1.1

Molecular and Neural Regulation of Sound Processing in the Cochlea

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Sound processing in the auditory system relies on the exquisite signal processing capabilities of the cochlea, such as the active mechanical processes in the auditory sensory organ that provide biological amplification of low-level sounds and enhance frequency selectivity. This review will discuss the emerging evidence of molecular and neural mechanisms that regulate cochlear processing capabilities to enhance signal detection and conditioning. The gain, and hence sensitivity of the auditory hair cells is under the control of both local molecular processes and descending neural pathways from the brainstem, ensuring that these cells are operating optimally. Research from our group shows that these molecular processes involve a novel purinergic signalling system operating via purinoceptors (Housley et al., 2001, *Audiology and Neuro-Otology, 7*, 55-61). The descending auditory pathways that innervate the sensory cells and auditory afferent neurons may also have a more complex role in auditory processing possibly improving the detection of signals in background noise by dampening the response of the cochlea to noise. There is evidence that cochlear biomechanics and the activity of these pathways may be enhanced by auditory training (Perrot et al., 1999, *Neuroscience Letters, 262*,167-70). Abnormalities of these descending pathways and regulatory mechanisms may underpin many forms of hearing impairment ranging from tinnitus and the lack of ability to hear in background noise to sensorineural deafness.

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1.2

Tactile Perception Can Resolve Visual Ambiguity

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When confronted with visual information for which two distinct interpretations are equally consistent, our phenomenal experience often alternates between the two. Can unambiguous tactile information resolve visual ambiguity? We created computer animation displays in which 240 dots appeared to be randomly distributed across the surface of a globe rotating about its vertical axis. The rotation direction of the visual globe (VG) was ambiguous, thus appearing at times to rotate clockwise, at other times anticlockwise. We also mounted a physical globe (PG) on a rotating shaft controlled by a motor, and positioned it at the same location that the visual globe appeared to occupy in space. In our first two experiments observers simultaneously grasped the PG as they viewed the VG, and reported the apparent rotation direction of the VG. In a third experiment observers were first exposed to the PG, then released their grasp and reported the rotation direction of a subsequently viewed VG. Although simultaneous perception biased the appearance of the VG, prior exposure to the PG had no influence on the appearance of the VG. Finally, we used fMRI to reveal the response in MT+ to a rotating VG, PG, and imagined globe. In the visual and physical conditions, but not in the imagined condition, moving stimuli yielded stronger MT+ activation. We conclude that touch can directly activate neurons commonly believed to register visually perceived motion, thus influencing our visual account of the world.

1.3

Neural Mechanisms of the McCollough Effect

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The McCollough Effect (ME) is a contingent visual after-effect that involves associations between orientation and colour. It is induced by viewing a pattern of alternating black and coloured lines of a particular orientation. When a black and white grid of the same spatial frequency and orientation is viewed later, the white lines appear to be tinted with the complimentary colour of the induction stimulus. Given a long enough induction period, this effect, can last hours or even days. A recent study by Humphrey et al., (*Psychological Science*, 1999, 10, 444-448) localised the *perception* of the ME to the fusiform gyrus (V4) using fMRI. However, the neural mechanisms that produce this phenomenon are still unknown. The present study hypothesises that plastic mechanisms such as long-term potentiation (LTP) or long term depression (LTD) might be involved. LTP and LTD, like the ME, are both associative and long lasting. Electroencephalography was used to investigate whether such mechanisms underlie the induction of the ME. This was done by comparing the event related potentials (ERPs) produced by viewing achromatic grids before and after induction of the ME. A significant increase in post-induction ERPs were observed indicating that LTP or LTD may have occurred. This difference was localised in V1, suggesting that *induction* the ME occurs early in cortical processing.

1.4

One Good Turn Deserves Another

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The time to determine if a rotated letter is a normal or mirrored version increases as a function of the stimulus orientation. Both mirrored and normal versions show the same effect of orientation, which is consistent with the notion that the stimulus is mentally rotated to the upright prior to the determination of the mirror/normal status. In addition to this increase over plane orientation is the finding that responses to mirrored stimuli are consistently slower than responses to normal stimuli. This latter finding is generally not investigated. Results from an EEG investigation suggest that this additional delay may be due to flipping the mirrored stimuli after the rotation to the upright. This would suggest that the mirror/normal difference may also be due to mental rotation.

1.5

Manipulating Perceptual Information And Cricket Bowling: A Case Study

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Few studies have examined the effect of manipulating multiple sources of information in real world tasks, such as cricket bowling run-ups. In this pilot study, a professional bowlers' run ups under three different visual informational constraints (normal match conditions, stumps only, and crease markings only) were filmed using a panning camera operating at 50 Hz. The distance of each footfall from the crease was calculated, with standard deviation of each footfall placement around the mean distribution taken as a measure of inter-trial variability. Similar levels of variability at front-foot contact (s= 0.08 m, 0.08 m, 0.04 m) were seen in all conditions, however the manipulation of information resulted in different patterns of footfall during the run-up and different mean distances of final footfall from the crease line (0.35 m, 0.21 m, 0.04 m). Findings suggest that the presence of the umpire and/or stumps is an important informational constraint necessary for successful bowling. This case study of one professional cricketer highlighted the need for further research with a group of highly skilled cricketers as well as the need for skill level comparisons with intermediate and club players. The relationship between task constraints of practice and competition is an applied issue of note to consider in future work.

2.1

Examination of the Use of Weights to Reduce Tremor and Improve Function in Ataxia

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The purpose of this study was to examine the common clinical practice of adding weights to the upper limb to reduce the ataxia in patients with cerebellar lesions. Two questions were asked. First, is there a learning effect after the weights have been worn for some time? Second, what is the mechanism underlying their effect? Five subjects were tested under four conditions: without weights, immediately after the addition of weights, after practising with the weights for 30 min, and after the removal of the weights. In each condition, they carried out two functional tests: the nine-hole peg test and the spiral test. In addition, activity of the biceps and triceps was collected during a finger-nose test. There was no difference in the scores of the two functional tests between either condition without weights versus either condition with weights. However, the traces from the spiral test were noticeably smoother. The amount of activity in biceps but not in triceps was increased during the conditions with weights compared to without weights. However, there was no change in the timing of the muscle activity. It appears that the addition of weights reduces tremor but not to the extent that function is improved, even after practice. The mechanism by which this happens appears to be a mechanical one, i.e. the weights require more muscle activity in the primary agonist which has a dampening effect on the amplitude of the tremor.

2.2

Proprioceptive and Timing Control of Multijoint Movement Sequences

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The coordination of hand opening during passive and slow voluntary arm movements ("frisbee task") is based on proprioceptive feedback. However, during rapid movements, this control may depend on internal models of the ongoing movement. This research examined whether both types of control existed in the coordination of a primary elbow extension movement (60°: durations 600, 800, 1066, 1421 ms) and secondary hand movement which occurred at an elbow angle of 30°. Ten subjects performed two experiments during which vision of the arm was occluded but the targets were visible. Experiment A: 1. Practice with visual feedback (VF) via a computer screen; 2. No VF; 3. No VF with biceps vibration (50 Hz) on 16 catch trials; Experiment B: 1. Practice with continuous biceps vibration and VF; 2**.** Vibration and no VF; 3. No VF with no vibration on 16 catch trials. In Experiment A vibration caused a reduction in the primary movement amplitude. For Experiment B "removal" of vibration caused an increase in the primary movement amplitude. There was no effect on movement duration. For both experiments the secondary movement was unaffected by vibration and covaried with primary movement duration. Proprioceptive feedback was used to control the primary movement but not the secondary movement. Instead, the secondary movement appeared to be controlled by an internal model that provided a representation of the intended time of thumb release.

2.3

Bilateral Training for Hemiplegia Rehabilitation

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A recent development in physical rehabilitation techniques for hemiplegia was investigated. Single-case research by Mudie and Matyas indicated that practicing motor tasks bilaterally (as if the movement were mirrored on the other side of the body) produced a rapid and substantial improvement in subsequent unilateral movement quality. It was speculated that the bilateral movement caused transcallosal disinhibition of ipsilateral pathways, and that these ipsilateral pathways were then permanently unmasked by long-term potentiation. A replication study was performed to confirm the behavioral phenomenon. However, several single-case experiments indicated that bilateral movement practice had no therapeutic effect. The replication study used the same multiple-baseline single-case design, similar kinematic variables, and similar participants to the original study. In contrast to the previous study, however, there was no ongoing verbal instruction or feedback offered to participants after the motor tasks had been explained. Verbal feedback and instruction are well-established motor learning variables in literature on neurologically intact humans, and are already commonly used in the clinical practice of movement rehabilitation. The current findings suggest that the improvements seen in previous studies were unlikely to be due to transcallosal disinhibition. If this were the case, disinhibition would be expected to occur as an inherent feature of bilateral movement performance. As the effect occurred only in the studies that included verbal feedback and instruction, it is now hypothesized that the improvement in movement quality was due to the utilization of these motor learning principles.

2.4

Observation of Goal Directed Action Modulates the Sensorimotor Mu Rhythm

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Recent animal and neuroimaging studies indicate that motor areas of the brain may play a role in the representation of the goal-directed actions of others. In the present studies we measured changes in the electroencephalographic mu rhythm to index activation of the sensorimotor cortex. In our first experiment using right hands only, mu rhythm amplitudes were significantly lower during observation, execution and imitation of a precision grip relative to the observation of simple hand extension without object interaction. In our second experiment we replicated and extended this finding to the observation of both left and right hands. Electromyographic recordings from hand/arm muscles showed no measurable muscle activity during all observation conditions. In both experiments scalp current source density maps were consistent with mu generation in sensorimotor cortices and were highly congruent across observation and execution conditions consistent with the hypothesis of an observation-execution matching system. In the second experiment we added a condition where subjects observed grip formation without grip performance. Mu rhythm amplitudes were significantly attenuated in the grip observation condition relative to the grip-formation observation condition. This novel finding shows that the sensorimotor mu rhythm is more strongly activated by the observation of goal-directed actions than by the mimicry of those actions. It is proposed that this enhanced activation is due to the activation of either a different or more salient motor schema.

2.5

Brain Potentials Elicited by Goal-Directed Hand Formations in Static Visual Displays

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Converging evidence from human neuroimaging studies have demonstrated that distributed neural systems, including the superior temporal sulcus, inferior parietal lobule and Broca's area, are strongly activated by either observation or execution of dynamic, goal-directed motor behaviours. In the present study we wished to determine if specific neural systems could similarly be activated by static visual displays of goal-directed behaviours. High-density Event-Related Potentials (ERPs) were collected from seven neurologically normal, right-handed individuals while they observed randomly presented pictures of left and right hands. The hands either grasped an object (Object condition), mimicked grasping in the absence of the object (No-object condition) or mimicked grasping with the object located displaced in the picture (Displaced-object condition). In comparison to the control conditions (No-object & Displaced-object), Object ERPs showed increased amplitude for a 260 ms positive component located at temporal electrodes (T5/T6). Similar results were obtained when stimuli were presented in a blocked condition, ruling out the possibility that the effect is due to subjective evaluation of the probability of the stimulus type. These results indicate that object-directed hand formations may recruit specialized neuronal populations at a relatively early stage of visual-perceptual processing.

2.6

Human Corticospinal Excitability During a Precued Reaction Time Paradigm

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The purpose of this study was to investigate the time-course of corticospinal excitability during reaction time (RT), and compare the excitability when a precue provided either information, completely specifying the upcoming movement, regarding the direction of the upcoming movement, or providing no information at all. Ten healthy, right-handed subjects performed a 4-choice RT task which involved flexion and extension of the dominant wrist. Transcranial magnetic stimulation (TMS) was presented at random intervals over a period of 120 ms prior to the subject's non-stimulated voluntary electromyography (EMG) activity onset. We found that for *flexor carpi radialis* (FCR) during flexion movements, corticospinal excitability increased approximately 105-110 ms prior to non-stimulated EMG onset in the Full and Direction conditions, but did not increase until approximately 40 ms prior to EMG onset in the None condition. The delayed onset of cortispinal excitability in the None condition possibly reflects the prolonged period of time selecting the desired response. The slope for the relationship of MEP amplitude as a function of time did not differ between the Full and Direction conditions, suggesting that motor cortex excitability is not altered in the specification of movement extent. The slope in the None condition was much steeper than in the other two conditions, reflecting an increase in gain in the corticospinal pathway (presumably at the level of M1) in response to the uninformative precue.

2.7

Changes in EEG Associated with Response Type, Parameter Precuing and Reaction Time

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We investigated in human participants (n=2) the relationship between response (None, Verbal, Motor) and precue parameters (All, Partial) on the latency and amplitude of the electroencephalogram (EEG) and reaction time (RT). Parameter precues were presented via a visual display containing four red LED's corresponding to four targets, two either side of a green centre LED. Illumination of one target LED precued direction and extent of the motor response (DKEK – direction known, extent known); two LEDs to one side of centre precued direction but not extent (DKEU); two LEDs spaced equally either side of centre precued extent but not direction (DUEK). A precue (500 ms) was followed by a variable (1, 1.5, 2 s) foreperiod then the imperative stimulus (specific target LED) occurred. In the "None" condition, participants just observed the precue and stimulus. For the "Verbal" conditions participants responded "Yes" when the stimulus appeared and in the "Motor" condition participants moved the pointer (attached to a manipulandum) as quickly and accurately as possible to the target when the stimulus occurred. Each participant received 18 blocks of 75 trials in a single session. Trials were blocked by response type (3) and precue (3), two blocks each. For the motor response, RT was shortest for DKEK (241 ms) and longer for DKEU (282 ms) and DUEK (296 ms) respectively. Within the EEG, visual evoked potential (VEP) latency remained unchanged across None, Verbal, and Motor response conditions. Contingent negative variation (CNV) was observed only in the Motor response conditions. Within the Motor response condition CNVs were larger (greater amplitude) to the DKEK (simple RT) precue than to the DKEU and DUEK (2-choice RT) precues. Furthermore, CNVs were larger at central than at occipital recording sites.

2.8

Lateral Asymmetry in the Effectiveness of Contraction of the First Dorsal Interosseous Muscle

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The first dorsal interosseous muscle performs clutching and gripping movements of the hand. Force and leverage parameters of this muscle expressed in its contractile and elastic elements are factors influencing effectiveness of the overall range of its behaviour. Our work checked the relationship between the quality and quantity of the lateral performance produced by this muscle and the asymmetrical profile of an individual. Five healthy strongly right-handed young males were recruited for the study. Maximum force of the muscle was measured using a specialised dynamometer. Participants pushed the button as strongly as possible in response to stimulus. The thumb was initially abducted between 83-90 degrees. The same subjects participated in Magnetic resonance imaging in order determine the characteristics of leverage of the muscle. Establishment of the pivot was derived from magnetic resonance images and standardised. The longitudinal orientation of the muscle was analysed from a range of images and longitudinal axes lines established. Both hands of each subject were scanned in a sequenced protocol. Our calculations defined the torque of left and right muscles in our subjects. It is interesting that the force and entire torque of the 1st dorsal interosseous in the dominant hand was sometimes less that the torque in the subdominant hand. This would tend to support our impression that anatomical and hemispheric asymmetry is not totally related.

2.9

Selective Increased Cortical Excitability Induced by Interventional Paired Associative Stimulation

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Paired associative stimulation (PAS) has received increased attention as a means for invoking plasticity in the cortex through an LTP-like mechanism. Significant enduring increases in corticomotor excitability have been demonstrated following sessions of PAS. In this study, PAS involved peripheral electrical stimulation applied over the median nerve at the elbow. Subsequently, a magnetic stimulus was applied over the area of the motor cortex associated with the flexor carpi radialis (FCR) muscle. The timing of the magnetic stimulus coincided with the arrival of the peripheral afferent stimulus at the motor cortex. Participants (n = 10) received PAS at 0.05 Hz for 30 mins. Pre- and post-intervention stimulus-response curves were constructed from motor evoked potential amplitudes collected from FCR and extensor carpi radialis (ECR). Only FCR demonstrated a significant increase in slope post-intervention, while the antagonist muscle (ECR) did not. PAS was therefore effective in producing a selective increase in excitability of the cortical motor area associated with FCR, a muscle innervated by the nerve that was peripherally stimulated. These results suggest that PAS may provide a well-controlled means of altering cortical excitability and may be a useful tool in the area of motor rehabilitation.

3.1

Selective Silencing of Honey Bee (*Apis mellifera* L.) Dopamine Receptor Genes Using RNA Interference Techniques

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RNA interference (RNAi) is a novel molecular biological approach that has been developed as a tool for gene silencing. Double-stranded RNA (dsRNA) introduced into cells is reported to suppress gene expression in a highly selective manner. We have examined the effects of dsRNA on 2 honey bee dopamine receptor genes expressed in insect (*Spodoptera frugiperda*, Sf9) cells. The dopamine receptor genes, *Amdop1* (Blenau et al., (1998) *J Neurochem* 70:15-23) and *Amdop2* (Humphries et al., (2003) *J Neurobiol* 55:315-330) were transfected into Sf9 cells using a plasmid vector expression system. Measurements of intracellular cAMP following treatment with dopamine were used to confirm that AmDOP1 or AmDOP2 receptors were functional in these cells. Activation of either receptor increases levels of intracellular cAMP. Sense and antisense mRNA was synthesized by *in vitro* transcription and annealed into dsRNA. Co-transfecting cells with dsRNA derived from a 350bp sequence of *Amdop1* abolished AmDOP1 receptor activity, but had no effect on receptors encoded by *Amdop2* indicating the specificity of RNA interference in this system. Co-transfecting cells with dsRNA derived from *lacZ*, a gene encoding β-galactosidase, had no effect on dopamine-induced cAMP responses in cells expressing either, AmDOP1 or AmDOP2 receptors. These results indicate that RNAi can be used to selectively block dopamine receptor expression *in vitro*. Our goal now is to determine the selectivity and longevity of the gene-silencing effects of treating honey bees with dsRNA *in vivo*.

3.2

Effects on Synaptic Transmission in the Striatum of Modulating the Firing of Substantia Nigra Dopamine Neurons, *In Vivo*

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Substantia nigra dopamine neurons are thought to change their firing patterns in response to the predictability of rewards. An unexpected reward activates the neurons to fire bursts, however this reward responsiveness is lost when the reward is fully predicted. Furthermore, omission of an expected reward results in an inhibition of dopamine cell firing at the time the reward was expected. These changes in tonic firing are thought to play a role in learning, however little is known about the cellular effects of these changes. We examined these effects by measuring synaptic plasticity in the target area of the dopamine neurons, the striatum. Intracellular records were made from striatal spiny projection neurons in urethane-anaesthetised rats. A stimulating electrode or an ejection pipette containing gamma-aminobutyric acid (GABA) was placed in the substantia nigra to activate or inhibit dopamine cell firing, respectively. Post-synaptic potentials (PSPs) were evoked by applying test pulses to cortex and measured before and after applying a brief treatment to substantia nigra. High-frequency electrical stimulation to substantia nigra (6 x 50 pulses at 100Hz) induced potentiation of corticostriatal PSPs (+18 ± 10% after 20 minutes) whereas GABA ejection (1M, 24nl), which directly inhibited substantia nigra cell firing, induced depression (-14 ± 4% after 20 minutes). These results suggest that brief changes in dopamine cell firing can induce lasting changes in synaptic strength in the striatum.

3.3

Acute Effects of 6-hydroxydopamine (6-OHDA) on Dopaminergic Neurons of the Substantia Nigra Pars Compacta (SNc) in the Rat Brain

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6-OHDA is a neurotoxin which has been implicated in degeneration of SNc neurons in Parkinson's disease, and frequently used to produce animal models of the disease. The aim of our study, conducted on midbrain slices (250 μm) obtained from young Wistar rats, was to determine acute electrophysiological and morphological effects of this toxin (0.25 – 2.0 mM; 10 – 20 min) on SNc neurons, using three approaches: extracellular recording, whole-cell patch clamping (under IR-DIC optics) and fluorescence imaging with Lucifer Yellow (LY). In most experiments, 6-OHDA was protected from oxidation by ascorbic acid and N_2, whilst in some the oxidized form of the toxin was used. Extracellular recording revealed concentration-dependent change in the tonic, pacemaker-like, firing. In whole-cell voltage clamp, exposure to protected 6-OHDA resulted in a rapid and irreversible decrease in cell membrane capacitance (by 39 ±10 pF; from 173 ±35 pF; n = 5) and a transient decrease in cell membrane resistance. Oxidized 6-OHDA induced an inward current (depolarization in current clamp), with no change in membrane capacitance. In most cases, loading cells through the patch pipette with LY showed no clear signs of morphological damage of proximal dendrites following toxin exposure. In some cases however, cell membrane blebbing was observed. These results demonstrate that 6-OHDA produces rapid, dose-dependent and irreversible changes in the electrophysiological parameters of nigral dopaminergic neurons, with some evidence of acute morphological damage.

3.4

Forgetting is a New Learning: Evidence from the Activity of Dopamine Neurons in Behaving Rats

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Previous studies in monkeys showed that dopamine cells might provide a “prediction-error” function in reward-dependent learning. After extensive training in instrumental conditioning tasks midbrain dopamine neurons reduce their responses to rewarding events if these are predicted by prior signals, and develop responses to the predictive signals. If predicted reward is omitted, these cells are said to be inhibited at the time reward would normally be delivered. However there has been little study of the effect of continued omission of rewards (in behavioural terms, an extinction procedure), on responses to the signals. We examined the effect of extinction procedures in putative dopamine cells recorded in thirsty and freely-moving rats performing a classically conditioned task. After conditioning, cells responded to the click sound of a solenoid delivering liquid reward, and after further conditioning, to a tone signal predicting the onset of the click. Extinction procedures consisted of disconnecting the fluid line (dissociating the click from reward), or dissociating the tone from the click. Cells generally reduced or lost completely their responses within 50–100 trials. However, re-testing later or the next day revealed partially restored responses. Further, loss of responses was in some cases accompanied by superposition of an overt inhibitory response, suggesting a specific mechanism affecting the cells activity. These extinction patterns of dopamine neurons match features of the extinction pattern of classical conditioning, suggesting that a developed inhibition mechanism is involved in extinction – and that it is a distinct process with a specific neural basis, i.e. is a new learning, as originally suggested by Pavlov.

3.5

Responses of Rat Prefrontal Cortex Cells to Reward-Predictive Stimuli in an Associative Learning Task

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Prefrontal cortex (PFC) is a possible source of afferent drive to midbrain dopamine neurons, which are selectively activated by unpredicted reward-related signals. To investigate the role of PFC in processing reward-related information, we are recording single neuron activity under conditions previously used to test dopamine cells. To date, random fluid rewards have elicited responses in 19/45 medial PFC cells, 4 excited and 13 inhibited. However, in all but two cases the response was related to licking, rather than to fluid delivery. A total of 9/42 cells responded to randomly delivered tones (7 inhibited, 2 excited). So far, very little evidence of response plasticity has been seen, either development or change of responses subsequent to pairing of sensory stimuli with rewards, or extinction/habituation of pre-existing responses by repeated exposure. These findings are in contrast to dopamine cells, which show almost no relation to licking movements, show more excitations than inhibitions, and are very plastic in this task. The latency for inhibitions to tone stimuli (mean 40 ms) appears similar to that of dopamine cells in the same task (mean 53 ms). For the two excitatory responses obtained to date both had shorter latencies (18, 20 ms) than typical for DA cells (mean 80 ms). Further experiments will increase the sample size, extend to recording from orbitofrontal cortex, and test the effect of dopamine agonists and antagonists on cortical responses.

3.6

Prolactin Activation of the STAT-signalling Pathway in Cultured Hypothalamic Dopaminergic Neurons

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We have previously demonstrated that prolactin activates tyrosine hydroxylase (TH) activity and mRNA expression in hypothalamic dopaminergic neurons maintained in cell culture. Interestingly, while the increase in activity was suppressed by specific inhibitors of protein kinase A, protein kinase C, MAP-kinase and CaMKII, the increase in mRNA expression was unaffected by these agents suggesting the involvement of an alternative signalling pathway. Prolactin mediates its actions via type I cytokine receptors which can couple to the JAK/STAT signaling pathway. Immunocytochemistry revealed that prolactin caused STAT5b (but not STAT1, 3 or 5a) to undergo nuclear translocation and phosphorylation in some, but not all, of the TH-positive neurons in culture. Using an antibody against phospho-STAT5 this response was detectable after 5 minutes (approx. 30% of TH positive neurons) and reached a maximum between 15 to 30 minutes (60%) but then declined by 1 hour (40%) to reach near basal levels by 4 hours (little detectable staining). As with the increase in TH mRNA expression prolactin-induced STAT5 phosphorylation and nuclear translocation was unaffected by the protein kinase inhibitors mentioned above. Our results suggest the involvement of multiple signalling pathways in prolactin regulation of dopaminergic hypothalamic neurons which differentially regulate TH activity and TH expression.

3.7

Angiotensin II Activates Tyrosine Hydroxylase Activity and Gene Expression in Cultured Hypothalamic Dopaminergic Neurons

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Angiotensin II (AII) stimulated a time- and concentration-dependent increase in tyrosine hydroxylase (TH) activity in rat hypothalamic dopaminergic neurons maintained in culture. This AII-induced response was suppressed by specific inhibitors of protein kinase A, protein kinase C and CaMKII but not by their inactive analogues. While PD 98059, an inhibitor of the MAP-kinase pathway, reduced basal TH activity an AII response was still detectable. Coincident with this increase in TH activity AII-stimulation resulted in enhanced phosphorylation of the TH ser-19, -31 and -40 residues. In addition to stimulating TH activity the AII-induced a time-dependent increase in TH mRNA expression. In contrast to TH activity this latter response was unaffected by inhibitors of protein kinase A or CaMKII, but abolished by PD 98059 or the protein kinase C inhibitor bisindolylmaleimide I. Interestingly, AII responses were observed in cultures prepared from female but not male rat pups. Examination of AII-stimulated TH activity in hypothalamic slices prepared from adult animals confirmed this sexual dimorphism and supported the role of the specific protein kinases noted above. It can therefore be concluded that AII can regulate both the activity and expression of TH in hypothalamic neurons employing multiple, but only partially overlapping signalling pathways.

4.1

Perirhinal Cortex and Recognition Memory: A 3T fMRI Study.

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It has recently been proposed that two independent mnemonic networks subserve two different forms of memory. One network is involved in the recall of episodic information and consists of a network of structures including the hippocampus and the anterior thalamic complex. The second network is believed to be involved in recognition tasks that primarily involve familiarity judgements, and this system includes the perirhinal cortex and the medial dorsal nucleus of the thalamus (see Aggleton and Brown *Behavioral and Brain Sciences, 22*, 425-489, 1999). In the current study we used 3-Tesla fMRI in a familiarity judgement task (old vs new) of words or pictures. Stimuli consisted of a baseline condition (fixation cross) and 3 experimental blocks (no words (or pictures) were repeated; 10% of the items repeated; 50% of the items repeated). It was found that the word and the picture conditions displayed different patterns of activation. However, on the whole, some support was provided for Aggleton and Brown's proposal. In these recognition tasks, no activation in the hippocampus was observed. Significant activation in parahippocampal areas, including the perirhinal area, was observed, however. In addition, activation in areas of the thalamus outside the anterior thalamic region, and including the medial dorsal nucleus, was also observed.

4.2

Can Idiothetic Information Acquired During Piloting be Used in Dead Reckoning?

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It has been suggested that normal rats are able to navigate using both piloting (i.e. allocentric cues such as visual information) and dead reckoning (i.e. egocentric cues such as vestibular information) strategies in a visually rich environment. Furthermore, when vision is restricted, dead reckoning strategies can be flexibly selected by the rats. The present study explored this issue further in a rat foraging (i.e. food carrying) task. Twenty-six male Wistar rats were trained to search for large food pellets on an open table and then carry the food home to eat. The results from a probe test using a novel starting location under normal light were consistent with previous reports that normal rats favour using allocentric cues when they are available. However, it took the rats multiple trials to learn new home location when they were in the dark. These results suggest that switching between allocentric and egocentric cues is not as flexible as previously suggested. The effects of peripheral vestibular damage on performance in this task remain to be determined.

4.3

Electrical Stimulation of the Amygdala and Fear

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Electrical kindling of the amygdala is a widely used animal model of temporal lobe epilepsy, and increased emotionality is well documented following amygdaloid kindling. The underlying process (i.e. electrical stimulation, afterdischarge (AD) or seizure evolution) responsible for kindling-enhanced fear and anxiety is unclear. We report here that subthreshold AD electrical stimulation of the basolateral amygdala enhances fear responding as measured by fear-potentiated startle in laboratory rats. Following Pavlovian fear conditioning (light + footshock pairings) rats were extinguished to the conditioned stimulus. One group of animals received a subthreshold AD stimulation of the amygdala after each light presentation, and on subsequent testing stimulated animals exhibited significant fear-potentiated startle. Electrical stimulation of the amygdala context-specifically restored previously-extinguished fear responding in another group of experimental animals. The possibility that electrical activation of the amygdala produces unconditioned fear was considered, and animals were uniformly unable to acquire fear-potentiated startle using electrical stimulation of the amygdala as the unconditioned stimulus. These results were interpreted to suggest that amygdaloid stimulation activates learned fear neural representations reinforcing existing excitatory stimulus-affect connections. This phenomenon may play a role in the resistance to extinction and fear reinstatement observed in the present study and may contribute to seizure-associated fear. Considering the essential role of the amygdala in fear learning and memory, a similar excitatory mechanism involving fear reinforcement may underlie the extinction deficits and persistent fear responding that characterize posttraumatic stress disorder.

4.4

Hippocampal Complex-Spike Cell Movement-Related Firing is Driven by Motor Efferent or Proprioceptive Systems

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Rat hippocampal complex-spike cell firing rate is positively correlated with the velocity of a freely moving animal. This information may be important for navigation processes. The information that drives complex-spike cell movement-related firing could potentially originate from sensory flow (such as optic flow, olfactory flow), motor efferent, proprioception, or vestibular systems. A previous study from this lab demonstrated, however, that vestibular lesions did not change firing rate-velocity correlations in freely moving rats. The purpose of this study was to investigate what other information might be utilised. In the first experiment, 49 hippocampal complex-spike cells were recorded while rats foraged freely in a linear track. In separate recording sessions the rats ran with either a vertical or a horizontal grating pattern on both sidewalls. These patterns gave the rats two different levels of optic flow stimulation.Changes in optic flow were shown to affect place field size but did not affect the relationship between velocity and firing rate. In the following experiment, hippocampal CA1 place cells were recorded as rats were passively moved along a linear track. Complex-spike cells decreased their firing rate during passive movement and the relationship between animal velocity and complex-spike cell firing rate was lost. This indicates that hippocampal complex-spike cell movement-related firing is driven by motor efferent or proprioceptive systems rather than from optic flow or vestibular information.

4.5

Effect of Rearing Environment on an Object Recognition Memory Task

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Rats reared in enriched environments are believed to have superior performance in a number of memory tasks compared to rats raised in impoverished environments. The purpose of the present experiment was to investigate the effects of rearing environment on a commonly utilised object recognition memory test. Eight rats were reared in each of three environments – isolated, social, and enriched – from day 40. Beginning at approximately day 170, rats individually explored an arena containing two identical Lego objects for two five-minute training sessions each day for three days. Prior to session two on the third day, one of these familiar objects was exchanged for a novel object. When the amount of time each rat spent exploring each object was analysed for the first two minutes of this test session, there was a significant environment effect, a significant object effect, and a significant interaction. Further analysis of the time exploring the novel object as a ratio of total exploration time also revealed a significant environment effect. A post-hoc analysis determined that rats reared in the social environment spent a significantly greater proportion of their total exploration time exploring the novel object than did rats reared in the enriched group. This research indicates for the first time that rearing environment affects exploration of a novel object.

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

4.6

Multiple Partially Independent Sources of Theta Activity in the Hypothalamus

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Injections of benzodiazepines into the supramammillary nucleus or the posterior hypothalamus can alter the frequency of hippocampal theta rhythm and change behaviour. We attempted to localise rhythmical activity, synchronous with hippocampal theta, within the hypothalamic area with stepped arrays of chronically implanted electrodes. There were multiple sites showing such activity and the extent of synchrony varied both with site and with the behavioural state of the animal. No site appeared to provide a master control of all other sites. The occurrence of theta activity in each site also showed only partial overlap with hippocampal theta. The results are consistent with the control of the frequency of theta being an emergent property of a distributed network of nuclei.

4.7

Thalamo-Cortical Function Compared in Recall and Recognition Mnemonic Tasks with Theta Activity

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Aggleton and Brown (*Behavioral and Brain Sciences, 22*, 425-489 (1999)) have recently proposed that two independent mnemonic networks subserve two different forms of memory. One network is involved in the recall of episodic memory and includes the hippocampus and the anterior thalamus. The second network, that includes the perirhinal cortex and the medial dorsal nucleus of the thalamus, is believed to be involved in recognition tasks that primarily involve familiarity judgements. It is likely that theta-rhythmic activity will be generated in participating nuclei of these circuits when they are engaged in mnemonic processing. Further, as the thalamic components of the two circuits differentially project to neocortex, it is possible that differential topographies of scalp-recorded theta will be observed when one or the other circuit is engaged in mnemonic processes. Here we compared a within-session repeating word recognition task with a task that involved recall from a previously learned list. The recall task and the recognition task displayed different patterns of theta activation. The former was associated with greater inferotemporal (fusiform) and middle/medial frontal lobe theta activity in the period 200 and 500 ms after the visual presentation of a word, whereas the latter displayed greater orbital frontal theta activity within the same time period. These results provide some general support for Aggleton and Brown's theory.

5.1

Effects of Associative Stimulation on Neocortical LTP in Freely Behaving Rats

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Associativity is an attractive property of LTP as a memory model. Associativity refers to the ability of input pathways to interact cooperatively during LTP induction. Specifically, a 'weak' pathway (one that does not potentiate when tetanized by itself) can potentiate if it is tetanized simultaneously with a 'strong' pathway. Associative effects have been demonstrated in the hippocampus and anesthetized neocortex, but associativity has not been tested in the neocortex of freely behaving rats. The present experiment sought to test associative stimulation on LTP induction in the motor cortex of chronically prepared rats. The thalamocortical input (weak pathway) was tetanized simultaneously with the callosal input (strong pathway). The results show that the weak pathway did not potentiate following associative stimulation. Remarkably, the thalamocortical pathway depressed following tetanization, an effect that was exacerbated by associative stimulation. However, LTP in the strong callosal pathway was facilitated by associative tetanization. The results show that associative phenomena behave differently in the neocortex of awake rats.

5.2

Experience-Dependent Reversal of Lateral Perforant Path Synaptic Plasticity in the Hippocampus

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Long-term potentiation (LTP) of synaptic transmission in the hippocampus can persist for months after induction (Abraham, Logan, Greenwood, Dragunow, 2002, *The Journal of Neuroscience, 22(21)*, 9626-9634), suggesting that the hippocampus may have the capacity to participate in the storage of long-term memory. However as this persistence occurs in the absence of many new learning opportunities, LTP in these studies may be artificially prolonged compared to normal retention of synaptic weight changes in the hippocampus. The present research investigated the effect of complex environment (CE) exposure on LTP and heterosynaptic long-term depression (LTD) in the lateral perforant path of the hippocampus. Adult male Sprague-Dawley rats were chronically implanted with a recording electrode in the dentate hilus and stimulating electrodes in both the medial and lateral perforant paths. After stable recordings of field excitatory postsynaptic potentials (fEPSPs) were established, a high-frequency tetanus was applied to either the lateral and medial pathways together or just the medial pathway. This resulted in strong LTP (56 ± 3%; n = 3) and heterosynaptic LTD (-40 ± 7%; n = 3) in the lateral path synapses, respectively. At 14 days post-tetanus, animals were exposed to a CE for seven consecutive nights. Lateral LTP and LTD were both reversed by exposure to the CE. These results demonstrate that, like medial path LTP, the persistence of lateral path LTP and LTD is experience-dependent. These data suggest that, under naturalistic environmental conditions, hippocampal synaptic plasticity may normally persist for only short periods of time.

5.3

Long-Term Potentiation (LTP) of Human Auditory Evoked Potentials

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In a previous EEG study, we found that a short period of high-frequency visual stimulation induced LTP-like changes in the visual-evoked potential recorded non-invasively from electrodes over the human visual cortex. In the present study we used a series of 1000 Hz tone pips to measure a baseline Auditory Evoked Potential (AEP). Subjects subsequently received either two minutes of silence (Control Condition) or a high frequency train of auditory stimulation (Tetanus Condition) and baseline AEPs were again recorded. Results indicate that only when the Tetanus Condition is presented do the second baseline AEPs significantly increase. This suggests that our high frequency auditory stimulation is acting similarly to high-frequency electrical stimuli employed in neurophysiological studies in animals, and induces plastic changes in the system. This is significant because our paradigm indicates that LTP can be induced non-invasively in humans, in both the visual and auditory domains, using manipulations of the sensory stimuli themselves.

5.4

An Antibody to Amyloid Precursor Protein Reduces Long-Term Potentiation in Anaesthetised Rats

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Amyloid-β has been extensively studied as a causative agent in the onset of Alzheimer's disease. Less attention has been paid to the possible role played by secreted-amyloid precursor protein (sAPP), a neurotrophic fragment cleaved from the same precursor protein as amyloid-β. Exogenous sAPP enhances the learning ability and memory of rats, while conversely, blocking endogenous sAPP disrupts memory and learning. On the molecular level, exogenously applied sAPPα enhances hippocampal long-term potentiation (LTP) of synaptic transmission *in vitro*. The present research investigates the role of endogenous sAPP in the induction of LTP *in vivo*. Adult male Sprage-Dawley rats were anaesthetised with urethane, and acutely implanted bilaterally with an electrode and a 30-gauge cannula in the dentate gyrus, and with a stimulating electrode in the perforant path. After 30 min of baseline recordings, either an antibody targeted to sAPP, a control antibody with no target sequence, or saline was injected into the dentate gyrus. LTP was induced 30 min after the injection, and was monitored for 3½ hours. The control antibody and saline groups did not differ and were combined to form a single control group. At 3½ hours post-induction, the anti-APP group showed a significant decrease in the amount of LTP of the field excitatory post-synaptic potential response (26 ± 2%, n=5, $p<0.0001$), compared to the combined control group (57 ± 12%, n=7). Therefore, the endogenous release of sAPP in the hippocampus may contribute to the induction of LTP. These results are consistent with the proposed facilitating role for sAPP in learning and memory.

5.5

GABA-A and Nicotinic Receptors do not Mediate the Inhibition of Long-Term Potentiation by Amyloid-β

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The level of soluble amyloid-beta (Aβ) is elevated in brains of Alzheimer's disease patients and correlates with the degree of memory impairment. This impairment may be due to the fact that Aβ inhibits long-term potentiation (LTP) of synaptic transmission, a putative neural mechanism underlying learning and memory. This experiment investigated potential receptor targets of Aβ that may mediate the inhibition of LTP. Experiments were conducted in rat hippocampal slices (400 μm). Field excitatory postsynaptic potentials were recorded in the stratum radiatum of area CA1, following stimulation of the Schaffer collateral afferents. To test whether $A\beta_{1\text{-}40}$ impairs LTP induction through up-regulating GABA-Aergic inhibtion, high-frequency stimulation (HFS, 100 Hz) was delivered either in the presence of the GABA-A antagonist picrotoxin (100 μM) or in picrotoxin plus $A\beta_{1\text{-}40}$ (200 nM). HFS, in the presence of picrotoxin alone elicited 26 ± 7% LTP (n=4). $A\beta_{1\text{-}40}$ pre-incubation significantly reduced LTP to 5 ± 5% (n=4; Student's $t(6)=2.45$, $p<0.05$). In the second experiment we tested whether nAChRs, which avidly bind Aβ, mediate the inhibition of LTP by Aβ. However, neither a low dose of the nAChR antagonist methyllcaconitine (100 nM), which selectively blocks α-7 nAChRs, nor a non-selective higher dose of the drug (1 μM) prevented the inhibition of LTP by $A\beta_{1\text{-}40}$. These findings indicate that neither GABA-A nor nACh receptors mediate the inhibition of LTP by Aβ.

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5.6

Injury-Induced Alterations in Limbic Functional Circuitry

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Cognitive deficits persist in patients who survive traumatic brain injury (TBI). Lateral fluid percussion brain injury in the mouse, which mimics human TBI, resulted in hippocampal-dependent cognitive impairment, similar to retrograde amnesia often associated with TBI. To identify potential substrates for the cognitive impairment, we evaluated limbic excitability, regional neuronal loss and inhibitory synaptic transmission. Input/output curves recorded in slices of injured brain demonstrated increased excitability in the dentate gyrus in concert with decreased excitability in area CA1 compared to sham controls. Design-based stereological procedures quantified fewer neurons, approximately 40%, throughout the entire hippocampus in the injured compared to the uninjured brain. This neuronal loss may contribute to the observed regional excitability shifts. In surviving dentate granule neurons, spontaneous miniature inhibitory post-synaptic currents (mIPSCs) were smaller and less frequent in injured versus uninjured brains. Whereas, mIPSCs recorded in surviving area CA1 pyramidal neurons of injured brains were larger than those in uninjured brains. Together, these alterations suggest that limbic information processing is mishandled in the injured brain. This study demonstrates for the first time that brain injury uniquely disrupts limbic function in terms of inhibitory synaptic function, uniform neuronal loss, and regional, but opposing, shifts in circuit excitability, which may underlie injury-associated cognitive impairment.

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5.7

Reversal of LTD by D1/D5 Receptor Activation is Dependent on the Timing of the Activation and the Magnitude of the LTD

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In contrast to findings reported by other laboratories, we have reported that activation of dopamine D1/D5 receptors alone in area CA1 of rat hippocampal slices does not induce the stable late phase of long-term potentiation, but rather reverses the long-term depression (LTD) chemically induced by bath application of N-methyl-D-aspartate. The present study examined the effect of D1/D5 receptor activation on synaptically induced LTD. Field excitatory postsynaptic potentials were recorded in area CA1 of hippocampal slices prepared from 6-7 wk male Sprague-Dawley rats. The D1/D5 receptor agonist SKF38393 (100 μM), applied immediately after a mild low-frequency stimulus (LFS, 3Hz, 1200 pulses, 1 mV) reversed the LTD induced by LFS alone (1 ± 4% vs –16 ± 4% respectively, $p<0.01$). In contrast, similar transduction pathway activation by β-adrenergic receptor stimulation did not reverse this LTD (-12 ± 3%). Direct activation of the intracellular pathway linked to the D1/D5 receptor by the adenylate cyclase activator forskolin (10 μM) reversed this mild LTD if applied immediately after LFS (-4 ± 4%, $p<0.05$), but not when applied 60 min post LFS (-11 ± 13%). A more robust LTD induced by 2400 pulses was not significantly reversed by SKF38393 when applied immediately after LFS (–25 ± 3% vs –14 ± 4%, respectively). These findings indicate that de-depression of synapses is specific to D1/D5 receptor activation and is dependent on the timing of the activation and the magnitude of the LTD.

5.8

The Level of Protein Tyrosine Phosphorylation Regulates the mGluR-Dependent Depression of the Slow Afterhyperpolarization in CA1 Pyramidal Neurons of the Rat Hippocampus

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We have previously described a persistent depression of the slow afterhyperpolarization (sAHP) and consequent increase in excitability engendered by activation of Group I metabotropic glutamate receptors in hippocampal CAl pyramidal neurons. In this study, we investigated whether these changes are dependent on tyrosine phosphorylation or dephosphorylation. Intracellular current-clamp recordings were made from rat CAl pyramidal neurons in acute hippocampal slices maintained in vitro at 32.5 degrees C. The sAHP depression and excitability increase induced by the Group I mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) was not altered by pre-exposure to the tyrosine kinase inhibitor, lavendustin A, indicating that activation of tyrosine kinase is not necessary for these changes. However these changes were prevented by to the tyrosine phosphatase inhibitor, orthovanadate. Since the inhibition of tyrosine phosphatases permits tyrosine phosphorylation, we tested whether such a response is critical for the effects of orthovanadate. Preincubation in lavendustin A plus orthovanadate rescued the mGluR-dependent changes, suggesting that the effects of orthovanadate are due to an increase in tyrosine phosphorylation. Overall these data suggest that the signaling pathway(s) by which mGluRs depress the sAHP is regulated by a balance between tyrosine phosphorylation and dephosphorylation of an unidentified phosphoprotein, such that activation of the pathway by mGluRs is prevented by tyrosine phosphorylation and permitted by dephosphorylation.

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5.9

Increased Sensitivity of Hippocampal Neurons to Domoic Acid Over Weeks in Culture

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Aged CNS exhibits heightened sensitivity to excitotoxins such as domoic acid (DOM). Interestingly, primary cultures of hippocampal neurons undergo changes over time which resemble cellular changes during brain aging. To assess cytotoxicity in this model of CNS vulnerability, we examined sensitivity to DOM at 8 and 23 days *in vitro* (DIV) and the effectiveness of receptor-specific blocking agents as neuroprotectants. Cell viability was assessed by morphological (appearance and cell count) and biochemical (LDH release and calcein fluorescence) techniques. At 23 DIV, neurons exhibited heightened sensitivity to DOM relative to 8 DIV (approx. EC_{50} = 500 nM vs 1.75 µM, respectively). Neither L-type VSCC blocker nimodipine (5 µM) nor NMDA receptor blocker MK-801 (10 µM, or a cocktail of the two) promoted cell survival, suggesting calcium through these channels is not contributory to DOM toxicity. Vitamin D (50 nM), which down regulates L-channels and imparts protection vs. glutamate toxicity, failed to protect neurons exposed to DOM. The AMPA/KA receptor blocker CNQX (25 uM) provided complete protection at 8 DIV, but was only moderately effective at 23 DIV, right-shifting the DOM EC_{50} to 2.75 uM. This finding is consistent with recent patch clamp studies showing robust increases in AMPA currents in hippocampal neurons between 8 and 23 DIV (L. Brewer, personal comm.) and confirm a prominent role of AMPA receptors in DOM cytotoxicity, as seen in murine cortical neurons (Larm et al., 1997).

6.1

Combined Methamphetamine and MDMA Administration: Effects on Behaviour and Neurotoxicity

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Methylenedioxymethamphetamine (MDMA) and methamphetamine (METH) are widely used drugs of abuse in Australia. Used together intentionally, or unintentionally as Ecstasy 'pills' containing various concentrations of METH, both have been identified as neurotoxins of the dopamine and serotonin systems. The effect of co-administration of METH and MDMA on brain and behaviour in humans or rats, has yet to be addressed. In this study, male Albino Wistar rats received four injections over 8h of either low or high MDMA (2.5 mg/kg; 5 mg/kg), low or high METH (2.5 mg/kg, 5 mg/kg), low MDMA/METH combination (1.25 mg/kg + 1.25 mg/kg), high MDMA/METH combination (2 mg/kg + 2 mg/kg) or vehicle. Increased activity was apparent in all groups, with both MDMA and high combo groups showing significantly higher average temperature, whilst high METH and both combo groups displayed severe stereotopy. Behavioural tests of anxiety four weeks later indicated increased anxiety in both high and low combination groups, beyond that seen in either drug group alone. Combined administration lead to decreased levels of dopamine, 5-HT and 5-HIAA in several brain regions. These results suggest that combined methamphetamine and MDMA administration, even at low doses, can lead to long-term changes in the brain and behaviour. This has important implications for future public awareness.

6.2

Activation of Caspase-3 in Rat Cerebellar Purkinje Cells Following Ethanol Exposure During the Third Trimester Equivalent of Development

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Exposure of the developing fetus to alcohol may result in brain dysfunction and is considered to be the leading cause of mental retardation in the Western world. Recent studies have shown that binge-like ethanol exposure in the neonatal rat brain results in extensive loss of cerebellar Purkinje (P) cells. This study aimed to determine the time of onset of P cell death by detection of active caspase-3 using immunohistochemical labelling. Detection of active caspase-3 indicates that cells have entered the apoptotic pathway. On PN4, Sprague-Dawley rat pups were given ethanol (4.5 g/kg ethanol as a 10.2% (v/v) solution in two doses two hours apart) to mimic a binge-like exposure. Animals were killed by intracardiac perfusion under deep anaesthesia (pentobarbitone) at 30 minute intervals for five hours and hourly up to 14 hours post ethanol delivery. Following routine wax histology, 5 µm thick parasagittal midvermal cerebellar sections were incubated with an antibody for active caspase-3. Labelled cells were visualised with AEC. Semi quantitative methods were used to determine the ratio of labelled P cells per total P cells in each lobule. Results show that apoptotic P cell loss begins within 4 hours and is maximal at eight hours post-ethanol exposure. P cell loss is more extensive in the anterior and posterior cerebellum. Determination of the interval between ethanol exposure and the onset of irreversible cell death established the window of time available for therapeutic intervention (e.g. blocking the apoptotic cascade).

6.3

Apoptotic Purkinje Cell Death in the Neonatal Rat Cerebellum Following a Single Exposure to Ethanol on Postnatal Days 0 to 4

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The cerebellar Purkinje cells (Pcells) have been studied extensively in the rodent, and a temporal window of vulnerability to ethanol-induced death exists from postnatal day (PD) 4 to 6. The endpoint of this temporal window has been thoroughly investigated, but the time of onset has not. This study aimed to determine the earliest timepoint postnatally following exposure to ethanol, at which Pcells express active caspase-3, a key enzyme involved in the initiation and regulation of apoptotic cell death. On G22 (PD 0), the pups of timed pregnant Sprague-Dawley dams were randomly assigned to groups – alcohol-exposed (AE), intubation controls, and suckle controls (SC) – and to days PD 0-4. On each day, pups were perfusion-fixed at 8, 10, and 12 hours after the initial ethanol exposure. Cerebelli were removed, wax-embedded, and serial 5 µm-thick sections cut. Sections were immunolabeled for active caspase-3 and the number of caspase-3 positive Pcells counted using the physical disector method. The number of labeled Pcells in the cerebellar vermis was significantly greater ($p<0.05$) in ethanol-treated animals compared to controls for all days studied (e.g. mean number of caspase-3 positive Pcells: AE = 74.33 compared to SC = 18.00 for PD1). This study shows that the window of vulnerability for Pcells to ethanol exposure during development is longer than previously thought.

6.4

Down-Regulation of Serotonin Transporter Binding Sites in MDMA Self-Administrating Rats

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Reductions in markers of serotonin integrity were observed in humans who are heavy users of MDMA (Ecstasy). While these studies suggest that chronic misuse of MDMA may have marked neurotoxic effects, the human data have been questioned because of polydrug abuse and co-morbid psychiatric conditions that limit the validity of observational data from human users. The inherent confounds in human studies of MDMA exposure can be addressed by examining MDMA self-administering rats. Self-administration by rats has predictive validity in terms of identifying factors that contribute to and result from human drug-taking. We report here that serotonin transporter sites are reduced significantly in the brains of rats trained to self-administer MDMA. Rats self-administered MDMA intravenously (1.0 mg/kg/infusion) during 17 daily 2-hr sessions. Total exposure to MDMA averaged 540 mg/kg across the 17 day exposure period. Rats were killed two weeks after the last drug-taking session and radioligand binding assays were performed on membrane homogenates of the frontal cortex, striatum, hippocampus and brainstem. The results demonstrated a significant reduction in the density of serotonin transport sites in MDMA self-administering rats as compared to controls across regions. Autoradiographic localization of serotonin transporters showed a marked reduction in the dorsolateral sectors of the frontal cortex and hippocampus from self-administering rats. Densities of serotonin binding sites labelled with [3H]paroxetine were decreased to a comparable level in tissue from self-administering rats and from rats given experimenter-administered MDMA (10.0 mg/kg at 2 hr intervals for a total of 40.0 mg/kg, IP).These results suggest that MDMA may be neurotoxic to serotonergic system following drug self-administration in rodents.

6.5

5-HT2C Receptor Status Following MDMA Exposure

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National reports suggest that there is an increase in the use of synthetically made recreational drugs such as 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'). MDMA is an amphetamine derivative and therefore induces hyperactivity in a similar manner to other structurally related stimulant drugs. In addition to the acute behavioural effects of the drug, there are reports suggesting neuroanatomical and neurochemical changes to rat and primate brains as a result of MDMA exposure. Such changes include initial serotonin (5-HT) depletion, reduced tryptophan hydroxylase activity and loss of certain serotonergic axons. As a result of altered serotonergic transmission, it has also been reported that there are changes in function and density of various 5-HT receptors. Several serotonin receptors have been implicated in the hyperactivity induced by MDMA. It has been demonstrated that systemic administration of specific 5-HT2C receptor antagonists potentiate the hyperactivity induced by MDMA. This potentiation has been purported to be dose-dependent. The 'potentiation effect' was used to study the status of 5-HT2C receptors in the rat brain following exposure to a neurotoxic MDMA regimen. Rats exposed to MDMA (4 x 10 mg/kg MDMA injections were administered at 2h intervals) underwent activity testing two weeks after the MDMA exposure whereby RS102221 (5-HT2C antagonist) was administered in conjunction with 10mg/kg MDMA. Rats previously exposed to MDMA were supersensitive to the ability of RS102221 to potentiate MDMA-produced hyperactivity.

6.6

The Effects of Chronic Self-Administration of MDMA on Memory Function in Rats

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Although acute administration of MDMA ('ecstasy') produces memory-task deficits, there is debate as to whether chronic exposure produces ongoing memory impairments. The aim of the current study was to investigate the effects of chronic self-administration of MDMA on memory function in rats using a delayed matching-to-sample (DMTS) task. Rats were pre-trained to perform the DMTS task prior to a period of being trained to self-administer MDMA or acting as yoked saline controls. The effects (in terms of delay-dependent and delay-independent aspects of task performance) were assessed at various intervals subsequent to the rats being returned to the original DMTS task. The implications for understanding the neurotoxic effects of chronic MDMA exposure on memory-task performance will be discussed.

6.7

Influence of Drug-Associated Stimuli on MDMA Self-Administration

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A number of studies have suggested that exposure to stimuli associated with self-administered drugs of abuse may contribute to relapse. The influence of conditioned stimuli on the maintenance of self-administration of MDMA (ecstasy) has not, however, been systematically investigated. This study was designed to determine whether omission of a stimulus that had been paired with self-administered MDMA would influence the maintenance of self-administration. During self-administration training, self-administered MDMA infusions were always paired with the illumination of a light. On test days, self-administered MDMA was delivered either with or without the MDMA-associated cue. Data will be presented to compare the influence of the drug-associated stimulus on self-administration of cocaine and MDMA. These findings will be discussed with respect to the factors that contribute to drug-taking and with respect to the abuse liability of MDMA.

7.1

Unstable or Inaccessible? Investigation of a Two-Dimensional Model of Fluent Aphasia

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Fluent aphasia is a language impairment characterised by word finding difficulties and sometimes problems understanding words. Recent theoretical work suggests that fluent aphasic individuals may vary along two dimensions. First, they may vary as to the *locus* of their deficit, that is, whether the impairment involves semantic (meaning based) or phonological (sound based) processing (Foygel & Dell, 2000). Second, individuals may vary as to the *nature* of their deficit - that is, whether the problem involves a difficulty accessing linguistic representations or an instability in the representations themselves (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997). The present study examines several variables that may distinguish aphasic participants along one or both of the theoretical dimensions. These variables include the nature of the errors produced (sound or meaning based), the types of words that are most difficult (for example, long or short words, common or rare words, and concrete or abstract words), and the presentation modality of the words (auditory or visual presentation). Data obtained from two aphasic participants suggests they both have a similar locus of impairment (phonological), but differ as to the nature of that impairment. This is demonstrated most clearly in: a) their differential sensitivity to modality of presentation, and b) the differences in their error types, most particularly the relative rates of whole word and single sound errors. Data on two additional participants is currently being analysed.

7.2

A Web-Based Program for Comparing Different Ways of Delivering and Evaluating Paired-Associate Learning: Application to Vocabulary Learning in a Foreign Language

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Learning and recall are often studied in the context of paired associate material. This paper presents a web-based program that allows subjects to interact with paired associates online. The system trains the subject on sets, or “lessons”, of paired associates in a cue/response format. After a cue has been displayed the subject is required to enter the appropriate response, using either text-input or multiple-choice. Feedback is given after each choice. The sequence in which items are presented can vary according to a previously designed paradigm, and/or to the particular subject’s ongoing performance. Subsequent retention is measured using a related test program. All of each subject’s activity is logged and is then available to the experimenter via a web interface. The system has been used to study the acquisition of Japanese vocabulary in English speakers with no prior experience of Japanese. A two-way ANOVA indicated that there were significant effects on retention at test of lesson number, and of the algorithms controlling the order and selection of items at acquisition. There was no interaction between these factors. We anticipate that this system will greatly facilitate the study of the many factors influencing learning and memory for various types of material.

7.3

Independent Components of the P600 Help to Identify Specific Features of Syntactic Processing

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The P600, an event-related potential (ERP) evoked by anomalous aspects of sentence structure, is likely to represent a summation of a number of neural processes that unfold at similar latencies post stimulus. Independent component analysis (ICA) provides an elegant way in which to separate out the discrete neural processes that contribute to the P600 potential. Such analyses mean that P600s elicited by different stimuli can be described and compared more precisely in terms of their spatial and temporal dynamics. This represents an advance over simply describing overall differences in latency and scalp distribution. ICA was performed on two different P600 ERPs from two studies. One ERP was collected from sentences where the subject could not form a single syntactically acceptable structure. The other was collected from sentences where the subject could form a syntactically acceptable structure, but where agreement features in that structure were violated. Preliminary results show that several of these independent components from the two ERPs are similar. Comparison of the ICAs that are shared by the two and those which are exclusive to either paradigm can help to distinguish neural processes that underlie general syntactic processing from other processes that are more specific such as identification of agreement features.

7.4

Contrasting Effects of Phonological Priming in Aphasic Word Production

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Two fluent aphasics, IG and GL, performed a phonological priming task in which an auditory prime was repeated, then a target picture was named. The two patients both had "output anomia": they had difficulties naming pictures and finding words during conversation, but were at or near ceiling on lexical comprehension tasks. Despite their superficial similarities, however, IG and GL responded very differently to priming: IG's naming was facilitated (both accuracy and speed) only by begin-related primes (e.g. ferry-feather), whereas GL benefited significantly from end-related primes (e.g. brother-feather) and showed only a non-significant trend towards facilitation with begin-related primes. The results demonstrate that output anomia can exhibit finer fractionations. They are consistent with the notion that word production involves two major stages: lexical selection and phonological encoding. The results also provide further support for a sequential model of phonological encoding.

7.5

Orthographic and Phonological Processing in the Normal and Dyslexic Brain: An fMRI Study

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In individuals with phonological dyslexia, the primary cognitive impairment is thought to involve the inability to represent or recall speech sounds (phonological representations). However, the *neural* basis of these deficits remains unclear. In a follow-up experiment from our earlier fMRI research (19th AWCBR), we used 3 Tesla fMRI during three linguistic tasks to help determine areas of concurrent activation that differ in the dyslexic brain compared to non-impaired readers (n=7). Five cycles of blocks were followed by 30 second rest periods: Block 1 (baseline Letter-Case Decision), Block 2 (Orthographic Decision; e.g., DEAP, Is it a real word or nonword?), Block 3 (Lexical Access; BRANE, Is it a real word or nonword?), Block 4 (Phonological Decoding; e.g., PHOKS, Does it sound like a real word?). As expected, controls showed concentrated activation in left hemisphere language areas and bilateral activation during lexical decision. Although the dyslexic subject showed activation in the same inferior fronto-temporal regions, the activation was maximal in the right parietal (BA 7) and occipital cortex (BA 18), possibly due to compensatory activity. Interestingly, the dyslexic subject also showed maximum activation in the cerebellum during the phonological task, a finding that would not have been predicted based on the temporal processing theory of dyslexia.

7.6

A Quantitative Sentence Production Test in Aphasia

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Aphasia is an acquired language impairment affecting the production and/or comprehension of spoken and written language. Cognitive investigations into aphasia have focused extensively upon the production and comprehension of single words. However, people suffering from aphasia can present with intact single word production, but can experience difficulties when required to produce whole sentences. At present most tests of aphasic sentence production are qualitative only. For example, they involve examining the spontaneous speech of the individual and describing the main presenting factors. The present study set out to construct a quantitative test aimed at providing an objective measure of aphasic sentence production ability. Pictures depicting sentences were constructed and those pictures with an 85% agreement in the 'normal' population (age groups: under 30, 30 – 49, 50 and above) were included and normed in the final set of pictures. This set of pictures was administered to fluent and non-fluent aphasic patients. The results show a quantitative discrimination between the heterogenous forms of the aphasic syndrome, indicating that our test will be a valuable contribution to the area of neuropsychological testing of sentence production in aphasia.

8.1

Revealing GnRH Neuronal Morphology Using Transgenic Mice: Have We Underestimated Their Connectivity?

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Despite the broad literature on substances that apparently regulate GnRH neurons, ultrastructural studies suggest that GnRH soma and proximal dendrites receive relatively few synaptic inputs. However, these techniques are biased towards the analysis of portions of the neuron containing GnRH peptide. Using transgenic GnRH-GFP mice, fluorescing GnRH neurons were identified in 2-300 μm thick coronal brain slices and filled with the small molecular weight and highly diffusable molecule biocytin in whole-cell mode. Cells were subsequently visualized with an avidin-conjugated fluorophore and their morphological characteristics analysed by confocal microscopy. In total, 42 GnRH neurons from 7 adult male and 6 diestrous female mice were examined. Surprisingly, we have found that GnRH neurons possess remarkably long dendritic processes, in some cases extending over 1500 μm distal to the cell body. Dendrites were decorated with numerous dendritic spines (up to 10 spines/10 μm) throughout their length and we estimate that individual GnRH neurons have in excess of 400 spines. As spines are thought to represent only excitatory inputs, total synaptic input will be substantially larger than this. The GnRH soma also exhibited various types of spiny protrusions including 1-3 filapodia, normally only observed in developing neurons, and up to 40 classical spines per cell. In contrast to previous ultrastructural studies demonstrating gender differences in synaptic input, the present study found no sexually dimorphic characteristics of somal or dendritic spine density. Individual GnRH neurons displayed a range of spine densities that did not correlate with their anatomical location or orientation (horizontal verses vertical dendrite extensions). Using a technique in which the full extent of the GnRH neuron can be visualized, we have been able to define a previously unrecognised GnRH morphology of extensive dendritic lengths and abundant somal and dendritic spines. This suggests that GnRH neurons receive extensive synaptic input.

8.2

Direct Membrane Effects of Noradrenaline on the Gonadotropin Releasing Hormone (GnRH) Neurones in GnRH-GFP Transgenic Mice

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Noradrenergic pathways have long been known to regulate the pulsatile release of gonadotrophin secretion from the pituitary gland. How noradrenaline (NA) achieves this is unknown but the simplest mechanism would involved the direct regulation of the gonadotrophin-releasing hormone (GnRH) neurones by NA. Using GnRH-GFP transgenic mice in which the GnRH neurones fluoresce, we have examined here whether NA exerts direct actions upon these cells using gramicidin-perforated patch electrophysiology. Both male and female GnRH neurones were found to be hyperpolarized by bath application of NA (1-100 μM) without desensitization. This was dependent upon intracellular signalling pathways as NA failed to influence GnRH neurones in the whole cell recording mode where cell contents are dialysed with the pipette solution. The hyperpolarizing effects by NA were maintained in the presence of tetrodotoxin (0.5 μM) indicating that they were direct upon the GnRH neurone. We also investigated the adrenergic receptors related these effects on GnRH neurones. The hyperpolarizing effects of NA were blocked by prazosin, the α_1 adrenergic antagonist, and mimicked by phenylephrine, an α_1 adrenergic agonist. However, isoproterenol, a β adrenergic agonist, also induced hyperpolariztion of the GnRH neurones. These data demonstrate that NA acts directly upon GnRH neurones through both α_1 and β receptors and suggest the mechanism through which the brainstem NAergic pathways regulate gonadotrophin secretion.

8.3

Rapid Estrogen Actions upon GnRH Neurons

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Gonadal steroids exert potent modulatory actions upon multiple neuronal networks. In addition to classical genomic mechanisms of action, estrogen also has poorly understood rapid, non-genomic effects on neurones. We have examined whether the gonadotropin-releasing hormone (GnRH) neurones, that regulate fertility, are also influenced by estrogen in a non-genomic manner. Using GnRH-GFP transgenic mice we undertook gramicidin perforated-patch recordings of GnRH neurones in the acute brain slice preparation. Estrogen rapidly depolarized approximately 40% of GnRH neurones. To evaluate rapid estrogen actions *in vivo*, ovariectomised, wild-type mice were given estrogen and the phosphorylation of CREB examined in GnRH neurones using immunocytochemistry. An increase in CREB phosphorylation within GnRH neurones was observed 15 min following estrogen administration and found to be both time- and dose-dependent. Studies in estrogen receptor (ER) knockout mice were undertaken to evaluate the role of classical ERs. Whereas ERα knockout mice displayed a normal response, estrogen was unable to phosphorylate CREB in GnRH neurones in the ERβ knockout mouse. A final series of *in vitro* experiments demonstrated that estrogen acted directly upon GnRH neurones to rapidly phosphorylate CREB and that estrogen must pass through the cell membrane to achieve this effect. Together, these experiments demonstrate that estrogen rapidly alters GnRH neuron membrane excitability and intracellular signalling. This latter action appears to require a novel cytoplasmic interaction between estrogen-ERβ.

8.4

The Effects of Cortical Spreading Depression on Striatal Spiny Projection Neuron Activity

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A transient depression of cortical neuronal activity can be induced by the application of potassium chloride (KCl) onto the brain surface. This depression passes from neuron to neuron in a wave-like fashion and is termed spreading depression (SD). It has been reported that some SD waves are transmitted to subcortical nuclei, including the striatum, which receives vast cortical innervation, terminating at the level of the spiny projection neuron. The aim of the study was to determine the effect of cortical SD on the activity of the striatal spiny projection neurons, as measured intracellularly in anaesthetised animals. The response to cortical SD (induced with 3M KCl) was recorded in nine spiny projection neurons displaying a down state potential of at least -60 mV. Three neurons showed large transient depolarisations within 12 $\pm$ 3.9 mins of SD induction. The other six neurons showed varying degrees of response to SD induction. Typical responses included smaller depolarisations (<20 mV), often followed by hyperpolarisation, a decreased amplitude of the UP/DOWN state transitions and the loss of action potential firing. These results show that cortical SD can have significant effects on striatal spiny projection neuron activity. This must be taken into consideration when measuring striatal synaptic responses and cellular properties after the induction of SD.

8.5

Noradrenaline Transporter: Visualisation Using Green Fluorescent Protein

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The noradrenaline transporter (NAT) is responsible for the removal of noradrenaline from the synapse following release by sympathetic neurons. It thus plays a vital role in monoamine neurotransmission in both the central and peripheral nervous system. The NAT is inhibited by antidepressants and psychostimulants (cocaine, amphetamines). The NAT may be dysregulated in affective disorders such as depression and ADHD. Recently the NAT has been shown to be regulated by alterations in its distribution between plasma membrane and intracellular pools. To study intracellular trafficking we have fused NAT to enhanced-green fluorescent protein (EGFP-NAT) and expressed the transporter in model cell lines. Expression of EGFP-NAT gave similar levels of noradrenaline uptake to the wild-type transporter. The transporter has been localised by fluorescence in epithelial and neuronal cell lines. We present results using EGFP-labelled transporter demonstrating the importance of the C-terminus of the NAT for targeting to neurite tips (equivalent to axon terminals) in PC12 cells. We have also used EGFP-NAT to investigate the effect of alterations to this region on protein stability and intracellular trafficking. EGFP-NAT will prove valuable for further studies of the localisation, internalisation and recycling of the transporter, as well as studies of transporter oligomerisation and the interaction of NAT with other proteins. This research may yield insight into the mechanism of control of noradrenergic signalling, and how this mechanism is disrupted in pathological states.

8.6

AAV-Mediated Neuroserpin Expression in Dorsal Root Ganglion Cell Cultures

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Neuroserpin, a member of the serine protease inhibitor (serpin) family, is expressed in most brain regions. However, the physiological role(s) of neuroserpin is still unclear. The most likely inhibitory target for neuroserpin is the enzyme tissue plasminogen activator (tPA) which is involved in synapse formation, neuronal plasticity and neuronal death.Previous *in vitro* studies from our group show that neuroserpin can alter neurite outgrowth in AtT20 [Hill et al. 2000. *Biochem J*, 345: 595-601] and PC12 [Parmar et al. 2002. *J Neurochem*, 82: 1406-1415] cell lines. To extend these studies, we are investigating the role of neuroserpin in nerve cell regeneration using primary dorsal root ganglion cultures. As neurons are generally refractory to common transfection procedures, we have used recombinant adeno-associated viral vectors (AAV) to mediate gene transfer. The effectiveness of AAV transduction has been studied in PC12 and HEK-293 cells with different AAV serotypes. The study showed that different cells types respond differently to different AAV serotypes and the level of transduction varied. Transduction of DRG cell cultures with AAV-GFP showed GFP expression in both glial and neuronal cells. Assessment of transduction with different serotypes is ongoing. Once optimal transduction of DRG neurons has been achieved, the effect of neuroserpin expression on DRG cultures will be investigated.

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8.7

Cannabinoid CB1 Receptor Protein Expression in the Rat Hippocampus and Entorhinal, Perirhinal, Postrhinal and Temporal Cortices: Regional Variations and Age-Related Changes

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Cannabinoids have been shown to disrupt memory processes and these effects occur primarily through cannabinoid CB1 receptors in the brain. The present study investigates, for the first time, the regional variations and age-related changes in CB1 protein expression in the hippocampus and its neighbouring entorhinal, perirhinal, postrhinal and temporal cortices using Western blotting. In young adult rats, CB1 protein was highly expressed in the hippocampus and within the hippocampus, the greatest density of CB1 protein was located in CA1. When a comparison was made between young (4-month-old) and aged (24-month-old) rats, CB1 protein expression was significantly increased in the aged entorhinal and temporal cortices and was significantly decreased in the aged postrhinal cortex. The present study demonstrates region-specific changes in CB1 protein expression during ageing and further suggests that cannabinoid CB1 receptors may contribute to the aging process.

8.8

Mitochondria Respiratory Chain Activity in the Vestibular Nucleus and Cerebellum

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Neural mitochondria, (i) produce ATP for general cell function and to maintain membrane potentials, (ii) regulate cellular [Ca^{2+}] and, therefore, regulate the release of neurotransmitters at the synapse and modulate axon membrane excitability, and (iii) regulate cell death and survival pathways. Therefore, mitochondria have a primary role both in neural plasticity and in various neural pathologies. Since most work on mitochondria-related neural disorders has been in studies on the fore- and midbrains, mitochondria in the hindbrain have received little attention. We isolated mitochondria from the vestibular nucleus complex (VNC) in the brainstem and from the caudal cerebellum and characterised respiratory chain activity by measuring oxygen consumption during oxidative phosphorylation and by measuring mitochondria respiratory enzyme complex activity. Our results are comparable to measurements taken from mitochondria isolated from hippocampus, both from our own work and from previously published studies. However, the VNC is considerably smaller than previously studied brain regions, including the hippocampus. To obtain an adequate volume of mitochondria we pooled tissue from 10 rats for each assay. This is problematic for experimental and ethical reasons. In addition, mitochondrial respiratory chain activity is highly sensitive to hypoxia, and lengthy dissection procedures can increase the duration of ischaemia in dissected tissue. Therefore, increased enrichment of brain mitochondrial isolates is required in order for experiments on brain regions of similar size to the VNC.

Gene Expression of Glutamic Acid Decarboxylase, GABA Receptor Subunits and the GABA Transporter in the Vestibular Nucleus and Cerebellar Flocculus of the Rat: Effects of Unilateral Labyrinthectomy

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The spontaneous recovery of ocular motor and postural function following a peripheral vestibular lesion is known as vestibular compensation, a useful model of CNS plasticity. To elucidate the role of the GABAergic neuronal system in vestibular compensation, we investigated the effects of unilateral labyrinthectomy (UL) on changes in the mRNA expression of GABA-related molecules in the vestibular nucleus complex (VNC) and cerebellar flocculus of the rat using a real-time quantitative RT-PCR method. The expression of genes encoding the GABA synthesizing enzymes GAD65 and GAD67, the $GABA_A$ receptor $\alpha 1$ subunit, the $GABA_B$ R1 subunit, and the neuronal GABA transporter GAT1, could be detected in the VNC. $GABA_A$ $\alpha 1$ and $GABA_B$ R1 subunit mRNA were upregulated in the ipsilateral VNC at 6 hs post-UL but decreased in expression thereafter. However, both GAD65 and GAD67 mRNA were upregulated in the bilateral VNC at 50 hs after the UL. In the flocculus, GAD65 mRNA expression (but not GAD67 mRNA expression) was bilaterally upregulated at 50 hs after the UL. GAT1 mRNA expression was initially upregulated in the ipsilateral VNC following UL and then underwent a bilateral increase. Although it remains to be seen whether these changes in gene expression reflect changes in protein expression, it is possible that the increase in GAD 65 and GAD67 mRNA expression could reflect an increase in GABA synthesis and release in the ipsilateral VNC during the development of vestibular compensation. The increase in the expression of GAT1 mRNA in the ipsilateral VNC may, in turn, be a response to the need for increased reuptake of GABA. One possibility is that once resting activity has been restored in the ipsilateral VNC through increased intrinsic excitability, increased tonic inhibition of ipsilateral VNC neurons by the contralateral VNC and the flocculus could increase the dynamic response of the type I VNC neurons to horizontal head rotation through disinhibition. Such a process would contribute to the restoration of type I responses in the ipsilateral VNC of the compensated animal.

A Test of the Right Hemisphere Dysfunction Theory of Attention Deficit Hyperactivity Disorder

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Normal right-handed adults tend to bisect horizontal lines to the left of the objective centre, a phenomenon labelled ‘pseudoneglect’. This is thought to reflect the right hemisphere’s ability to direct attention to both sides of contralateral space. Previous research has found that children (ages 10 to 12 years) show a slight rightward bias, suggesting that developmental maturation of the corpus callosum occurs during this period (Hausmann, Waldie, & Corballis, 2003, *Neuropsychology, 17*, 155-160). In contrast, individuals with attention deficit hyperactivity disorder (ADHD) may not show the same rightward to leftward shift in bias as they mature, possibly due to a chronic disturbance in the right frontal lobe network (Sheppard, Bradshaw, Mattingley, & Lee, 1999, *JNNP, 66(1)*, 57-63). In the present study, ten ADHD children ages 7 to 12 years performed two line bisection tasks: a manual version and a computerised version (which requires less motor activity - the computer mouse is used to bisect lines). As predicted, children with ADHD demonstrated a significant rightward bias during manual line bisection. Of particular interest was the finding that the rightward bias was slightly reduced during the computerised version. This suggests that visuo-motor integration is an important component of manual line bisection performance and has implications for the right hemisphere dysfunction theory of ADHD.

9.2

Turn That Frown Upside Down: Effects of Thatcherisation on ERP Responses to Rotated Faces

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The "Thatcher illusion" is the phenomenon whereby a face whose eyes and mouth have been inverted appears grotesque in an upright orientation, but normal in an inverted position. The normal appearance of inverted thatcherised faces has been attributed to a decrease in configural and an increase in feature-based processing with face inversion. An outstanding issue is whether the decrease in configural processing and an increase in featural processing is a continuous process or reflects two distinct processing systems. We investigated the effect of thatcherisation on ERPs to thatcherised and normal faces at varying orientations. The ERPs paralleled the perceptual illusion, with large effects of thatcherisation for upright faces but no significant effects when the faces were presented upside-down. The effect of thatcherisation on upright faces was apparent in early visual (P1) and face-specific (N170) ERP components, reflecting attentional engagement due to unpleasantness of thatcherised faces. The effect of thatcherisation was also evident over two later components: the P250 component, which has been related to recognition mechanisms engaged by varying configurations within individual faces; and a late parietal component which may reflect task-specific demands dependent on featural processing. The effect of thatcherisation on the P250 and late parietal components decreased as the faces were rotated in 60-degree steps away from the upright. This decrease was gradual for the P250 component, but stepwise for the late parietal component.

9.3

The Neural Response to Sub-Threshold Stimuli

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Although the effect of the presentation of sub-threshold stimuli on subsequent behaviour has been the frequent focus of research, an understanding of the underlying neural response during the actual presentation of these stimuli has proved more elusive. A recent study (Dehaene et al., 2001, *Nature Neuroscience, 4*, 752-758) did successfully find activation to the sub-threshold presentation of words. The present study employs this paradigm to further understand the quantitative and qualitative distinctions between sub/supra-threshold evoked responses. Specifically, this study addresses whether the imaged neural response attained by Dehaene was a reflection of the extraction of the word's abstract identity, as was evidenced by his behavioural measures, or the result of lower level processing.

9.4

Traumatic Brain Injury Rehabilitation Outcomes Across Cultures

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Evidence suggests that there is an over-representation of Maori and Pacific Peoples sustaining traumatic brain injury (TBI) in proportion to their populations in New Zealand compared to Pakeha. However, research efforts investigating rehabilitation outcomes have failed to take into account the multi-cultural make-up of TBI individuals unique to New Zealand. This study is an exploratory investigation aimed at identifying how Maori and Pacific people experience post-acute community rehabilitation following mild to moderate TBI, whether outcomes differ across Maori, Pacific and Pakeha cultures, and to identify any service delivery needs that may be distinct from Pakeha. Thirty-three participants (11 Maori, 11 Pacific and 11 Pakeha) and a selected family member partook in an interview which included the Neurobehavioural Cognitive Status Examination (Cognistat), the Brain Injury Community Rehabilitation Outcome Scales (BICRO-39 Scales), the Beck Depression Inventory-II (BDI-II), the Impact of Event Scales-Revised (IES-R), the Client Satisfaction Questionnaire (CSQ-31), and a semi-structured interview. Results indicated that all participants were at a similar level of general cognitive functioning. Level of handicap increased following TBI and decreased following rehabilitation, with no difference across cultures, and suggesting effectiveness of rehabilitation. Forty-two percent of the sample were clinically depressed (half of whom were Pakeha), and 24% of the sample showed mild signs of post-traumatic stress (almost all of whom were Maori or Pacific). Ninety-seven percent of the sample were generally satisfied with their rehabilitation service. Implications of universalities and differences across cultures will be discussed.

9.5

Implicit and Explicit Memory in Schizophrenia

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This research investigated whether the core memory deficit in schizophrenia is better characterised by the implicit/explicit retrieval distinction or the perceptual/conceptual processing distinction. Priming was measured across three experiments using a range of implicit and explicit memory tasks that relied on perceptual or conceptual processing. A read–generate manipulation was employed to operationally define tasks as perceptual or conceptual. Experiment one compared people with schizophrenia and controls on the implicit word fragment completion task (perceptual), and the explicit semantic cued recall task (conceptual). People with schizophrenia displayed intact priming on the implicit perceptual task and were impaired on the explicit conceptual task. Experiment two compared people with schizophrenia and controls on the implicit category association task (conceptual) and the explicit word stem cued recall task (perceptual). People with schizophrenia were impaired on both the implicit conceptual task and the explicit perceptual task. Experiment three explored this finding further by comparing people with schizophrenia and controls on implicit and explicit versions of the word fragment and semantic tasks that adhered to the retrieval intentionality criterion. Priming in people with schizophrenia was intact on the implicit perceptual, implicit conceptual and the explicit perceptual tasks, while priming was impaired on the explicit conceptual task. Despite the inconsistency in results between Experiment two and Experiment three, the findings indicate that dissociations among memory tasks in this clinical population may be better explained in terms of various memory systems rather than by a processing framework of memory.

9.6

Everyday Action Performance in Mild to Moderate Alzheimer's Disease: A Single-Case Examination

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In clinical settings, such as rehabilitation centres, it is frequently argued that people with Alzheimer's dementia (AD) perform routine everyday tasks more effectively in their home environment than in the clinical environment. The current study examined the performance of everyday tasks by four people with mild to moderate AD (MMSE >18). A set of everyday tasks were assessed using a protocol developed by Schwartz and colleagues. Performance of the everyday tasks was examined in the participants' homes under both experimental conditions manipulating working memory demands (dual-task, distraction) and under naturalistic conditions. Neuropsychological test performance was also obtained. Results are examined in terms of the relationships between novelty and complexity of a task, subsequent task performance and neuropsychological test performance. The relevance of these findings to clinical settings is discussed, as is the theoretical basis of everyday action performance.

9.7

Styrene Exposure in the Boat Building Industry: Neuropsychological and Neurophysiological Effects

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New Zealand's internationally renowned boat building industry commonly utilises plastic composites comprising the organic solvent styrene. Prolonged or excessive exposure to organic solvents has been linked to Organic Solvent Neurotoxicity (OSN). OSN symptoms include mood changes, fatigue, and concentration, learning and memory problems that may be irreversible. Previous studies have measured behavioural and cognitive changes in solvent-exposed workers using neuropsychological tests, and EEG studies have reported longer latency and/or smaller amplitude P300 event-related potentials. This pilot study found a high prevalence of solvent-related symptoms in twenty-nine styrene-based boat builders. Six boat builders and seven control subjects underwent neuropsychological tests and an auditory "oddball" test designed to elicit the P300, on four occasions at monthly intervals. An ABAB design was used, with condition A being a morning non-exposed session for both groups, and condition B being an afternoon session following styrene exposure for the boat builders. Urine analysis indicated styrene exposure was generally low. The boat builders performed significantly more poorly on three neuropsychological tests across both conditions. P300 latency differentiated both groups and conditions, however. Both groups showed longer latencies and smaller amplitudes in condition B, but latency was significantly more prolonged in the styrene-exposed men. This finding suggests further research may be warranted to ensure that current exposures do not pose a health risk to workers.

Mental Rotation and Cognitive Action Representation an EEG Study

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Research into image transformations using mental rotation has, in general, focused upon simple stimuli that do not possess action representation content. Our work seeks to extend such traditional research through a synergistic approach, combining a traditional mental rotation paradigm (Shepard, R.N., & Metzler, J. 1971, *Science*, Mental rotation of three-dimensional objects., 171 (972), 701-703) and three representationally disparate stimuli (1 - a flat hand, 2 - a hand grasping a small object and 3 - a hand making an identical grasping motion to 2 but without the object). High-density Event-Related Potentials (ERPs) were collected from twelve neurologically normal, right-handed males while they performed a left/right judgement upon randomly ordered rotated images of the three stimuli (0°, 60°, 120°, 180°, 240° and 300°). Reaction time results replicated those of previous authors (for review see Kosslyn, S.M, 1980, *Image and Mind*. Cambridge, MA: Harvard University Press) and support the notion that subjects were actually performing a mental rotation of the images. Differences, however, were observed between the two non-object stimuli (flat and empty grasp) and the object grasp stimuli. The object grasp stimuli demonstrated an increased negativity with a latency of 260ms and a spatial location lateralised to the left anterior occipital/posterior temporal areas. These preliminary findings add support to the growing body of evidence for the involvement of occipital/temporal regions in the processing of cognitive action representation.

Apoptotic Cell Death in the Developing Granular Layer and White Matter of the Rat Cerebellum Following a Single Ethanol Exposure on Postnatal Day 4: A TEM Study

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Binge ethanol exposure during the brain growth spurt results in a permanent deficit of granule cells in the mature rat cerebellum. Altered proliferation and cell death consequent to postsynaptic target loss are thought to contribute to the granule cell deficit. This study investigated the role of acute cell death in the internal granular layer (IGL) and developing white matter (DWM) following brief exposure to ethanol on postnatal day 4 (PN4). On PN4 Sprague-Dawley rat pups were assigned to the ethanol exposure group (4.5 g/kg/day ethanol) or the control group (sham intubation). Animals were killed from 1hr to 30hrs post ethanol delivery. Semi-thin sections, 1 µm thick, from cerebellar vermal lobule IX were analysed for the presence of pyknotic nuclei and a pyknotic index (PI) assigned. Pyknotic nuclei, indicating cell death, were seen infrequently in control animals at all time points (PI:0-7.9) Exposure to ethanol increased the pyknotic index: significant cell death was detected at 4 hrs (PI:23.4), with a peak at 10 hrs (PI:81.1), returning to control levels at 21 hrs (PI:4.7). TEM analysis revealed that the degenerating cells exhibited the morphological features of apoptosis. These data indicate that developing cells in the IGL and DWM are vulnerable to the direct toxic effects of ethanol. Cell death is initiated soon after ethanol exposure and occurs via apoptosis.

10.2

Apoptosis in Mouse Gastrulation Embryos: The Effects of Blood Ethanol Concentration on Cell Death Following a Single Ethanol Exposure

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A single intraperitoneal injection of ethanol during gastrulation results in extensive cell death in the embryo (Dunty et al., 2002). This study was undertaken to evaluate the acute effects of binge ethanol exposure, via gavage, on the ectoderm of the gastrulation embryo. Timed pregnant mice (C57BL/6J) were divided into three groups. On gestational day (GD7.5), dams were gavaged with 4.5, or 6.5 g/kg ethanol (20% v/v). Control animals received an equivalent volume (to 6.5 g/kg ethanol group) of 0.9% NaCl. Dams were killed by cervical dislocation 10 hrs after ethanol delivery. Small lengths of uterus, containing an embryo implantation site, were removed and fixed in 4% paraformaldehyde. Cell death was examined using TUNEL staining on 5 um thick wax sections. Section location within the embryo was matched between embryos. The pyknotic index (PI) for the ectoderm of each embryo was determined from the number of TUNEL(+) nuclei per 100 epithelial nuclei in the ectodermal layer. The 4.5 g/kg and 6.5 g/kg ethanol doses resulted in peak BACs of 314.68 ± 20.87 mg/dl and 583.01 ± 25.81 mg/dl respectively. The PI for intubation controls was 2.14 ± 0.08. The 6.5 g/kg ethanol group showed a significant increase in cell death (PI: 9.38 ± 2.07, $P<0.05$). However, the 4.5 g/kg ethanol group there was no significant increase in cell death (PI: 3.55 ± 0.4). Ethanol exposure on G7.5 results in an increased cell death that appears to be dose-dependent. These results confirm that ethanol exposure during gastrulation, when a women may not realize that she is pregnant, causes cell death in the developing ectodermal layer. This may result in altered brain development and permanent brain damage.

10.3

Progressive Ratio as a Measure of the Relative Reinforcing Effectiveness of MDMA ('ecstasy') and Cocaine

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We have recently reported reliable self-administration of MDMA (ecstasy) in laboratory rats. MDMA supported robust, dose-dependent self-administration, extinguished when saline was substituted for the drug and was reinstated when MDMA was again available. MDMA self-administration compared favourably to results we have previously obtained for cocaine self-administration and efficacy and potency of the two drugs in reinforcing operant behaviour was similar. In the present study a progressive ratio procedure was used in order to compare reinforcement strength and incentive to self-administer the two drugs. Within each self-administration session, the number of responses required to obtain an infusion of either cocaine or MDMA (ratio) was progressively increased. The session terminated when the ratio failed to maintain responding. This ratio, termed the break point was obtained for self-administration of the two drugs. The data will be discussed with respect to comparative abuse liability of cocaine and MDMA.

10.4

Effects of Exposure to Neurotoxic Doses of MDMA on the Behavioural Response to the Serotonin 2C Agonist, *m*-CPP

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3,4 – Methylenedioxymethamphetamine (MDMA; 'ecstasy') is an increasingly popular drug of abuse. There is a wealth of evidence that administration of MDMA results in neurotoxicity. Specifically, MDMA has been shown to significantly decrease regional brain 5-HT content and to produce 5-HT nerve terminal degeneration. Recently, it was reported that exposure to MDMA might also decrease the density of 5HT2C receptors. In the present study, the functional status of 5HT2C receptors in MDMA-exposed and control rats was compared by examining effects of selective drugs on locomotor activity. In control rats, MDMA (20.0 mg/kg, ip)-produced hyperactivity was potentiated by pre-treatment with selective 5HT2C antagonists whereas pre-treatment with the 5HT2C agonist, *m*-CPP, produced hypolocomotion. In order to determine whether MDMA preexposure altered these effects, rats were injected with MDMA (4 x 10mg/kg MDMA at 2 hr intervals) or the saline vehicle 2 weeks prior to behavioural tests. We have previously shown that this exposure regimen is neurotoxic to serotonin systems. On the test day, the potency and efficacy of *m*-CPP in producing hypolocomotion was determined and compared for the 2 groups. Results will be discussed in terms of the behavioural and neurochemical consequences of MDMA exposure.

10.5

The Effects of Stimulant Medication on the Cognitive Processes of Children with ADHD

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Children with Attention-Deficit Hyperactivity Disorder commonly experience deficits in cognitive processes that are associated with particular neurological structures. This study examines the magnitude and clinical significance of stimulant medication effects on these processes in 25 ADHD children using the Cognitive Attention System (CAS) and the Test of Everyday Attention for Children (TEA-Ch). The CAS is based on the neuropsychological work of Luria (1966, 1973, 1980) and includes tests of planning, attention, simultaneous and successive processing, which he conceptualised as interdependent and related to identifiable neurological areas. The TEA-Ch is based on Mirsky's (1991) model of distinct attentional functions that are associated with specific cerebral regions and includes tests of focused, sustained, shifting and divided attention. Results were contrasted with a normal control sample. On the CAS, ADHD children performed significantly worse than controls on measures of planning, attention and simultaneous processing. Stimulant medication effects failed to reach statistical significance for any measures of PASS processing. However an examination of the clinical significance of effects indicated that 88% of children exhibited normalised overall cognitive functioning when treated with stimulant medication. On the TEA-Ch, ADHD children showed deficits in sustained, shifting and divided attention, evidencing statistically significant improvement on measures of sustained and shifting attention with medication. These findings suggest that these neuropsychological models of cognitive and attentional functioning may provide a useful perspective in the conceptualisation of deficits associated with ADHD and for examining medication response.

11.1

Age-Related Changes in Glucocorticoid Receptor Protein Expression in the Rat Hippocampus and Parahippocampal Region

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Glucocorticoids are involved in the regulation of central nervous system function. The hippocampus and the adjacent entorhinal, perirhinal and parahippocampal (postrhinal in rodents) cortices are critical for normal learning and memory. It has been shown that hippocampal glucocorticoid receptors (GRs) play an important role in age-related cognitive decline. At the present time, however, there is limited information about whether there are age-associated changes in GRs in the parahippocampal region and there are no previous studies on age-related changes in GR protein expression in the sub-regions of the hippocampus using the Western blot technique. In the present study, we investigated GR protein expression in the dorsal and ventral hippocampus, and the entorhinal, perirhinal, postrhinal and temporal cortices, as well as the CA1, CA2/3 and dentate gyrus (DG) in aged (24 months old) and young adult (4 months old) rats. Overall, there were no age-related changes in GR protein levels in the dorsal and ventral hippocampus and the entorhinal, perirhinal, postrhinal and temporal cortices. GR protein levels were, however, significantly decreased in the aged CA2/3 and increased in the aged DG subregions of the hippocampus. The present study demonstrates that region-specific changes in GR protein expression occur during aging and provides further evidence for a contribution of glucocorticoid receptors to the aging process. An investigation of how these changes correlate with age-related learning and memory impairments is currently underway.

11.2

Preclinical Neuropathology in Ovine Batten Disease

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The neuronal ceroid lipofuscinoses, (NCLs, Batten disease) are fatal inherited human neurodegenerative diseases characterised by massive brain atrophy and the accumulation of fluorescent organelles in most cells throughout the body. These were thought to be the product of accelerated lipid peroxidation, similar to the normal age pigment lipofuscin and an "accelerated aging" scenario was advanced. Batten disease also occurs in animals and much has been found from the study of a flock of affected sheep. Biochemical studies revealed that the stored cytosomes result from the specific lysosomal accumulation of a protein, subunit c of mitochondrial ATP synthase, not lipid peroxidation, but the relationship between subunit c storage and neurodegeneration is not understood. Cells from foetal sheep brains have been cultured for an *in vitro* disease model. Cultures from 60-day foetuses were mainly neurons with a range of morphologies, GABA and glutamate immunostaining, and calcium binding protein distribution. Cultures from older brains contained fewer neurons but they were more complex. Subunit c accumulation was observed in non-astrocytic glial cells. A parallel study of preclinical *in situ* pathological changes revealed region-specific pathological changes at 12 days, including storage body accumulation, immunostaining for astroglial and microglial activation, and activation of perivascular macrophages in white matter. This early activation of microglia *in vivo* and in culture suggests that glial cells may be important in pathogenesis.

11.3

AMPA/Kainate Receptor Ligands Reduce Constitutive GTPase Activity in Young but not Aged Hippocampus

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Brief exposure to either kainic acid (KA) or domoic acid (DOM) induces a lasting tolerance to these excitotoxins in young, but not aged hippocampus. To determine whether G-protein coupled receptors (GPCRs) play a role in tolerance induction, high affinity GTPase activity was assessed using hippocampal membrane preparations from young (2-3 month old) and aged (26-29 month old) SD rats. Basal GTPase activity and GTPase stimulation by the positive control baclofen did not differ between groups. However, KA and DOM significantly reduced GTPase activity in young, but not aged samples. The selective KA receptor agonists ATPA and SYM-2081 also reduced constitutive GTPase activity in young samples, as did the AMPA/KA antagonists CNQX, NBQX, NS-102, GYKI52466 and GAMS, and the mGluR receptor antagonists AIDA and CPPG. In aged hippocampus, comparable reductions in GTPase activity were only seen in the presence of NS-102, AIDA, GYKI52466 and GAMS. The AMPA-selective agonist FW, which does not induce tolerance, had no effect on young samples and only slightly reduced constitutive GTPase activity in aged samples. These findings suggest that tolerance to excitotoxins in young hippocampus is mediated via a reduction in the constitutive activity of GPCRs, and this neuroprotective mechanism is lost in aged brain.

11.4

Identification of a Role for the Intracellular Serine Protease Inhibitor raPIT5a in Apoptosis/Necrosis

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The *ser*ine *p*rotease *in*hibitors (serpins) are a diverse and abundant protein superfamily fundamental to the maintenance of proteolytic homeostasis in virtually all living systems. While the extracellular roles of this highly influential class of protease inhibitors are well defined, few physiological targets or functions have been identified for intracellular serpins. Our laboratory has cloned a member of this subfamily, termed raPIT5a. Analysis of mRNA expression in adult rat brain indicated low level expression of raPIT5a transcripts in a number of brain regions. raPIT5a can form a stable inhibitory complex with the serine protease granzyme B suggesting a role in regulating neuronal cell survival. PC12 cell lines overexpressing raPIT5a showed increased cell viability following insult with the neurotoxin 6-hydroxydopamine and the reactive oxygen species hydrogen peroxide. Expression of raPIT5a protein was increased following severe hypoxic-ischaemic injury in a well established rat brain model. These results support a role for raPIT5a as a regulator of cell death in nerve and endocrine cells.

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11.5

Spatial, Visual and Verbal Working Memory in Older Adults: Changes with Age

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Working memory is known to lose capacity with increasing age. Little, however, is known of whether different types of working memory change at the same rate. Sixty-two individuals, 18 men and 44 women, aged between 18 and 57 years (M = 38.34; SD = 12.26) completed a listening span version of Daneman and Carpenter's (1980) reading span task, a dot memory task, and an irregular polygon with articulatory suppression task in a study designed to examine whether performance on spatial and visual memory tasks would decline as a function of chronological age, whether performance would decline to a greater or less extent than found in verbal memory, and whether verbal, visual, and spatial memory could be measured as separate memory representations. The results indicated that there was a significant negative relationship between age and verbal memory, and age and spatial memory. The relationship between age and visual memory, although negative, was not significant at the $p<0.05$ level. A test for the equality of correlations for dependent samples (Cohen & Cohen, 1983) showed significant differences among the correlations between age and verbal, visual and spatial memory, with age correlating with verbal memory to a greater extent than to either of the other memory systems. Correlations between verbal, visual and spatial memory task scores were all non-significant and below 0.25, therefore each memory task appeared to be tapping a distinct type of memory.

11.6

Normative Cognitive Test Scores and Factors Influencing Memory in Post-Menopausal Australian Women

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Normative cognitive test values for the ageing, Australian-born population is not readily available, as most data is derived from the North American population. The effect of declining hormone levels on memory in post-menopausal women is also poorly understood. Women (n=257) aged 56-67 years (mean= 60), who are part of the Melbourne Women's Midlife Longitudinal Health Project were administered a battery of 14 neuropsychological tests. Tasks included three verbal memory measures; (a shortened version of the California Verbal Learning Test II, a 10-item supraspan word list, and the East Boston Memory Test); and one non-verbal memory measure (the Faces subtest of the WMS-III). Education was significantly related to memory performance, and there was a non-significant trend for test scores to decline with age. Self-rated mood was unrelated to test performance. Mean scores were stratified by education (less than 12 years, 12 or more years) and age (56-59, 60-67 years). Women who reported memory problems or hot flushes did not perform differently on word lists. Scaled normative data were constructed for the CVLT, recognition of Faces, Verbal Fluency, The Boston Naming Test and Block Design. These population-based normative data will facilitate future investigations of effects of ageing, hormones and dementia in Australian women.