1.1

Lateralisation of Cognitive Processing in Response to Low- and High-Spatial Frequency Visual Stimuli

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Under the global-precedence hypothesis (Navon, 1977) global and local features of visual stimuli are processed independently, with processing of global features preceding that of local features. Furthermore, there is a functional lateralisation of global and local processing, with global-processing preferentially occurring in the right hemisphere and local-level processing in the left hemisphere (e.g. Fink *et al.*, 1996; Han *et al.*, 2002; Yamaguchi *et al.*, 2000). However, it has also been suggested that the brain does not differentially process local and global information *per se*, rather that each hemisphere is specialised for processing different relative *frequencies* of visual information (Sergent, 1982), with the right hemisphere specialised for processing the lower-frequency information within a visual scene and the left hemisphere for higher-frequency information. The differences observed between local and global features merely reflect the fact that local information is typically carried at high spatial frequencies while global information is carried at low spatial frequencies. Using high-density 128-channel electroencephalography, the present study examined both the temporal sequence and the lateralisation of low- and high-frequency visual processing by presenting sine- and square-gratings to subjects and asking them to make either a sharp/fuzzy (high frequency) distinction or a thick/thin (low frequency) distinction. The aim was to determine whether cognitive processing of low- and high-frequency visual information is lateralised in the human brain.

1.2

Brain Event-Related Potentials Reflect Individual Differences in Interrogative Suggestibility

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Interrogative suggestibility (IS) refers to the tendency, under interrogation, to yield to leading questions (Yield), and to shift one's responses under pressure (Shift). Suggestible individuals are prone to confess to crimes they have not committed. Brain ERPs were measured in high- and low-suggestible groups of individuals while they underwent a well-established protocol for measuring individual differences in IS. Brain ERPs elicited by pictures that were either relevant, or irrelevant, to the story used in the protocol, showed significant differences between groups identified as high and low suggestible, either in terms of Yield, or a measure of false recognition that correlated with it. These ERP differences, which emerged at latencies greater than 211 ms, help to shed light on possible neurocognitive substrates of IS, and have important implications for the forensic assessment of suggestible individuals in cases involving possible false confessions.

1.3

Asymmetrical Visual Field Effects in Redundancy Gain and in Priming of Mirrored Images

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A redundancy gain occurs when two identical copies of an image are processed faster than a single copy. This is often reported when one copy is presented to either visual field (i.e. to either hemisphere), indicating that the two hemispheres cooperate with one other, rather than inhibit one other. This gain from identical image copies could not be based on visual-spatial homotopic connectivity between the two hemispheres. The current results find only asymmetric patterns of such redundancy gain: where images presented only to the left visual field (LVF) enhance priming during subsequent presentations to both visual fields. In contrast, images presented initially to the right visual field (RVF) enhance priming by a single, left-right mirrored copy presented to the other (left) visual field. Such facilitation is created by visual-spatial homotopic connectivity that only occurs when the left hemisphere is receptive because it is not pre-occupied with viewing an image of its own.

1.4

Neuromagnetic Imaging Reveals Primary Motor Cortex Activation During the Observation of Oro-facial Movements

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The direct-matching hypothesis of action representation states that actions of both the self and other share a common motoric neural representation. In support of this a number of MEG/EEG studies have shown modulation of endogenous sensorimotor (mu and beta) rhythms during the observation of hand movements suggesting primary sensorimotor cortices help to achieve a representation of the actions of others. In this experiment we wished to determine whether similar responses would be obtained during the observation of oro-facial movements. Neuromagnetic recordings (151 channels, CTF Systems) were obtained from six healthy subjects while they (1) observed a video of an experimenter making oro-facial movements (2) imitated the same movements and (3) observed hand movements. Source scanning using synthetic aperture magnetometry (SAM) was used to find changes in source power between these active conditions compared to pre-stimulus control conditions where no movement occurred. Statistical group analysis of SAM images showed increased activation of primary motor cortex and also occipital and parietal regions in all conditions. Analysis of virtual SAM sensors from sensorimotor areas showed event-related desynchronisation of mu and beta bands following the onset of movement in all three conditions. The comparable activations across conditions provide evidence that the direct-matching system in humans plays a role in achieving a representation of the oro-facial gestures of others.

1.5

EEG and Blinking Attention

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The accuracy of detecting a pre-specified probe letter in a rapid visual serial presentation (RSVP) paradigm is typically very high even under presentation rates of 8-11 items per second. Probe detection performance drops, however, if subjects are required to identify a unique target item (a white letter) that is presented 200-500 ms prior to the probe item. Performance typically, although not always, remains at the single task control levels if the probe item is presented at 100 ms post target, or at post target intervals greater than 500 ms. This temporary drop in probe detection performance is referred to as the "attentional blink". Recent findings using dual stream presentations have suggested that the attentional blink is attenuated for stimuli presented to the right hemisphere. We recorded EEG from subjects performing a standard attentional blink task and found that the ERPs in response to the probe item was reduced during the blink period. Source localisation of the difference wave suggested decreased activity in the left temporal and left frontal lobe areas. Use of nonmeaningful symbols, thought to be processed in the right hemisphere, resulted in a much smaller attentional blink and showed reduced activity in the right temporal lobe and left frontal regions. These results are consistent with the suggestion that the attentional blink may, in part, be a result of the identification process of the target stimuli combined with an update of semantic memory rather than a "blink" of visual attention.

1.6

Neural Correlates of Mood Congruence in Memory

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Emotional information is better remembered when a subject's mood at the time of retrieval matches it in valence (positive mood, positive material). An associative memory model predicts that this 'mood congruent' facilitation is due to the reactivation at retrieval of emotional regions which became associated with the valenced information at encoding. We tested this model by training subjects with positive and negative words, and then manipulating their mood at the time of retrieval while using functional magnetic imaging to monitor brain activity. Subjective ratings of mood indicated that our manipulation was successful, heart rate variability measures differed significantly between moods, and behaviour performance showed a strong trend towards memory facilitation for the congruent compared to incongruent test condition. In the functional data, conjunctions between valence specific activity evoked at encoding and the simple effects of congruent mood during retrieval of similarly valenced words, revealed strong shared activity in regions which have been linked to the processing of emotional information. For positive valence, these included the subgenual cingulate and medial orbitofrontal cortices. For negative valence they included medial orbitofrontal cortex and a region boardering caudate nucleus. To further examine mechanisms for the congruency effect, we compared the neural responses to mood congruency in correctly remembered items (R) with correctly rejected (CR) distracter items. Our observation that no brain region activated in the R congruency > CR congruency contrast, while several regions activated in the CR congruency > R congruency contrast suggests that mood congruent facilitation may act at the level of *attempts* to recall information, rather than at the level of successful recollection. The specific regions of activity we observed included right dorsolateral prefrontal cortex, posterior cingulate, and precuneus. These are believed to be involved in monitoring of memory functions, source memory, and memory related imagery respectively. We therefore conjecture that these are the processes facilitated by congruency.

1.7

Stimulus Control of Working Memory Cells

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The capacity of memory is, even though impressive, not limitless. Therefore it is important to control the load on memory i.e. to forget irrelevant information. The present study investigated the influence of cues to remember or forget on the neural mechanism believed to mediate rehearsal (delay activity).

We recorded from 124 cells in the 'prefrontal cortex' of pigeons, a structure crucial for the executive control of behavior and working memory. We found that during the retention period of a working memory task (delayed-matching to sample task) 66.9% of the cells showed delay activity when instructed to remember. When instructed to forget, delay activity was greatly abolished (in 88.2% of all instances of delay activity). The neural data reflected the behavioral data, with high performance after cues to remember (79.2% correct) and a drop to chance-level (44.4% correct) after cues to forget.

We conclude that active rehearsal and therefore working memory depend on the relevance of a stimulus, allowing selective memory for relevant information only. Hence selective rehearsal provides a means to control the load on working memory.

1.8

Does Memory Retention Require Synaptic Stability or Synaptic Plasticity?

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Memory storage is believed to involve long-term potentiation (LTP) and long-term depression (LTD)-like changes in synaptic weights within relevant neural circuits. Indeed, LTP and LTD can be as stably maintained as long-term memories, and synaptic spines can show stable structure for equally long periods of time. It is not yet possible, however, to record from or image single synapses during memory storage and retention.Thus the intuitively appealing hypothesis that long-term memory requires equally persistent physiological mechanisms remains untested. Interestingly, a number of lines of evidence are now pointing to the opposite hypothesis, i.e. that synaptic weights remain plastic while memories are retained, although these experiments too are inconclusive. An alternative approach to addressing these questions is through connectionist neural networks, which have the advantage of allowing one to continuously monitor individual connection weights during learning and retention. In these models it can be clearly shown that a network will undergo dramatic alterations in connection weights in order to preserve previously learned information while learning new information. This finding accords with larger scale theories of neocortical learning mechanisms, which emphasize an adaptive learning process that operates during repeated rehearsal/learning trials to ensure that new learning does not cause catastrophic interference and loss of old memories. Thus the physiological and modelling data suggest that the duration of synaptic change does not necessarily define memory persistence, and that a careful management of synaptic stability vis a vis synaptic plasticity is likely to be required for optimal memory retention in real neuronal circuits.

2.1

Blockade of N-methyl-D-aspartate (NMDA), Alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA), Kainate, or Dopamine (DA) D_2 Basolateral Amygdala (BLA) Receptors Before Administration of Five Unsignalled Footshocks Prevents the Reinstatement of Fear-Potentiated-Startle (FPS)

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The BLA contains NMDA, AMPA, kainate, and DA D_2 receptors and neurobiological events within the amygdala mediate conditioned fear. Long-term-potentiation occurs in the amygdala during fear conditioning and is linked to fear-memory storage. Fear learning involves NMDA, AMPA, kainate and dopaminergic receptor mediated processes and enhanced amygdaloid synaptic transmission facilitates fear-memory retrieval and makes fear expression possible. Fear extinction learning, which is not forgetting, also relies on amygdaloid NMDA receptor activation. Fear-reinstatement has been demonstrated behaviourally using the FPS paradigm but the biochemical events involved in FPS reinstatement have not been elucidated. Thus, the present study independently examined the effects of NMDA, AMPA/kainate and DA D_2 receptor antagonists on fear-reinstatement using a FPS paradigm. Over ten days, rats with cannulae targeting the BLA were baselined, fear-conditioned, pretested, fear-extinguished then infused with either, (±)-2-Amino-5-phosphonopentanoic acid {(AP5); 2.5µg/0.5µl, 1.25µg/0.5µl; n=12 each}, 6-Cyano-7-nitroquinoxaline-2,3-dione disodium {(CNQX); 5.0µg/0.5µl,-2.5µg/0.5µl; n=12 each}, raclopride-L-tartrate (8.0µg/0.5µl, 4.0µg/0.5µl, 2.0µg/0.5µl; n=12 each) or phosphate buffered saline (PBS; 0.5µl, n=12), before exposure to five unsignalled footshocks. FPS reinstatement was assessed 24-hours later. PBS-infused rats showed FPS reinstatement whereas, rats infused with AP5, CNQX, or the two higher doses of raclopride failed to exhibit FPS reinstatement.This finding suggests that these drugs impaired amygdaloid fear-memory retrieval processes by preventing the re-excitation of neurons and pathways that became linked during fear-conditioning. Thus, fear-reinstatement was blocked whereas, extinction was left intact.

2.2

Pedunculopontine Tegmental Nucleus Controls Conditioned Responses of Midbrain Dopamine Neurons in the Freely-moving Rat

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The pedunculopontine tegmental nucleus (PPTg) is an important source of afferent input to the ventral midbrain (substantia nigra, (SNc) and ventral tegmental area (VTA)) and may be involved in driving midbrain dopamine (DA) cell responses to reward-predicting sensory stimuli. We obtained direct evidence in behavioral animals to support this hypothesis. (1) We first compared the responses of DA cells and PPTg cells of rats in a classic conditioning task, in which a tone or light was used as the conditioned signal predicting delivery of sweetened water reward. The result showed that PPTg cells respond to auditory and visual stimuli at shorter latency than do dopamine cells (e.g. 7ms vs. 80ms to tone), that suggests that signal flow may relay at PPTg and than to DA cells. (2) We then tested if the sensory responses of VTA/SNc neurons to conditioned signals are affected by inactivating the PPTg. VTA/SNc neurons were recorded by using chronically implanted extracellular electrodes, and the PPTg temporarily inactivated during task performance by the infusion of 0.5 µl of 1% lignocaine via a guide cannula. Control infusions of saline were performed in some cases. The results show that ipsilateral inactivation of the PPTg can suppress sensory responses of DA cells. These data provide functional evidence that PPTg plays an important role in selectively mediating conditioned responses of dopamine neurons in reward learning.

2.3

Dopamine Receptor Contributions to Reward-Oriented Visuo-Spatial Processing in Rats

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Humans, as well as monkeys and rats, are equipped with neural circuits that predict the availability of reward during the performance of goal-directed behaviour. Using an asymmetrical reward spatial-choice task in monkeys, Lauwereyns and colleagues (2002a,b) previously showed that responses are faster and more accurate in a direction associated with reward as compared to a direction associated with no reward. Based on this research, we aimed to develop an analogue of the asymmetrical reward paradigm (ARP) in rats using a lever-press task. Fifteen male Sprague-Dawley rats responded faster (i.e., showed decreased median reaction times) in a direction associated with a high magnitude of reward. After 40 trials during the ARP, an automatic reward-value lever reversal occurred, with all rats learning the reversed stimulus-reward association within a few trials. A further aim of our research was to assess the effects of systemic administration of selective dopamine D1 (*SCH-23390*; 0.005, 0.01 and 0.02 mg/kg) and D2 (*eticlopride;* 0.025, 0.05 and 0.1 mg/kg) receptor antagonists on task performance. The reward factor amounted to ~20% of behavioural variability in the saline baseline condition, but only 10-15% in the dopamine-antagonist conditions. Overall slowing in motor performance was approximately 10-15% compared to saline baseline; however the absolute difference between high and low reward tended to decrease in size. Furthermore, after high doses of both antagonists, the reward-reversal proved to be particularly challenging, with some rats being unable to complete any further trials in the session. These findings suggest important roles for D1 and D2 dopamine receptors in the implementation of reward value during visuo-spatial processing.

2.4

Modelling Midbrain Dopamine Neurons With the Temporal-difference (TD) Learning Algorithm

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The TD learning algorithm implements the reinforcement learning paradigm and learns associations between stimuli and rewards by improving reward predictions through an error-signal dependent weight update. It has been suggested that dopamine cell activity may correspond to the prediction error of a neural TD algorithm. However, previous models did not account for persistent responding to both predictive signals and predicted rewards that we have observed in rat dopamine cells during learning. Many previous models used only the immediate previous state for their weight update. We modified this by employing weight changes that could extend back multiple time steps across the temporal representation of signals within a trial. We then explored a range of values for the key model parameters alpha (learning rate for synaptic weights across trials) and lambda (the recency weighting factor for temporal representations of signals within a trial). We found a specific range of values (low alpha, high lambda) defining a region of parameter space in which there were persistent responses to both cues and rewards. This suggests that lambda is a vital parameter for the model to successfully account for the full range of dopamine cell behaviours. High values of lambda indicate that representations of signals occurring early in the trial are still able to be modified by later events.

2.5

Alterations in Synaptic Protein Expression Associated with the Maintenance of Long-Term Potentiation

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Persistence of long-term potentiation (LTP) at rat perforant path synapses in vivo requires new protein synthesis and gene transcription, although it is not well understood how these processes maintain synaptic enhancement. This study aimed to determine whether elevated NMDA-glutamate receptor expression, previously reported to be associated with LTP, occurs as part of a more widespread change in synaptic protein expression. Western blot analyses of dentate gyrus cellular homogenates prepared 48 hours after LTP induction, showed no change in the expression of presynaptic protein synaptophysin, suggesting no change in synapse number. Expression of the AMPA-glutamate receptor subunit, GluR1, was elevated (45±20%, $p<0.01$, $n=11$) in these extracts, but no increase was observed after analysis of cell surface GluR1 expression. Interestingly, NMDA receptor subunit NR1 expression was increased in this preparation (22±7%, $p<0.05$, $n=6$). These data suggest that LTP maintenance is associated with increased synaptic surface expression of NMDA receptors. Furthermore, as there is no corresponding increase in GluR1-containing AMPA receptors, this implies that LTP maintenance is associated with formation of new silent synapses, perhaps in readiness for further plasticity. The overall increase in GluR1 levels may reflect a reserve pool primed for rapid insertion at such silent synapses following subsequent activity.

2.6

Long Term Potentiation in the Human Visual Cortex: An fMRI Study

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Applying functional magnetic resonance imaging (fMRI) techniques, hemodynamic responses elicited by flashing checkerboards were measured both before and after a photic tetanus (PT) was delivered. Previously, recorded with EEG, it has been shown that rapidly presented sensory stimulation induces long-lasting plastic changes within the human sensory cortex. In the present experiment, subjects were presented with 2 runs of checkerboards flashed very slowly to the left and right visual fields, separated by a run of 2 minutes where the subjects solely stared at a fixation point. Subsequently, subjects were shown a train of the same checkerboards presented at a much faster rate to one hemifield. Lastly, subjects were again presented with a run of the slow rate checkerboards. As this was a pilot study, 2 subjects were tested using two different inter stimulus intervals (4 sec and 30 sec) for the slow presentation rate. Hemodynamic responses were compared across runs to determine the effects of the PT. In both subjects, results showed that the hemodynamic responses in the visual cortex, primarily areas 18 and 19, were significantly increased only after the administration of a PT and did not change between the first two blocks of baseline testing. These results further support that Long Term Potentiation can be demonstrated within the human visual cortex. Furthermore, we can conclude that the changes induced by the PT are possibly occurring within the secondary visual cortices.

3.1

$GABA_A$ Receptor Subunit mRNA Expression in Human Brain and Evidence for Changes in Schizophrenia

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We investigated the distribution and density of $GABA_A$ receptor α1 and β3 subunit mRNAs in various regions of the human brain using standard radioactive *in situ* hybridisation techniques; including middle frontal cortex (MFC), hippocampus, superior temporal gyrus (STG), polar temporal cortex, primary visual cortex and cerebellum. Tissue was obtained from the New South Wales/NISAD Tissue Resource Centre with ethical approval. Both subunit mRNAs were detected above background in all regions investigated, with β3 subunit mRNA expressed at lower levels than α1 subunit mRNA except in the hippocampus. Given the published evidence for alterations in $GABA_A$ receptor expression in schizophrenia, we investigated changes in mRNA density in the MFC and anterior STG; two key cortical regions implicated in the symptoms of schizophrenia. A trend was observed for increased expression (by 16%) of α1 subunit mRNA in the MFC of schizophrenic compared with non-psychiatric control subjects (n=6). A converse decrease in expression (31%, n=6) of this subunit was found in the anterior STG. Moreover, the pattern of expression in these two regions was reversed for β3 subunit mRNA in schizophrenic brain (31% decrease in MFC and 13% increase in STG). Although the present investigation was limited by availability of tissue and the inherent variability between subjects, the current data extend the literature on the distribution of $GABA_A$ receptors in human brain and provide further evidence for altered expression in schizophrenia.

3.2

Is Connecting Genetic Lesions to Cellular Disruption Sufficient to Understand Inherited Neurodegenerative Disease? Lessons from Ovine Batten Disease

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The modern paradigm is that understanding the genetic lesion in genetic diseases will lead to understanding the pathogenesis, simply by following the route from the genetic lesion to aberrant protein affecting cell function, leading to symptoms. This works well for many diseases, including inherited lysosomal deficiencies such as the developmental bone disease, pycnodysostosis, caused by a defect in cathepsin K. Bioinformatics people even argue that such an understanding can be gained *in silico.*

Studies of brains of sheep with presymptomatic Batten disease (neuronal ceroid lipofuscinosis) a fatal inherited neurodegenerative disease, highlighted serious limitations of this approach. Glial cell activation preceded neurodegeneration by several months. Activation began in specific foci, foremost affected being regions associated with clinical symptoms later. Activated astrocytes and clusters of activated microglia were present in outer layers of occipital and somatosensory cortical regions at only 12 days. Activation and transformation of microglia to brain macrophages spread from vertically integrated circuits, preceded neuronal loss and did not parallel storage body accumulation. There are suggestions that the progressive involvement of glial cells from well-defined foci is a phenomenon shared with other lysosomal storage diseases, including the mucopolysaccharidoses, Tay-Sachs disease, Sandhoff's disease and gangliosidoses.

These studies suggest that the modular cell driven approach to understanding pathogenesis in these diseases will not suffice alone, and it will need to be integrated with developmental knowledge.

3.3

Role of RAGE in the Pathogenesis of Huntington's Disease

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Increased expression of RAGE (Receptor for Advanced Glycation End Products) and accumulation of β-amyloid-like fibrils have been implicated in the pathogenesis of some neurodegenerative diseases including Alzheimer's disease.We have investigated the expression of RAGE in the hypoxic-ischemic rat brain injury model and in the caudate nucleus (CN) of Huntington's disease (HD) human brains using *in situ* hybridization and immunohistochemistry. The results showed RAGE expression in dying CA1/2 neurons of rat hippocampus following ischemic stress. Increased expression of RAGE, observed in neuronal and glial cells in HD CN, correlated with the known pattern of cell death seen in HD CN. These results suggest that RAGE may have a role in neuronal cell death and in the pathogenesis of HD. To clarify this, functional studies are being undertaken in our laboratory. We propose to over-express RAGE in neuronal/glial cell lines, and in cell lines expressing huntingtin protein, using cell-specific tetracycline (Tet)-inducible expression system. The construct with RAGE, inducible by tetracycline, has been designed using molecular cloning techniques. The plasmid pIRES-EGFP has been modified to express RAGE under the CMV promoter with or without the Tet-operon upstream of the promoter. The plasmid rtTA-M2 has been modified to replace the CMV promoter regulating expression of Tet-activator with either neuronal specific NSE or glial cell specific GFAP promoter. This approach will allow us to assess the role of RAGE in neuronal / glial cell death and in the pathogenesis of HD.

3.4

Opiates Modulate Progression of Simian AIDS/Neuro-AIDS

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Intravenous opiate abuse is a major risk factor in AIDS. Since opiates modulate immunity and *in vitro* HIV production, they have been suspected of directly altering AIDS progression. However, epidemiological data are equivocal on this point. We have been using simian AIDS models to study this matter. SIVsmm9 was injected into rhesus macaques dependent on morphine (n=19) or saline controls (n=18). An overall retardation in AIDS progression rate was seen in opiate-exposed monkeys ($p<0.05$), along with alterations in neurological outcomes. Still, an immediate type hypersensitivity (type-III) response to morphine developed for two opiate-dependent monkeys, accelerating their progression to AIDS, while truly long term survivors (> 4 yr) were equal in number for morphine and saline groups. Alternatively, collaborative studies from Puerto Rico using a 3-virus cocktail of much more virulent (and neurovirulent) SIV/SHIV strains than SIVsmm9 have shown that AIDS progression can be uniformly accelerated in opiate-dependent monkeys. Thus, opiates appear to modulate AIDS progression in conditionally variable ways so that retardation and exacerbation of AIDS progression by opiates are not mutually exclusive outcomes. These data clarify the quandary over mixed epidemiological findings in this area, while impacting on public-health, therapeutic, and prophylactic thought about how to deal with the AIDS situation in drug addicts.

3.5

Reduced Activity of the External Globus Pallidus During Catalepsy in the Awake Rat

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The current model of basal ganglia functioning postulates the existence of an 'indirect' pathway from the D2-dopamine receptor expressing-striatal output neurons to the external segment of the globus pallidus (GP). Lack of dopamine would decrease inhibitory activity of GP neurons, leading to increased activity of the output nuclei and suppression of movement. To test the model, we are recording single neuron activity of the GP in the awake rat, during equivalent resting periods before and after systemic injection with either the D2 receptor antagonist Raclopride or vehicle. Raclopride produced catalepsy as revealed by the grid test (average grid time before and after Raclopride injection 1.2 and 59.0s, respectively). To date, mean firing rates and firing patterns of 25 Raclopride and 22 control cells were analyzed. Baseline mean firing rate before injection (19 spikes/s) was similar to results from two other different studies (20 spikes/s and 22 spikes/s, respectively) conducted in anaesthetized rats. We report a significant decrease ($p<0.004$) of the mean firing rate under Parkinsonian conditions. Mean coefficient of variation also decreased after Raclopride injection, from 1.156 to 1.009 ($p<0.002$). These results suggest that in conscious animal, Parkinsonian akinesia is associated with decreased rate and increased regularity of firing in the GP, consistent with predictions of the standard model.

3.6

Hippocampal Nitric Oxide Synthase and Arginase and Age-Associated Behavioural Deficits

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Increasing evidence suggests that nitric oxide (NO), generated by nitric oxide synthase (NOS) from L-arginine, plays an important role in the aging process. The present study investigated age-related changes in NOS and arginase, an enzyme shares the substrate with NOS, in the sub-regions of the hippocampus and their correlations with animals' performance in the open field, T-maze and water maze tasks. Aged rats (24 months old) showed reduced exploratory activity and poorer spatial learning and memory relative to the young adults (4 months old). Significant increases in total NOS activity were found in the aged dentate gyrus and a dramatic decrease in endothelial NOS expression was observed in the aged CA2/3. Activity and protein expression of inducible NOS were not detected in any sub-region of the hippocampus. There were no age-related changes in total arginase activity or arginase I and arginase II protein expression. Multiple regression analysis revealed significant correlations between NOS/arginase and behavioural measures in both the aged and young groups. In conjunction with our previous findings, the present results provide further support for the involvement of NOS/NO and arginase in the normal aging process. A highly significant positive correlation between CA1 eNOS protein expression and the swimming speed in the water maze task may reflect a relationship between the local cerebral blood flow and neuronal activity.

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3.7

Chlormethiazole: Mitochondrial Energetic Preservation Following Hypoxia-Ischaemia

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Transhemispheric diaschisis is described as remote changes occurring in the contralateral hemisphere corresponding to ipsilateral damage. We have previously shown that following cerebral hypoxia-ischaemia (HI), the contralateral hemisphere hippocampus suffers significant suppression in electrophysiological activity and a reduction of mitochondrial energetics at 3-days post-HI. Mitochondria have been shown to be specifically damaged by oxidative stress arising during ischaemia, resulting in diminished respiratory function and ATP production. The present study evaluated the extent of mitochondrial damage in cortical and cerebellar regions following an HI-insult. Mitochondrial dysfunction was assessed using oxygen electrode-derived respiratory measurements and mitochondrial respiratory enzyme kinetic (Complex I-IV) assays, in tissue homogenates from control, sham, HI + saline and HI + chlormethiazole (CMZ) treatments. Mitochondrial FAD-linked (succinate-driven) respiration was assessed 1- and 3-days post-HI from ipsilateral and contralateral cortex and cerebellum. Respiratory function from the ipsilateral cortex was impaired at both 1- ($P<0.001$) and 3-days ($P<0.001$) post-HI, whereas, both contralateral cortex and cerebellum only revealed a respiratory impairment at 3-days post-HI ($P<0.05$). CMZ treatment provided significant protection against HI-induced mitochondrial dysfunction at all time points and regions assessed. This focused study demonstrates that, both mitochondrial respiratory function and activities are impaired by an HI-insult in the ipsilateral and contralateral regions of cortex and cerebellum. The study further extends the understanding of CMZ's neuroprotective properties, whilst reinforcing the evidence against the use of the contralateral hemisphere as an internal control.

4.1

Binge Ethanol Exposure Induces Apoptotic Granule Cell Death in the Developing Rat Cerebellum

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Binge-like ethanol exposure during the neonatal period results in permanent granule cell loss in the rat cerebellum. However, the temporal window of vulnerability of this cell population has not been clearly defined. This study used caspase-3 immunolabelling to identify cells of the external granule layer (eGL) most likely to proceed down a pathway of apoptotic cell death, to determine this temporal window. On a set day (PD 0-10), the pups of timed pregnant Sprague-Dawley dams were randomly assigned to one of two groups – alcohol-exposed (AE), and sham-intubation controls (IC). Each day, pups were perfusion-fixed at 10 hours after the initial ethanol exposure. Cerebella were removed, wax-embedded, and serial 5um-thick sections cut. Sections were immunolabelled for active caspase-3 and the total number of caspase-3 positive cells in the whole cerebellar vermis were counted using the physical disector/fractionator method. The mean total number of labelled eGL cells was significantly greater ($p<0.05$) in ethanol-treated animals compared with controls for postnatal days 0-5 (e.g. PD 2: AE = 1,249.46 ± 410.08 (mean ± SD); IC = 423.25 ± 216.48 (n = 6/group/timepoint). This study shows that the developing granule cells of the eGL are vulnerable to ethanol-induced apoptotic cell death. This has implications for binge alcohol consumption in the third trimester of human pregnancy.

4.2

Activation of Caspase-3 in Cerebellar Purkinje Cells of the Four Day Old Rat Following Binge Ethanol Exposure

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Exposure of the developing fetus to alcohol is considered to be the leading cause of mental retardation in the Western world. Binge-like ethanol exposure in the neonatal rat brain results in extensive cerebellar Purkinje cell (Pcell) loss and motor dysfunction. This study investigated the lobular pattern of the initiation and duration of apoptotic Purkinje cell death using activated caspase-3 as a marker of apoptosis. Four day old Sprague-Dawley rat pups were given ethanol (4.5g/kg) in 2 doses 2 hours apart). Control animals were sham intubated. Animals were killed at set time intervals post ethanol delivery. Activated caspase-3 was detected in 5μm thick midvermal sections and visualised with AEC. Semi quantitative methods were used to determine the ratio of labelled Pcells per total Pcells within each lobule. Ethanol-induced caspase-3 activation in Pcells was variable across lobules. Caspase-3 activation had occurred by 4 hours and was maximal at 10 hours post-ethanol. The extent and rate of subsequent caspase-3 activation differed between lobules. Ten hours after ethanol exposure 68% of lobule IX Pcells were positive for active caspase-3, whereas only 18% in lobule VI were labelled. The lobular basis of ethanol-induced caspase-3 activation in Pcells will be compared to the total Pcell loss per lobule in the mature cerebellum following the same ethanol exposure paradigm. Investigation of the lobular variation in ethanol-induced Pcell death provides a model system to investigate mechanisms of ethanol induced apoptotic cell death.

4.3

Endocannabinoids Mediate Group I mGluR Modulation of GABAergic Synaptic Transmission in Midbrain Periaqueductal Grey Neurons

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The midbrain periaqueductal grey (PAG) is a major site of cannabinoid-mediated analgesia in the central nervous system. This study examined the possible contribution of endocannabinoids to the actions of the group I metabotropic glutamate receptor (mGluR) agonist, DHPG, on GABAergic synaptic transmission in PAG neurons in vitro. In brain slices, superfusion of DHPG (30 μM) reduced the rate but not the amplitude of spontaneous miniature inhibitory postsynaptic currents (mIPSCs) in all PAG neurons tested. The DHPG-induced decrease in mIPSC rate was concentration-dependent (EC_{50} = 1.4 μM) and reversed by the group I/II mGluR antagonist MCPG (1mM). In slices pre-treated with the CB_1 receptor antagonist AM251 (3 μM), DHPG produced either no effect or dramatically increased mIPSC rate. The DHPG-induced increase in mIPSC rate was abolished by the non-selective transient receptor potential (TRP) channel antagonist ruthenium red (3 μM), but not by the vanilloid receptor (TRPV1)-selective antagonist iodo-resiniferatoxin (0.3 μM). Ruthenium red did not prevent DHPG-induced inhibition of mIPSC rate in the absence of AM251. These results are consistent with previous studies in hippocampus and cerebellum demonstrating group I mGluR-mediated inhibition of synaptic transmission via endocannabinoids acting at presynaptic CB_1 receptors. In addition, in PAG, this CB_1 receptor-mediated inhibition masks a novel facilitatory action of group I mGluR activation on GABA release, possibly involving presynaptic TRP channel activation.

4.4

Cannabinoid CB1 Receptor Protein Expression in the Rat Choroid Plexus: A Possible Involvement of Cannabinoids in the Regulation of Cerebrospinal Fluid

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Cannabinoid CB1 receptors in the brain are expressed on axon terminals presynaptic to neurons that express fatty acid amide hydrolase (FAAH). Postsynaptic FAAH catalyses endocannabinoids which act as short range transmitters. It has been previously shown that FAAH is also expressed in the epithelial cells of the choroid plexus. Using immuno-histochemisty, we found that CB1 receptor protein is also expressed in choroid plexus epithelia. This is consistent with the hypothesis that FAAH in choroid plexus epithelial cells catalyses endocannabinoids close to their site of action. Cannabinoids may then act directly on choroid plexus cells, and thereby contribute to the regulation of the composition of the CSF.

4.5

Influence of Drug-Associated Stimuli on MDMA Self-Administration – Part two

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Cues associated with self-administered drug infusions acquire properties that appear critical to the maintenance of drug-taking. For example, cocaine self-administration requires the continued presentation of cocaine-associated cues and the omission of these cues leads to extinction of responding. Like cocaine and other stimulant drugs, MDMA is positively reinforcing and animals will reliably perform operant responses in order to obtain drug infusions. The extent to which MDMA-associated cues influence self-administration has not been investigated. In the present study rats were trained to self-administer MDMA according to an FR-1 schedule of reinforcement. Contingent with the infusion of MDMA was the presentation of a light stimulus. Following acquisition and a criterion number of drug/stimulus presentations, the ability of the light stimulus alone, the drug stimulus alone or neither stimulus to maintain self-administration behaviour was determined. Omission of the light stimulus led to rapid extinction of responding, comparable to the removal of both the light and drug stimuli. Omission of the drug stimulus resulted in a slight reduction in responding, however, responding seemed to be maintained by the continued presentation of the light stimulus. These data will be discussed with reference to the role of MDMA-associated stimuli in maintaining self-administration behaviour.

4.6

The Effects of Binge Ethanol Exposure in Very Early Gestation on Fetal Outcome in the C57BL/6J Mouse

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Alcohol exposure on a single day of gastrulation can induce different levels of acute cell death in the ectoderm that are blood alcohol concentration (BAC) dependent. Most previous studies have looked at embryonic development as this paradigm of ethanol exposure can be embryo lethal. It is unknown what effect such exposure has on fetal outcome. 8 - 10 week old C57BL/6J mouse were exposed to ethanol (either 6.5 g/kg E, or 3.0 + 1.0 + 1.0 + 1.0 + 1.0 g/kg E) via intra-gastric intubation at gestational day (G) 7.5. Offspring were raised to postnatal day (PN) 60 then killed, or embryos were removed from the pregnant dam on G18.5. In the PN60 group, binge-like alcohol exposure (6.5 g/kg E) significantly lengthened gestation (20.09±0.33 days; 3.0+1.0x4 g/kg E:18.92±0.08; C:19.07±0.17).Litter size at PN60 was significantly decreased with a single binge ethanol exposure (5.00±0.60) compared to the other groups (3.0+1.0x4 g/kg E: 7.33±0.61; C: 7.86±0.96). In both PN60 and G18.5 groups, the ratio of abnormal offspring was significantly increased in 6.5 g/kg E but not in 3.0+1.0x4 g/kg E. Body weight from PN0 to PN60 and whole brain weight were not affected by ethanol exposure. This study is the first thorough examination of the long-term effects of binge-alcohol exposure during gastrulation on fetal outcome. Binge alcohol on G7.5 caused a significant decrease in litter size and increased abnormal offspring.

4.7

The Effect of Neonatal Ethanol Exposure and Motor Learning on Purkinje Cell Dendritic Spines in the Sprague Dawley Rat

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Exposure of the neonatal rat to binge-like ethanol exposure results in cerebellar Purkinje cell (Pcell) deficits and motor dysfunction in the mature rat. Training on a set of complex motor tasks results in an increase in Pcell dendritic spine synapses in the paramedian lobule (PML) and improved motor performance. The purpose of this study was to investigate the effects of neotnatal ethanol exposure and motor training on the linear density of Pcell dendritic spines. Rats were exposed to ethanol (E-5.25 g/kg/day) or sham-intubated (I) on postnatal day (PD)4-9. On PD30, rats in each group were assigned either to a rehabilitation condition (RC) given 20 days of training on motor tasks, or to a cage condition (CC). Rats were killed at PD50. Sagittal PML sections were processed for transmission electron microscopy. Estimates of the number of spines per unit length of Pcell spiny dendrite were made from serial ultra-thin sections of randomly selected transverse dendrites. Neonatal ethanol exposure resulted in a significant decrease in linear spine density. E-RC animals had significantly more spines per unit length than E-CC animals. RC did not alter linear spine density in I animals. The increase in synapse number per Pcell seen following training on complex motor tasks is paralleled by a change in linear spine density on the Pcell dendritic branchlets.

5.1

Grip Strategy Affects Force Control in Simple Lifting Tasks

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Ten healthy adult subjects lifted a small, special-purpose manipulandum using three different grip strategies, *viz*, the normal "precision grip" between index finger and thumb tips (lateral pinch), a pinch grip with the fingers oriented downwards (downward pinch) and a "key grip" between the thumb and the side of the index finger. The weight of the device was changed randomly after every 10 lifts so that the subject did not know the weight of the object before beginning each series of lifts. The sequence of grip type and hand used was also varied randomly. When lifting a new load, subjects always used a stronger grip force than was required, then reduced this particularly in the next two lifts to a force that matched the load quite accurately, at least with the two pinch grips. Subjects' ability to scale the grip force to load force efficiently in subsequent lifts was not affected by grip type or hand. However, the grip force was significantly greater with the key grip than with either of the precision grips in both hands. There was no overall difference between the hands, but there the pattern of learning differed, with the dominant hand improving more consistently across the 10 lifts. These findings suggest that the types of alternate grip strategies used by patients with limited fine motor control in disorders such as stroke may partly explain the excessive grip forces used in object manipulation.

5.2

Corticospinal Excitability During a Choice-Hand Reaction Time Task

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Fourteen neurologically healthy, right-handed subjects performed a reaction time (RT) task, which involved wrist flexion or extension of either the left or right hand to one of three fixed target locations. A precue provided information regarding the location of the imperative target. Transcranial magnetic stimulation (TMS) was delivered over either hemisphere in two experimental sessions. TMS was delivered at set times during the foreperiod, and at random intervals during RT and following EMG onset. Surface electromyography (EMG) was recorded from the *flexor carpi radialis* (FCR) and *extensor carpi radialis* (ECR) of both hands. The amplitude of the motor evoked potentials (MEPs) recorded in the contralateral FCR and ECR were assessed, as was the velocity of the involuntary stimulus-evoked hand movement. In the responding agonist there was an increase in corticospinal excitability. There was also an increase in the stimulus-evoked velocity in the direction of the impending movement. There was no modulation of the responding antagonist during RT. During the foreperiod there was a decrease in excitability, which was independent of target location. During RT, when the responding hand was required to flex, the corticospinal excitability of the non-responding agonist mirrored that of the responding agonist. This constraint is likely due to the coupling of homologous muscles. When the responding hand was required to extend, the excitability of the non-responding hand suggested directional tuning dependent upon the extrinsic location of the target. This is perhaps due to activation of directionally tuned neurons within the cortex.

5.3

Cortical Excitability During Inhibition of a Pre-Planned Response

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The purpose of this study was to investigate the temporal and spatial modulation of corticospinal excitability when the participant was both able and unable to inhibit a pre-planned response. A volitional inhibition paradigm involving the sweep hand of a clock was used with the pre-planned response being to lift a finger from a button when the sweep hand reached 800 ms of a 1 s revolution. On some trials, the clock hand sweep would stop prior to 800 ms and the subject would attempt to inhibit their response. Transcranial magnetic stimulation was applied over a range of times throughout the clock hand sweep. Electromyography was used to record motor evoked potentials from the left *extensor indices proprius* (EIP) and *abductor digiti minimi* (ADM) of eight participants. When the clock hand reached 800 ms and the subject lifted their finger, there was an increase in corticospinal excitability of both the response muscle EIP, and the control muscle ADM. When the clock hand stopped unexpectedly 170 ms prior to the anticipated response, excitability increased in the control muscle ADM but not in the response muscle EIP. Results indicate that inhibition may function selectively to temporally modulate motor output.

5.4

Does Having to Remember Verbal Precue Information Slow Motor Preparation?

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If the Chinese proverb "I hear and I forget; I see and I remember…" is correct, remembering verbal precue information might result in slower motor preparation than visual precue information. The effects of precue modality (Auditory, Visual) and precue parameters on reaction time (RT), electromyography (EMG) and the electroencephalogram (EEG) amplitude were examined. A single-handed manipulandum incorporated a target response panel containing red LED's embedded within four targets, two either side of a green central LED. Visual precues were presented via the target LED's. Three parameter precue conditions were investigated: one target LED lit (DKEK – direction known, extent known); two target LED's lit (DKEU – direction known, extent unknown); two target LED's lit (DUEK – direction unknown, extent known). Auditory (verbal) precues indicated the conditions: e.g., 'left-long', 'left' or 'short'. A precue (500 ms) was followed by a variable (1000, 1500, 2000 ms) foreperiod then a visual stimulus. Participants moved the attached pointer quickly and accurately to the correct target upon stimulus onset. Eight participants received 18 blocks of 50 trials each. Each block included one precue modality and parameter condition. For all parameter conditions, the auditory precue resulted in a faster RT than a visual precue. Within precue modalities, RT was shortest for DKEK, longer for DKEU and longest for DUEK. Contingent negative variation (CNV) amplitudes were greatest in DKEK and smallest in DUEK, with larger CNV's at central (CZ) recording sites. Auditory precues resulted in less change in CNV amplitude than visual precues. CNV and RT appear to be sensitive to the modality of the precue when stimulus modality is unaltered.

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5.5

Cortical Influence Over Infantile Breathing-Swallowing Coordination

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The brainstem has been shown to be the primary controller of breathing-swallowing coordination (BSC), although the cerebral cortex may also contribute. The comparison of BSC during wakefulness and sleep may clarify the role of the cortex due to the difference in the level of conscious cortical activation between these two conditions. Ten healthy full-term infants were monitored longitudinally during wakefulness and sleep on seven occasions within the first three months of life. Concurrent measurements of submental muscle activity, thyroid acoustics and nasal airflow were made in order to categorise swallows into one of five respiratory-phase categories: mid-inspiratory, inspiratory-expiratory, mid-expiratory, expiratory-inspiratory and respiratory pause. Repeated-measures ANOVA revealed a phase-by-condition interaction (F = 8.009, p = .002) for mid-expiratory and respiratory-pause swallows. There was an age-by-phase interaction (F = 4.982, p < .001) with the frequency of mid-pause swallows declining at two and three months of age. The coordination of breathing and non-nutritive swallowing in healthy human infants during wakefulness is different from sleep, particularly from one week of age, suggesting that the cortex may be involved in BSC by one week of age.

5.6

Effects of Concurrent Cognitive and Physical Loading on Reaction Time and Force

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Voluntary movement performance will ultimately deteriorate when tasks are performed with sufficient intensity and/or duration. The extent to which cognitive and physical activity changes independently and/or interactively during concurrent tasks is not clear. We examined the effect of a sustained concurrent cognitive and physical loading task on fractionated reaction time, error rate, and force performance. Cognitive loading was manipulated through visually precued simple, 2-choice and 4-choice reaction time conditions. Physical loading involved sustained isometric elbow flexion (30% maximal voluntary contraction force), until the target force could not be maintained for three consecutive seconds (Task failure). Twenty-four healthy right-handed participants (22.8 ±3.0 years; 73.7 ±11.5 kg; 1.74 ±0.1 m) were tested. Following task failure (about 8 minutes) reaction time and premotor time had increased significantly (16% and 23%, respectively, $p < .05$). Neither motor time nor error rate changed. Even when force production was no longer required, reaction time and premotor time remained 8% greater than baseline fractionated reaction time performance ($p < .05$). There were no significant interactions between reaction time performance and cognitive load during the concurrent task. The increase in premotor time following task failure provides evidence that decision making time is slowed when the capability to maintain performance diminishes, independent of changes in muscle function and error rate, or cognitive demands of the task.

5.7

Neuro-Muscular Factor in Stiffness of the Distal Hand Muscle *in vivo*: The Lateral Approach (Preliminary Results)

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Stiffness of muscle exerts important peripheral influences upon motor performance. Values of muscle stiffness between left and right hands in right-handed people are not represented in literature. We measured muscle stiffness with a unique sensing device with interpretive software. The pressure sensor was positioned on the muscle surface and lowered gradually - compressing the muscle at a constant rate- 0.25 mm/s. The instantaneous force of muscle resistance and the level of spatial (vertical) deformation was measured, involving the belly of the first dorsal interosseous muscle during rest. External force was applied in a dorsal-ventral direction. Control data was sourced from a homogeneous rubber phantom. Nine right-handed, untrained young males. Muscles from both hands were studied with three data acquisitions per side. Instantaneous forces and Hook's moduli were analysed over each 0.25 mm of deformation. Individual covariances were graphically represented. In comparison to the phantom each subject demonstrated specific waves, representative of the stretch and tendon reflexes of the muscle fibres. The muscle from the dominant hand produced waves of greater amplitude. The covariance indices between ipsilateral trials were much less on generalised muscle tissue in comparison with the phantom. Non-dominant muscle demonstrated a significantly lower level of covariance, possibly attributable to the prevalence and influence of contractile elements resultant from spinal reflexes. These results profile subcortical and intrinsic muscular influence on handedness.

5.8

Further Neuro-Structural Characteristics of the First-Dorsal Interosseous: Possible Peripheral Factor of Handedness

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Peripheral factors involved in lateralization of motor behaviour are infrequently presented in the literature. Clinical references contain contradictory statements of the differential force generated by the muscles of the dominant and non-dominant hand. Our study emphasized "peripheral" factors involving the axis of tension of the muscle, and aimed to establish the lateral difference of the angle of projection of the First Dorsal Interosseous muscle (FDIM) to the osseous components of the thumb. Structural MRI generated anatomical images of the muscular and osseous compartments of both hands. Slice contours were extracted and reconstructed with specialized software (CAD-2004). In the osseous compartment centres of mass of the carpal, metacarpal and the distal phalanges were volumetrically assigned. The centre of rotation in the carpal-metacarpal articulation was identified. Segmental analysis of each muscle contour enabled construction of a geometrical axis of active tension of the muscle. This line was translated and spatially localized in relationship to the reconstructed integrated osseous axis of the thumb. The angle of intersection of these lines indicates the projected attachment to the FDIM. Nine young, untrained, right handed males. Both hands were imaged with the thumb abducted and adducted. Preliminary data indicates that the angles were dissimilar on the left and right hands. We hypothesize that magnitude of the angle has some influence in production of the maximal force of the muscle in addition to muscle fibre recruitment and has a relation to handedness.

6.1

Measures of Impulsivity: Approaches and Clinical Usefulness

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Impulsivity and disorders of impulse control have frequently been a fundamental etiological concept in theoretical models of the behaviour exhibited by clinical populations such as those with head-injury or substance abuse. Such theoretical considerations have guided the development of assessment instruments to assist with prognosis and diagnosis for such groups. In the substance-abuse area, two different theoretical approaches have guided test development and usage. One follows the tradition that dimensions such as impulsivity are personality characteristics. The Eysenck Impulsivity-Venturesomeness-Empathy Scale (IVE) and the Barratt Impulsivity Scale (BIS-11) are examples. The other approach is to view dimensions such as impulsivity as reflecting some learnt or acquired cognitive-behavioural capability. For example, the theory underlying the Dysexecutive Questionnaire (DEX) views impulsivity as arising from a lack of planning ability or, alternatively, as an inability to inhibit inappropriate responses. The present study examines the inter-relationships among these scales (DEX, IVE and the BIS-11) and assesses their usefulness for prediction and diagnostic classification. A total of 293 normal participants and 49 opiate-dependent participants were administered the DEX, the IVE and the BIS. Discriminant Function classification analyses with cross-validation showed the DEX to be superior at classifying participants according to group membership (normal vs. risk for opiate dependency). The best predictor (discriminating) variable from each scale were: Social Regulation (DEX), impulsivity (IVE) and motor-planning (BIS). The different approaches represented, and dimensions measured, by the DEX, IVE and BIS each have merit. Overall the conclusion is made that the DEX more accurately identifies people at risk for opiate addiction than previously developed personality measures.

6.2

Construct Validity of the Dysexecutive (DEX-S) Questionnaire

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The self-rating Dysexecutive Questionnaire (DEX) is a recently developed standardized self-report measure of behavioural difficulties associated with executive functioning such as impulsivity, inhibition control, and monitoring and planning. It is a scale beginning to receive broad use with neurologically impaired populations. However, few studies have examined its factor, concurrent or predictive validity. The present study administered the DEX-S (self monitoring form) to 293 normal participants and 49 clinical participants and its construct (factor) validity examined. A series of factor analyses were evaluated to determine the best factor solution for this scale. This was found to be a 4-factor solution with factors best described as: inhibition, intention, social regulation, and abstract problem solving. The first 2 factors replicate factors from the 5-factor solutions recommended by previous studies and the 3-factor solution produced less interpretable and less parsimonious factors. It is argued the 4-factor solution found in the present study represent a more stable and valid factor solution than those reported previously.

6.3

Dysexecutive Symptoms and Impulsivity in Opiate Users

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The study of executive cognitive functioning (ECF) and impulsivity in opiate users has not received much research attention to date. This study examines self-report measures of ECF, impulsivity, and affective state (anxiety and depression) in both non-opiate dependent and opiate dependent individuals. A cross-sectional between-subjects design compared performance between two groups. The university students completed the self-report measures in group format within a classroom. The opiate dependent individuals completed the self-report measures in the clinic waiting area, or in private rooms when preferred, prior to their appointments. The two groups were comprised of first year university students (n= 293) and opiate dependent individuals (n= 186). All participants completed the Behavioural Assessment of Dysexecutive Syndrome (BADS) DEX-S questionnaire, the I_7 Impulsiveness Questionnaire, the Barratt Impulsiveness Scales (BIS-11), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI). A 3-factor solution for the DEX-S emerged from the combined samples. All three DEX-S factors correlated significantly with self-reported symptoms of impulsivity and affective state in each group. The heroin dependent group also reported significantly higher scores than the control group on all 3 DEX-S factors. This study established a relationship between a self-report measure of ECF and self-report measures of affect and impulsivity. It furthermore confirmed that heroin users report greater symptoms in each of these domains compared with non-users. It is suggested that affective and impulsive symptoms may represent behavioural manifestations of ECF disturbances, or an impulsive cognitive style. This may set the stage for drug use and dependency, and may also serve to maintain an established addiction, consistent with the concept of neurocognitively-mediated substance use vulnerability.

6.4

Patients With Multiple Forms of Anosognosia and Multiple Forms of Hemineglect; Evidence for a Syndrome of Unawareness?

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Previous studies have found that (i) anosognosia and persisting hemineglect (HN) do not necessarily co-occur, (ii) anosognosia usually resolves after the acute stage (iii) visual neglect plus anosognosia for hemiplegia predicts a poor recovery from hemiplegia. Over 18 months in a population of 1 million, we identified only 13 adults (16- 65 yrs) with HN persisting >3 months. Three to 22 months post-CVA, 9 were assessed for visual and personal HN, anosognosia for visual and personal HN, and hemiplegia. Lesion locations were analysed in detail from MRI brain scans. Our results demonstrated that (i) all participants demonstrated visual and personal HN, and two or three types of anosognosia, (ii) severe visual and personal neglect were frequently associated with a severe anosognosia for these disorders, but hemiplegia was less frequently associated with anosognosia for hemiplegia (iii) anosognosia was not correlated with recovery from hemiplegia, and (iv) all participants had large lesions including 3 or more cortical or subcortical areas, as well as, in all cases, the basal ganglia, but the lesions of two participants did not involve the parietal lobe. Although patients demonstrated a range of patterns of severity across the different types of anosognosia and HN, it is argued that the different forms of neglect and anosognosia will influence one another and thus could be conceptualised as a syndrome of unawareness.

6.5

Assessment of Affective Prosodic Memory: Implications for Neuropsychology

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There are currently no standardised tests of affective prosodic memory for people with brain injury. The aim was to begin to develop a brief, computerised measure of short-term affective prosodic memory and sensitivity to proactive interference, while holding constant set-size variables (Nelson et al., 1992), and using principles of memory task classification (Humphreys et al., 1994). The procedure involved two cued recall tasks, allowing a comparison between prosodic and phonological memory. For each of 16 trials, participants heard four words, spoken in different emotional tones (happy, sad, angry or neutral). In each trial, they then read aloud four digits, in a distractor paradigm. They then saw a face which acted as a memory cue: In the prosodic task, the face showed an emotional expression matching one of the four words (e.g., a happy face indicated that participants were to recall the word said in a happy tone). In the phonological task, the face showed a mouth position representing the ending-sound of one of the four words. The task was developed over successive experiments. Overall performance was shown to be significantly stronger in the phonological than in the prosodic task. It was also found that performance declined significantly during the 16 trials, reflecting the build-up of proactive interference.This applied to both phonological and prosodic memory. The results have implications for clinical neuropsychological assessment, paving the way for a prosodic memory test that considers the overall level and pattern of performance.

6.6

Affective Working Memory – What Do You Feel About It?

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While there has been a considerable amount of research and theory development in both auditory-verbal and visuo-spatial working memory, the concept of affective working memory appears relatively recently in the literature on affect and memory. Affective working memory has been conceptualized as a special category of working memory which is linked to the amygdala-dependent emotional arousal system in the production of immediate conscious emotional experience. It has been postulated that neural connections between the prefrontal cortex and amygdala play a crucial role in affective working memory, linking components of the prefrontal cortex involved in working memory with the amygdala and related structures implicated in emotional memory (Davidson & Irwin, 1999; LeDoux, 2000). A study was devised to test the concept of affective working memory using a standard working memory experimental paradigm – the cued recall paradigm. Three cued memory tests were developed utilizing **semantic, phonological**, and **affective** speech/language cues. The number of correct target recalls under each condition were examined using analysis of variance which produced a significant main effect for memory task, F (2, 34) = 91.35, $p < .001$, and a significant interaction effect between task and trials, F (6, 102) = 2.99, $p < .05$). The results demonstrated significant differences between semantic, phonological, and affective working memory and, in particular, suggest that affective working memory is substantially different from the "phonological loop" component of the auditory-verbal working memory model.

6.7

The Role of the Amygdala in Emotion Recognition in Normal Aging

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This study examined emotion recognition in normal aging. We consistently find deficits in older adults' ability to identify three emotions: anger, sadness, and fear, but not happiness, surprise, and disgust. Anger, sadness and fear have all been tied to the amygdala. For this reason we examined older adults' ability to predict the dangerousness of persons based on photos of their faces, because this task has also been shown to tap amygdala functioning. We found that, relative to younger adults, older adults were worse when predicting dangerousness in faces but not in situations. Their ability to predict dangerousness in situations shows that their difficulties are restricted to faces. We also used an eye tracker to examine whether older adults' impairments on face tasks stem from a failure to study the same areas of the face as younger adults. For instance, research shows that the eyes provide more information about emotions than the mouth. However, we found that older adults look to the eyes as much as younger adults do, and are thus receiving identical information about faces and emotions as are young adults. We conclude that older adults' difficulties are not due to differences in the facial information they perceive. Instead, they are in making sense of face and emotion information, a classic role of the amygdala. Our findings tie in with recent evidence of advanced cell death in the amygdala with aging, and a reduction in amygdala activity when viewing emotion faces.

6.8

Temporal Dynamics of Task Specific Hemispheric Lateralisation

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A recent functional magnetic resonance imaging (fMRI) study has shown left-hemispheric activation with a language-related task and right-hemispheric activation with a visuospatial task, even though the stimuli were the same for the two tasks (Stephen *et al.*, *Science*, 2003, 301, 384-386). Using a similar paradigm, we investigated the temporal sequence of events associated with this type of task-specific hemispheric lateralisation using event-related potentials (ERPs). The stimuli for both tasks were four-letter words with either the second or the third letter printed in red. The language-related task was a simple letter-detection task whereby the participants were required to determine whether a target letter was present. In the visuospatial task the participants determined the location of the red letter. Task-related ERP modulation was found over the N1 component (180-220 ms) and a later time period spanning 296-500 milliseconds. The visuospatial task elicited a greater N1 response over the left hemisphere compared to the language-related task. The visuospatial task also elicited increased negativity over the right parietal electrodes between 320-400 ms, while the language-related task elicited greater negativity over the left anterior and posterior electrode sites between 296 and 500 milliseconds. The present findings suggest that the ERP correlates of letter-detection start earlier and last longer than the ERP correlates of the red-letter location task and that they depend on different neural mechanisms as determined by scalp topography.

7.1

Getting Wired on Estrogen and Leptin: Development of Forebrain Circuits Mediating Reproduction and Feeding

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Developmental mechanisms specifying the pattern of connections that form between limbic-hypothalamic nuclei are major determinants of the functional properties of these forebrain neural circuits. Although it is clear that sex steroid hormones play an important role in determining patterns of connectivity between sexually dimorphic nuclei, the cellular mechanisms underlying the developmental actions of these hormones are only now beginning to be elucidated. The anteroventral periventricular nucleus (AVPV) plays a critical role in the neural control of ovulation and is unusual among sexually dimorphic nuclei in that it is larger in females. We have used the AVPV as a model system for studying how sex steroid hormones specify sexually dimorphic neural connections in the mammalian forebrain. The results of both in vivo and in vitro experiments indicate that estrogen acts directly on the AVPV through an ER dependent mechanism to induce formation of sexually dimorphic afferents to the AVPV. Moreover, genetic and pharmacological evidence indicates that both BDNF and a secreted semaphorin are involved. Thus, estrogen acts at the level of the AVPV to regulate expression of these guidance molecules to sexually differentiate its inputs by regulating axonal targeting through ER dependent signaling pathways.

The development of hypothalamic circuits that control feeding also appears to be directed by peripheral endocrine cues. A core hypothalamic circuit has been defined that mediates the regulatory actions of the adipocyte hormone leptin on feeding and energy balance. Neurons in the arcuate nucleus of the hypothalamus (ARH) play a key role in conveying the regulatory effects of leptin to other parts of the hypothalamus and we recently defined the postnatal development of ARH projections. Because there is a postnatal surge in circulating leptin levels preceding its regulatory action on body weight, leptin has been postulated to function as a developmental signal. Therefore, we investigated whether leptin deficiency alters the normal developmental pattern of projections from the ARH. The results indicate that ARH projection pathways are severely disrupted in leptin deficient (ob/ob) mice, remain stunted in adult ob/ob mice, and leptin treatment in adulthood does not restore the wild type pattern of projections. However, both the pattern of ARH projections and food intake can be rescued by neonatal leptin treatment. These findings suggest that the postnatal leptin surge is a key developmental signal affecting the architecture of hypothalamic circuits mediating feeding in much the same way that sex steroids specify patterns of connectivity between forebrain regions involved in reproduction.

7.2

Hyperphagia in the Pseudopregnant Rat is Associated with Normal Hypothalamic Response to Leptin

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During pregnancy a state of leptin resistance develops that facilitates the hyperphagia required to meet the high energy demands of pregnancy and lactation. It is likely that the changing hormone levels associated with pregnancy are responsible for inducing the loss of leptin responsiveness in the brain. The aim of this experiment was to examine the behavioural response to leptin in pseudopregnant rats. These animals have an identical hormone profile to the first half of pregnancy, but do not form a placenta, allowing the effects of hormones of maternal origin to be distinguished from those from the placenta. Proestrous Sprague-Dawley rats were mated with vasectomised males to induce pseudopregnancy. On day 9 of pseudopregnancy (following a 23 hour fast), leptin (4μg in 2μl) or vehicle (artificial CSF) was injected intracerebroventricularly, then food intake measured over the subsequent 3 and 24 hours. Food intake and body weight were significantly increased during pseudopregnancy compared with cycling control rats. Leptin administration significantly suppressed post-fasting food intake in both control and pseudopregnant rats. These data demonstrate that changes in maternal hormones during pseudopregnancy induce a significant increase in appetite and food intake, similar to that observed during pregnancy. The absence of leptin resistance during pseudopregnancy, however, suggests that placental-derived hormones must contribute to the changing hypothalamic response to leptin observed during pregnancy.

7.3

Identification of Mouse MC4R Gene Promoter Sufficient to Impart Brain Specific Expression *in vivo*

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Loss of one functional melanolcortin-4 receptor (MC4R) allele in either mouse or human leads to obesity. As a first step for developing a model to study regulation of the MC4R promoter *in vivo*, we developed a mouse transgenic line and determined whether ~1kb mouse MC4R promoter was sufficient to direct tissue specific MC4R expression. Approximately 1kb mouse MC4R together with 5'UTR sequence (-1096 to +426bp) was fused to a nuclear localized LacZ reporter gene and the construct injected into pronuclei from FVB mice. Five transgenic lines were identified as carrying autosomal transgene insertions and three of these had significant brain LacZ staining. None of the lines showed significant transgene expression in kidney, liver, lung, or testis. The three lines that showed brain transgene expression also showed transgene expression in a few cells in heart. The pattern of transgene expression in the brain for the three lines differed markedly. Two lines showed expression mostly limited to either the ventral preoptic area or the frontal and dorsal regions of the cortex. The third line showed wide spread transgene expression in brain with a pattern remarkably similar to endogenous MC4R mRNA expression. In conclusion, ~1kb mouse MC4R promoter is sufficient to direct gene expression to the brain, and specifically to regions that express endogenous MC4R mRNA.

7.4

Confocal Imaging of Ligand-Induced Internalisation of GFP-tagged Melanocortin-4 Receptors Stably Expressed in HEK293 Cells

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Melanocortin-4 receptor (MC4R) is the most widely expressed MCR subtype in the brain. Mutations in one allele of the MC4R gene are a common monogenetic cause of human obesity, accounting for ~ 4% of childhood morbid obesity. Homozygote MC4R gene knockout mice are more obese than heterozygote MC4R gene knockout mice. This observation suggests that the abundance and regulation of MC4Rs at the plasma membrane plays a role in the development of obesity. To study MC4R trafficking we developed a chimeric human MC4R (hMC4R) fused with green fluorescent protein (GFP) at the C-terminus, and stably expressed in HEK293 cells. Receptor function (as assessed by adenylyl cyclase assay) showed that hMC4R-GFP is comparable to wild-type receptor (EC_{50} = 1.3 ± 0.36 nM and 2.3 ± 0.81nM, respectively). To quantify the time-course of receptor trafficking, hMC4R-GFP expressing cells were stimulated with either a-MSH or desacetyl-α-MSH for different time points, fixed with paraformaldehyde, and then the membranes were labelled with $DiIC_{18}$(3)-DS to demarcate cell boundaries. This provides a means with which to distinguish membrane and cytosolic GFP fluorescence in digital image processing. We showed that α-MSH is more potent than desacetyl-a-MSH at inducing hMC4R internalisation. Since the expression level of MC4R in the cell-surface membrane is important for MC4R signaling, the different regulation of hMC4R signalling by α-MSH and desacetyl-α-MSH may ultimately influence energy homeostasis.

7.5

Interleukin-6 Stimulates STAT3 Phosphorylation and Nuclear Translocation in Bovine Adrenal Medullary Chromaffin Cells

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Interleukin-6 (IL-6) is a cytokine released from immune cells in response to inflammation. We have examined the action of IL-6 on adrenal medullary chromaffin cells because such an interaction could allow the immune system to influence the body's acute response to stress. In other cells IL-6 signalling is mediated by the tyrosine phosphorylation and nuclear translocation of STAT3 (signal transducer and activator of transcription 3). Medullary cells were isolated from the bovine adrenal by collagenase digestion, purified and maintained in culture for 1-3 weeks. Chromaffin cells were identified by immunostaining for tyrosine hydroxylase and STAT3 signalling monitored using activation state-specific antibodies. Even under basal conditions STAT3 was highly localized to chromaffin cell nuclei. While STAT3 was not itself phosphorylated its nuclear localization was reduced by the tyrosine kinase inhibitor AG490. Incubation with IL-6 increased the level of STAT3 nuclear staining and more strikingly resulted in a time- and concentration-dependent phosphorylation of nuclear STAT3. This response was seen with IL-6 concentrations as low as 10 pmol and was evident after 5 min incubation, maximal after 30 min but then declined back to basal levels by 60 min. Thus adrenal chromaffin cells respond to IL-6 with a rapid but transient activation STAT3. Such a response is likely to result in the regulation of chromaffin cell gene expression thus ultimately influencing the adrenal medullary response to stress.

7.6

Brain Myostatin: a Central Regulator of Homeostasis

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We have identified myostatin (Mstn) neurons in the brains of rats and sheep. Mstn perikarya are predominantly located in the horizontal and vertical limbs of the diagonal band, but are also widely distributed throughout the cortex, hippocampus and the lateral hypothalamus. Ir-Mstn, presumably terminals, are located in the ventral margins of the lateral ventricles, PVN, ARC and SON. To confirm this finding, Western blotting showed ir-Mstn in the hypothalamus and cortex and RT-PCR confirmed Mstn mRNA. We further showed that ir-Mstn increased in perikarya of rats fasted for 24 h and, using Western blotting, we showed that the abundance of Mstn increased in the hypothalami of sheep fasted for 3 d and those that were septic. To determine the function of brain Mstn, male sheep were injected with Mstn either ICV (vehicle or 0.025, 0.05, 0.1 nmol/kg BW) or IV (vehicle or 0.5 nmol/kg BW). After ICV injection, there was a rapid and dose-dependent decrease in secretion of insulin ($P<0.001$), which resulted in hyperglycemia ($P<0.001$) and increased concentrations of FFA ($P<0.001$). In addition, Mstn reduced secretion of LH ($P<0.001$) and increased secretion of GH. In contrast, IV injections of Mstn were limited in effect. We speculate that Mstn neurons play an important role in regulating energy balance and homeostasis.

7.7

Recent Insights into Insulin-Relaxin Family Peptides and Receptors in Brain

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Recent studies have identified various orphan-GPCRs as putative receptors for relaxin-family peptides, including LGR7 for relaxin/relaxin-3, LGR8 for INSL3 and GPCR135 for relaxin-3. Anatomical studies have revealed discrete populations of neurons in rat/mouse brain that express relaxin, relaxin-3 and relaxin binding sites, but studies of the precise neuroanatomical associations of these receptors and ligands are still required. In collaborative studies using a range of techniques and experimental models, we have documented: *(i)* the broad distribution of LGR7 mRNA and/or immunoreactivity in rat/mouse brain - particularly in cortico-thalamic, limbic and hypothalamic areas; *(ii)* the restricted but abundant expression of relaxin-3 in the nucleus incertus (NI) with prorelaxin-3 immunoreactive fibres topographically distributed in target areas of NI afferents in rat forebrain; and *(iii)* the restricted presence of LGR8 mRNA within rat intralaminar thalamic nuclei. In functional studies in rat, we have demonstrated: *(i)* inhibition by rh-relaxin of synaptically-induced pyramidal neuron activity in basolateral amygdala (BLA) of neonatal brain slices; *(ii)* dose-dependent inhibition by rh-relaxin of memory consolidation, following bilateral injections into BLA after inhibitory avoidance training; and *(iii)* complex effects of synthetic INSL3 on parafascicular neuron activity, including hyperpolarization and decreased input resistance. These findings provide evidence for actions of relaxin-family peptides in somatosensory-autonomic-endocrine pathways, via different GPCRs.

8.1

Hunting for Novel Receptors in GnRH Neurons

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The gonadotropin-releasing hormone (GnRH) neurons are responsible for regulating fertility in all mammals. As such, an understanding of the factors controlling their activity is essential to facilitating progress in the treatment of infertility. As a result of the scattered distribution of the GnRH neurons in the brain, it has been difficult to obtain information on the types of receptors expressed by these cells. We have recently made GnRH promoter-GFP transgenic mice that enable us to visualize living GnRH neurons in the acute brain slice. To evaluate the complement of receptors expressed by these cells we have harvested the cell contents of individual GnRH neurons for RT-PCR amplification and subsequent microarray analysis. These studies have identified the presence of over 50 different neurotransmitter receptor subunit mRNAs in GnRH neurons. One unexpected family of receptors identified was that of the somatostatin receptors (sstr2, sstr3, sstr4). Immunocytochemical experiments using a sstr2-lacZ knockin transgenic mouse verified the presence of sstr2 gene expression in a sub-population of GnRH neurons. Gramicidin, perforated-patch-clamp electrophysiological studies revealed a direct and potent inhibitory effect of somatostatin upon the electrical activity of the majority of GnRH neurons. These results indicate that the previously unsuspected neuropeptide somatostatin is likely to be an important modulator of GnRH neuron activity *in vivo*. Overall, this microarray strategy has provided a significant resource with which we can decipher further the neurobiology of the GnRH neuron.

8.2

Molecular Determinants of Stress Modulation in GnRH Neurons

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Neurons that synthesize and secrete gonadotropin-releasing hormone (GnRH) represent the neural control point for fertility modulation in vertebrates. Although these cells are ideally situated to be an integration point for the feedback of environmental stress on reproduction, there is little evidence that molecules involved in stress reception and response influence GnRH neurons directly. Single cell microarray interrogation of the GnRH neuron transcriptome (Todman et al., 2004) revealed several candidates for conveying stress signals to GnRH neurons. Interestingly, the variety of molecular classes and potential pathways represented, suggested that different mechanisms might exist for responding to qualitatively different stressors. We now report the expression validation of a subset of these transcripts using single cell RT-PCR from individual GFP-expressing transgenic GnRH neurons, corroborating and extending our microarray findings. We selected genes for validation based on their involvement in a variety of stress pathways, including the immune response. This set includes interleukin-1 receptor accessory protein, prostaglandin E receptor type 2, corticotropin releasing factor receptor type 1, and arginine-vasopressin receptor type 1b. We found that all microarray-identified genes were expressed in GnRH neurons, but that their expression patterns were heterogeneous. The majority of genes were expressed singly, although some GnRH neurons also exhibited co-expression of multiple molecules. Our findings underscore the emergent theme of heterogeneity in the GnRH neuronal population and suggest that unique subsets of GnRH neurons exist to convey particular stress modalities within the network.

8.3

Morphological Changes in Gonadotrophin-Releasing Hormone (GnRH) Neurons During Postnatal Development

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The activation of GnRH neurons in adolescence is considered to be the critical event underlying the onset of puberty. Despite its critical importance, the mechanisms underlying this activation of the GnRH neurons remain unknown. We have recently established a new method for visualising the whole of the GnRH neuron and its dendritic architecture *in situ*. Using this methodology we have set out to examine whether the numbers of dendritic spines (the sites of excitatory synaptic input) on GnRH neurons are different in pre- and post-pubertal male mice. Acute brain slices allowing living GnRH neurons to be visualised were prepared from GnRH-GFP juvenile (day 10-12) and adult (~d60) male mice. Individual GnRH neurons were patched and filled with biocytin that was subsequently revealed with avidin-conjugates. The biocytin filling revealed extensive dendritic extensions in both juvenile and adult GnRH neurons. Unexpectedly, however, we found that GnRH neurons in juvenile mice exhibited a markedly more complex dendritic architecture than those of adult GnRH neurons. In contrast, preliminary data suggests that dendritic spine density on the GnRH cell bodies and dendrites is not substantially different between juvenile and adult mice. These observations suggest that the adult-type pattern of dendritic architecture in GnRH neurons is not established until relatively late in the post-natal period. This may reflect a process of network formation, whereby the GnRH neurons initially produce widely-projecting dendrites to initiate connections, and that this is followed by a period of dendritic pruning, prior to puberty whereby successful connections are strengthened and maintained.

8.4

Central Administration of the Estrogen Antagonist ICI-182,780 Alters LH Pulse Frequency in Estrogen-Treated Ovariectomised Rats

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The overall aim of this research program is to determine whether changes in the concentrations of ovarian steroids are responsible for bringing about the reduction in neuroendocrine dopamine neuron activity resulting in late pregnancy hyperprolactinemia. In order to develop a method for manipulating estradiol activity within the brain, without compromising peripheral steroid actions, the present experiment tested the effectiveness of intracerebroventricular administration of the pure estradiol receptor antagonist ICI-182,780 in overcoming estradiol negative feedback of gonadotrophin-releasing hormone (GnRH) pulse frequency. Crystalline ICI-containing cannulae (18G) were stereotaxically implanted into a lateral ventricle of estrogen-treated ovariectomised rats. Three days later, blood samples were collected every ten minutes for three hours and analysed for pulsatile luteinizing hormone (LH) secretion; a reliable index of GnRH pulse frequency. An increase in LH pulse frequency in ICI-treated animals was observed compared to control animals (4.0±0.6 vs. 2.4±0.5 pulses/3hrs). In addition, ICI treatment resulted in an increase in pulse amplitude and mean LH concentration over the three-hour period ($P<0.05$). We therefore conclude that ICI had a central effect to block estradiol action on GnRH neurons. This confirms that this method successfully delivers ICI to brain tissues, and thus can be used to alter central effects of estrogen in experiments using pregnant rats.

8.5

The Role of Estrogen Receptors in Estrogen Positive Feedback in GnRH Neurons

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During the estrous cycle estrogen stimulates gonadotropin releasing hormone (GnRH) neurons to evoke the luteinising hormone (LH) surge that initiates ovulation. GnRH neurons express estrogen receptor beta (ERβ) whereas their primary afferents are thought to express estrogen receptor alpha (ERα). We used estrogen receptor knock out (ERKO) mice to examine the involvement of these receptors in the estrogen stimulation of GnRH neurons to induce the LH surge. It is well established that activated GnRH neurons express the immediate early gene cFos at the time of the LH surge. Thus ERKO mice and wild-type litter mates (n=5/6 per group) were transcardially perfused at the time of the LH surge and their brains collected for immunohistochemistry with antibodies against GnRH peptide and cFos. Plasma samples were also collected at the time of perfusion to confirm the presence of an LH surge. The percentage of GnRH cells positive for cFos in wild-type mice was 24±7% at the time of the surge. ERβKO mice expressed cFos in a similar proportion of cells (28±8%) whereas ERaKO mice expressed virtually no cFos (0±7%). ERαKO mice also did not exhibit an LH surge. These results suggest that ERβ expressed by GnRH neurons is not necessary for the stimulatory effects of estrogen in these cells. In contrast, it appears that ERα cells within the GnRH neuronal network are critical.

8.6

The Potential of Inducing Pituitary Dysfunction by the Use of GnRH-toxins

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The brushtail possum is a major pest in New Zealand and a significant research effort has been initiated to devise methods of fertility control to manage its population. The central role of GnRH in reproduction is well known, and it has frequently been used as a target to control reproductive function. For example, it has been used to deliver various cytotoxic compounds to specifically disrupt gonadotroph function. The aims of the current study were to 1) determine the rates of internalisation of GnRH in gonadotrophs from male and female possums; and 2) determine if GnRH conjugated to a plant-derived toxin, namely pokeweed antiviral protein (PAP), would specifically kill cells expressing GnRH receptor, namely, gonadotrophs. Experiments were conducted *in vitro* utilising immortal cell lines (αT3, CHO) and possum pituitary cells in primary culture. Peak internalisation of GnRH occurred at 15 and 30 minutes for aT3 and possum pituitary cells, respectively. Whilst internalisation rates for cells from male and female possums were similar, cells from male pituitaries bound more total GnRH. The GnRH-PAP conjugate was shown to specifically kill αT3 and possum pituitary cells, however the proportion of cells killed was lower than expected. Results from the current study demonstrate the potential of using a GnRH-toxin conjugate to disrupt pituitary function in the possum.

8.7

Endogenous Secretory Patterns of Prolactin in the Brushtail Possum

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The recent development of a homologous radioimmunoassay utilizing recombinant possum prolactin has enabled the accurate elucidation of endogenous secretory patterns of prolactin in the brushtail possum *(Trichosurus vulpecula)* for the first time. The aims of this study were to measure prolactin concentrations at frequent intervals over an entire lactation and oestrous cycle, as well as identify areas of localisation of prolactin-synthesizing and storage cells within the pituitary gland of the possum. During lactation, mean plasma prolactin concentrations were basal until 15 weeks after parturition. Thereafter, prolactin levels increased markedly to reach a peak at 19-20 weeks post-parturition and returned to baseline 5-9 weeks later to coincide with observed weaning at 19-27 weeks after parturition. Prolactin concentrations were highly variable during the oestrous cycle except for immediately prior to the preovulatory LH surge when prolactin levels appeared to be tightly regulated. Prolactin concentrations were basal immediately prior to the surge and two pulses of prolactin were detected 2-5 hours prior to, and during the preovulatory LH surge in 4/5 possums. In situ hybridisation and immunocytochemistry revealed that lactotroph cells capable of expressing and storing prolactin were compartmentalised within the anterior pituitary gland. In conclusion, endogenous secretory patterns of prolactin suggest involvement in galactopoiesis, and distinct regulation around the time of the preovulatory LH surge support a role for prolactin in reproduction in the possum.

8.8

Control of Prolactin Secretion in the Brushtail Possum (*Trichosurus vulpecula*)

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In eutherian mammals, the secretion of prolactin (Prl) is largely under inhibitory control via the hypothalamus, however, stimulatory factors also play important roles. Whilst Prl is known to be important for lactation and ovarian function in some marsupial species, the factors that regulate Prl secretion in marsupials has not be extensively characterised. The aim of this study was to determine whether the secretion of Prl in a marsupial, the brushtail possum, is regulated by similar mechanisms to eutherian mammals. Adult female possums with pouch young (>117 days) were treated with reagents known in other mammalian species to either increase (TRH) or decrease (cabergoline) Prl secretion. Administration of TRH resulted in an acute 15-fold increase in plasma Prl concentrations. Short-term exposure to cabergoline (1x75ug; i.m.) reduced plasma concentrations of Prl to baseline levels for approximately 24h, but did not affect the bodyweights of suckling pouch young. Longer-term exposure to cabergoline (6x75ug at 12 hourly intervals) diminished plasma Prl concentrations until 24h after the last injection. Moreover, bodyweights of pouch young decreased over the treatment period indicating that Prl is important during late lactation. When a TRH challenge was administered to cabergoline-treated animals, the Prl surge was attenuated 5-fold compared to saline-treated animals. Results demonstrate that the regulation of Prl in possums is similar to other mammals, however, possums seem to be less sensitive to the dopamine agonist cabergoline.

8.9

Lactation Alters Prolactin-Induced STAT5b Signalling in Hypothalamic Neurons

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During lactation, gonadotrophin-releasing hormone (GnRH, the central hormonal driver for reproduction) secretion is inhibited. One likely hormonal mediator of this is prolactin, the secretion of which is itself dramatically enhanced during lactation due to reduced activity of inhibitory tuberoinfundibular dopaminergic (TIDA) neurons. Prolactin signalling in TIDA neurons utilises the transcription factor STAT5b. This project aimed to determine whether prolactin also signals via STAT5b in GnRH neurons, and if lactation alters this in TIDA or GnRH neurons. Lactating rats or normally cycling (diestrous) rats (n=5) received prolactin (250 μg sc) or vehicle 40 minutes before perfusion. Sections containing the arcuate nucleus and preoptic area were immunohistochemically stained to identify STAT5b translocation into the nucleus of TIDA or GnRH neurons, respectively. In diestrous rats, prolactin induced a 3-fold increase in the percentage of nuclear STAT5b-translocated TIDA neurons ($P=0.01$ vs. vehicle-treated); this was not seen in TIDA neurons in lactating rats or in GnRH neurons from either group. To determine if GnRH neuronal activity was affected by prolactin, we measured co-localization of these neurons with pCREB, which is activated by a range of signalling pathways. In lactating rats only, prolactin caused a 2.5-fold decrease in the percentage of GnRH neurons co-stained for pCREB ($P<0.05$ vs. vehicle-treated). We conclude that (1) during lactation prolactin signalling is suppressed in TIDA neurons, and (2) prolactin does not act directly on GnRH neurons via STAT5b signalling, but may alter cell signalling during lactation.

8.10

The Presence of a Male Mouse Advances Maternal Behavior in Virgin C57B6 Mice

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There is evidence that at least some maternal behaviors are dependent on prolactin action in the brain. It has been shown that pheromones carried by male mouse major urinary proteins lower serum prolactin levels in female mice. This study aimed to determine if such pheromones might affect maternal behavior. Virgin C57B6 mice were housed in split cages with a male mouse, a female mouse, or alone, for more than 10 days. They were then exposed daily for 4 days to three pups placed at opposite corners of the cage from the nest, and observed for pup directed behavior. Virgin mice housed with a male were significantly faster ($p<0.05$) to retrieve all three pups on the first day of testing compared to mice housed alone. Both of these groups became faster at retrieving pups on subsequent days. Virgins housed with another female took a similar time to retrieve pups on the first of testing, as the mice housed alone, but this group did not become significantly faster on subsequent days, and by the third and fourth day of testing were significantly slower than both other groups ($p<0.05$). It appears that pheromonal interactions can alter maternal behavior in virgin C57B6 mice.

8.11

Increased Expression of Prolactin Receptor mRNA in Oxytocin Neurons in the Maternal Rat Hypothalamus

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During late pregnancy and lactation, when circulating levels of prolactin are high, prolactin receptor protein is upregulated in several areas of the hypothalamus, including the supraoptic and paraventricular nuclei. The aim of this study was to identify, in these two nuclei, the relative proportions of oxytocin and vasopressin-secreting magnocellular neurons that express prolactin receptor mRNA and to determine whether levels of expression change during pregnancy and lactation. Dual-label *in situ* hybridisation histochemistry was performed on brain tissue from groups of cycling, pregnant and lactating rats. Sections were hybridised with an ^{35}S-labelled nucleic acid probe that specifically detected the long form of the prolactin receptor together with digoxygenin-labeled RNA probes to detect either oxytocin or vasopressin mRNA. In the supraoptic nucleus, in all three groups, the majority (84-89%) of oxytocin neurons expressed prolactin receptor mRNA whereas colocalisation in vasopressin neurons was markedly lower (< 20%). In the paraventricular nucleus, prolactin receptor mRNA was also predominantly present on oxytocin neurons. The proportion of oxytocin neurons showing co-localisation increased significantly ($p<0.05$) during pregnancy and remained high during lactation. As in the supraoptic nucleus, prolactin receptor mRNA was detected in relatively few vasopressin magnocellular neurons and did not change during pregnancy and lactation. The presence of prolactin receptor mRNA on oxytocin neurons suggests that prolactin can act in the brain to directly modulate the activity of magnocellular neurons.

8.12

STAT-Signalling in Bovine Adrenal Medullary Chromaffin Cells

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STAT (signal transducers and activators of transcription) proteins are an important latent signal molecule in many cells. In response to cytokine receptor activation they become phosphorylated and translocate to the cell nucleus to regulate gene transcription. As part of an investigation into the interaction between cytokines and the neuroendocrine system we have examined STAT signaling in adrenal medullary chromaffin cells. Medullary cells were isolated from bovine adrenal glands, purified and maintained in culture for 1-3 weeks. Chromaffin cells were identified by tyrosine hydroxylase immunostaining and STAT expression was determined using activation state-specific antibodies. Immunoblotting demonstrated the presence of specific members of the STAT family, namely STAT1, 2, 3, 5a and 5b. Interferone-a stimulated a time- and concentration-dependent phosphorylation of STAT1. This response was evident after 10 min incubation, maximal after 30 min and required concentrations of interferon-α as low as 100 pmol. Immunocytochemistry confirmed that phosphorylated STAT1 nuclear translocation occurred in chromaffin cells. Interferone-α also stimulated a smaller increase in the phosphorylation of STAT 2 and 3, although nuclear translocation could not be confirmed in chromaffin cells. Interferon-α did not activate STAT5a or 5b, nor were these STAT proteins responsive to inteleukin-1, 2 or 6. In contrast interleukin-6 activated STAT3 and, to a lesser extent, STAT1. STAT proteins expressed in chromaffin cells can therefore be differentially activated by specific cytokines, suggesting a potentially complex interaction between the immune system and the adrenal medullary stress response.

9.1

Purinergic Regulation of the Endocochlear Potential and Hearing Sensitivity

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The sound transduction process in the cochlea is driven by the endocochlear potential (EP, +100mV) in the endolymph bathing the apical surface of hair cells. These studies investigated the role of endogenous adenosine triphosphate (ATP) in regulating EP via ATP-gated ion channels (P2X receptors) in cells lining the endolymphatic compartment (Thorne et al., 2004 JARO, 5:58-65). The EP and cochlear partition resistance (CoPR: change in voltage resulting from current pulses introduced into endolymph) was measured in anesthetized guinea-pigs. Introduction of ATP into endolymph caused a dose-dependent reduction of EP and CoPR. Both were blocked by the P2X2 receptor antagonist PPADS. This indicates that ATP in endolymph can alter EP by activating a P2X2-mediated shunt conductance in the endolymphatic compartment. Introduction of PPADS alone caused a small increase in EP implying that endogenous ATP has only a small effect on EP under basal conditions. Preliminary studies show that noise exposure (12kHz, 110dBSPL) causes a decline in the EP and CoPR which is partially blocked by PPADS. These data provide support for a role of ATP in regulation of EP and consequently humoral regulation of hearing sensitivity under loud sound stress. Thus, the ATP-mediated cochlear shunt appears to be activated by ATP released into the cochlear fluids by stress such as noise exposure or hypoxia, to reduce EP and hearing sensitivity.

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9.2

Noise Exposure Up-Regulates NTPDase3 Expression in Rat Cochlea

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Stimuli such as noise or hypoxia can induce a release of intracellular ATP into the cochlear fluid spaces. At high concentrations, ATP may exert cytototoxicity acting on specific $P2X_7$ receptor subunits thus contributing to the pathophysiology of noise-induced cochlear injury. Ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases) are pivotal to regulation of extracellular nucleotide concentrations and P2 receptor signalling in the cochlea. Here, we characterize the distribution of NTPDase3 in cochlear tissues and investigate the effect of noise exposure on NTPDase3 expression. NTPDase3 immunoreactivity was observed at the nerve terminals of inner and outer hair cells and spiral ganglion neurons, suggesting the involvement in auditory neurotransmission. The discrete distribution of NTPDase3 corresponds to the reported distribution of $P2X_7$ receptor, which plays a role in cell death via apoptosis or necrosis. Quantitative real-time RT-PCR demonstrated up-regulation of NTPDase3 mRNA transcript levels in the cochlea exposed to noise, whilst semi-quantitative immunohistochemistry revealed increased NTPDase3 translation in the synaptic regions of the inner and outer hair cells. The results suggest a role for NTPDase3 in regulating ATP signaling associated with auditory neurotransmission, and the potential neuroprotective nature of noise-induced up-regulation of this ectonucleotidase in the cochlea.

Supported by the Health Research Council of New Zealand and Lottery Grants Board. Study approved by the University of Auckland Animal Ethics Committee.

9.3

Reduced K_v1 but Normal Ca_V Expression in the Auditory Brainstem of Congenitally Deaf (*dn/dn*) Mice

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Principal neurons of the medial nucleus of the trapezoid body (MNTB) form an integral component of the sound localization pathway. In congenitally deaf (*dn/dn*) mice the firing properties of the MNTB neurons are dramatically altered due to a down regulation of K_v1 channels (Leao et.al. in press). Preliminary calcium imaging experiments suggest that the resting calcium concentration in *dn/dn* MNTB principal cells is higher than in neurons from normal mice, however the exact concentration of calcium is yet to be determined. We hypothesized that the change in potassium channel expression may be mediated by altered intracellular calcium levels, perhaps due functional differences of the voltage-gated calcium channels. We examined the properties of voltage-gated calcium currents, and concluded that there was no difference between normal (CBA) and *dn/dn* MNTB principal cells in the amplitude of the calcium current at 0mV (-263 ± 59pA in normal, n=9 ; and -333 ± 70pA in *dn/dn*, n= 7). In addition, both normal and *dn/dn* mice express the same compliment of calcium channel types in roughly the same proportion (L-type-normal, $14 \pm 5\%$, n=4; *dn/dn*, $21 \pm 4\%$, n=5: N-type- normal, $30 \pm 4\%$, n=7; *dn/dn* $34 \pm 9\%$, n=5: P-type- normal, $32 \pm 4\%$, n=3: *dn/dn*, $25 \pm 8\%$, n=3: Q/R-type normal $28 \pm 9\%$, n=3: *dn/dn* $28 \pm 5\%$, n=3). This indicates that potassium channel and calcium channel expression are regulated by different mechanisms. It is unlikely that differences in the expression levels or properties of voltage-gated calcium channels underlie an increased intracellular calcium concentration in *dn/dn* principal cells.

9.4

Ageing and Auditory Stream Segregation

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Neuroelectric scalp recordings have facilitated our understanding of changes in central processing that contribute to age-related cognitive deficits. Neuroelectric studies with young adults have demonstrated modulation of auditory sensory organisation by top-down neural processes when attention is directed to a prescribed auditory schema. In the current study, elderly adults (mean age = 74 years) were presented with 3-tone sequences of high or low tones (single stream) and sequences of alternating high and low tones (dual stream) under ignore and attend conditions. Under attend conditions, participants were instructed to direct their attention towards either high- or low-pitched tones and detect within-stream order reversals of the 3-tone sequences. Results showed that no neuroelectric, attention-related components were obtained under ignore conditions, or under attend conditions to the non-target auditory stream. However, attention related components were obtained for correctly identified target stimuli in both single and dual stream attend conditions, demonstrating that the elderly were well able to segregate the high- and low - pitched streams. But, unlike their younger counterparts, no neuroelectric index of automatic stimulus grouping was observed for the reversed-order tones under the dual stream condition. This suggests that detection of sequential order changes for the elderly does not proceed at the same level of automaticity observed for young adults, but probably draws on higher-order central processes, possibly reducing neural resources available for other cognitive processes.

9.5

Exploring the Relationship Between Language and Short-Term Memory: Evidence From Aphasia

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Traditional models of verbal short-term memory view it as separate and distinct from the language system. However, recent evidence suggests these two systems are highly interdependent – indeed it has recently been argued that verbal short term memory emerges from the language system's ability to sustain activated linguistic representations over a short period. An interesting source of evidence for investigating these issues is the performance individuals with aphasia (acquired language impairment). In this study, five fluent aphasics and six age-matched controls were examined on a range of digit and word span tasks. Two of the aphasics had a deficit in semantic processing, and the remaining three had an impairment in phonological processing. Four span tasks were administered: i) digit span, ii) word span for words of high vs. low imageability; iii) word span for phonologically confusable vs. nonconfusable words, and iv) word span for words vs. nonwords. Sequences were presented auditorily, and, where possible, visually as well. The patterns of performance for semantically-impaired and phonologically-impaired aphasics were quite distinct: the semantically-impaired group, like normals, showed strong effects of phonological confusability, and a superiority for auditory over visual presentation; however, they showed reduced imageability effects relative to controls. The phonologically-impaired group, on the other hand, showed normal imageability effects, but reduced phonological confusability effects, and little or no benefit for auditory over visual stimuli. These results are consistent with the hypothesis that short term memory relies heavily on the language system, and that both semantic and phonological systems co-operate to support short term memory. An impairment to one results in over-reliance on the remaining system, which gives rise to a highly predictable pattern of errors in their short-term memory performance.

9.6

A Test of the Magnocellular Deficit Theory of Dyslexia in an Adult Sample

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An influential theory of dyslexia is based on the premise that individuals with the disorder have impaired sensitivity to rapidly changing stimuli in the visual and auditory modalities, due to a dysfunction in the magnocellular channel of the visual system and its analogue in the auditory pathway. The deficit in the auditory system is thought to cause difficulties in the segmentation of speech and the formation of accurate phonological representations, leading to problems in making the grapheme-phoneme correspondences necessary for reading. In a sample of 14 adults with persistent reading difficulty and 18 controls, visual contrast thresholds were measured in response to an 8Hz flickering Gaussian blob as well as a slowly modulated 8c/deg Gaussian windowed grating. Auditory thresholds were measured in response to a 1 sec burst of white noise, amplitude modulated at 100Hz or 1Hz. The adult reading difficulty group exhibited normal thresholds to rapidly changing stimuli in both modalities, but showed some insensitivity to the 1 Hz amplitude modulated auditory stimulus. Inspection of individual data showed that this finding was due to a subset of six individuals, all of whom had marked reading difficulties, although three individuals with similar levels of reading difficulty had thresholds within the normal range. Sensitivity to amplitude modulation at slower rates has been shown to be important for segmentation of the speech stream, and so may be implicated in the reading difficulty of the affected individuals. A magnocellular deficit cannot explain this impaired sensitivity, which may be the result of a reduced auditory short-term memory span.

9.7

Semantic Priming and Semantic Interference in Aphasic Word Retrieval

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One method of studying normal word production is to manipulate the context in which production occurs. For example, in the semantic priming task a related prime word presented prior to the production trial is generally found to facilitate naming. In contrast, other tasks may elicit inhibitory effects. In Humphreys et al's (1995) "postcue" procedure, where two pictures are displayed, and one is later cued to be named, naming latencies are actually *slowed* if the pictures are related. Since these tasks appear to tap into different aspects of the word production process, they may prove useful for studying aphasic word production. In this study, seven aphasics (three anomic, two Broca's, one transcortical motor, one borderline conduction/Wernicke's) were compared with age-matched controls on two tasks, one designed to elicit semantic facilitation, and the other inhibition. In Experiment 1, participants completed a priming task, in which they had to say aloud a written/spoken prime word, then name a picture. For the controls, naming latencies were significantly shorter following semantic primes. However, of the seven aphasics studied, only two showed significant effects: one demonstrated facilitation, and the other inhibition. In Experiment 2, the same participants were tested on a "postcue" type procedure, in which they saw two pictures and were then cued to produce both their names in a specified order. In contrast to the semantic priming study, no effects of semantic relatedness were found for controls or aphasics. We discuss implications of these results for models of word production in general, and theories of aphasic word production impairments in particular.

10.1

Connexin Expression in the Human Brain

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The connexin protein forms the basic subunit of a gap junction channel which serves for direct cell-to-cell coupling and the exchange of ions and chemical messengers. Recently, changes in gap junction expression in neurological disease processes have become an area of intense interest. The need to screen for connexin expression quickly and cost-effectively has directed attention to opportunities afforded by microarray technology. This technology involves spotting probes onto slides with their subsequent hybridisation to a fluorescently labelled target cDNA or cRNA pool. The aim of our study was to validate the design of a 'boutique' microarray chip to screen for mRNA for all the reported human connexins. Oligonucleotides of 50-base length were designed from the sense strand of the connexin coding sequences. Twenty custom-designed probes, fourteen of them showing cross-species human/rat alignment, and twenty probes for the human connexin sequences designed by the German company MWG were incorporated into the connexin array along with five positive and five negative controls (50 probes in total). The array was tested on rat brain, heart, liver and lens and on human tissue (brain only). The initial tests were validated by performing 'dye reversal' control hybridisations. Results confirm that our array design is reliable, has a consistent target binding pattern and can detect differential connexin gene expression in both human and rat tissues. The array has significant applications in the rapid screening of connexin expression in neurological diseases.

10.2

Postnatal Changes in Mitochondrial Energetics

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Brain damage following a stroke is a result of the inability of adult neurons to tolerate greater than three minutes of oxygen deprivation. In contrast, neonatal neurons have the unique ability to survive hypoxia/ischaemia (HI), for up to 6 times longer than adult neurons. The increased tolerance to HI-insult suggests that neonatal neurones respond to oxygen deprivation in a fundamentally different way to adult neurones. During normoxia, oxidative phosphorylation (ATP production) occurs at the mitochondrial ATP-synthase complex. However, during HI the ATP-synthase runs in reverse, pumping protons from the mitochondrial matrix into the cytosol and consuming ATP. In order to survive prolonged periods of oxygen deprivation cells must limit the amount of ATP consumed in this manner. There are two ways to limit ATP hydrolysis by the ATP-synthase; (*i*) reduce proton leakage across the mitochondrial inner membrane or (*ii)* inhibit the electron transport chain (ETC). Non-synaptosomal forebrain mitochondria were isolated from mixed sex Sprague-Dawley rats between PND1 and PND90 through differential centrifugation. Assessment of mitochondrial energetics through complex assays revealed an age-associated increase in activity for complex II-III ($p < 0.001$), V ($p < 0.001$) and the mitochondrial membrane integrity marker citrate synthase ($p = 0.007$). A small non-significant increase in complex I was also seen. The comparative reduction in isolated mitochondrial complex activity may indicate that the ETC is inhibited in neonate brains and thereby depress reverse ATP-synthase activity.

10.3

Isodomoic Acid C Exhibits Low KA Receptor Affinity and Reduced Functional Potency *in vitro*, and Fails to Induce Tolerance to Subsequent Domoic Acid Exposure

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In hippocampal region CA1, domoic acid (DOM) produces transient hyperexcitablility followed by a dose dependent suppression of population spikes. Several isomers of DOM have been identified, and the aim of the current study was to determine effects of isodomoic acid C (Iso-C) recently isolated from commercial shellfish. Hippocampal slices were obtained from 2-3 month old male Wistar rats and maintained in a Kerr Tissue Recording Chamber (ADInstruments, Sydney). Orthodromically evoked population spikes were recorded in CA1 before and after exposure to DOM and Iso-C. Iso-C produced transient hyperexcitablity and dose dependent suppression of population spikes in area CA1, but was approximately 34-fold less potent than DOM (EC_{50} DOM = 125 nM; Iso-C = 4.2 µM). In young hippocampal neurons, DOM preconditioning induces tolerance to subsequent DOM exposure via KA, but not AMPA receptors. However preconditioning with 1 or 5 µM Iso-C did not induce tolerance to subsequent DOM. Competitive radioligand binding studies using SF-9 insect cells expressing homomeric GluR-6 KA receptors showed the affinity of Iso-C to be 290-fold lower than DOM (IC_{50} DOM = 5 nM; Iso-C =1450 nM). Our results suggest that the effects of Iso-C are due to the activation of AMPA receptors alone.

10.4

Age-Related Increases in Severity of Domoic Acid-Induced Seizures

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During an incident of human domoic acid (DOM) poisoning elderly people were more susceptible to the neurological effects of DOM than young adults. Here we examined DOM-induced seizures in young (3 month) and aged (22-27 month) Sprague Dawley rats. Animals were observed for 2.5 hours following injection of saline, 0.5, 1 or 2 mg/kg i.p. DOM. A concentration-dependent increase in behavioural scores was evident in both age groups in response to DOM. Lower doses of 0.5 or 1 mg/kg DOM in young, and 0.5 mg/kg DOM in aged, promoted low level seizure behaviours such as freezing, squinting, mastication and panting. Higher doses (2 mg/kg in young and 1 mg/kg in aged) produced a typical progression of behaviours from stage 1 (belly-crawling, facial tremors, wet dog shakes) to stage 2 (prolonged scratching/foot biting, forelimb clonus), and ultimately stage 3 seizures (rearing-praying, salivation and tonic-clonic convulsions). Cumulative behavioural scores indicated an age-dependent susceptibility to DOM, with aged animals exhibiting significant reductions in latency to onset, as well as increases in frequency of head tics, scratching, rearing-praying and tonic-clonic seizures. Analysis of serum collected 2.5 hours after injection indicated a weak correlation between serum DOM and cumulative behavioural score. Our analysis of DOM in aged rats provides further evidence that susceptibility to excitotoxins is increased with age. (Supported by the Neurological Foundation of New Zealand).

10.5

3D Models of Blood Flow in the Cerebral-Vasculature

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The Circle of Willis (CoW) is a ring-like arterial structure located in the base of the brain, responsible for the distribution of oxygenated blood throughout the cerebral mass. Among the general population, only 50% have a complete CoW, and absence of vessels is common. Cerebral infarction can result when an afferent blood vessel to the brain is occluded, and may be more severe with certain CoW anatomical variations. A 3D computer model has been developed based on the results of a Magnetic Resonance Angiogram of a patient's cerebral vasculature and a numerical algorithm to simulate the body's autoregulation mechanism. The intention of the present study was to simulate different pathological states, including different vessels missing from the circle and varying degrees of stenosis in an afferent Internal Carotid Artery. Results show that the CoW is remarkably resilient to a stenosis in one of the Internal Carotid arteries. Because of their small diameters the communicating arteries act almost as barriers within the circle significant as amounts of blood do not flow through them unless there is significant blood pressure asymmetry. Peripheral resistances decrease to increase blood flow through the communicating arteries which also increases afferent flow, even when the Internal Carotid artery is subjected to a pressure drop. This indicates that 'pressure' is the more physiologically correct boundary condition as opposed to the specification of an inlet 'velocity profile'.

10.6

Multi-Site Recordings of Somatosensory Evoked Potentials in Freely Moving Rats

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Multi-site recording techniques have been used for characterizing the activities of large populations of neurons involved in brain processing. The aim of this study is to evaluate the multi-site recording technique for brain activities and utilize signal analysis for decomposing the underlying information for freely moving rats. In our study, male Wistar rats were first anesthetized for the implantation of a multi-wire electrode into the primary somatosensory cortex (SI). To eliminate the need for a cable and improve the wireless transmission quality, a Bluetooth-based telemetry data acquisition system is designed which can be mounted at a rat's backpack to record signals from awake, chronically implanted rat. During the experiment, sessions of somatosensory evoked potential (SEP), induced by electrical stimulus at rat's tail base, were recorded. Using multi-site recordings, independent component analysis (ICA) was used to remove the electrical stimulus artifacts. The decomposed signals, reconstructed from selected components based on cumulative power spectra, were represented in a topographic form in order to observe the spatiotemporal distribution of the rat's brain. Our results indicated that the application of an ICA can extract the dominant components of SEPs related to drowsy and awake states of somatosensory stimuli on the subject animal. The techniques developed in this study would benefit neuroscience studies of awake, freely moving rats while performing neuropsychological task.

10.7

Evolution of Brain Development in Primates and Hominids

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In the past 2 million years, since *Homo erectus*, both the extent of adolescence and cranial capacity have increased in the hominid line. In primates, adolescent development includes specific changes in cortical neuroanatomy (late synaptic growth and pruning in frontal and temporal lobes), so we can make some inferences about how neural development may have evolved in hominids. This paper presents evidence for three key points. 1) Extension of childhood and adolescence may have been an important genetic change underlying brain expansion in hominids. I present analyses showing that in primates, extent of childhood and adolescence is strongly related to neocortex size (r-squared=0.90). 2) Though humans appear to be an outlier among primates in the extent of childhood and adolescence, human data lies exactly on the regression line for nonhuman primates relating neocortex size and development. 3) Extent of childhood and adolescence is most strongly related to size of lateral prefrontal cortex, which handles domain-general cognitive abilities, rather than size of the more "social" areas, orbitofrontal cortex and limbic system. I conclude that "Machiavellian social intelligence" was not the driving force behind expansion of brain size. Rather it was the domain-general abilities subserved by the frontal lobes (recursion, executive control, future planning, generativity) that made expanded brains advantageous. A longer adolescence in hominids allowed more time for synaptic development in frontal areas, leading to more computational power being available for these cognitive abilities.

11.1

Manipulation of the Brain Angiotensin System for the Treatment of Parkinson's Disease

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Manipulation of the renin-angiotensin system is beneficial in the treatment of cardiovascular disease in humans. Here, we demonstrate that manipulation of the brain angiotensin system may be also beneficial in neurotoxin-induced models of Parkinson's disease (PD). Primary ventral mesencephalic (VM) cultures from E15 rats were cultured in the presence of the mitochondrial complex I inhibitors: rotenone and MPP^+. Rotenone (20 nM) reduced the number of dopamine (DA) neurons identified by the tyrosine hydroxylase (TH^+) immunoreactivity by 50% and MPP^+ (5 mM) by 25%. When angiotensin II (Ang II) (100 nM) was added in the presence of the angiotensin type 1 receptor (AT_1R) antagonist, losartan (1 mM) rotenone- and MPP^+-induced DA neuronal loss was significantly reduced. By contrast, when Ang II (100 nM) was added in the presence of the AT_2R antagonist PD123319 (1 μM), DA neuron loss was unchanged for either neurotoxin. Cultured TH^+ neurons expressed AT_1, but not AT_2 receptors, while other cell types expressed both AT receptors. *In vivo*, TH^+ neurons also expressed only the AT_1 receptor. Furthermore, initial results show that when C57BL/6 mice were pretreated with 30 mg/kg losartan prior to MPTP (20 mg/kg) injections, both MPTP-induced behavioral and pathological deficits were significantly reduced. Our results suggest that manipulation of the brain angiotensin system may prevent the onset of hallmarks associated with neurotoxin-induced Parkinsonism and may provide a novel therapy for PD.

11.2

Posture and Limb Tremor Relations in Parkinson's Disease

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The ability to minimize oscillatory motion that arises from whole body sway or segmental tremor is essential for many everyday tasks. Under most situations, neurologically normal subjects are able to effectively dissociate the impact of postural sway from tremor in the upper limb. However, it is unclear whether individuals with amplified tremor output, such as Parkinson's disease (PD), are able to effectively dissociate their postural sway from their amplified tremor. The relation between resting tremor, postural tremor and postural sway was examined in 10 elderly and 8 PD subjects (on and off medication) who completed a pointing task while standing on a force platform. Tremor was recorded from the hand and index finger segments of each limb using uniaxial accelerometers. Both PD and elderly subjects were able to effectively dissociate the low frequency, high amplitude oscillations of whole body motion from tremor in the upper limb. The frequency profile for sway for all subjects was characterized by a single peak between 0-1 Hz. In contrast, the upper limb tremor for the PD and elderly subjects was characterized by a dominant peak between 5- 8 Hz and 8-12 Hz respectively. Where the PD patients displayed greater tremor, a greater degree of coupling between A/P and M/L sway was seen. Increased coupling of tremor between the hand and finger of a single limb was also observed.

11.3

Using Biological Feedback for the Treatment of Children with Scoliosis

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A method of biological feedback (BF) therapy allows the patients to develop of the optimal diaphragm-relaxation type of breathing with the maximal level respiratory arrhythmia of the heart, controlled by channels of vision and hearing feedback. In this case a patient is an active member of process of treatment. 54 patients with the scoliosis of various stages have taken part in clinical investigations. Computing system was used for the treatment and for the assessment of functions of autonomic nervous system. The effect of BF therapy was estimated by Baevsky's index of tension (BIT). In healthy children the BIT was 1-1.5. At 70% of the patients the BIT is varied in limits 2.5-12. These results show the hyper sympathetic influences and the tension of compensatory mechanisms by these patients. After treatment with using of BF therapy the BIT is varied in limits 1.0-5.4. At 20% of the patients the BIT is varied in limits 0.3-0.8. These results show the hyper parasympathetic influences. After treatment we can observe the increase of BIT up to 0.6-1.5. At 10% of the patients have the BIT like in healthy children, i.e. 1-1.5. Index of the balance of sympathetic and parasympathetic influences is varied in limits 90-280. Our results shown that the biological feedback therapy leads to the normalization of the functions of autonomic nervous system.

11.4

Is Automaticity of Walking Regained After Stroke?

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The aim of this study was to determine whether people who have completed rehabilitation after stroke have regained a level of automaticity of walking comparable to healthy elderly people. Twenty stroke subjects and 20 healthy elderly controls and 20 healthy young controls were tested. To quantify the automaticity of walking subjects were required to walk simultaneously while performing an additional task(s).Subjects walked under four counterbalanced conditions: a single walking task, a dual-cognitive task, a dual-manual task and a triple task. Walking velocity, cadence, stride length and step length were analysed. Stroke subjects walked slower ($p = 0.001$), took shorter strides ($p = 0.002$) and fewer steps/min ($p = 0.04$) than elderly controls. Velocity declined significantly across conditions from the single to the dual-cognitive to the dual-manual and finally to the triple task ($p < 0.001$). Both stroke and elderly groups showed similar deterioration in walking velocity across conditions ($p = 0.99$) while the deterioration in the young subjects was significantly less than for healthy elderly subjects ($p=0.04$) and the stroke subjects ($p=0.02$). This group of rehabilitated stroke subjects display the same level of automaticity of walking as elderly controls, but both elderly controls and stroke subjects are less automated than young controls. This suggests that during rehabilitation every effort should be made to improve motor impairments, ie, strength and dexterity, so that the walking performance which is learnt and hence automated, is optimal.

11.5

Abnormal Motor Cortex Inhibition in Focal Hand Dystonia

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Single- and paired-pulse transcranial magnetic stimulation was used to investigate corticospinal excitability and intracortical inhibition respectively in focal hand dystonia (FHD). Motor evoked potentials (MEPs) of forearm muscles (flexor and extensor carpi radialis muscles: FCR and ECR) were examined in six patients with FHD and age-matched controls across four wrist angles (±15º and ±37º) with participants at rest and during 80° amplitude passive movement at 0.2 Hz. Confirming previous results, corticospinal excitability was greatest with the muscle in the shortened position (+37º for FCR and -37º for ECR) both at rest and during passive movement. There were no group differences in measures of excitability suggesting normal sensory receptor functioning in FHD. There was a significant interaction between group and joint angle on the right/affected side in the measure of intracortical inhibition (ICI). During static flexion phases of the FCR muscle, the least amount of inhibition for controls occurred at the most flexed phase (37º) and the greatest inhibition occurred at 15º. For the patients, this pattern of ICI was in the opposite direction, with the greatest amount of ICI occurring at 15º rather than 37º. During FCR extension phases for the controls, the most extended phase (-37º) had the least amount of ICI and at -15º controls demonstrated greatest amount of ICI. For the patients, the pattern of ICI was reversed, with the greatest amount of ICI at -37º. It appears that while there were changes in ICI across flexion and extension phases for both groups, the pattern of ICI was in the opposite direction for the patients compared to controls. These results support the growing body of evidence that patients with focal hand dystonia are characterized by abnormalities in inhibition within the motor system, in this case within motor cortex.

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