right inferior frontal areas, whereas during sublexical analysis general occipital and cerebellar activity was observed. Dyslexics may indeed depend more on the right side of their brains instead of the left, but only during particular linguistic tasks.

Poster 4.11

Neurophysiological Correlates of the McCollough Effect: Evidence for Neuronal Plasticity?

B. M. KNIGHT, J. P. HAMM, I. J. KIRK and M. C. CORBALLIS

Research Centre for Cognitive Neuroscience, Department of Psychology, University of Auckland, Auckland, New Zealand

The physiological mechanisms underlying the long-lasting orientation-contingent colour aftereffect (McCollough Effect – ME) remain unclear. Whereas early explanations suggested a process of neuronal fatigue, recent models of the ME implicate synaptic plasticity in visual cortex. Work in our lab has demonstrated that plasticity can be measured non-invasively in human visual cortex following the rapid presentation of checkerboard stimuli. A 9Hz photic tetanus was found to persistently increase the amplitude of a component of the visual evoked potential (VEP), whereas 1Hz stimulation was found to reduce the amplitude of the same component, possibly reflecting synaptic depotentiation or depression. This study aimed to investigate the relationship between the ME and this rapidly induced form of visual cortex plasticity. Electroencephalography (EEG) was used to measure VEPs elicited by achromatic gratings from eighteen participants before and after the rapid presentation of alternating red and green vertical and horizontal gratings. The induction gratings were presented at one of three frequencies: 15Hz, 9Hz and 1Hz. Preliminary analysis shows that the amplitude of a late positive component (the P2) of the VEP evoked by achromatic gratings was significantly altered ($p<0.05$) following 15Hz and 1Hz induction; a 15Hz induction tetanus led to a significant increase of the P2, whereas 1Hz induction led to a significantly decreased P2. No significant change was observed following 9Hz induction. These findings are consistent with the notion that rapidly induced neuronal plasticity underlies the ME.

Poster 4.12

Development of Virtual Reality Environment for Behavioral Study of Rats

H. Y. LEE[1], M. D. KUO[1], Y. S. OU-YANG[2] and J. J. J. Chen[2]

[1]Department of Management Information Science,
Far East University, Tainan County, Taiwan, ROC
[2]Institute of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan, ROC

Recent developments in information technology have facilitated the use of virtual reality (VR) techniques for simulation surgery, rehabilitation training, and cognitive neuroscience studies. Several VR studies have demonstrated that it is feasible for animals to interact with VR by using rewarding scheme and visual cues for attention processes, spatial memory, and executive functions. This study aimed to develop an animal behavior testing environment with immersive VR which allowed us to interact with the animal responses to the stimulations in a limited space. We integrated the dome screen for displaying visual stimuli and a motion detection subsystem for sensing the animal's intention. In our self-design animal cage, the front hemisphere screen connected the outer cage in one-degree-of-freedom for pitch rotating which ensures the animal is constrained at optimal view point during the experiment. The intentions of animal were detected by a body position sensing device, which sent rotation and yaw angles via TCP/IP transmission to alter VR generation. A camera was mounted behind and slightly above the animal which allowed the experimenter to observe the locomotion of the rat and to synchronize the recording of brain activity. Validation tests of animal behaviors on the developed VR system were performed based on the visual interaction to the animal behavioral studies.

Poster 4.13

Mitochondrial Stress and Inflammation in the Diabetic CNS

R. D. MARTINUS and W-W HWANG

Department of Biological Sciences, School of Science and Engineering,
University of Waikato, Hamilton, New Zealand

There is compelling evidence linking brain inflammation and mitochondrial dysfunction (via reactive oxygen species) to a number of age associated neurodegenerative diseases (such as Alzheimer's and Parkinson's Diseases). However, the underlying molecular mechanisms responsible remain unknown. The diabetic CNS shows similar neuropathology to the ageing brain and other neurodegenerative conditions. Using the diabetic CNS as a model system we have recently demonstrated for the first time the expression of the mitochondrial stress protein (cpn60) in the hippocampus as a function of mitochondrial oxidative stress. In this study we investigated the relationship between expression of cpn60 and pro-inflammatory cytokines in the CNS of streptozotocin induced diabetic rats. TNF-a immunostaining was observed in neuronal cells in the cortex, pyramidal neurones in the CA1/CA3 regions of the hippocampus and in the thalamus. Immunostaining for TNF-a was not seen in any of the untreated control brain regions. Double immunostaining with ant-cpn60 antibodies indicated a strong correlation between expression of TNF-a and mitochondrial stress in neuronal cells in the diabetic CNS. We propose a novel hypothesis linking mitochondrial dysfunction and inflammation in the CNS via the expression of cpn60.

Poster 4.14

Abnormalities in Somatosensory Psychophysical Functions After Stroke

T. A. MATYAS, F. D. FISHER and L. M. CAREY

La Trobe University and National Stroke Research Institute, Melbourne, Australia

Conscious experience, safety, motor performance and rehabilitation are adversely influenced by somatosensory loss following stroke. Psychophysical functions estimated by direct scaling methods have the potential to provide: (1) theoretically interesting observations into the effects of brain damage; and (2) a clinically applicable measurement method that is more comprehensive and more practical than estimation of detection or discrimination thresholds via indirect scaling, the dominant quantitative approach in neurological literature. Hypotheses derived from psychophysical theory and somatosensory neuroscience were therefore investigated in two studies employing stroke (n = 31 and n = 40) and matched healthy control samples. Participants responded via cross-modality matching methods to unsighted passive wrist position or punctate pressure stimuli (Semmes-Weinstein monofilaments). Test durations were briefer than required for indirect scaling methods. Psychophysical scatterplots using data obtained from contralesional limb performance were compared to scatterplots obtained from healthy controls and ipsilesional limbs. Statistical analyses of parameters extracted from individually fitted psychophysical functions were consistent with hypotheses predicting increased neural noise, attenuated gain in encoding, or both. Abnormalities over specific segments of the stimulus ranges were also observed, consistent with an encoding hypothesis assuming tuned neurons. These findings confirm expectations that direct scaling offers a more informative and more efficient assessment methodology. Associations with data on lesion type and stroke history are being investigated.

Poster 4.15

The Acute Effects of Benzylpiperazine on Human Working Memory and Vigilance Using EEG Recording

B. RUSSELL, V. K. LIM and I. KIRK

School of Pharmacy, Department of Psychology,
University of Auckland, Auckland, New Zealand

"Party pills" are becoming increasingly popular with conservative estimates from 2005 suggesting that approximately 150,000 doses/month were sold. Healthy right-handed males, between 18-40 years of age were recruited to perform several tasks while recording a 128-lead electroencephalogram (EEG) followed by a single oral dose of BZP (200 mg) or a placebo, waiting for 2 hours and then repeating the tasks while recording a further EEG. The tasks used i.e. Sternberg, Poffenberger and the P300 using an auditory oddball paradigm are typically used to assess working memory, inter hemispheric transfer times, and vigilance. It was expected that the BZP would act as a typical psychostimulant similar to others such as caffeine or nicotine and improve working memory and vigilance. However preliminary data suggests that these tests may not be appropriate for measuring the effects of this drug because there was no observable alteration in either the latency or amplitude of event related potentials.

Poster 4.16

Event-Related Potentials during the Auditory Discrimination Oddball Task in the Rat

S. SAKATA and M. HATTORI

Department of Behavioral Sciences, Hiroshima University, Hiroshima, Japan

Auditory event-related potentials (ERPs) were recorded from rats that were actively performing in a tone discrimination oddball task. Male Wistar rats were trained to press a lever within 2s after the onset of a short duration target tone (8kHz, 50msec). Rats were given a food pellet (45mg) as a reward only when they correctly responded to the target tone. A stimulus presentation was scheduled every 4.5s and could be one of three alternatives. The probability of the stimulus being the target tone was 15%, of no tone (empty stimulus) was 15% and of a non-target standard tone (4kHz, 50msec) was 70% with the alternatives presented in a random order. After reaching the learning criterion, rats were chronically implanted with seven electrodes targetting the frontal cortex, parietal cortex, anterior cingulate cortex, hippocampal areas CA1 and CA3, striatum and septum. The target tone elicited P1, N1, P2, N2 and P3-like potentials. P1 latencies were almost always around 35ms in all brain areas. N1 latencies were changed between 52 to 75ms. P2 were 75 to 140ms in wide varied. Cortex areas latencies were faster than sub-cortex areas. We utilized an animal model of ERPs to explore the relationship between these brain areas during performance of auditory discrimination task. The rodent may provide a useful model for investigation of the cognitive process in the neural sources of the human P3.

Poster 4.17

Kindling-Induced Plasticity Changes in the Lateral Amygdala

M. SCHUBERT[1,2], T. KASCHEL[2], C. DREPHAL[2] and D. ALBRECHT[2]

[1]Department of Physiology, University of Auckland, Auckland, New Zealand
[2]Institute of Neurophysiology, Universitätsmedizin Berlin, Berlin, Germany

Temporal lobe epilepsy is often accompanied by impairments of learning and memory. Mechanisms of learning and memory are based on synaptic plasticity, which can be analyzing through long-term potentiation (LTP) and long-term depression (LTD). fEPSP recordings were performed in the lateral amygdala (LA) in horizontal brain slices. In untreated animals, we observed that high frequency stimulation (HFS) induced stable LA-LTP that was dependent on NMDARs and kainate GluR5, not on L-type VGCCs. Low-frequency stimulation (LFS) caused a stronger LA-LTD than theta pulse stimulation (TPS) and was dependent on NMDARs as well as group II mGluRs. In the kindling model of epilepsy Wistar rats were kindled through daily administration of brief electrical stimulations to the left basolateral amygdala. 48 h after the last induced epileptic seizure (kindling), we observed a significant impairment of HFS-induced LTP, the magnitude of which was dependent on the number of prior stage V seizures. The specific kainate GluR5 agonist, ATPA (2000 nM), removed the kindling induced LA-LTP impairment. The specific $GABA_A$ receptor antagonist, SR 95531 (100 nM, partial blockade), did not abolish the kindling-induced impairment of LA-LTP. LFS and TPS elicited no LTD but LTP in the LA of kindled rats. In conclusion, this kindling-induced impairment of LA-LTP might be as a result of functional changes such as the up-regulation of transmitter receptors, involved in mediation of plasticity in the amygdala.

Poster 4.18

Bring the Noise: A Search for Stochastic Resonance in the Auditory System

D. SHEPHERD and M. J. HAUTUS

University of Auckland, Auckland, New Zealand

The extraction of meaningful signals from a background of random noise is the concern of both electrical engineers and observers relying on their biological sensory apparatus. Traditionally, noise in dynamical systems has been viewed as counterproductive, but, it seems, in certain nonlinear systems a weak signal can be made more apparent by the presence of noise. This phenomenon has been termed Stochastic Resonance, and generally concerns a cooperative effect that arises out of the coupling between deterministic and random dynamics in nonlinear systems. However, to play a constructive role in the elucidation of weak signals in nonlinear systems the noise must be of an optimal level. Stochastic Resonance has been applied to the domain of human sensory systems with varying success and this talk reports on three studies dedicated to finding evidence of stochastic resonance in the human auditory system. In the first two studies observers were asked to discriminate between pairs of 1000-Hz sinusoids embedded in varying levels of noise. The studies differed in that one involved the use of a six-point response scale and analysed the data within the framework of signal detection theory, while the other employed a conventional two-alternative forced choice response regime returning percent correct scores. A third experiment involved the detection of a 1000-Hz sinusoid presented in a noise background varying in both bandwidth and level. Evidence supporting the existence of stochastic resonance was weak, and theoretical and methodological factors will be discussed in light of these results.

Poster 4.19

Cortical Inputs to Cholinergic Interneurons in the Striatum of the Rat: Optimisation of Methods

R. J. SIZEMORE, J. N. J. REYNOLDS and D. E. OORSCHOT

Department of Anatomy and Structural Biology,
University of Otago, Dunedin, New Zealand

Cholinergic interneurons account for less than 1% of the total number of neurons present in the striatum of the rat brain and display a synchronous pause in their tonic firing pattern during reward-related learning. It is hypothesised that a fast conducting crossed-corticostriatal pathway is involved in synchronising the pause reponse. This study aimed to investigate synaptic connections between crossed cortico-striatal neurons and cholinergic interneurons in the striatum through labelling cortical neurons by intracellular filling with biocytin and double immunolabelling cholinergic interneurons for m2-muscarinic acetylcholine (m2) receptors and choline acetyltransferase (ChAT). Three antidromically-activated corticostriatal neurons were recovered from intracellular electrophysiological experiments by incubating fixed vibratome sections in an avidin-biotin complex. Neurons were stained with nickel chloride intensified 3,3'-diaminobenzidine tetrahydrochloride. Somas and apical dendrites were filled but axons were not. Double immunolabelling was optimised by trailling monoclonal and polyclonal antibodies for m2 and ChAT on fixed vibratome sections with two different immunohistochemical protocols. A novel protocol, which yielded good staining with minimum background, used a blocking solution containing bovine serum albumin (BSA) and cold water fish skin gelatin and washing steps using acetylated BSA. Best results were achieved using a polyclonal rabbit anti-m2 antibody and a monoclonal mouse anti-ChAT antibody with the novel protocol. Ongoing work aims to combine cortical neuronal labelling and axon tracing with double immunolabelling to confirm synaptic connections between crossed-corticostriatal neurons and cholinergic interneurons.

Poster 4.20

Eye Movement Control and Cognition in Parkinson's Disease

S. VAN STOCKUM, M. MacASKILL,
J. DALRYMPLE-ALFORD and T. J. ANDERSON

Department of Psychology, University of Canterbury, Christchurch, New Zealand

Investigations of eye movement control report a loss of response inhibition in Parkinson's disease (PD), consistent with impaired prefrontal-basal ganglia circuitry. The same neural connections are also involved in cognitive processes. This study explored the potential association of impaired oculomotor control with cognitive deficits in PD. Eighteen non-demented PD patients (MMSE>26) and eighteen controls completed a range of oculomotor and neuropsychological tasks. The PD group made more inhibitory errors in the antisaccade (37% vs 22%, $p<0.01$) and delayed prosaccade tasks (42% vs 20%, $p<0.01$) and generated more express saccades (very fast reflexive responses) in prosaccade tasks (21% vs 15%, $p=0.051$) compared to controls. PD patients who made a high proportion of inhibitory errors in the delayed saccade task had lower scores on the memory and visuospatial perception tests ($r=-0.73$ and $r=-0.58$, $p<0.01$). In contrast, the proportion of errors in the antisaccade task was not significantly associated with any neuropsychological test scores. In both groups, the proportion of errors on the antisaccade task was associated with the proportion of express saccades in prosaccade tasks ($r=0.70$, $p<0.01$). The proportions of inhibitory errors in the two tasks were associated with each other in the control group, but not in the PD group. We conclude that different neural mechanisms may be involved in saccadic disinhibition in delayed and antisaccade tasks in PD. Delayed response tasks may be more useful in the investigation of cognitive impairment in PD than antisaccade tasks.

Poster 4.21

The Profile of Subventricular–Derived Neuroblast Migration into the Quinolinic Acid (QA) Lesioned Adult Rat Striatum

A. S. TATTERSFIELD[1], A. P. KELLS[1], R. L. M. FAULL[2],
S. M. HUGHES[1] and B. CONNOR[1]

[1]Department of Pharmacology, [2] Department of Anatomy, University of Auckland, Auckland, New Zealand

We have previously demonstrated doublecortin (Dcx) positive neuroblast migration in the QA lesioned striatum. Here we investigate the timing of subventricular zone (SVZ) progenitor proliferation and neuroblast migration in relation to lesioning. Rats received a unilateral striatal injection of either QA or vehicle. Groups received BrdU on either day -5, -2, -1 or 0 prior to QA or saline, or on day 0, 1, 2, 3, 5, 7, 14, or 30 after QA or saline. Dcx-positive and BrdU/Dcx co-labelled cells in the lesioned striatum were quantified. Similar patterns of migration were observed in each group with a significant increase in Dcx positive cell numbers observed in the QA lesioned groups compared with shams ($P < 0.05$). There was a significant difference in the number of BrdU/Dcx co-labelled cells between the lesioned groups ($P < 0.01$) but not between shams ($P = 0.77$). Cells proliferating within 2 days of lesioning generated significantly more BrdU/Dcx co-labelled cells in the striatum compared to shams ($P < 0.05$). These results demonstrate that cell loss following QA lesioning results in an acute rather than chronic migratory response. Specifically, the majority of neuroblasts migrating into the damaged striatum are generated from SVZ progenitor cells that were proliferating prior to or immediately following the QA lesion, with reduced recruitment observed at later time points.

Poster 4.22

Brain Reactive Autoantibodies in Autoimmune Diseases, Psychiatric Disorder (Psychosis) and Neurologic Disorder (Epilepsy): Preliminary Results

S. K. TIN[1], J. THUMBOO[1], E. C. LIM[2], S. A. LIM[3], A. PAN[3] and K. Y. FONG[1]

[1]Department of Rheumatology and Immunology, [2]Department of Psychiatry, [3]Department of Neurology, Singapore General Hospital, Singapore

We identified autoantibodies reacting with mammalian brain membrane proteins in Systemic Lupus Erythematosus patients. These autoantibodies were found to be significantly associated with neuropsychiatric disorders (psychosis and/or seizure) in lupus patients. In this study, we aim to determine the prevalence and association of these autoantibodies with other autoimmune diseases, neurologic patients (epilepsy), psychiatric patients (psychosis). We recruited 100 healthy controls, 100 unselected lupus patients, 20 RA patients, 20 OA patients, 20 PsA patients, 20 AS patients, 20 APS patients, 21 psychiatric (psychosis) patients and 5 neurologic (epilepsy) patients. Standard western blot application, using pig brain membrane proteins, was employed to detect brain reactive autoantibodies in patients' sera. The demographic and clinical data were recorded from chart review. The brain reactive autoantibodies were detected in 10 % (n=10) of lupus patients. None of controls, other autoimmune patients, the psychotic patients and epileptic patients showed presence of these autoantibodies. Neuropsychiatric manifestations (psychosis and/or seizure) were significantly associated in 60% (n=6) of BRAA-positive lupus patients (p<0.0001). In conclusion, the brain reactive autoantibodies are present only in lupus patients and not in patients with other autoimmune diseases, psychosis and epilepsy. Although these autoantibodies are significantly associated with psychosis or seizure in lupus patients, they may confer different role in pathological mechanism with regards to psychosis and/or seizure in lupus.

Poster 4.23

Chronic Treatment with Alprazolam Enhances 5-HT_{2A} Receptor-Mediated Inhibition of a Panic-Like Behavior in the Rat Dorsal Periaqueductal Gray

H. ZANGROSSI and V. BORTOLI

Department of Pharmacology, University of São Paulo, Ribeirão Preto, Brazil

The dorsal periaqueductal gray (DPAG) has been critically associated with the mediation of escape, a panic-related defensive behavior. Long-term treatment with antipanic drugs such as imipramine and fluoxetine enhances the inhibitory effect on escape induced by intra-DPAG administration of 5-HT_{1A} and 5-HT_{2A} agonists. Thus, it has been proposed that sensitization of these 5-HT receptors in the DPAG is involved in the mode of action of antipanic drugs. We investigated whether sensitization of 5-HT_{1A} and 5-HT_{2A} receptors in the DPAG is also observed after treatment with alprazolam, a benzodiazepine receptor agonist that is effective in treating panic disorder. The results showed that intra-DPAG injections of the 5-HT_{1A} and 5-HT_{2A} agonists, 8-OH-DPAT and DOI respectively, raised the threshold of aversive electrical stimulation for inducing escape. The inhibitory effect of DOI was significantly higher (p<0.05) in animals receiving long-term treatment with alprazolam (2 mg/kg, 21 days, i.p.) than in saline-injected rats [aversive threshold (mean $\pm$ SEM, μA): sal = 29.0 $\pm$ 2.4; alp = 54.0 $\pm$ 5.3]. Chronic treatment with alprazolam tended (p=0.09) to increase the inhibitory effect of 8-OH-DPAT. Subchronic treatment with alprazolam was without effect. Therefore, as reported previously with the 5-HT acting drugs imipramine and fluoxetine, long-term treatment with alprazolam sensitizes 5-HT_{2A} receptors in the DPAG, strengthening the view that these receptors are involved in the mode of action of different classes of antipanic compounds.

5.1

Time-Course Assessment of Muscle Tone in Raclopride-Treated Parkinsonian Rats

J. J. J. CHEN[1], Y. N. WU[1], H. Y. LEE[2] and B. I. HYLAND[3]

[1]Institute of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan, ROC
[2]Department of Management Information Science, Far East University, Tainan, Taiwan, ROC
[3]Department of Physiology, University of Otago, Dunedin, New Zealand

The aim of the present study was to establish quantitative methods to provide time-course assessment of the alternations of muscle tone of parkinsonian (PD) rats. A portable and miniature biomechanical stretching device was established to manually stretch the hindlimb of awake PD rats treated by raclopride (5mg/Kg, i.p.). From the measured angular displacement angle and reactive torque of sinusoidal stretches at 4 varied frequencies, viscoelastic components of the muscle tone can be derived. In addition, non-invasive multi-electrode was applied to record the tonic and phasic activities of the gastrocnemius muscle for five hours. For comparison, traditional behavior bar test was used as a reference. Our biomechanical measurements showed not only increase in stiffness but also increase in viscous components. Similarly, increase in amplitude of electromyography (EMG) as well as decrease in median frequency of EMG were observed which also indicated an increase in muscle tone after raclopride injection. Moreover, the viscosity and stiffness components of stretched limb increased and sustained for at least five hours. Future development of this study is to extend these assessment methods to assist the experimenters in evaluating the time-course changes of abnormal muscle in chronic PD rat model for evaluating the development of novel treatments.

5.2

Neuro-Musculo-Skeletal Couplings in Rhythmic Multijoint Arm Movement

A. dE RUGY[1], S. RIEK[1], Y. OYTAM[1] and R. G. CARSON[1,2]

[1] School of Human Movement Studies, University of Queensland, Brisbane, Australia
[2] School of Psychology, Queen's University Belfast, Northern Ireland

We investigated the coordination between rhythmic flexion-extension (FE) and supination-pronation (SP) movements at the elbow joint-complex, while manipulating the intersegmental dynamics by means of a 2-degrees of freedom robot arm. Previous behavioral studies revealed the in-phase pattern of coordination (supination synchronized with flexion) to be predominant, i.e., to be established spontaneously by participants. In this study, we investigated whether there is a neuromuscular organization optimized to exploit the biomechanical coupling introduced by the bi-functional muscle Biceps Brachii (BB). This particular muscle acts both as a flexor and supinator at the elbow joint complex. EMG activity of the BB was recorded together with other arm muscles during rhythmic FE and SP movements performed separately and in combination. Rhythmic SP movement was also produced while passive FE was imposed by the motorized robot arm. BB was activated to a greater degree during FE and SP movements performed in combination than separately, and also more strongly during SP performed in combination with passive FE movement than in isolation. These results reveal exploitation of the dual mechanical action of the BB, and suggest that proprioceptive feedback is implicated in the spontaneous generation of the in-phase pattern.

5.3

Functional Magnetic Imaging (fMRI) During Simple and Complex Movements in Controls and Patients with Basal Ganglia Dysfunction

V. K. LIM, C. C. WU, J. P. HAMM, T. ANDERSON R. CUNNINGTON and I. J. KIRK

Department of Psychology, University of Auckland, Auckland, New Zealand

Individuals with Focal Dystonia (FD) and Parkinson's disease (PD) have demonstrated impairments in processing and integrating afferent information from the periphery. This study examined sensorimotor integration, as indexed by the blood oxygenation level-dependent (BOLD) response in 14 controls, eight patients with dystonia and, to date, three PD patients. Participants were required to perform either simple tapping or complex (Luria finger apposition task) tasks in time with an auditory metronome. For the simple unimanual task, controls demonstrated contralateral activation of the sensorimotor cortices, basal ganglia and ipsilateral cerebellum. For the complex unimanual task there was both ipsilateral and contralateral activation in the sensorimotor region and basal ganglia. Preliminary analyses suggest that individuals with dystonia have, relative to controls, larger activations of areas within the basal ganglia and the thalamus. Although more PD patients are required to confirm this, the three PD patients tested so far showed little activation within the basal ganglia and thalamus. Thus, the fMRI BOLD signal in the basal ganglia and the thalamus can be detected in both simple and complex unimanual movements. This is clearly important for investigating movement and sensory integration for patients with changes in the basal ganglia.

5.4

Globus Pallidus Activity in a Rat Model of Parkinson's Disease and the Effect of Treatment with L-DOPA

B. I. HYLAND and M. OCHI-SHINDOU

Department of Physiology, University of Otago, Dunedin, New Zealand

Treatment of Parkinson's disease with the dopamine precursor L-DOPA eventually loses effectiveness and is often limited by dyskinesia. Previous studies suggest that L-DOPA may have minimal effect on the indirect pathway through the basal ganglia. We investigated this by recording single unit activity in a key indirect pathway nucleus, the globus pallidus (GP), in the chronic unilateral 6-OHDA lesion rat model. Compared to GP cells from sham lesioned animals (n = 94), cells (n = 122) in lesioned animals had lower mean firing rate ($p=0.0014$, unpaired t-test) and increased coefficient of variation of interpsike intervals ($p=0.0016$) indicating more irregular spike firing pattern. These cells also had increased autocorrelation peak amplitude, ($p=0.0002$) and % of spikes in burst, ($p<0.0001$), both markers of increased burst incidence, but decreased mean intraburst firing rate ($p=0.0086$) suggesting reduced intensity of bursts. L-DOPA treatment, which significantly improved measures of usage of the affected limb, did not significantly alter any of these measures (n = 40 cells), although there may have been a trend for increase in baseline firing rate ($p = 0.0529$, paired t-test). Lack of a normalizing effect of L-DOPA on GP activity may contribute to the side effect profile of L-DOPA. However the possibility that subgroups of neurons in GP may be differentially affected remains to be ruled out.

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5.5

Adenosine A2A Receptor Stimulation does not Change Activity of Substantia Nigra Pars Reticulata Neurons in the Freely Moving Rat

C. VOICU and B. I. HYLAND

Department of Physiology, University of Otago, Dunedin, New Zealand

The adenosine A2A and dopamine D2 receptors are highly expressed and co-localised in the striato-pallidal neurons. In a previous study we reported reduced activity of rat globus pallidus neurons following adenosine receptor stimulation. However, the effects of adenosine receptor manipulation on neural activity of basal ganglia output structures are unknown. We recorded single neuron activity of the substantia nigra pars reticulata during equivalent resting periods before and after systemic injection of adenosine A2A receptor agonist CGS21680 (dose=5 mg/kg, n=45 cells) and compared this with the effect of the dopamine D2 receptor antagonist raclopride (2 mg/kg, n=50), or vehicle (n=16). Both drugs produced catalepsy, albeit of different quality: increased rigidity and average grid time (2s to 75 s) after raclopride injection, and flat body position and increased average bar time (2 s to 31 s) after CGS21680 injection. Mean firing rates and firing patterns of recorded cells were analysed. Raclopride slightly reduced firing frequency (22±7 Hz before, 18±6 Hz after injection, $p<0.002$) and increased the percentage of spikes found in bursts (57±17% to 69±17%, $p<0.001$). CGS21680 did not significantly change either frequency (21±7 Hz before, 19±6 Hz after injection, $p<0.1$) or pattern of discharge (58±21% and 57±23% spikes in bursts, before and after injection, respectively, $p<0.5$). These data suggest that changes in the firing pattern, rather than frequency, might be responsible for akinesia and rigidity in Parkinsonian states.

5.6

Cortical Voluntary Drive to Wrist Extensors Measured with Transcranial Magnetic Stimulation

M. LEE, J. SAYDE, M. HSU, J. BARTON, S. C. GANDEVIA and T. J. CARROLL

Health and Exercise Science, School of Medical Sciences, University of New South Wales, Sydney, Australia

Twitch interpolation with transcranial magnetic stimulation (TMS) was recently introduced to estimate cortical voluntary drive to human elbow flexors during exercise. This method, unlike twitch interpolation with peripheral nerve stimulation, provides an estimate of cortical activation which is directly proportional to voluntary force. Todd et al (2003) have shown that during an elbow flexion contraction the size of the extra force produced by TMS (superimposed twitch, ST) decreases linearly with increase level of voluntary force >50% of maximum. This relationship can be used reliably to extrapolate cortical motor output at rest (resting twitch, RT), and subsequently used to calculate voluntary activation using the conventional formula: voluntary activation (%) = (1 – ST / RT) x 100. The purpose of this study was to examine the validity and test-retest reliability of twitch interpolation with TMS to measure cortical activation of the wrist extensors. Seven healthy subjects participated in two identical experiments separated by at least 48 hours. The subjects performed voluntary contractions with their right wrists matching 0, 12.5, 25, 37.5, 50, 67.5, 75, 87.5 and 100% of MVC during which TMS was applied to evoke ST. We showed that the amplitude of the ST decreases linearly between 25 and 100% MVC in the wrist extensors. Extrapolation of this linear regression can be used reliably to estimate RT and voluntary activation on different days.

6.1

Cannabinoid Receptor Down-Regulation In The Ventral Cochlear Nucleus in a Salicylate Model Of Tinnitus

J-H. BAEK, Y. ZHENG, P. F. SMITH and C. L. DARLINGTON

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

Cannabinoid CB1 receptors have not been systematically investigated in the brainstem cochlear nucleus. Using immunohistochemistry and stereology, we showed that a large number of neurons in the rat cochlear nucleus possess cannabinoid CB1 receptors. Following salicylate injections that induced the behavioural manifestations of tinnitus, the number of principal neurons in the ventral cochlear nucleus expressing CB1 receptors significantly decreased, while the number of CB1-positive principal neurons in the dorsal cochlear nucleus did not change significantly. These results suggest that CB1 receptors in the cochlear nucleus may be important for auditory function and that a down-regulation of CB1 receptors in the ventral cochlear nucleus may be related to the development of tinnitus.

6.2

Synapse Elimination in the Cochlea: A Model for Synaptic Remodeling

L-C. HUANG[1], P. R. THORNE[2], G. D. HOUSLEY[1] and J. M. MONTGOMERY[1]

[1]Department of Physiology, [2]Discipline of Audiology, FMHS, University of Auckland, Auckland, New Zealand

Synapse elimination and axonal retraction play an integral role during development to ensure the correct wiring of the brain. The major obstacle to understanding this process is the absence of a CNS model system. Before hearing is established (postnatal day 12), innervation of the outer spiral bundles (OSB) to the outer hair cells (OHC) includes transient type I afferent nerve fibres, stabilised type II afferent nerve fibres and efferent nerve fibres. However, little is known about the mechanism driving this activity-independent retraction of type I afferent nerve fibres from OHC. To study the development of the OSB, dextran was applied as a neuronal tracer to the mouse vestibulocochlear nerve to label primary auditory neurones (SGN). The components of the dextran-labelled nerve fibres were identified by performing immunohistochemistry for peripherin (as a marker for type II SGN) and choline-acetyltransferase (ChAT; as a marker for efferent fibres) during cochlear synapse re-organisation. The results showed that dextran-labelled OSB projecting to OHC were not co-localised with peripherin or ChAT up to postnatal day 6. This suggests that during this period, it is possible to selectively identify type I nerve fibres under OHC. This will provide a powerful tool to demonstrate the dynamics between synaptic proteins and afferent nerve fibres during the time-frame of synapse re-organization as the type II nerve fibres supplant the type I fibres innervating the cochlear OHC.

6.3

Why is the Vestibular Inner Ear Necessary for a Normal Hippocampus?

P. F. SMITH

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

Many studies in animals and humans have shown that damage to the balance organs in the inner ear (the vestibular system) is associated with memory impairment, especially, but not exclusively, spatial memory impairment. Recently, we have demonstrated that patients with bilateral vestibular deafferentation, but with hearing preserved, exhibited a selective bilateral atrophy of the hippocampus of approximately 17%, which correlated with spatial memory impairment as measured using a virtual Morris water maze (Brandt, Schautzer, Hamilton, Markowitsch, Kalla, Darlington, Smith and Strupp., *Brain* 128 (2005) 2732-2741). Animal studies have also shown that vestibular damage causes a dysfunction of place cells and theta EEG activity, as well as changes in the expression of N-methyl-D-aspartate (NMDA) receptors and nitric oxide synthase (NOS) in the hippocampus. Why should the hippocampus be so sensitive to changes in sensory input from the vestibular inner ear? This paper presents the hypothesis that, due to the evolutionary significance of the otolithic vestibular receptors (the utricle and saccule) in sensing gravitational vertical, the hippocampus may have developed a greater reliance on the vestibular system than on other channels of sensory information. This hypothesis is supported by recent evidence of memory impairment in astronauts exposed to microgravity.

6.4

Surface Imaging Microscopy of the Mammalian Cochlea

P. R. THORNE[1], D. K. M. DREAVER[1], D. A. GERNEKE[2,3], G. B. SANDS[2,3] and G. D. HOUSLEY[2]

[1]Section of Audiology, [2]Department of Physiology and [3]Bioengineering Institute, University of Auckland, Auckland, New Zealand

The location of the cochlea in the temporal bone provides challenges for detailed morphological analysis. Microscopy procedures involve dissection or sectioning which destroys interrelationships between specialised tissues and limits precise quantitative analysis of structures for correlation with function. We report a new method using microCT and Surface Imaging Microscopy (Gerneke et al. in preparation) to image and reconstruct the entire cochlea. SIM involves ultra-milling of resin-embedded tissue and imaging the sample surface. The ultramill and imaging equipment are on a high-precision, computer-controlled three-axis translational stage enabling registration of optical sections. For microCT the mouse cochlea was fixed (2.5% glutaraldehyde) and imaged in a Skyscan 1172 micro-CT scanner. 856 two-dimensional images (5.5 mm) were obtained in the axial orientation and the cochlea reconstructed in transverse orientation using Voxx. For SIM, the cochlea was decalcified (4% EDTA, 10 days), embedded in resin and sequentially milled at 3 mm increments. After each step the surface was stained (2% Toludine Blue). A digital camera was used to acquire a matrix of 10 overlapping images for 410 planes using a 10x immersion lens on the optical microscope. Excellent images were obtained at 0.3µm pixel resolution showing cellular detail. The cochlea was reconstructed using custom software written in LabVIEW™. This method shows considerable promise as a technique for 3D high resolution imaging of the cochlea to aid investigations of the spatial relationships between tissues and their function.

6.5

Impairment and Recovery on a Spatial Forced Alternation Task Following Bilateral Vestibular Deafferentation

Y. ZHENG, M. GODDARD, C. L. DARLINGTON and P. F. SMITH

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

Over the last decade, accumulating evidence has suggested that vestibular information may contribute to higher cognitive function, especially spatial learning and memory. However, very little research has been done on the long–term effects of vestibular lesions on spatial learning and memory. The present study used a spatial forced alternation task in a T-maze to test learning and memory in rats at 3 weeks, 3 months and 5 months following bilateral vestibular deafferentation (BVD). The animals were given 20 days of testing at each time point. BVD rats made significantly fewer correct choices at all time points when compared with the sham rats. However, a close examination of the animals' performance showed that the percentage correct choice for BVD rats was at chance level at 3 weeks post-op, but was significantly above chance on the last testing day at 3 months and on most of the testing days at 5 months post-op. The results support the view that vestibular information contributes to spatial learning and memory and suggest, for the first time, a possible rehabilitation therapy that might be useful in the treatment of patients with vestibular disorders.

6.6

Effects of Bilateral Vestibular Deafferentation on Performance in an Elevated Plus Maze in Rats

C. L. DARLINGTON, Y. ZHENG, M. GODDARD and P. F. SMITH

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

It has been reported that patients with bilateral vestibular damage have a higher incidence of conditions such as agoraphobia, other anxiety disorders and depression. However, this issue has never been studied in experimental animals. The present study tested anxiety related behaviours in rats at 3 weeks, 3 months and 5 months following bilateral vestibular deafferentation (BVD) using an elevated plus maze. The number of entries into either the open or enclosed arms and the time spent in each arm was recorded for 5 min. There was no significant difference in either the percentage time spent on the open arms or the percentage of open arm entries between the sham and BVD rats at 3 weeks after the surgery. However, BVD rats spent significantly more time on the open arms and made significantly more open arm entries than the sham rats at both 3 months and 5 months after the surgery. Our results demonstrate for the first time that BVD rats displayed an anxiolytic-like behaviour on an elevated plus maze. They also suggest that anxiety related problems in patients with bilateral vestibular damage are far more complicated than expected and further studies are needed.

7.1

AM-36 and Minocycline Reduce Retrograde Microglial Activation in the Spinal Cord Following Focal Head Injury in Rats

R. M. WESTON, J. K. CALLAWAY, S. J. FEENEY and B. JARROTT

Howard Florey Institute, University of Melbourne, Parkville, Australia

Focal brain lesions can also lead to cell damage and inflammatory changes in areas remote from the lesion site, including the corticospinal tract (CST) of the spinal cord. We have evaluated the potential neuroprotective activity of minocycline and AM-36 on this remote injury at 3 days following cortical cold injury (CCI) in rats. Although both drugs had no significant effect on the lesion size, both minocycline and AM-36 effectively reduced functional deficits, assessed using the grid walking test (P<0.05). AM-36 and minocycline treatment prevented CCI induced activation of microglia in the terminal area of CST (P<0.001) as visualized by OX-42 immunohistochemistry. Additionally, CCI induced an increased expression of iNOS and TNF± in the CST terminals particularly within microglial cells as visualized by double-label immunofluorescence (P<0.001). Both minocycline and AM-36 strongly inhibited the number microglia exhibiting iNOS immunoreactivity in the CST by ~55% and ~50% respectively (P<0.0001). Similarly, AM-36 treatment diminished TNFα immunoreactivity within microglia by 50% (P<0.0001). Conversely, minocycline increased the number of microglia expressing TNFα by 10%. These results indicate that AM-36 has effects comparable to minocycline in modulating microglia function, and thus both drugs may be effective in reducing inflammation following neurodegenerative conditions. Findings from this study demonstrate the importance of inflammatory changes in the CST and that these changes contribute to functional deficits seen following stroke and head trauma.

7.2

Neuroblast Migration into the QA Lesioned Adult Rat Striatum: A Retroviral Tracing Study

A. L. MCGREGOR, R. J. GORDON and B. CONNOR

Department of Pharmacology, University of Auckland, Auckland, New Zealand

We have previously demonstrated increased proliferation of subventricular zone (SVZ) progenitor cells, migration of neuroblasts into the damaged striatum, and formation of new neurons in a rat model of Huntington's Disease (HD). To extend these findings, we investigated the profile of SVZ-derived neuroblast cell migration into the quinolinic acid (QA) lesioned striatum using retroviral (RV) labeling techniques. Adult male Wistar rats received a unilateral striatal injection of QA or vehicle. To confirm the origin and track the migration of neuroblasts, animals also received a unilateral SVZ injection of a retrovirus expressing Green Fluorescent Protein (RV-GFP) on days 5 and 2 prior to lesion, on the day of lesioning, or 2, 5, 7, 14 and 30 days after QA lesion (n=5 per group). GFP-labeled cells were allowed 5 days of exposure to the QA lesioned environment before the animals were killed. SVZ-derived neuroblasts labeled with RV-GFP 2 days prior to, or on day 0, 2, 5 and 7 in relation to the QA lesion were observed within the lesioned striatum in addition to the RMS. SVZ-derived neuroblasts labeled with RV-GFP 2 days prior to, or on the day of QA lesioning showed the greatest extent of migration into the striatum. Understanding the mechanisms controlling SVZ progenitor cell proliferation and migration in the diseased adult brain may help in the development of new therapeutic strategies for the treatment of neurological disorders.

7.3

Expression of Aquaporin-1 & 4 in Optic Nerve After Traumatic Brain Injury

H. P. CHOTALIYA[1], S. K. SAGGU[1], R. J. CASSON[1] and M. N. GHABRIEL[2]

[1]Department of Ophthalmology and Visual Sciences [2]Department of Anatomical Sciences, University of Adelaide, Adelaide, South Australia

Damage to the visual system often occurs after head injury. Aquaporin-1&4 water channels are implicated in the pathogenesis of brain edema after head trauma, the role of water channels in optic nerve edema after head injury is still not explained. The current research aims to explore the morphological changes and to study the change in the expression of Aquaporin-1&4 in the rat optic nerve after blunt head trauma. For the study, 16male Sprague Dawley rats were perfused at various time intervals (control, ½hr, 1hr and 5hrs) after subjecting to blunt head trauma. Optic nerves were taken for immunohistochemistry on paraffin-embedded sections and light microscopy on resin sections. Light microscopy revealed axonal swelling after 1hr of injury with no morphological changes seen at 5hrs. AQP-1&4 molecular expression reduced at 30min and decreased significantly after 1hr after injury ($p<0.05$). No statistically significant difference was observed in immunostaining after 5hrs of injury. AQP-1&4 water channels initially decrease within the first hour of head injury during which the optic nerve edema appears. The AQP-1&4 expression returns back to normal after 5hrs of injury with the disappearance of axonal swelling. This suggests that the water channels may play a significant role in driving the water flux and preventing early optic nerve edema.

7.4

In vivo Seizure Induction by Domoic Acid and Isodomoic Acids-A and -C

P. M. SAWANT[1], D. O. MOUNTFORT[2], P. T. HOLLAND[2], L. RHODES[2], A. I. SELWOOD[2] and D. S. KERR[1]

[1]Department of Pharmacology & Toxicology, University of Otago, Dunedin, New Zealand
[2]Cawthron Institute, Nelson, New Zealand

Domoic acid (DOM) is a potent seizurogenic algal excitotoxin and natural isomers of DOM can occur in relative abundance. To date, little is known of the biological properties and selectivities of DOM isomers *in vivo*. Previous *in vitro* work indicates that, like DOM, both isodomoic acid-A (Iso-A) and Iso-C produce hyperexcitability and dose-dependant suppression of population spikes in hippocampal CA1 (EC_{50}'s: 125 nM, 1.3 μM and 4.1 μM, respectively). Ki values for displacement of ^{3}[H]-kainate from homomeric GluR6 KA receptors prepared from an SF-9 insect cell receptor expression system are 4.9 nM (DOM), 130 nM (Iso-A) and 1176 nM (Iso-C). In the present study, we investigated the functional potency of DOM, Iso-A and Iso-C in adult male Sprague Dawley rats *in vivo*. With approval of the University Animal Ethics Committee, animal behaviours were observed for 2.5 hours following intrahippocampal injection of toxin (3 to 3000 pmoles per microlitre of injected fluid volume) and were scored on a 5-point rating scale. DOM, Iso-A and Iso-C produced significant dose- and time-dependent increases in seizure activity; doses producing half-maximal cumulative seizure scores (ED_{50}) were 48, 69, and 1310 pmoles, respectively. In contrast to our *in vitro* findings, the present *in vivo* results indicate that DOM and Iso-A are functionally equipotent and Iso-C is markedly less potent. Taken together our results suggest that the neuroexcitatory effects of Iso-A in CA1 involve both AMPA and KA receptors, while Iso-C likely involves the activation of AMPA receptors alone.

7.5

Bumping to the Right: A Consequence of Pseudoneglect?

M. E. R. NICHOLLS[1], A. LOFTUS[1]. K. MEYER[2] and J. B. MATTINGLEY[1]

[1]Department of Psychology, University of Melbourne, Melbourne, Australia
[2]Department of Psychology, Ruhr-University Bochum, Germany

Patients with right parietal damage can exhibit signs of spatial neglect where they ignore the leftward features of their environment – causing them to bump into the left-side of doorways. In contrast, the normal population shows a mild attentional bias *towards* the left. Self-report measures reveal a trend toward more collisions to the right in everyday settings. We sought to obtain a quantitative measure of lateralised bumping in a laboratory setting. Participants (n=277) walked though a narrow doorway and the experimenter recorded whether they collided with the left, right, neither or both sides. Unilateral activation of the hemispheres has been found to ameliorate the effects of spatial neglect. We investigated the effect of activation by asking participants to move their left, right or both hands as they walked. In the both hands condition, which acted as a baseline, there were more right bumps than left bumps. The rightward bias was exasperated when the left hand moved, presumably because this movement activated the right hemisphere. In contrast, there were more left bumps when the right hand moved. The results demonstrate that bumping is not random and that we collide with the right side more often. The effect of hand-movement demonstrates that bumping, and by implication pseudoneglect, is brought about by an imbalance of activation between the hemispheres.

7.6

Predictive Eye and Arm Movement in Parkinson's Disease

Y. SHIRAKURA, M. R. MacASKILL, N. McGRANE,
M. KHASHRAM and T. J. ANDERSON

Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand

It is known that Parkinson's disease (PD) results in characteristic abnormalities in saccadic performance measured in the laboratory. However, the relationship between eye and somatomotor functions has not been well studied. We therefore investigated the relationship between eye and arm movement. PD patients and controls were instructed to perform comparable predictive tasks for eye and arm movement, which involved following targets on a computer screen. Eye and arm movements were measured with infrared video oculography and magnetic field disturbance respectively. Saccadic eye movements and arm reaching movements in response to horizontal targets alternating predictively at either 0.7Hz, 0.5Hz, 0.4Hz or 0.2Hz were recorded in each case. Latency, velocity and movement amplitude of eye and arm movement were compared between groups and between eye and arm. PD subjects anticipated stimulus movements to a significantly greater extent than controls in saccadic tests. This increase in prediction could be a compensatory strategy for the inaccuracy of initial eye movement in PD subjects. No increase in prediction, but a longer movement time was observed in arm movements of PD subjects. These observations suggest that PD patients employ different compensatory strategies to overcome impairment of eye and arm movement. Such a difference could be attributed to the presence of an obligatory pause required between successive saccades, but not between successive arm movements.

8.1

Extending the Kuramoto Model to Encompass Neuronal Synchronisation

D. CUMIN[1] and C. P. UNSWORTH[2]

[1]*Department of Anaesthesiology,* [2]*Department of Engineering Science, University of Auckland, Auckland, New Zealand*

Synchronisation of neurons is thought to play a role in memory, learning and epilepsy. We have extended the Kuramoto model for studying synchronisation to more appropriately model neural activity. Our model incorporates time-varying natural frequencies, time-varying coupling strengths and different network configurations. These extensions allow for more realistic attributes of neurons to be accounted for and therefore more appropriate modelling of neuronal synchronisation. We performed numerical simulations on an N=4 coupled oscillator network and qualitatively showed the effects of altering the aforementioned parameters individually and in combination. Our results show that synchronisation increases with increasing coupling strength over time and also with decreasing spread of natural frequencies over time. We showed that synchronisation is strengthened with larger networks and more connectivity and that these effects can all be combined to modify the level of synchronisation in the system. This work paves the way for more physiologically-linked studies and potentially a deeper understanding of neural processes.

8.2

Validation of Numerical Fluid Simulations in the Circle of Willis Using Phase Contrast MRI

J. N. FINK, S. MOORE, S. WELLS, R. WATTS and T. DAVID

Christchurch School of Medicine and Health Sciences, University of Otago, Christchurch, New Zealand

Blood flow to the human brain is maintained relatively constant within a broad range of arterial blood pressure by a process known as autoregulation. Autoregulation is a local control mechanism, mediated by vasoconstriction or dilation of the cerebral arterioles via a process which is dependent on changes in extracellular CO_2 concentration and pH. Our research group has developed a unique mathematical model of the cerebral autoregulation mechanism coupled into 1, 2, and 3D models of the cerebral vasculature, which incorporates important measurable physiological parameters which determine vascular flow, such as CO_2 concentration. We have also developed a technique to quantitate blood-flow within the major afferent and efferent brain arteries of the Circle of Willis using phase-contrast MRI. In this experiment we measured the cerebral blood flow of 5 healthy volunteers under four experimental conditions of inspired gas: (i) room air; (ii) 2.5% CO_2 mixed with air; (iii) 5% CO_2; (iv) hypoxic normocapnia. Measured changes in cerebral blood flow are used to validate numerical fluid simulations of the mathematical model.

8.3

The Dynamics of the Transition from Slow-Wave Sleep To REM Sleep: (1) Experimental data

L. VOSS[1], J. W. SLEIGH[1], M. WILSON[2], D. A. STEYN-ROSS[2] and M. STEYN-ROSS[2]

[1]Department of Anaesthesia, Waikato Clinical School, University of Auckland, Auckland, New Zealand,
[2]Department of Electronic Engineering and Applied Physics, University of Waikato, Hamilton, New Zealand

Despite advances in our understanding of the correlation between neurophysiological function and global brain states, the function of sleep remains elusive. Data from rats suggests that the *transition* from SWS-to-REM sleep is important for certain neuroplastic changes during sleep. We have developed a continuum model of the interactions between populations of inhibitory and excitatory cortical neurons to describe the features of the SWS-to-REM transition. In order to validate this model, we have obtained detailed measurements of changes in spectral content, and local field potential correlation during the SWS-to-REM transition in S-D rats. We implanted tungsten stereotrodes into the parietal cortex (0.5mm). The stereotrode consisted of two insulated microelectrodes (3µm diameter) separated by 200µm. After full recovery, cortical local field potential data was collected while the animals slept naturally. Transitions from SWS to REM sleep were identified offline and electrocorticogram (ECoG) activity spanning each transition extracted for analysis. In SWS the rat cortex showed activity in the ~0.5-2Hz band. This pattern shifted to a transitional state (lasting only 5-15s) where the cortex jumped between the two states, before settling in the REM state, characterised by a strong ~8Hz oscillation. The transitional period was characterised by a strong surge in coherent activity between cortical sites. We have compared this pattern of activity with the output from simulations run using our theoretical model.

8.4

The Dynamics Of The Transition From Slow-Wave Sleep To REM Sleep: (2)Theoretical Modelling

J. W. SLEIGH[1], M. T. WILSON[2], D. A. STEYN-ROSS[2], M. STEYN-ROSS[2] and L. VOSS[1]

[1]Department of Anaesthesia, Waikato Clinical School, University of Auckland, Auckland, New Zealand
[2]Department of Electronic Engineering and Applied Physics, University of Waikato, Hamilton, New Zealand

The cortical transition from slow-wave sleep(SWS) to the rapid eye-movement(REM) pattern, occurs abruptly; and is driven by a linear progressive increase in cholinergic input from the brainstem into M1 receptors in the cortex. We used a continuum model of the interactions between populations of inhibitory and excitatory cortical neurons to describe the features of this transition. The cortical effects of various neuromodulators were described on a 3D domain (fast synaptic connectivity, neuronal excitability, and mean soma potential). In addition: (i) neuronal excitability fluctuates inversely with a pre-synaptic firing-rate, and (ii) a Hebbian change in synaptic weights occurs between correlated neuronal populations. The model was implemented using simulations run in Matlab, and showed quantitative agreement with the experimental data obtained from sleeping rats. Increasing cholinergic effect caused the model to move from a 0.5-2Hz SWS-like pattern to a REM-like state (8Hz). We conclude that it is possible to use a continuum method to model the SWS-REM transition realistically. Plasticity effects are required to produce an accurate model. We speculate that SWS-induced changes in synaptic weights may form an important part of the function of sleep - to reorganise cortical information handling capacity.

8.5

The Critical-Slowing Challenge for Neurophysiologists

D. A. STEYN-ROSS[1], M. L. STEYN-ROSS[1], M. T. WILSON[1] and J. W. SLEIGH[2]

[1]Department of Physics & Electronic Engineering, University of Waikato, Hamilton, New Zealand,
[2]Department of Anaesthetics, Waikato Hospital, Hamilton, New Zealand

The neuron is an excitable membrane. When sufficiently aroused by input current, the neuron will fire off an action-potential spike. We have demonstrated theoretically that this abrupt change in cell behaviour—from quiescent rest to active spiking—is a biophysical phase change that shares many of the statistical properties of classical thermodynamic phase transitions in physics. Our analysis of the simplified neuron equations of H.R. Wilson tells us that the approach to the critical point of spiking threshold can be detected and quantified in terms of the altering responsiveness or susceptibility of the neuron to low-level white-noise stimulation. Near threshold, the noise-evoked membrane voltage fluctuations grow in amplitude while slowing in frequency, becoming much more correlated in time. Collectively, these altered properties are called "critical slowing down", and they arise because one of the system eigenvalues is moving perilously close to zero. When the eigenvalue crosses the zero axis, fluctuations grow exponentially, and a spike is born. To date, these ideas remain theoretical. Our challenge to the neurophysiology community is: Using a current-clamped single-cell configuration with controlled noise input, can you demonstrate that a near-threshold resting neuron exhibits critical slowing in the fluctuations of its membrane potential?

8.6

Including Higher-Order Statistics in Cortical Mean-Field Modelling

M. T. WILSON[1], J. W. SLEIGH[2], M. L. STEYN-ROSS[1] and D. A. STEYN-ROSS[1]

[1]Department of Physics and Electronic Engineering, University of Waikato, Hamilton, New Zealand
[2]Waikato Clinical School, University of Auckland, Hamilton, New Zealand

Mean-field models have been applied with varying degrees of success to address various electroencephalogram (EEG) phenomena, for example, those of the slow-wave sleep (SWS) to rapid-eye-movement (REM) sleep transition, the wake-unconscious transition of anaesthesia, and gamma, spindle and cortical slow- oscillations of sleep. Dynamic changes in average synaptic weights can be considered through fluctuations in the soma potentials using a Hebbian-style rule. However, since such models deal with macro-column averages of properties such as cell connectivity they are not well suited to memory and learning applications where individual synaptic weights can be important. In this presentation we develop the mean-field approach mathematically to consider the standard deviation of the synaptic weights within a macrocolumn. This allows us to work with distributions of weights rather than single values. Specifically, we develop a set of equations for the rate of change of the standard deviations with time and show analytically and numerically that they will increase if the means increase, and vice-versa. This implies that changes in standard deviation will be large when there are strong correlations between neurons, such as during the jumps between the 'up' and 'down' states of SWS. This naturally suggests that the cortical slow oscillation is important for memory and learning, since it results in changes to the synaptic weights distribution.

9.1

The Role of Biologically Based Conceptualisations of Impulsivity in the Addictions

N. J. LOXTON, S. DAWE and M. J. GULLO

School of Psychology, Griffith University, Mt Gravatt Campus, Queensland, Australia

Impulsivity has been consistently found to play a role in the vulnerability to addictive behaviour. However, current conceptualisations of impulsivity propose at least two independent dimensions; 1) reward drive (RD), reflecting individual differences in mesolimbic dopaminergic activation, and 2) rash impulsiveness (RI), putatively reflecting orbitofrontal functioning. These dimensions are proposed to play specific roles in the vulnerability to addictive behaviours and in the progression from experimental substance use to chronic abuse and dependence. In this paper we present results from two of our recent studies. In both studies participants completed self-report questionnaires on alcohol use, risky behaviour, RD and RI. In the first study using 191 undergraduate students, both dimensions were predictive of current levels of drinking. RD but not RI was associated with earlier onset of drinking, whereas RI was associated with length of frequent drinking. In the second study using 288 high school students, both dimensions were again associated with current levels of drinking. RD but not RI was associated with participation in high risk sports whereas RI was associated with rule breaking. Generally, although RD and RI were both associated with current levels of hazardous drinking, the two dimensions were differentially associated with early onset drinking/participation in high risk sport (RD) and long-term drinking/rule breaking (RI). These studies support the current notion that multiple dimensions of impulsivity may assist in further understanding the complex pathways to addiction.

9.2

Quantitative Distribution of Endocannabinoid Component MRNA in Mouse Brain: Effects of Cannabinoid Tolerence

S. A. ROBINSON and R. E. LOIACONO

Department of Pharmacology, Monash University, Melbourne, Australia

CB_1 cannabinoid receptors are highly expressed in the mammalian brain. These receptors are targeted by Δ^9THC, but also by endogenously synthesised compounds: endocannabinoids such as N-arachidonoyl-ethanolamine (anandamide) and 2-arachidonoyl-glycerol (2AG). The synthesis and degradation of these endocannabinoids depends on various enzyme systems. *N*-acyl-phosphatidylethanolamine phospho-lipase D (NAPE-PLD) synthesises anandamide; the diacylglycerol lipase isoforms DAG-lipase α and β synthesise 2AG. Monoacylglycerol lipase (MAG-lipase) degrades 2AG; fatty acid amide hydrolase (FAAH) degrades anandamide. The first aim of this study is to localise components of the endocannabinoid system in mice. CB_1 receptor, NAPE-PLD, DAG-lipase-α and DAG-lipase-β, MAG-lipase and FAAH mRNA were measured in normal C57/BLJ6 mouse brains using *in situ* hybridisation histochemistry (ISHH). CB_1 receptor mRNA was highly expressed in the cortex, thalamus and hippocampus. FAAH mRNA expression correlated with high levels of CB_1 receptor mRNA in the cortex, thalamus and hippocampus. DAG-lipase-β mRNA was found to be enriched in the hippocampus and the frontal cortex, while DAG-lipase-^{2} mRNA was found at lower levels in the hippocampus and frontal cortex. MAG-lipase mRNA is enriched in the cortex, caudate, as well as in pyramidal and non-pyramidal cells of the hippocampus. The second aim was to examine regulatory changes in the endocannabinoid component mRNA following tolerance in response to chronic treatment with the CB_1 receptor agonist WIN55212-2. Mice were subcutaneously injected with WIN55212-2 twice daily for 15 days; the initial dose was 3mg/kg; the dose was doubled every 3 days to a final dose of 48mg/kg. WIN55212-2 differentially affected the distribution of the endocannabinoid mRNA.

9.3

Cholinergic Interneurons in the Striatum: It's Time to Pause and Take Notice

J. N. J. REYNOLDS

Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand

Cholinergic neurons in the striatum are local-circuit interneurons that normally exhibit uninterrupted tonic firing activity, continuously releasing acetylcholine. However, they begin to display a transient cessation in activity in response to a previously neutral stimulus, following repeated pairings with a reward. Intriguingly, the pause response is acquired by cholinergic neurons that are sparsely distributed throughout the striatum. Thus, after conditioning, the stimulus elicits a synchronous pause in these widely-spaced neurons. Because acetylcholine is rapidly degraded by acetylcholinesterase, pauses may globally decrease acetylcholine levels in the striatum for 100-200 ms following the stimulus. How are these pauses synchronised across the striatum and what is their significance to striatal function? Both questions may be addressed by considering recent evidence regarding dopamine-dependent synaptic plasticity of cortical synapses within the striatum. Firstly, work from our laboratory suggests that reward-related activity of dopamine cells strengthens common excitatory inputs to cholinergic neurons, thus engaging an intrinsic mechanism that synchronously ceases tonic firing. Secondly, a decrease in muscarinic receptor tone appears to enable dopamine to induce either depression or potentiation of cortical synapses with spiny output neurons in the striatum. Thus, cholinergic neurons 'learn' to respond to a significant stimulus and the resulting pause may signal to spiny neurons that the time is right to modify their active synaptic inputs. Cholinergic interneurons might therefore play a previously unappreciated frontline role in the reinforcement of actions associated with rewarding stimuli.

9.4

Mapping the Crossed-Corticostriatal Pathway Using Antidromic Activation

M. D. BARRY, D. E. OORSCHOT and J. N. J. REYNOLDS

Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand

The axonal projections of a cortical neuron can be determined by attempting to activate it antidromically within a putative target area using electrical stimulation. With this technique, we aimed to map the distribution within the cerebral cortex of neurons that project to the striatum on the opposite side of the brain. Experiments were performed on urethane-anaesthetised Wistar rats using *in vivo* intracellular and extracellular recording techniques. Bipolar stimulating electrodes were inserted into the striatum and cemented in place, and glass recording pipettes were inserted into the motor and pre-motor cortex in the opposite hemisphere. Mapping was performed by systematically varying electrode co-ordinates. Pyramidal neurons (n = 105) were recorded in Layers III-V of the rat motor and pre-motor cortex. Five of these neurons were able to be antidromically activated from the contralateral striatum. This was determined by the presence of an action potential with a constant latency (7.4 ± 3.3 ms, mean ± SD) despite increasing stimulus current (0.6 to 5.0 mA) and by a positive collision test where possible. Their cell bodies were located between 1180 μm and 1620 μm from the brain surface, at similar anteroposterior (3.1 ± 0.5 mm referenced to bregma) and mediolateral (2.6 ± 0.7 mm) stereotaxic co-ordinates. These results suggest that crossed-corticostriatal neurons are located within similar geographic locations in Layer V of the rat motor and pre-motor cortex. This information will inform future experiments investigating crossed-corticostriatal circuitry.

9.5

Effects of Repeated Exposure to MDMA in Rats

S. SCHENK

School of Psychology, Victoria University of Wellington, Wellington, New Zealand

Recreational use of ± 3,4 methylenedioxymethamphetamine (MDMA; ecstasy) is increasing across the globe. The consequences of such use are, however, poorly understood. Our laboratory has been examining the effects of repeated exposure to MDMA using animal models. Repeated intermittent exposure resulted in sensitised behavioural responses. The dose-effect curve for MDMA-produced hyperactivity was shifted leftward for rats that received 5 daily injections of 10.0 mg/kg/day. In contrast, a more chronic dosing regimen resulted in tolerance to the behavioural effects of MDMA. This was manifest as a rightward shift in the dose-effect curve for MDMA-produced hyperactivity and in the ability of MDMA to increase latencies to emerge from a hide box to an open field environment. These data suggest differential neuroadaptations as a function of dosing regimen comparable to effects produced by repeated exposure to other psychostimulant drugs.

9.6

Induction of Visual Responsiveness in Striatal Spiny Neurons by Disinhibiting the Superior Colliculus

J. M. SCHULZ[1], P. REDGRAVE[2] and J. N. J. REYNOLDS[1]

[1]Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand
[2]Department of Psychology, University of Sheffield, Sheffield, UK

It has recently been suggested that subcortical pathways, which originate from brainstem structures, including the superior colliculus (SC), and project via the thalamus to the basal ganglia might be a source of short-latency sensory input. The present electrophysiological findings support this idea. We recorded intracellularly from striatal spiny neurons of urethane-anaesthetised rats while presenting visual stimuli. At baseline, neurons were either visually non-responsive (n=9), or responded weakly in a stochastic manner (n=6). After local injection of bicuculline into the SC, all neurons (n=15) exhibited strong visual responses consisting of immediate depolarising transitions to the 'Up state' at latencies of ~100 ms. Visual responses persisted only as long as visual evoked potentials could be observed in the SC (8-15 min), indicating that the SC may be the primary source of visual input. Prior administration of alpha-methyl-para-tyrosine (300 mg/kg i.p.; n=7), known to deplete releasable dopamine stores, had no detectable effect on the visual responses in comparison with neurons from control animals (n=8). This demonstrates that striatal visual responses are not mediated by the dopamine release known to be evoked in the striatum by this protocol, favouring the tecto-thalamo-striatal transmission route. However, the contribution of alternative cortical pathways simultaneously opened by bicuculline ejection cannot be completely excluded at present.

9.7

Cortical Stimulation Evokes Postsynaptic Potentials and Slow Afterhyperpolarisations in Striatal Cholinergic Interneurons *In Vitro*

M. J. OSWALD, D. E. OORSCHOT and J. N. J. REYNOLDS

Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand

Acetylcholine is released by cholinergic interneurons in the striatum through tonic firing activity. This activity can be modulated by cortical and thalamic excitatory afferents, however the mechanism is poorly understood. Using rat brain slices (400 µm) cut at an oblique angle to the horizontal axis, intact cortico-striatal connections were found. Cholinergic interneurons were identified by their relatively large size using infrared/differential interference contrast microscopy, and recorded in current clamp mode. Cortex stimulation (0.5-5 mA biphasic pulses at 0.1 Hz) evoked depolarising postsynaptic potentials (PSPs) of up to 5 mV. Subthreshold depolarising PSPs were followed by a slow afterhyperpolarisation (sAHP) lasting 100 to 500 msec. The sAHP is an intrinsic membrane mechanism, and its amplitude and duration was directly proportional to the degree of membrane depolarisation. The sAHP was also present in a few cases following cortical stimulation, however, after blocking GABA-A receptors with bicuculline (30 µM), all neurons tested showed a sAHP. Bicuculline uncovered a number of additional excitatory events of long latency (up to 25 msec to peak), which summed to a large-amplitude multi-component depolarising PSP preceding the sAHP. These results suggest that by increasing the amplitude of the preceding synaptic depolarisation, the sAHP can be increased in amplitude or appear *de novo*. Potentiating the depolarising effect of cortical inputs and inducing a sAHP may underlie the appearance of the pause response after reward-related learning.

10.1

Expression and Localization of Voltage Gated Sodium Channels in Mouse Retina

B. J. O'BRIEN[1], K. M. BUMSTED O'BRIEN[1], S. R. LEVINSON[2] and J. H. CALDWELL[2,3]

[1]Department of Optometry & Vision Science, University of Auckland, Auckland, New Zealand
[2]Department of Physiology and Biophysics, [3]Department of Cell and Developmental Biology, University of Colorado Health Sciences Center, Denver, CO, USA

Until recently, expression of voltage gated sodium channels (VGSCs) in the retina have been thought to be restricted to retinal ganglion cells (RGCs). Over the past several years, however, each of the other retinal cell classes has been demonstrated to have sodium currents. The mammalian VGSC gene family consists of nine different types of alpha subunits. Each alpha subunit has a unique set of physiological properties and pattern of expression in the nervous system. Through recent developments of VGSC subtype specific antibodies and characterization of the mouse genome, we have now examined the expression (RT-PCR) and localization (immunostaining) of VGSCs in the mouse retina. Clear immunostaining of RGC axons with antibodies to Nav1.2 and Nav1.6 was found, as observed previously. In addition to RGC axons, Nav1.6 co-localized with glutamine synthetase, a marker for Müller glia. Antibodies to Nav1.4 normally associated with skeletal muscle, also stained Müller cells. Nav1.3 stained horizontal cells and an unknown population of amacrine cells. Nav1.8 stained both starburst amacrine cells and a sub-population of large ganglion cells. Punctate labelling of rod and cone synapses was observed for Nav1.9 in the outer plexiform layer. While immunostaining for six different VGSCs was observed, expression of all nine VGSCs in the retina was implicated by RT-mPCR. The role of each subtype in retinal physiology will be important to determine.

10.2

The Spatial and Temporal Pattern of Optic Nerve Degeneration After Excitotoxic Retinal Injury

S. K. SAGGU[1], H. P. CHOTALITA[1], Z. CAI [2], P. BLUMBERGS[2] and R. J. CASSON[1]

[1]Department of Ophathlmology and Visual Sciences, Royal Adelaide Hospital, Adelaide, South Australia
[2]Department of Neuroscience, IMVS, Adelaide, South Australia

N-Methyl-D-Aspartate (NMDA), an excitatory neurotransmitter, is implicated in the pathogenesis of stroke, neurotrauma and various neurodegenerative disorders, including glaucoma. Although, the effect of NMDA-induced excitotoxicity on neuronal somata is described, the effect on axons after somal excitotoxic injury has not been reported. This research aims to study the spatial and temporal pattern of changes in the rat optic nerve secondary to excitotoxic retinal ganglion cell (RGC) damage following intravitreal injection of NMDA. For the study, 30 Sprague-Dawley rats were perfused at various times (0hrs, 2hrs, 6hrs, 24hrs, 72hrs & 7days) after intravitreal injection of 5microl of 4mM NMDA into one eye. Eyeballs and optic nerves were dissected. 0.5micron resin sections were taken and stained with toluidine blue. Light microscopy was done and the number of damaged axons and myelin compared in proximal and distal axons. With light microscopy, no changes appeared in the optic nerve up to 24hrs. Degenerative changes: axonal swelling, axoplasmic clumping, myelin thickening and disruption developed at 72hrs and markedly increased at 7 days with early atrophic changes. Moreover, the distal axon showed significantly greater changes as compared to the proximal ($p<0.05$). Axonal degeneration commences after 24 hours of excitotoxic injury to RGCs. This progressive degeneration initially affected the distal axon and was consistent with "dying back" type of degeneration.

10.3

Morphological Characterisation of the Central Foveal Region in the Pigeon Retina

K. M. BUMSTED O'BRIEN[1], S. K. SHIN[1], H. R. LEE[1] and J. M. PROVIS[2]

[1]Department of Optometry and Vision Science, University of Auckland, Auckland, New Zealand
[2]Research School of Biological Science, Australian National University, Canberra, Australia

Visual acuity is mediated by the fovea, a small pit where the inner retinal neurons have been pushed aside, rods are missing and cones are packed at their highest density. While human foveal structure and development have been studied, an animal model where hypotheses formed in the human can be tested has been unavailable. This study aimed to characterise the adult and developing pigeon fovea to determine whether it is a good model of human foveal development. Adult and developing pigeon eyes were enucleated and fixed in 4% paraformaldehyde. The right retina of each animal was flatmounted and the photoreceptor density determined. The left eye was sunk in 30% sucrose, frozen sectioned, and stained with DAPI. In the pigeon, there is a significant increase in the number of foveal cones during development leading to a 3 fold increase in cone density in the adult fovea. Rods are not detected in the developing and adult fovea. The formation of the pit is first detectable by midgestation in a region of increased ganglion cell density, which then thins to form the well defined pit. These data indicate pigeon foveal development is similar to the human indicating that it is a useful and appropriate model to study the mechanisms underlying human foveal development.

10.4

Studies in Wild-Type and Relaxin-3 Knock-out/*LacZ* Knock-in Mice Reveal the Central Distribution of Relaxin-3 and GPCR135 and Suggest a Role in Attentional States, Behavioral Control and Stress Responses

C. M. SMITH[1], S. MA[1], P.-J. SHEN[1], S. W. SUTTON[2], F. LIN[1], J. D. WADE[1], R. A. D. BATHGATE[1], G. W. TREGEAR[1] and A.L. GUNDLACH[1]

[1]Howard Florey Institute, The University of Melbourne, Victoria, Australia
[2]Johnson & Johnson PR&D, San Diego, California, USA

The neuropeptide relaxin-3 is a newly discovered member of the relaxin peptide family and its expression and distribution, along with that of its cognate receptor - GPRC135 - have been mapped in rat brain. The present study establishes the central distribution of relaxin-3 and GPCR135 in mouse. Relaxin-3 knock-out/*LacZ* knock-in mice confirmed via X-GAL staining that the major source of relaxin-3 gene expression is the pontine nucleus incertus. Using a polyclonal antibody raised against a portion of prorelaxin-3 peptide and DAB immunohistochemistry, relaxin-3 positive nerve extensions were widely observed in adult C57BL/6 mouse brains, including the midline cortex, septum, hippocampus, midline and geniculate thalamic nuclei, anterior/posterior hypothalamus, and areas of midbrain and pons. GPCR135 mRNA distribution was examined using in situ hybridization histochemistry and GPCR135 binding sites were mapped by autoradiography of brain sections labeled with a selective, chimeric peptide ([^{125}I]-R3/I5). Receptor distribution was consistent with relaxin-3 afferent projections and earlier findings in rat. This anatomical data, combined with the demonstrated behavioural- and stressor-responsiveness of the nucleus incertus, suggest that relaxin-3/GPCR135 signalling plays a role in attentional/arousal states, behavioral control and stress responses; and forms the foundation of planned behavioral studies of relaxin-3 KO mice.

10.5

Variability of Two Paired Associative Stimulation (PAS) Protocols Used to Induce Neuroplastic Changes in Human Motor Cortex

M. V. SALE, M. C. RIDDING and M. A. NORDSTROM

Discipline of Physiology, University of Adelaide, Adelaide, Australia

Several protocols are used to induce neuroplastic changes in human motor cortex. One protocol, paired associative stimulation (PAS), combines peripheral electrical stimulation of the nerve innervating the target muscle with transcranial magnetic stimulation (TMS) of the hand region of motor cortex. Responses to PAS vary considerably between subjects, however the reasons for this are not well understood. In the present study we compared two forms of PAS, and assessed the reproducibility of results obtained by repeated testing of the same subjects. Subjects (n=20) were equally divided into two PAS protocol groups ("short" protocol – 11 mins of 0.2 Hz paired stimulation; "long" protocol – 30 mins of 0.05 Hz paired stimulation), and each subject was tested 3 times, at least 1 week apart. Both protocols induced significant facilitation of APB MEPs ($p < 0.05$), although the short protocol was more effective (51% increase in MEP amplitude *vs*. +11%). Both protocols had similar intra- and inter-subject variability. There was no consistent effect of session number on the effectiveness of PAS. APB MEP facilitation with both protocols was significantly larger for experiments conducted in the afternoon vs. morning ($p < 0.05$). Although circadian influences on learning and memory are well established, this is the first study to provide evidence for a circadian influence on PAS. This finding will allow us to control a substantial source of variability with PAS, and could potentially have wide-ranging implications for neuro-rehabilitation strategies reliant on the induction of neuroplastic changes in the brain.

10.6

The N400 in Response to Non-current Rehearsal Items

J. P. HAMM, S. ASHCROFT and I. J. KIRK

Department of Psychology, University of Auckland, Auckland, New Zealand

Stimuli which violate a semantic expectation tend to produce a more negative going ERP response than the ERP response to semantically expected items. This negativity is observed around 400 ms post stimulus onset and is referred to as the N400 effect. In his description of Global Workspace Theory of Consciousness, Baars uses the rehearsing of a list of items to indicate how only one item is conscious during a point in time. In this example, Baars suggests that only the currently rehearsed item is conscious while the other list items are non-conscious. One could extend Baars' example to suggest that all words in our lexicon are "non-conscious" when not currently active in our "Global Workspace", which raises the question of whether or not the N400 effect is similar for "non-conscious list items" and other "non-conscious" words. During the current experiment, subjects were required to rehearse a list of 5 words at a pace determined by their presentation rate on a computer monitor. After presenting the list at least once, the pace was maintained by simply presenting a central X. After a random number of X's were presented, a final test word was presented and the subject was required to indicate if the presented item was (match) or was not (mismatch) the expected list word. Mismatch trials could either include a "non-conscious" list item or a "non-conscious" non-list item. N400's were calculated for list and non-list words. The scalp topographies did not differ although the amplitude of the N400 was larger for non-list words. For the list words, there was no relationship between the amplitude of the N400 and the relative list position of the mismatch word compared to the expected word.

10.7

Involvement of Anterior Cingulate and Prefrontal Cortices in the Stroop Colour-Word Task: EEG and fMRI Studies

I. J. KIRK, K. J. BARNETT, S. L. FAIRHALL, A. C. MORTON and G. BADZAKOVA-TRAJKOV

Research Centre for Cognitive Neuroscience, Department of Psychology, University of Auckland, Auckland, New Zealand

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. It has been generally assumed that the anterior cingulate cortex (ACC) is involved in the attentional control necessary for conflict resolution in the Stroop task, and the majority of imaging studies support this. However, imaging work has also highlighted a role for structures in the prefrontal cortex. Further, several studies have suggested that the substrate of attentional control in the Stroop is the dorsolateral prefrontal cortex (DLPFC), and that the ACC is involved primarily in response selection or performance monitoring. We used EEG and fMRI to investigate a number of variations on the Stroop task. Comparison of the data, within and between experiments, suggests that a neural network that includes both ACC and DLPFC (and likely the ventral lateral prefrontal cortex as well) is involved in attentional control, and conflict resolution in the Stroop task. We also suggest that generally, it is perhaps an oversimplification to attempt to assign a particular cognitive construct to a particular neural substrate.

10.8

Variation in Frontal and Posterior Cortical Theta-range Rhythmicity in Differing Behavioural States

N. McNAUGHTON and C. K. YOUNG

Department of Psychology, University of Otago, Dunedin, New Zealand

Low frequency (theta-range) rhythms can be recorded from many structures in the brain involved in emotion, learning and memory. Human EEG recording has often focussed on frontal midline activity; and animal work has often focussed on posterior, hippocampal, activity. We investigated theta-range activity recorded concurrently from the hippocampus and from a variety of midline cortical sites in rats. We obtained power spectra and coherence relationships during 4 different spontaneous behaviours: immobility, grooming, movement (head turning and locomotion) and rearing. Frontal cortical rhythmicity was generally lower frequency than posterior and, in contrast to posterior, was more prominent during automatic behaviours (grooming and immobility) than voluntary behaviours (locomotion and rearing). However, frontal and posterior cortex theta rhythms were more coherent in voluntary behaviours than automatic behaviours. These findings suggest that separate brain networks use theta-range activity and that they can interact to produce coordinated activity under some conditions.

10.9

Effects of Aging on NMDA Receptor Subunits in Memory-Associated Brain Structures

P. LIU[1], P. F. SMITH[2] and C. L. DARLINGTON[2]

[1]Department of Anatomy and Structural Biology, [2]Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

The N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptors, is critically involved in learning and memory. The present study investigated the effects of aging on protein expression of NMDA receptor subunits in the hippocampus and its adjacent entorhinal, perirhinal, postrhinal and temporal cortices. Western blotting demonstrated significant decreases in NR1 expression in the ventral portion of the hippocampus ($p < 0.05$) and the entorhinal ($p < 0.05$) and postrhinal ($p < 0.005$) cortices in aged (24-month-old) rats relative to the young adults (4-month-old). There were significant decreases in NR_2A expression in the aged entorhinal, perirhinal and postrhinal cortices (all $P < 0.05$), but not in the hippocampus. When the sub-regions of the hippocampus were investigated, a dramatic decrease in NR1 expression was found in the aged CA2/3 ($p < 0.0005$) and there were no significant age-related changes in NR_2A expression. These results suggest the differential effects of aging on NMDA receptor subunits in memory-associated structures. Within the hippocampus, the aging process appears to affect NR1 greatly in the ventral portion, in particular the CA2/3 region.

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10.10

Aging-Related Decrease in Synaptic Protein Synthesis in Rat Hippocampus

W. C. ABRAHAM[1], D. GUÉVREMONT, J. M. WILLIAMS[2] and D. S. KERR[3]

[1]Department of Psychology, University of Otago, Dunedin, New Zealand
[2]Department of Anatomy and Structural Biology, [3]Department of Pharmacology & Toxicology, University of Otago Medical School, Dunedin, New Zealand

Aging is associated with cognitive changes, including a decline in the retention of new memories that is correlated with a decline in the protein synthesis-dependent stability of hippocampal long-term potentiation (LTP). Here, we ask whether aging is associated with a decline in either basal or pharmacologically stimulated synaptic protein synthesis. Hippocampal synaptoneurosomes were isolated from young (YA, n=21, 2-4 mo), middle-aged (MA, n=12, 14-16 mo) and old-aged (OA, n=11, 22-25 mo) Sprague-Dawley rats. Basal protein synthesis, assessed by ^{35}S-methionine incorporation over a 30 min period, was significantly reduced by 30% and 39% in OA compared to YA and MA rats, respectively. Stimulation of synaptic protein synthesis by a Group I metabotropic receptor (mGluR) agonist or by brain derived neurotrophic factor progressively declined with age, peaking at 62% and 76% reductions in OA animals, respectively. The former reduction may relate to reduced mGluR5b receptor expression which declined by 50% in Western blot analysis. In contrast, inhibition of L-type voltage-dependent calcium channels (VDCCs) by (+)-BAY-K8644 caused a progressive decline in basal protein synthesis with age, suggesting an increased contribution of VDCCs to basal protein synthesis. These findings demonstrate a dysregulation of basal and stimulated synaptic protein synthesis with aging that may contribute to decreases in the stability of both LTP and newly formed memories.

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