## Split Brain, Split Mind

## M. C. CORBALLIS

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

The split brain offers a unique opportunity to study mind-brain relations, since each disconnected half of the brain appears to act, in some ways at least, as a separate "mind." There are, however, many ways in which a split-brained person retains a mental unity. I will focus on visual connections and disconnections. Callosotomized people cannot compare visual stimuli presented in the opposite visual field even in terms of such simple dimensions as luminance or colour, but have little difficulty with these comparisons within visual fields. Yet they can judge apparent motion across the visual fields, and judge the alignment of sloping lines in the two fields. I will describe one remarkable split-brained man who not only fails on simple comparisons across fields, but also shows almost complete left hemineglect in simple reaction-time and in simple perceptual decisions. At the same time, however, he is able to integrate the two visual systems thought to underlie visual perception in the normal brain.

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## Is the Right Brain Left Behind in Dual Task Research?

M. S. RADEL<sup>a</sup> and K. MCFARLAND<sup>b</sup>

# <sup>a</sup> The Prince Charles Hospital, Brisbane, Queensland, Australia <sup>b</sup> School of Psychology, University of Queensland, Australia

Over the past decade, there has been continuing debate about the validity of the dual-task procedure as an index of lateralised cerebral processing. Despite evidence for the utility of dual-task methodology in providing an index of speech/language lateralisation in the left cerebral hemisphere, there remains a relative paucity of evidence with respect to its utility in lateralising those non-language functions for which the right hemisphere is superior. Part of the difficulty lies not only in producing a concurrent task for which the right hemisphere is clearly superior in the same way that speech/language is clearly mediated by the left hemisphere in dextrals but also in producing a motor task which demonstrates preferential right hemisphere mediation in the same way that variants of tapping tasks, requiring rapid fine-motor repositioning, have shown preferential left hemisphere mediation. A study was devised to examine the utility of a manipulospatial task in demonstrating selective left-hand disruption with the concurrent performance of a second task for which there is strong evidence of preferential right hemisphere processing, the mental rotation of figures. Response times for task completion were calculated for both left and right hands under Concurrent Task (motor task with mental rotation) and No Concurrent Task conditions. A repeated measures ANOVA showed a significant Hand x Condition interaction effect, F(1, 16) = 19.38, p < .001, which clearly demonstrated selective left hand disruption on the manipulospatial task with a concurrent mental rotation task. The results highlight the importance of carefully selecting both tasks in laterality dual task experiments so that both adequately engage the relevant processing capabilities of the hemisphere being examined.



## Concurrent-Task Assessment of Brain Functioning: Where to From Here?

## K. MCFARLAND

#### School of Psychology, University of Queensland, Australia

The past decade has seen considerable refinement of imaging technology that enables the study of the human brain at work. This has led to a profitable re-examination of many of the methods, procedures and paradigms developed in Psychology for examining sensory, motor and higher order cognitive functions. One particular behavioural assessment method developed largely in psychology and that has not been investigated in conjunction with brain imaging methodology is the concurrent-task (CT) procedure used for investigating brain lateralisation of cognitive functions. One reason for this neglect is that the CT procedure has relied on using equipment and task requirements that are not suitable for use with fMRI procedures (e.g. by requiring gross arm movements). A second reason for this neglect is that the CT procedure has by and large focused on examining the lateralisation of language functions to the neglect of right hemisphere functions, thus limiting its usefulness for assessing brain functioning as a whole and because of its failure to demonstrate doubledissociation of function. The study reported here successfully replicates past CT work using new experimental procedures and equipment which can appropriately be used with fMRI technology. These results established the utility of the CT methodology as a behavioural procedure and indicated that it can be used to assess the neurofunctional activity of a number of brain regions. This study not only establishes a CT procedure for use with imaging technology but also opens the way for its fMRI validation as an assessment instrument for use in clinical practice.

## Developmental Changes in Line Bisection: A Result of Callosal Maturation?

#### M. HAUSMANN, K. E. WALDIE, and M. C. CORBALLIS

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

Normal adults tend to bisect vertical lines to the left of the objective middle, especially when using the left hand. This bias has been attributed to the dominance of the right hemisphere in spatial attention (Bradshaw et al., 1986, Neuropsychologia, 24, 849-855). The left bias is still present, although typically reduced, if the right hand is used. For this dominance to persist when the right hand is used implies interhemispheric transfer of the attention-biased perceptual representation from the right hemisphere to the motor cortex of the left hemisphere. Due to the fact that the size of the corpus callosum increases up to about age 18 (Giedd et al., 1996, Developmental Brain Research, 91, 274-280), line bisection performance should vary as a function of age. We investigated line bisection in right-handed children and adults, classified into four different age groups: 10-12, 13-15, 18-21, and 24-53 years (N=98). All four groups showed the characteristic leftward bias when using the left hand. When using the right hand, the youngest group showed a rightward bias, whereas the other three groups all showed a leftward bias. This suggests a shift from contralateral to right-hemispheric control during puberty, and may reflect maturation of the corpus callosum.



Attentional Dynamics of Speech-Hand Gestures: Stabilisation of Functional Asymmetries

#### P. J. TREFFNER and M. PETER

## Centre for Active Visualisation, School of Information Technology, Griffith University, Gold Coast, Australia

Interest is rapidly growing in the hypothesis that natural language emerged from a more primitive set of linguistic acts based primarily on manual activity and hand gestures. Increasingly, researchers are investigating how hemispheric asymmetries are related to attentional and manual asymmetries (i.e., handedness). Both speech perception and production have origins in the dynamical generative movements of the vocal tract known as articulatory gestures. Thus, the notion of a "gesture" can be extended to both hand movements and speech articulation. The generative actions of the hands and vocal tract can therefore provide a basis for the (direct) perception of linguistic acts. Such gestures are best described using the methods of dynamical systems analysis since both perception and production can be described using the same commensurate language. Experiments were conducted using a phase transition paradigm to examine the coordination of speech-hand gestures in both left- and right-handed individuals. Results will address coordination (inphase vs. anti-phase), hand (left vs. right), lateralisation (left vs. right hemisphere), focus of attention (speech vs. tapping), and how dynamical constraints provide a foundation for human communicative acts. Predictions from the asymmetric HKB equation (e.g., Amazeen, Amazeen, Treffner, & Turvey, 1997, Attention and handedness in bimanual coordination dynamics. Journal of Experimental Psychology: HPP, 23, 1552-1560) confirm the attentional basis of functional asymmetry. Of significance will be a new understanding of the role of perceived synchrony ("P-centres") during gestural coordination.

#### Effects of Bimodal, Simultaneous Stimuli and Memorisation on Simple Reaction Time

#### J. G. ANSON and D. A. MURTAGH

## School of Physical Education, Neuromotor Control Laboratory and the Neuroscience Research Centre, University of Otago, Dunedin, New Zealand

Reaction time (RT) is shortest when uncertainty is minimal and the imperative stimulus is either auditory or tactile. Visual stimuli require more neural processing and result in longer RTs. Minimal uncertainty occurs when precise direction and distance parameters are precued (presented in advance) before the imperative stimulus occurs. This situation results in simple reaction time (SRT) and is exemplified by the start of a sprint race in track or swimming. In SRT, if both visual and auditory stimuli were presented simultaneously (bimodal presentation) RT would be predicted to reflect the duration required for auditory processing as only stimulus detection would be necessary for response initiation. Here, we report results from an SRT experiment that indicate a shortening of SRT accompanying bimodal (auditory + visual) stimuli. SRT was longest to a unimodal visual stimulus, shorter to a unimodal auditory stimulus and shortest when bimodal stimuli were employed. Furthermore, the augmenting effect of bimodal stimuli was not altered when memorisation of the precued parameters was required. One possible explanation for shorter SRT's to bimodal stimuli may be that attending to two stimulus modalities could increase attention and arousal to facilitate a gain in information processing speed that is greater than that which can be facilitated by auditory processing alone.

# Motor Imagery of Phasic Thumb Abduction Modulates Corticospinal Excitability, but not Intracortical Inhibition

#### C. M. STINEAR and W. D. BYBLOW

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

Like voluntary movement, motor imagery involves a muscle-specific increase in the excitability of the target muscle's motor cortical representation. Voluntary movement also involves a muscle-specific downregulation of intracortical inhibition (ICI), and an increase in spinal excitability. However, there is conflicting evidence of similar changes during motor imagery. Using transcranial magnetic stimulation (TMS), motor evoked potentials (MEPs) were evoked in abductor pollicis brevis (APB) and abductor digiti minimi (ADM) of the dominant hand in eight subjects, while they either rested, contracted their thenar muscles in time with a 1 Hz metronome, or imagined doing so. Magnetic stimuli were delivered during the 'on' and 'off' phases of the real and imagined movements. F-waves were also recorded from APB and ADM under rest and motor imagery conditions. It was found that both motor imagery and actual movement produced a muscle-specific, temporally modulated increase in corticospinal excitability. Actual movement also produced a muscle-specific, temporally modulated decrease in ICI, but motor imagery did not. The evidence of F-wave modulation was inconclusive. These results have potential implications for the use of motor imagery in neurological rehabilitation. Imagery may be more useful in a rehabilitation context when the aim is to maintain or increase the excitability of inhibitory interneurons and corticospinal neurons, rather than to decrease it.

#### **Muscle Tone: Problems of Assessment**

## J. M. AYERS<sup>a</sup> and J.G. ANSON<sup>b</sup>

# <sup>a</sup> School of Physiotherapy, University of Otago, Dunedin, New Zealand <sup>b</sup> School of Physical Education, University of Otago, Dunedin, New Zealand

The purpose of this study was to determine if muscle tone was assessed consistently by clinicians. Eight experienced physiotherapists were asked to assess the muscle tone of the leg of a stroke patient and of a subject with no neurological pathology. On completion of each assessment each clinician rated on a ratio scale, their overall impression of the subjects muscle tone. The importance of twenty four parameters in their assessment was rated on an interval scale. Clinicians and patients returned one week later to repeat the task. Analysis of results indicated a significant (p<0.05) difference in the tone ratings for the stroke and non stroke patients on both days. There was no significant difference (p>.05) in the ratings for each patient between day one and day two. The largest range of tone ratings was for the assessment of the non stroke patient on day one (42.3% - 71.2%). The smallest range was for the stroke patient on day two (79.8% - 99.0%). Intra clinician and inter clinician variability was found in the ratings of the parameters. Very low correlations (-.04 - .47) were found between the tone scale and the importance of each parameter. The clinicians indicated twenty four parameters additional to the twenty indicated in the literature. These results indicate that the concept of muscle tone is frequently subjective and should be interpreted cautiously carefully within the clinical setting.



## **Rope Jumping Performance Variability**

A. M. PELLEGRINI, L. H. SILVA and F. C. R. BUENO

Department of Physical Education, Labordam, Universidade Estadual Paulista, RC, São Paulo, Brazil

An experimental design with a secondary task was used to verify the variability in rope jumping. Six female and six male volunteers, university students, had their rope jumping performances video recorded under the following conditions: 1) jumping rope without a secondary task assigned (control); 2) jumping rope counting from one to ten as fast as possible; 3) jumping rope alternatively adding after ten 3 and 4 in the sequence (e.g. 9...10...13...17...20). The three conditions were performed initially in the subjects' natural rope jumping frequency and after a resting period in an imposed frequency of 1.66Hz. The dependent variable was the variability (SD) of relative phase (RP) defined for this study as the temporal difference from the loss of surface contact to the time the rope crossed the vertical line under the feet of the performer. Data from each cycle of the rope and of the jump were obtained from video analysis. ANOVA results revealed no differences among the mean RP of the three conditions in the subject's natural frequency. For 1.66Hz frequency, the post-hoc results indicated larger variability only under the condition with the heavier additional mental activity, when compared to the control condition. For all three conditions there were no differences between the two frequencies. It is suggested that rope jumping in the subject's natural frequency is not affected by a secondary verbal task. An imposed frequency coupled with an additional task can increase performance variability.

## A Comparison of Four Measures of Finger Tapping Speed

## M. CHRISTIANSEN and J. LEATHEM

Massey University, Wellington, New Zealand

The finger tapping test is a neuropsychological measure that assesses motor speed and motor control. A computer-mediated finger tapping instrument was developed. The purpose of this study was to obtain normative data for this instrument and to compare it to other traditional finger tapping devices. Normal volunteers (n=150) tested the Computer Finger Tapping Test (CFTT), the Halstead-Reitan Finger Tapping Test (H-R), a manual finger tapping test developed by Massey University, and the Western Psychological Services (WPS) digital finger tapping test. This sample of volunteers was stratified according to gender and age, with five age groups ranging from 15 years upwards. The CFTT showed similar psychometric properties to those of the other three tapping tests. Correlations between scores for the four tapping tests were obtained and these provided moderate to high values.



## A Kantian Analysis of Skill and Beauty

D. F. HIGHT<sup>a</sup>, D. WARD<sup>b</sup> and J. G. ANSON<sup>a</sup>

<sup>A</sup> Neuromotor Control Laboratory, School of Physical Education, University of Otago, Dunedin, New Zealand <sup>b</sup>Department of Philosophy, University of Otago, Dunedin, New Zealand

The relationship between the skillfulness of a movement and our aesthetic appreciation of it was philosophically explored. David Best proposed that in the appreciation of a movement, if it was considered efficient, it would also be considered beautiful, or aesthetic. Christopher Cordner disagreed, noting that some highly efficient movements afford very little aesthetic appreciation. The aesthetic theory of Immanuel Kant was used to understand the contention. Kant's aesthetic philosophy was seen to be commensurate with the understanding of motor learning first put forward by Nikolai Bernstein. His notion of the *reciprocity* of the agent with its environment, in the utilization, and not the suppression, of biophysical reactive phenomena, is key to understanding our aesthetic appreciation of a movement. Our perception of the locus of the *will* of the person within the creation of a movement generates, according to Kant, a dynamic interplay between the imagination and the understanding which results in the judgement of beauty. It is concluded that the contention between Best and Cordner can be fully resolved, and that dynamical theories of skill acquisition elucidate how Kant's aesthetic theory applies to movement.

## Possibility of the Dominant Upper Limb to Utilise Gravity More Effectively

B. GUTNIK<sup>a</sup> and G. HUDSON<sup>b</sup>

<sup>*a*</sup> School of Bioscience, UNITEC, Auckland, New Zealand <sup>*b*</sup> School of Engineering, UNITEC, Auckland, New Zealand

We investigated kinetic parameters of fast repetitive flexion-extensions of the forearm using a WACAM<sup>™</sup> graphic design tablet connected to an IBM PC. Rapid, harmonic-like (1.73 – 3.88 Hz, 21-106 mm amplitude) flexion-extensions of both forearms of 8 strongly righthanded young, blind-folded participants (females) were recorded over 20 seconds. The forearms were loaded with an extra 1-kg applied to the wrist joint. For analysis the trajectories were divided into acceleration and deceleration phases. The net forces and impulses were computed and averaged over the trial for each forearm. During acceleration upward the right forearms demonstrated higher magnitudes of force and larger impulses than the left, but remarkably, while accelerating downward, the left forearms consistently showed larger magnitudes of these parameters. Although movement initiation may be due to the motor cortex, the sequence of events is likely to be under subcortical or spinal-cord control. However, the lateral differences observed may be due to possible variations in the architectonics of left and right-limb muscles. In our previous experiments, muscles of the dominant extremity demonstrated greater stiffness than of the non-dominant. If the system is considered as a mass-spring model (two opposing forces from springs and force of gravity) the following explanation is possible. The downward movement of the non-dominant forearm involves contributions from both spring elements, whereas the dominant forearm in downward movement operates with only one resisting element and gravity force. This mathematical approach reflects closely the theoretical mechanical model.



## **DID NOT PRESENT**

#### Interaction of Sensory Systems for Support of Vertical Posture

#### V. I. KOBRIN, A. N. SINEL'NIKOVA, and A. A. BESNOSOVA

## Department of Physiology, State Classical Academy n. Maimonides, Moscow, Russia

Support of vertical posture is the outcome of an interaction of visual, vestibular and proprioceptive analysers. The degree of sharing of that or other analyzer in regulation of vertical stability varies and depends on environmental conditions, and the functional condition of the central nervous system (CNS). The purpose of the present work was to study the interaction of visual and proprioceptive analyzers in healthy individuals and in patients with children's cerebral paralysis (CCP) by varying proprioceptive load (PL), visual stimulation (VS) and visual biological feedback (VBF). The average frequency of oscillation of the center of the body gravity (CBG) in frontal and sagittal planes was measured for assessment of the vertical posture. The VBF was carried out as computer visualization of a signal from stabilographic platform and its monitoring of volunteers on the target of screen of computer. A standard test was used for VS. The test included five sequential stages of visual stimulation with simultaneous registration in the actual time scale of the position of CBG. The PL was carried out with the help of cosmic suit "Adeli". The oscillations of CBG healthy volunteers in frontal and sagittal planes depended on the direction of movement of a visual stimulus. With the PL the modulating influence of VS decreased. The vertical stability was reduced by the repeated training in the system of VBF in 60 percent of volunteers. For the patients with CCP, vertical stability did not depend on the direction of movement of the visual stimulus. A single PL increased the amplitude of oscillation of CBG in the frontal plane by the movement of VS to the left and downwards. With training in the system of VBF the vertical stability increased in 50 percent of the patients with CCP. Our results show that the damage of CNS in prenatal or early postnatal periods (an example of CCP) leads to the decrease of sharing the phylogenetically younger structure of the brain in regulation of vertical posture. At the same time, one can think, that the change of the modulating influence of single VS on initial vertical posture by increasing PL is stipulated by a modification of the interaction of sensory systems. Thus, the externally organized visual biological feedback allows the CNS to compensate insufficiency of the information, received by the initially weak afferent stream, for its functional adaptive reorganization.

# Entirely Intrasaccadic Target Blanking still Reduces Saccadic Suppression of Displacement

# M. R. MACASKILL<sup>a</sup>, H. DEUBEL<sup>b</sup>, T. J. ANDERSON<sup>a</sup> and R. D. JONES<sup>a</sup>

## <sup>a</sup>Department of Medicine, Christchurch School of Medicine & Health Sciences, Christchurch, New Zealand <sup>b</sup>Max Planck Institute for Psychology, Ludwig Maximilians University, Munich, Germany

Instantaneous object displacements occurring during saccades can go unperceived (saccadic suppression of displacement, SSD). A temporal blank between the successive target locations abolishes the effect, contrary to other forms of change blindness. SSD's function may be to bias the visual system to ignore small visual position errors after saccades in favour of assuming that the visual world is stable. Transient target disappearance violates the stability assumption, allowing displacement to be perceived. The optimum blanking period is > 100 ms, which is longer than the normal saccade duration, confounding whether it is the blank period per se, or its persistence into the succeeding fixation period, that causes the effect. We therefore examined the effect in a person with severely slowed saccades (due to spinocerebellar ataxia type 2), in whom saccades lasted hundreds rather than tens of milliseconds. A forced-choice response indicated whether a target was perceived to have been displaced leftward or rightward during a saccade (detected by infrared oculography). Blank periods increased the per cent correct for both the patient and for 4 controls even when the blank was entirely intrasaccadic. Transient visual instability can therefore disrupt SSD even when not extending into stable fixation periods. Small displacements during saccades are accessible to the visual system even if subsequently suppressed.



Separate Control of Decision Making and Arousal by the Behavioural Inhibition System

### N. MCNAUGHTON

## Department of Psychology and the Neuroscience Research Centre, University of Otago, Dunedin, New Zealand

Gray and McNaughton (The Neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system, Oxford: Oxford University Press, 2000) postulate that anxiety involves a Behavioural Inhibition System distributed between the septo-hippocampal system and the amygdala. When approach-avoidance conflict occurs, the septo-hippocampal system detects the conflict and generates behavioural inhibition. The amygdala increases arousal. The theory leaves unclear why hippocampal lesions (removing the conflict detector) allow increased arousal and how the amygdala increases arousal in the absence of such a conflict detector. However, Gray and Smith (An arousal-decision model for partial reinforcement and discrimination learning. In: Animal discrimination learning, edited by R. Gilbert and N. S. Sutherland, London: Academic Press, 1969, p. 243-272) show that decision is based on subtraction between approach and avoidance tendencies but arousal is based on addition. The Behavioural Inhibition System also acts on these two outputs differently. It is specific to avoidance with respect to decision making but general to approach and avoidance with respect to arousal. Combining these ideas yields a model in which there are separate means of detecting conflict, and separate outputs as a result of such detection, that the Behavioural Inhibition System uses to control decision making and arousal respectively. This raises the possibility that the outputs of the system may be different in conventional memory tasks as compared to tasks involving high levels of arousal.

## Does P3b Latency Reflect the Duration of Stimulus Evaluation? Disconfirming Evidence

## C. A. CHRISTENSEN, M. E. MCDADE and K. J. DRAKE

#### Department of Psychology, Vassar College, Poughkeepsie, New York, USA

According to the classic view the latency of the P3b evoked potential reflects the time taken for perceptual evaluation in cognitive tasks. This attribution stems from the often-replicated finding that degradation of stimuli delays the P3b peak. Consequently investigators often use P3b latency to estimate the duration of perceptual evaluation. We were not able to replicate the classic finding when care was taken to avoid confusing the P3b with the P4 peak that follows (Christensen, Davidheiser, Gibbons and Drake, 2000, Neurosci. Abstr., 26, 749.16). The latency and amplitude of the P4 peak increase when reaction times are prolonged, exactly the case on degraded trials. The P4 peak is easily misidentified as a delayed P3b when search windows are long enough to include both peaks which is a common practice. Despite our reservations we wondered whether the standard view might be supported if multiple stimuli were used instead of two stimuli in the two-choice discriminations used in the past. Instead we employed same-different discriminations that were graded in difficulty. The task was evaluated in 21 young adults using circles with wedges of various sizes removed and again with irregular polygons. Reaction times were significantly prolonged and accuracies reduced with both kinds of stimuli. Robust P3b peaks were also observed, but in neither case was the P3b peak delayed when the perceptual evaluation was difficult, calling the standard view into question.



# A Brain Event-Related Potential (ERP) Correlate of Individual Differences in Interrogative Suggestibility (IS)

R. HOWARD and J. GOH

#### Department of Social Work & Psychology, National University of Singapore, Singapore

Although it is known that individuals differ in their tendency to yield to leading questions in an interrogative interview, making them more or less suggestible, the neurocognitive mechanisms underlying this remain unknown. The present study explored these mechanisms using a well-known behavioural protocol for measuring interrogative suggestibility, Gudjonsson's Suggestibility Scales (GSS). The latter exist in two parallel forms, GSS1 and GSS2, where the sole difference is the narrative used for memory recall. ERPs elicited by story-relevant and story-irrelevant pictures were recorded, from midline electrodes, during the interval between immediate and delayed recall in groups of high- and low-suggestible participants. A 3-stimulus oddball paradigm was used where story-relevant and -irrelevant pictures each occurred on 10% of trials (rare targets), and geometric shapes on 80% (frequent non-targets). Participants (N=20) underwent the GSS1 protocol, such that GSS1 pictures were story-relevant and GSS2 pictures were story-irrelevant. The results indicated that a large frontal positivity occurring 300-600 ms post-stimulus was (i) modulated by the storyrelevance of the pictures and (ii) was of greater amplitude in suggestible than non-suggestible participants. The results shed light on the neural process underlying the formation of false memories: they suggest that frontal mechanisms thought to be important in controlling and monitoring memory recall processes may operate differently in subjects who falsely recall elements that were not present in the original narrative.

## Context-Processing Differs as a Function of Age: Convergent Evidence from Simultaneous CNS/ANS Measures

K. KANG<sup>a,b,</sup> L. WILLIAMS<sup>a,b</sup>, D. HERMENS<sup>a,b</sup>, A. HAIG<sup>a</sup> and E. GORDON<sup>a,c</sup>

<sup>a</sup> Brain Dynamics Centre, Westmead Hospital, Australia <sup>b</sup> Cognitive Neuroscience Unit, School of Psychology, University of Sydney, Australia <sup>c</sup>Department of Psychological Medicine, University of Sydney, Australia

Research suggests that simple reaction time (RT) is not affected by either age or the nature of the P300 ERP response, despite the fact that P300 is representative of contextual processing and is greatly affected by the age of the subject. However, there is evidence that P300 is not only modulated by pre-stimulus neural activation, but also represents only one step in the processing of contextually relevant information. The authors conducted an analysis of the effect of age on two measures of contextual processing (P300 ERP and Gamma-2 phase synchrony) and two variables that are considered to modulate these measures (pre-stimulus EEG Theta and autonomic arousal as indexed by tonic skin conductance level). Data were collected from 120 healthy subjects' (aged 11-70 yrs) performance in a conventional auditory oddball paradigm. All four measures showed significant changes across age with the largest apparent change being that of decreased arousal with increasing age, suggesting that changes in contextual processing may be subordinate to those in baseline neural function. In addition, significant functional relationships were found between pre-stimulus Theta and P300, and Gamma-2 phase synchrony and RT. These results fit with models of P300 and Theta as concomitants of selective sensory inhibition in attention processes, as modulated by the hippocampus and reticular nucleus of the thalamus. Further, the Gamma-2 response was interpreted as a second stage of contextual processing, involved in the binding of stimulus and response characteristics and being the possible cause of the lack of performance differences between age groups due to Gamma-2's own very large within-group variability. While this study elucidates the possible interrelationships between the variables underlying contextual processing, a future study with a larger number of subjects will be undertaken to explore these relationships.

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## The Neurocognition of Sentence Processing: An ERP Approach

P. COLLARD, J. M. MCALLISTER, and I. J. KIRK

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

The past decade has seen much exploitation of evoked response potential (ERP) approaches in the studying of the temporo-spatial aspects of the neurocognition of sentence processing. Such studies have identified reliable markers of syntactic anomaly such as Left Anterior Negativity (Neville et al., 1991, Journal of Cognitive Neuroscience, 3, 151 - 165) and the P600/Syntatic Positive Shift (Ousterhout & Holcomb, 1992, Journal of Memory and Language, 31, 785 - 806 and Hargoort, Brown and Groothusen, 1993, Language and Cognitive Processing, 8, 439 - 483). Possibilities for the analysis of existing data from sentence processing studies extend beyond ERP analyses. Using a Band Power method similar to the one outlined in Pfurtscheller & Lopes da Silva (1999, Clinical Neuropsychology, 110, 1842 - 1857), data from a study involving violation of subject verb agreement (e.g. 'The talented violinist begin to play.') were analysed. Initial results indicate that, relative to the same sentences being presented without morpho-syntactic violations (e.g. 'The talented violinist **begins** to play.'), these violations induce widespread patterns of synchronisation and desynchronistaion. These include, left temporal theta synchronizations (4 - 7 Hz) around 500ms post stimulus and left temporo-pariatal low beta desynchronisations (13 – 18 Hz) around 600ms post stimulus. Such results may be utilized in theories that seek to describe both the time course and neuroarchitecture of sentence processing.

### Differential Topographies Between Subtypes of Nouns and Verbs

## S. FAIRHALL

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

An associative model of neural connectivity posits that neural networks to stimuli will be made up of areas which are commonly activated together. This predicts that words that are connected to visual stimuli will have networks including the visual association cortex and that words that are connected to movement will have networks including the pre-motor and supplementary motor areas. The present study investigated the difference in event related potentials and spectral power to nouns with high and low imagability ratings and to verbs with high and low motor associations.



## The Children of Visual Hemineglect; Even More Bizarre Than Their Parents?

## J. A. OGDEN

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

Hemineglect is a neurological disorder that follows focal damage to one hemisphere of the brain, commonly the right. Following an acute brain lesion, hemineglect is quite common, but as it spontaneously resolves in most patients, persisting hemineglect is relatively rare. The hemineglect patient demonstrates a wide range of disordered behaviours, but all involve "ignoring" or "neglecting" stimuli (or images) in the side of space opposite to the brain lesion. Thus patients with left neglect might copy only the right side of a picture, or bisect lines to the right of the true centre. Neglect in the visual modality is the most common form of neglect, and in the past visual hemineglect was conceptualised as a single disorder. Over the past 15 years the study of neglect arena. In this paper some of the elegant and creative research paradigms used by cognitive neuropsychologists will be described. These studies demonstrate that visual hemineglect can be dissected into different subtypes, and that neglect behaviours can be influenced by a range of variables. The bizarre nature of neglect disorders is also underlined by these studies.

## Case Studies on a Unimanual and Bimanual Reaction Time Task in People with Unilateral Stroke

Y-C. SHEN and L. FRANZ

## Department of Psychology and Neuroscience Research Centre, University of Otago, Dunedin, New Zealand

This is a preliminary report on a series of case studies conducted on people with unilateral stroke resulting in hemiparesis. The experimental question of interest is whether bimanual coordination facilitates performance of the affected (damaged) hand on a simple motor task. The sample currently includes 7 individuals participating in repeated testing sessions over the course of 6 months, on a simple reaction time task that assesses response preparation time. The task involves speeded simple reaction time (RT) to a stimulus presented visually on a computer monitor. In different blocks of trials, the left hand performs alone, the right hand performs alone (unimanual), or both hands perform together (bimanual). Although data collection is still underway for the majority of participants and controls matched for age, sex, and handedness, we have analysed one complete set of data on one participant. This individual shows a complete lack of sensation in the impaired limb (as assessed by independent experiments conducted on sensation), but nonetheless shows marked synchrony in the bimanual task. In addition, he shows improvement across testing sessions on the RT task performed by the impaired limb. These data and those of control participants will be discussed.



Long Term Behavioural, Psychiatric and Cognitive Outcomes Following Mild Head Injury in Childhood

> A. MCKINLAY<sup>a</sup>, J. C. DALRYMPLE-ALFORD<sup>a</sup>, J. L. HORWOOD<sup>b</sup> and D. M. FERGUSSON<sup>b</sup>

Christchurch Movement Disorders Brain Research Group, <sup>a</sup> Psychology Department, Canterbury University, Christchurch, New Zealand <sup>b</sup> Christchurch Health and Development Study, Christchurch School of Medicine, Christchurch, New Zealand

The mixed evidence for adverse effects of mild head injury in childhood may reflect methodological problems. We examined long-term outcomes in mid to late childhood as a function of severity of mild injury and age at injury, using a large birth cohort and a fully prospective longitudinal design. Prior to age ten, 96 cases received outpatient medical attention only and 36 inpatient cases were hospitalised overnight. The remainder of the cohort (613-807, pending exclusions and missing data) provided a non-injured reference group. The inpatient group, but not the outpatient group, displayed increased hyperactivity/inattention and conduct disorder when rated by both mothers and teachers between ages 10-13 (ES, d = 0.65 to 0.84). These findings remained following statistical control for several pre-injury, family and demographic characteristics. Progressively increasing deficits were generally evident over ages 7-13, even when matched against a subset of children in the reference group who received equivalent ratings at age seven. At 14 to 16 years, there was also an increased likelihood of psychiatric outcomes (DSM-III-R) of ADHD, CD/ODD and substance abuse/dependence, but not anxiety, mood and alcohol abuse, especially in the inpatient subgroup injured prior to age five. No cognitive/academic deficits were evident for any group. These findings support the view that cases of more severe mild head injury in childhood produce some long-term adverse outcomes.

## A Test of the Magnosystem Theory of Dyslexia

## K. E. WALDIE, C. M. WHITE, S. M. H. ROLFE and I. J. KIRK

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

In individuals with developmental dyslexia, the primary cognitive impairment is thought to involve the inability to represent or recall speech sounds (phonological representations). A currently popular but controversial view of the neural basis of dyslexia is that reading impairments result from a "bottom-up" problem in processing rapidly sequenced auditory stimuli (the "magnosystem" theory). Dyslexics may not be able to fully utilize a left hemisphere timing mechanism to employ grapheme-phoneme correspondence rules rapidly enough to achieve reading fluency (Stein, 1994, International Journal of Psychophysiology, **18**, 241-249). We sought to determine whether children with phonological dyslexia (n=11)differed from children with general cognitive deficits ("garden variety poor readers;" GPRs, n=11), and from control children and adults (n=22) in their ability to discriminate auditory tones that varied according to frequency, tone length and ISI. Although dyslexics performed more poorly overall than the control groups, there were no differences between the children with dyslexia and the GPR group. Moreover, the dyslexics often performed better when the sound frequencies changed rapidly rather than slowly -a finding that would not be predicted by the magnosystem theory. A lateralised lexical decision task, used to assess hemispheric specialisation for reading, showed a left hemisphere advantage for all subjects. Taken together, although poor temporal processing appears to be associated with cognitive dysfunction in general, the magnocellular system may not be specifically involved. The findings also raise questions regarding the causal nature of timing deficits and reading impairment.



# Differential Processing of Fear and Happy Faces at Sub- vs Supra-Threshold Levels: An Event-Related Potential Study

## B. LIDDELL<sup>a</sup>, L. WILLIAMS<sup>a</sup> and E. GORDON<sup>b</sup>

 <sup>a</sup> School of Psychology, The University of Sydney, NSW, Australia, Cogntive Neuroscience Unit, The Brain Dynamics Centre, Westmead Hospital, NSW, Australia
<sup>b</sup> The Brain Resource Company, Suite 202, 55 Mountain Street, Ultimo, NSW, Australia

It has been proposed that there are two parallel neural pathways involved in the processing of positive versus negative emotions (Sokolov and Boucsein, 2000). In this study, we used fear and happy face stimuli as exemplars of the negative and positive emotion dichotomy and presented them either at a supra-threshold level (500ms) or at a sub-threshold level (10ms followed immediately by a neutral face stimulus for 150ms following a backward masking protocol). The first results of this study reveal that the processing of the sub-threshold fear condition is distinguished (enhanced amplitude) from the processing of the supra-threshold fear stimuli at the N2 ERP component. This component has been implicated in the more automatic aspect of emotion processing. The results also suggest that there is a distinction in ERP amplitude and latency in response to stimuli related to social survival (happy) versus those related to physical survival (fear). This distinction remains apparent even when faces are presented at a sub-threshold level. These findings have implications for understanding the cognitive neuroscience of emotion, and disorders involving these 'emotional brain' networks, such as post-traumatic stress and schizophrenia.

## Electrophysiological Correlates of own and Familiar Face Recognition

# D. WISWEDE, J. HAMM, W. CLAPP and M. CORBALLIS

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

Electrophysiological studies of face recognition have shown that the N170 component, which is increased after presenting face pictures, is not influenced by familiarity (Eimer, 2000, Clinical Neurophysiology, 111, 694-705). However, Porterfield and Tanaka (2001, unpublished) found an increased N170 after presenting the subject's own face. We used high-density EEG to examine the effect of face familiarity, not only on the wellexamined early components, but also on later stages of face recognition. Twenty subjects viewed frontal face pictures on a screen and were asked to detect a previously unknown target face within a sequence of familiar faces (classmates), unfamiliar faces, and the subject's own face. A slightly increased N170 was found over occipito-temporal areas only for the target face. The first effects of familiarity were found between 220 and 300 ms after stimulus onset and were strongest between 300 and 500 ms. The most pronounced N400s were elicited by the "own" and by the target face. Although subjects were not asked to pay attention to their own face, it elicited a positive peak on parieto-central areas around 400 ms, whereas the target face elicited a very similarly distributed component 80 ms later in time. LORETA source analysis showed temporal areas (STG, MTG and fusiform gyrus) to be activated by all face groups, whereas the fusiform gyrus and the frontal lobe appeared to be involved in familiarity judgements.



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## Hemispheric Interactions in Dual-Stream Tasks

#### A. HOLLÄNDER, M. C. CORBALLIS and J. P. HAMM

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

If observers are asked to detect two targets in a stream of stimuli presented rapidly to a single location, detection of the second target (T2) is typically impaired if it closely follows the first (T1), a phenomenon known as the attentional blink. In our study, we presented letters in two parallel streams, one in each visual field. The targets T1 and T2 could occur either in the same, or in opposite streams. Under the same stream condition there was an attentional blink, which occurred 200-400 ms after T1 presentation. This effect was much more pronounced when both targets appeared in the right stream, whereas none of the decrements was significant when the targets were in the left stream. Furthermore the results indicate that the attentional blink depends on the nature of the task to be performed on T1. We found that these deficits in detecting T2 required that observers both identify and locate T1; they did not occur when observers simply located which stream T1 appeared in. A surprising aspect of the present results is that presentation of T1 in one stream did not cause an attentional blink in the other. Thus, the mechanisms underlying the attentional blink appeared to be confined to one hemisphere, and in particular to the left hemisphere. This reinforces evidence that the left hemisphere is fundamentally a sequential processor, whereas the right hemisphere is more adept at processing even sequential information in parallel.

## Neuropsychological Outcome of Electrical Injury

## J. LEATHEM and J. TAYLOR

#### Massey University, Wellington, New Zealand

Electrical injury (EI) is associated with neuropsychological sequelae if there is either direct contact with the head, and/or hypoxia. A head injury may also have been sustained if the victim was thrown or fell as a result of the EI. In their review of eight studies involving 65 participants, Duff and McCaffrey (2001), conclude that EI is associated most frequently with memory difficulties (37%), followed by difficulty with attention (14.8%), motor speed (12.8%), information processing speed (12.5%) and higher executive function (9.6%). Depression and irritability are also apparent after EI (Barrash, Kealey & Janus, 1996; Plishkin, et al., 1999). Problems typically appear later than earlier, and are unrelated to severity of, physical injury, voltage exposure, litigation or previous psychiatric history. The neuropsychological results of four individuals who sustained EI and who subsequently sought medical attention for changes in memory and mood are reported. All injuries involved DC current and low voltage (<1000 volts) contact without loss of consciousness. All four reported everyday difficulties with attention, memory, depression and irritability, verified by a significant other. Formal cognitive assessment however revealed intact verbal/visual memory in all clients, with some individual specific difficulties.



# Evaluation of a Structured Group Format Memory Rehabilitation Program for Adults Following Brain Injury

### K. THICKPENNY

#### University of Auckland, Auckland, New Zealand

Memory impairments follow traumatic brain injury (TBI) and cerebral vascular accident (CVA). Memory deficits have a profound impact on the capacity to engage in rehabilitation and independent living. This study evaluated the effectiveness of an 8-session structured group format memory rehabilitation program for adults following TBI and CVA. Fourteen participants aged 16 to 50 years were randomly assigned to either wait-list control or experimental groups. Neuropsychological assessments of memory and memory related performance (i.e., verbal recall, visual recall, attention), and measures assessing functional and everyday memory were administered before the wait list (where applicable), before treatment, after treatment and at one-month follow-up. Results indicate that participation in the Memory Group significantly increased participants' knowledge of memory and memory strategies; significantly increased participants' use of memory aids and strategies as rated by participants and significant others; and significantly reduced behaviours indicative of memory impairment as rated by participants and significant others. Participation in the Memory Group also had a positive effect on participant performance on selected neuropsychological assessments of memory and memory related performance (i.e., California Verbal Learning Test: Long Delay Free Recall; Visual Paired Associates Subtest: Delayed; Logical Memory Subtest: Immediate and Delayed; and on a measure of visual attention response time). All the significant improvements outlined above exceeded those experienced by waiting-list controls. The positive effects of the group were maintained one-month after participation in the group. Clinical implications and future research will be discussed.

# Clarifying the Nature of the Link Between Posttraumatic Stress Disorder (PTSD) and Cognitive Functioning

#### A. DANCKWERTS and J. LEATHEM

#### School of Psychology, Massey University, Wellington, New Zealand

Of the symptoms associated with post-traumatic stress disorder (PTSD), impairment of memory is the most difficult to understand. Some suggest that the problem is caused by the chemistry of stress (cortisol) acting to depress right hippocampal function which in turn impairs hippocampal dependent learning and memory function. The pattern of learning and memory difficulty is similar to that experienced by people after traumatic brain injury (TBI), who experience learning and memory difficulties but have not been shown to experience hippocampal density loss. Examination of the research literature on PTSD raises questions regarding the assumptions and logic of some the associations made with regard to cognitive function, and methodological problems and concerns that appear to arise on several levels. These will be discussed in more detail in the presentation. A research programme will be discussed that proposes to clarify the true nature of PTSD-related cognitive impairment by using comprehensive neuropsychological assessment of attention and memory functioning in a comparison of civilian groups diagnosed with PTSD, and TBI groups with and without PTSD.



# A Study Investigating the Effects of Tai Chi Chuan in Individuals with Traumatic Brain Injury

## C. S. GEMMELL

#### School of Psychology, Massey University, Wellington, New Zealand

Tai Chi Chuan (or Tai Chi) is a Chinese Martial Art that has been shown to improve mood, balance, coordination, cardiovascular and respiratory functions, fatigue, general wellbeing, motor skills, and to reduce stress. Research on Tai Chi has mainly been conducted with older adults with little emphasis in other populations. This study explored whether Tai Chi had similar effects on individuals with traumatic brain injury (TBI). Eighteen participants with TBI, (nine females and nine males) either undertook a course in Tai Chi (N=9) or were on a waiting list (Control group, N=9). The Tai Chi group attended twice weekly, for 45 minutes over a 6-week period. Before and after each Tai Chi class the Visual Analogue Mood Scale (VAMS) was completed to determine whether there were any immediate effects on mood. Both groups also completed the Medical Outcome Scale Short Form 36 (SF-36) and the Rosenberg Self-Esteem Scale (RSES) (3 weekly) before, during, at the completion of the Tai Chi course, and 3 weeks after the experiment finished. Responses of the Tai Chi group were compared with the control group, to determine whether there were any group differences in physical and emotional functions, self-esteem, social functioning, and general perceptions of health. The results of this study confirm that Tai Chi improves mood in individuals with TBI. Individuals were less tense, afraid, confused, angry and sad, and felt more energetic and happy immediately after Tai Chi practice. No significant differences between groups were found for physical and emotional functioning.

## Motor Deficits and Recovery During the First 6 Months Following Mild-to-Moderate Closed Head Injury

#### M. H. HEITGER, T. J. ANDERSON and R. D. JONES

## Department of Medicine, Christchurch School of Medicine & Health Sciences, Christchurch, New Zealand

Diffuse axonal injury caused by mild-to-moderate closed head injury (CHI) is likely to affect the neural networks concerned with oculomotor and sensory-motor control. We compared mild-to-moderate CHI patients and matched controls at 1 week, 3 months and 6 months post injury on different types of saccades, oculomotor smooth pursuit, upper-limb sensory-motor performance, and the SF-36 health assessment survey. This interim analysis comprised 37 matched pairs at 1 week and 3 months and a subset of 28 pairs at 6 months. At 1 week, the CHI group demonstrated prolonged saccade latencies, increased directional errors and decreased saccade accuracy in combination with increased arm movement reaction time, decreased arm movement speed, and decreased motor accuracy and longer lags in the sensory-motor tests. Fast oculomotor smooth pursuit was mildly impaired. SF-36 was impaired on all 8 scales and summary scores. At 3 months, several oculomotor and sensorymotor deficits remained, indicating persistent cerebral dysfunction despite normalisation of the SF-36 scores. No deficits were found at 6 months post injury. These results support our earlier findings that mild-to-moderate CHI can cause impairment of multiple motor systems and suggest that these motor tests can provide sensitive markers of neurophysiological dysfunction in the brain. Furthermore, preliminary analyses indicate correlations between several motor measures at +1 week and SF-36 scores at +3 months, suggesting that computerized motor assessment might provide early indications of outcome following mildto-moderate CHI.



## Evaluation of Information Provided to People in New Zealand After They Have Experienced TBI

#### C. MOORE and J. LEATHEM

#### School of Psychology, Massey University, Wellington, New Zealand

This presentation will report on the outcomes of a survey distributed throughout New Zealand to a representative sample of GP's and all accident and emergency departments. In all, 244 valid surveys were returned, (229 from GPs and 15 from hospital Emergency Departments) giving a return rate of 50.1%. Included with the returned surveys, as requested were 145 samples of information that these agencies typically provide to patients. Overall, 45.9% of respondents (93.4% of hospitals & 42.8% of GPs) provided an information sheet to patients with a confirmed or suspected TBI, generally covering signs and symptoms, when to seek medical attention, and advice about pain relief, driving, alcohol and rest. Of the hospital information sheets, 92.9% had a FRE score of over 61 (the level recommended to be able to be read by 70% of the population), compared to 56% those provided by GP's. Information sheets ranged in length from ½ a page to 10 pages with those provided by hospitals generally longer than those provided by GP's (33.6 compared to 12.9 sentences). Other findings and recommendations for guidelines for information provided by health professionals about TBI will be presented.

#### **Detection of Focal Activity in the EEG**

B. VANRUMSTE<sup>ab</sup>, R. D. JONES<sup>ac</sup> and P. J. BONES<sup>b</sup>

 <sup>a</sup> Department Medical Physics & Bioengineering, Christchurch Hospital, Christchurch,New Zealand
<sup>b</sup> Department of Electrical and Computer Engineering, University of Canterbury, Christchurch, New Zealand
<sup>c</sup> Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand

We have developed an algorithm for detection of focal activity in the EEG. The EEG is divided into overlapping epochs, which are processed in two steps, as follows. The first step is singular value decomposition (SVD), which identifies the number of asynchronous active sources in an epoch. The algorithm proceeds to the second step if there is one dominant source. In the second step, EEG dipole source analysis, using a single dipole model, is applied to the EEG. This yields dipole parameters and a residual energy (RE), being the energy in the EEG which cannot be explained by the dipole model. The lower the RE the better the EEG represents activity coming from a single focal source. An EEG epoch triggers the detection algorithm when SVD indicates a dominant source and the RE is low. A validation of the algorithm has been carried out on a simulated EEG composed of alpha activity of 9 Hz and focal activity of 5 Hz with increasing amplitude, representing the start of a seizure. The focal activity was detected as soon as the energy contribution of this signal became higher than that of the alpha activity. The algorithm has also been applied to real EEG containing two spikes and an eye-blink artifact. The SVD indicated a dominant source active for all three events. The RE was low during all three events compared to the background EEG. These preliminary results indicate that the method can be used to detect seizure and spikes with a focal origin. In addition, the dipole parameters can provide valuable information on the location of the epileptogenic source.

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### Schizophrenia and Communication Between the Hemispheres

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## K. J. BARNETT, M. C. CORBALLIS and I. J. KIRK

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

It has been demonstrated that stimuli presented simultaneously to both hemispheres of the brain will be processed more rapidly than stimuli presented to only one hemisphere. It has been suggested that there may be a deficit in this "bilateral field advantage" in people with schizophrenia due to a lack of cooperation between the hemispheres. The paper presented will report preliminary results from behavioural data collected in order to study communication between the hemispheres of the brain in 10 participants diagnosed with schizophrenia and 20 controls with no psychiatric diagnosis. All participants underwent 256 trials in which they were required to judge whether basic computer presented stimuli ("A's" and "B's") were the same or different. Stimuli were presented rapidly to either a single visual field, or across both visual fields, and subjects made a "same" or "different" judgement. The data suggest a general slowing of response times and a deficit in the transfer of information between the 2 hemispheres in people with schizophrenia. Findings will be discussed in terms of the "laterality hypothesis" of schizophrenia, which argues for alteration of hemispheric functions and dysfunctional information transfer between the two cerebral hemispheres in those diagnosed with schizophrenia.

## Nitric Oxide Synthase and Arginase Expression in the Rat Hippocampus Following Unilateral Vestibular Deafferentation

#### P. F. SMITH, J. KING, Y. ZHENG, P. LIU and C. L. DARLINGTON

## Vestibular Research Group, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

Increasing behavioural, electrophysiological and biochemical evidence suggests that damage to the peripheral vestibular system results in dynamic changes in the hippocampus, some of which may be long-term. In order to better understand the possible relationship between changes in nitric oxide synthase (NOS) and arginase expression in the hippocampus following unilateral vestibular deafferentation (UVD), we used Western blotting to examine the expression of neuronal NOS (nNOS), endothelial NOS (eNOS) and arginase in the ipsilateral and contralateral CA1, CA2/3 and dentate gyrus (DG) in rats at 10 hs and 2 weeks following UVD, sham surgery or anaesthetic (fentanyl citrate/metotomadine) without surgery. Consistent with our previous studies, a decrease in nNOS expression was found in the ipsilateral DG at 2 weeks but not 10 hs post-UVD (p < 0.05). A significant decrease in eNOS was observed in the contralateral CA2 at 10 hs post-UVD (p < 0.01). eNOS expression was also increased in the contralateral DG at 10 hs post-UVD (p < 0.01). No significant changes in arginase expression were observed. These results add to the increasing evidence for complex changes in NOS expression in various subregions of the hippocampus following UVD.



# Contribution of Visual Cues and Vestibular Cues to Egocentric Spatial Memory in the Morris Water Maze

Y. ZHENG<sup>a</sup>, J. M. PEARCE<sup>b</sup>, P. F. SMITH<sup>a</sup> and J. P. AGGLETON<sup>b</sup>

<sup>a</sup> Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, New Zealand <sup>b</sup> School of Psychology, Cardiff University, UK

Twenty Lister Hooded rats (230-280g) were trained to swim to a submerged platform in a water maze that was at a fixed direction and distance from the start point. A different start point was used for each trial. The contribution of visual cues and vestibular cues were examined by comparing performance in the light and dark and by rotating the animals immediately prior to a test trial. The animals rapidly learnt to swim to the submerged platform. Although they initially took longer to find the platform in the dark, they improved to the same level as in the light after 5 days of training (P=0.1). Rotation significantly impaired the animals' performance when tested in the light (P<0.0031), but a much greater increase in latency was observed in the dark (P<0.0001). There was a significant interaction on the effect of rotation in light and dark conditions (P<0.0001). The results therefore supported and extended the notion that vestibular information is important for egocentric spatial memory.

## NMDA and AMPA Receptor Subunit Protein Expression in the Rat Hippocampus Following Unilateral Labyinthectomy

P. LIU, Y. ZHENG, J. KING, C. DARLINGTON and P. SMITH

## Vestibular Research Group, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

The hippocampus is critical for spatial information processing. Increasing behavioural and neurophysiological evidence suggests that vestibular-hippocampal interaction provides an important influence on hippocampal spatial representations. The aim of the present study was to address the issue of vestibular-hippocampal interaction from a neurochemical approach by examining the expression of the NR1 and NR2A subunits of the NMDA receptor and the GluR2 subunit of the AMPA receptor in the rat CA1, CA2/3 and dentate gyrus (DG) of the hippocampus at 10 hours and 2 weeks following unilateral vestibular deafferentation (UVD). We found that the only significant change in NR1 expression was decreased NR1 protein in the ipsilateral CA2/3 at 2 weeks in UVD rats compared to sham (SHAM) and anesthetic controls (CONT). Interestingly, although UVD resulted in significant decreases in NR2A expression in the bilateral CA2/3 at 2weeks post-op, a significant increase in NR2A expression was found in the ipsilateral CA1 at 10 hs post-op. Overall, there were no significant changes in GluR2 expression at 10hs or 2 weeks post-op in any region examined. The present findings demonstrate that peripheral vestibular damage can alter the expression of NMDA receptors in specific subregions of the hippocampus. Given the role of NMDA receptors in neuroplasticity, and learning and memory, these findings may account for the navigational deficits of humans with vestibular dysfunction.

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# Activation of the Hypothalamic-Pituitary-Adrenal Axis following Vestibular Deafferentation in Pigmented Guinea Pig

#### C. M. GLIDDON, C. L. DARLINGTON and P. F. SMITH

Vestibular Research Group, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago Medical School, University of Otago, Dunedin, New Zealand

This study was designed to determine if unilateral vestibular deafferentation (UVD) results in the activation of the hypothalamic-pituitary-adrenal axis in male pigmented guinea pigs. Salivary cortisol was measured in the morning and the night three days before the surgery to obtain baseline levels and four days following the UVD or sham operation. The type of operation (UVD or sham) did not significantly alter the cortisol levels. However, the level of cortisol over time and the interaction between the type of operation and time, were significantly different for the night cortisol values. There was no significant difference in operation type, time, or the interaction between operation and time for the morning cortisol levels. These results suggest that UVD activates the HPA axis as indicated by the elevation in cortisol levels and that reduction in cortisol does not occur until compensation of the static symptoms has occurred.

#### Mitochondrial Function in the Vestibular Nucleus Complex

## A. KHALESSI, J. C. ASHTON, I. A. SAMMUT, P. F. SMITH, C. L. DARLINGTON

#### Department of Pharmacology, University of Otago, Dunedin, New Zealand

Vestibular compensation (VC), the recovery process following unilateral vestibular deafferentation (UVD), is partly associated with a silencing and subsequent return of spontaneous resting activity (SRA) in the ipsilateral vestibular nucleus complex (VNC) following UVD. One possible explanation for the recovery of SRA is that the ipsilateral VNC neurons are silenced at UVD by excitotoxic levels of glutamate-induced intracellular calcium, and the recovery of SRA is due to a return to normal levels of intracellular calcium. Mitochondria are sensitive to calcium levels. Therefore, silencing of the ipsilateral VNC neurons may be associated with disruption of mitochondrial function post-UVD, and recovery of the mitochondrial function may help explain recovery of SRA (and, hence, VC). Testing this hypothesis requires measuring VNC mitochondrial function over the course of VC. However, no studies of mitochondria in the VNC have been published. We therefore developed a method for isolating mitochondria from the VNC. We then characterised mitochondrial function in our isolate using oxidative phosphorylation and mitochondrial complex activity assays. Here we describe our methods and compare our protocols and results to those for mitochondrial isolates from control (cerebellar) tissues and to previously published data on hepatic mitochondrial function. These results will provide baseline data for continued studies on mitochondrial function in the VNC during VC, and may demonstrate the potential for using VC as a model for recovery from diaschisis (secondary neural damage resulting from insults to brain tissue) and for the role of mitochondria in this process.



# The Effect of Low Body Temperature at Unilateral Deafferentation on Vestibular Compensation

# J. C. ASHTON, P. F. SMITH, C. L. DARLINGTON and C. GLIDDON

## Department of Pharmacology, University of Otago, Dunedin, New Zealand

Vestibular compensation, the recovery that follows unilateral vestibular deafferentation (UVD) is a model for central nervous system plasticity. Recovery from static symptoms of UVD may involve temperature dependent processes that modulate excitotoxic effects of UVD and/or the capability of the central nervous system for adaptive plasticity. To test for the effect of low temperatures at UVD on vestibular compensation we compared the rate of recovery and peak values for postural (roll head tilt, RHT, and yaw head tilt, YHT) and ocular (spontaneous nystagmus, SN) symptoms from three groups of female guinea pigs. Group 1 animals (n = 6) were maintained at 37°C throughout unilateral labyrinthectomy (UL) surgery. Group 2 animals (n = 6) were not temperature controlled, and group 3 animals (n = 5) were cooled with ice to 28°C throughout UL surgery. Cooled animals showed significantly higher rates of SN upon recovery from anaesthesia (p < 0.005), and were significantly slower to compensate (p < 0.005). Cooled animals were also slower to compensate for postural symptoms (RHT and YHT, p < 0.005), with 2 animals showing no compensation for YHT 52 hours after UL. Despite rectal temperatures between 31°C and 34°C during UL surgery, group 2 animals were not significantly slower to compensate than group 1 animals (p > 0.05 for all symptoms). We conclude that although strict temperature control during UL surgery may not be a critical factor for vestibular compensation, low temperatures during surgery exacerbate postural and ocular symptoms following UL and significantly slow recovery.

## NMDA and AMPA Receptor Subunit Protein Expression in the Rat Vestibular Nucleus Following Unilateral Labyrinthectomy

#### J. KING, Y. ZHENG, P. LIU, C. L. DARLINGTON and P. F. SMITH

## Vestibular Research Group, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

We examined the expression of the NR1 and NR2A subunits of the N-methyl-D-aspartate (NMDA) receptor, and the GluR2 subunit of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor, in the ipsilateral and contralateral vestibular nucleus complexes (VNCs) at 10 hs and 2 weeks following unilateral vestibular deafferentation (UVD) in rats, in order to directly test the hypothesis that the behavioural recovery following UVD ('vestibular compensation') is associated with an up-regulation of NMDA receptors. Using Western blotting, we found no significant changes in NR1 or NR2A expression at 10 hs or 2 weeks post-op. compared to sham and anaesthetic (fentanyl citrate/metotomadine) controls. However, we did find a significant (p < 0.01 and p < 0.05) increase in GluR2 expression in both VNCs at 10 hs but not 2 weeks post-op. These results add further evidence to the conclusion that NMDA receptors do not undergo up-regulation in the ipsilateral VNC during vestibular compensation.



# Nitric Oxide Synthase and Arginase Expression in the Rat Vestibular Nucleus Following Unilateral Vestibular Deafferentation

C. L. DARLINGTON, J. KING, Y. ZHENG, P. LIU and P. F. SMITH

Vestibular Research Group, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

Nitric oxide (NO) has been implicated in many forms of plasticity, including the process of CNS plasticity that occurs following unilateral deafferentation of the vestibular labyrinth (UVD). In order to better understand the possible relationship between the expression of nitric oxide synthase and arginase in the brainstem vestibular nucleus complex (VNC) following UVD, we used Western blotting to examine the expression of neuronal NOS (nNOS), endothelial NOS (eNOS) and arginase in the ipsilateral and contralateral VNCs of rats at 10 hs and 2 weeks following UVD, sham surgery or anesthetic (fentanyl citrate/metotomadine) without surgery. There were no significant changes in arginase or nNOS expression in the ipsilateral or contralateral VNCs at 10 hs or 2 weeks post-UVD However, eNOS expression showed decreased expression in the ipsilateral VNC at 2 weeks post-UVD (p < 0.01), with no change in the contralateral VNC or in either VNC at 10 hs post-op. These studies suggest that eNOS rather than nNOS may undergo changes in the ipsilateral VNC following UVD.

# A Mathematical Model of Ca<sup>2+</sup> Release in Single Cells Following Metabotropic Receptor Activation

W. G. GIBSON<sup>a</sup>, G. LEMON<sup>a</sup> and M. R. BENNETT<sup>b</sup>

# <sup>a</sup> The School of Mathematics and Statistics, University of Sydney, Sydney, Australia <sup>b</sup> The Neurobiology Laboratory, Department of Physiology, University of Sydney, Sydney, Australia

Agonist-induced activation of second messenger systems plays an important role in the mobilization of stored  $Ca^{2+}$  in neurons and in other cells. A first stage in this process is the binding of a ligand to a G-protein coupled receptor. This sets off a cascade of events leading to the activation of the enzyme phospholipase C (PLC) which hydrolyses the membranebound phospholipid, phosphatidylinositol 4,5-biphosphate (PIP<sub>2</sub>) to inositol 1,4,5trisphosphate (IP<sub>3</sub>) and diacylglycerol. This IP<sub>3</sub> diffuses into the cytosol and interacts with  $Ca^{2+}$  channels in the endoplasmic reticulum (ER) causing the release of stored  $Ca^{2+}$ . There is also a feed-back loop in which  $Ca^{2+}$  is an activator for the hydrolysis of PIP<sub>2</sub>. We present a unified mathematical model for these processes, starting from the binding of ligand to metabotropic receptors and leading, via a G-protein cascade, to the production of IP<sub>3</sub> and the release of Ca<sup>2+</sup> from the ER. The modelling falls into three linked modules: the first concerns the ligand-receptor binding and involves consideration of desensitization through phosphorylation and internalization of the receptors; the second concerns the G-protein cascade, leading to the production of IP<sub>3</sub> and the final section treats the IP<sub>3</sub>-induced  $Ca^{2+}$ release from the ER. A further extension of this work includes the IP<sub>3</sub>-induced translocation from the cell membrane of green fluorescent protein-tagged pleckstrin homology domain (PHD), thus allowing comparison with experimental results. Calculations were performed for both the equilibrium and transient surface receptor densities following the step application of uridine triphosphate (UTP) to cells containing  $P_2Y_2$  receptors and good agreement was obtained with the experimental results of Garrad et al. [J. Biol. Chem. 273: 29437-29444 (1998)] for both the time-dependence of the response and for the equilibrium receptor density as a function of UTP concentration. Results were also obtained for PHD fluorescence as a function of time following receptor activation and also as a function of agonist concentration and good agreement was obtained with the experimental results of Hirose et al. [Science, 284: 1527-1530 (1999)] for the application of ATP to purinergic receptors in MDCK cells.

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## Chlormethiazole: Neuroprotection Following Hypoxia-Ischaemia

# A. N. CLARKSON, D. S. KERR, and D. M. JACKSON

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand Hypoxia-ischaemia (HI) produces long-term cortical and sub-cortical damage. Chlormethiazole (CMZ), a GABA<sub>A</sub> receptor agonist, is neuroprotective in many stroke models. In the present study CMZ's neuroprotective properties were examined in a modified 'Levine' rat pup model. CMZ (or saline) was administered subcutaneously via implanted minipumps at approximately 600mg/day/kg b.w. Following left carotid artery occlusion coupled with 60 minutes hypoxia (6%  $O_2$ ) CNS tissue changes were assessed. Triphenyltetrazolium chloride (TTC) stained serial whole brain sections quantified lesion extent ipsilateral and contralateral to the occlusion. Evoked field potential analysis (population spikes and field EPSP's) was used to assess hippocampal CA1 neuronal activity in vitro at 3 and 14-days post-HI. Extensive CNS lesions were present 3-days post-HI ipsilaterally, with no apparent anatomical damage contralaterally. CMZ decreased the lesion size ipsilaterally (49  $\pm$  24mm<sup>3</sup> (n=7, CMZ treated, standard error of the mean)) compared to saline treated ( $128 \pm 14$  mm<sup>3</sup> (n=6; p < 0.05)). Contralaterally evoked neuronal responses were impaired at 3-days  $(3.98 \pm 0.31 \text{ mV} \text{ (pop. spike amplitude: n=26 slices)})$  compared to controls  $(6.19 \pm 0.26$  mV (n=25; p <0.001)), and 14-days post-HI (4.19 \pm 0.22 mV (n=23)) compared to controls (5.88  $\pm$  0.25mV (n=25; p <0.001)). Electrophysiological measurements could not be made ipsilaterally. CMZ significantly reduced the HI-induced impairment at 3-days (5.60  $\pm$  0.26mV (n=23) vs. 3.98  $\pm$  0.31mV (n=26; p<0.001)), and at 14-days post-HI (5.79  $\pm$ 0.18mV (n=25) vs. 4.19  $\pm$  0.22mV (n=25; p <0.001)), suggesting the CMZ provides both anatomical and functional neuroprotection.

## Effects of Bilobalide, the Sesquiterpene of *Ginkgo Biloba*, on GABA-Mediated Currents Modulated by GABA<sub>A</sub> Modulators

S. H. HUANG<sup>a</sup>, R. K. DUKE<sup>a</sup>, M. CHEBIB<sup>b</sup>, G. A. R. JOHNSTON<sup>a</sup>, K. SASAKI<sup>c</sup> and K. WADA<sup>c</sup>

<sup>a</sup> Department of Pharmacology, Faculty of Medicine, University of Sydney, Australia <sup>b</sup> Faculty of Pharmacy, University of Sydney, Australia <sup>c</sup> Department of Hygienic Chemistry, Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Japan

Bilobalide is one of the active constituents of the *Ginkgo biloba* leaf extract widely employed to treat symptoms associated with mild-to-moderate dementia. There is evidence literatures indicating that at least some of the beneficial effects of the extract are mediated through GABAergic neurotransmission. The extract significantly decreases social interaction in rats acting oppositely to diazepam, a benzodiazepine site agonist of GABAA receptors (Chermat et al., 1997). The extract and bilobalide also shorten barbital-induced narcosis in mice (Brochet et al., 1999). Barbiturates act by facilitating GABA-mediated Cl<sup>-</sup> currents at GABA<sub>A</sub> receptors and this action can be antagonised by the channel blocker picrotoxinin. Picrotoxinin is a noncompetitive antagonist of GABA<sub>A</sub> receptors that influences actions of GABA<sub>A</sub> modulators. With the use of 2-electrode voltage clamp electrophysiology, bilobalide was examined for its effects on direct and enhanced GABA actions by diazepam, pentobarbitone and steroid recorded from human  $\alpha_1\beta_2\gamma_{2L}$  GABA<sub>A</sub> receptors expressed in *Xenopus* oocytes and compared to the effects of picrotoxinin. In this study, we found that bilobalide, which is structurally similar to picrotoxinin, is also a noncompetitive antagonist that influences actions of GABA<sub>A</sub> modulators. In conclusion, bilobalide may mediate some of the effects of the Ginkgo extract by acting at GABA<sub>A</sub> receptors.



## Kainic Acid-Induced Tolerance to Kainic Acid in Rat Hippocampus

## B. R. HESP, T. WRIGHTSON, and D. S. KERR

## Department of Pharmacology & Toxicology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

The excitotoxin domoic acid acts at both KA- and AMPA-sensitive glutamate receptors and induces tolerance against subsequent domoic acid insult in rat hippocampus. To determine the receptor specificity of this effect, tolerance induction was examined in vitro in hippocampal slices from young male S.D. rats, using evoked field potential analysis of CA1 population spike amplitude, spike area, and EPSP slope in response to Schaffer-collateral stimulation. Slices were preconditioned by 30 min exposure to low-dose kainic acid (KA; 500 nM) to selectively activate KA-sensitive glutamate receptors, or the AMPAreceptor selective agonist S-fluorowillardiine (FW; 50 - 250 nM). Following washout, tolerance induction was assessed by administration of 2 to 4  $\mu$ M KA or 100 – 250 nM FW (respectively), for 30 minutes. FW preconditioning failed to induce tolerance to subsequent challenges with FW. In contrast, KA preconditioning induced a significant tolerance to a subsequent KA challenge. Population spikes in control slices were significantly reduced relative to baseline after 30 minutes of 2  $\mu$ M KA (spike area; mean % change + sem: -77.0  $\pm$ 13.1%; n=6) but were largely unaffected by 2  $\mu$ M KA after preconditioning (-24.6 ± 14.8 %; n=7; p<0.05). Similar results were seen following 20 min exposure to 4  $\mu$ M KA (-99.0  $\pm$ 1.2%; n=6 versus  $-41.0 \pm 14.1\%$ ; n=9; p<0.05). These findings provide evidence that a potentially neuroprotective mechanism is triggered by selective activation of KA-sensitive glutamate receptors.

## Effects of the Cannabinoid Receptor Antagonist SR141716 on Morphine-Induced Place Conditioning and Locomotor Sensitisation

# M. E. SINGH<sup>a</sup>; A. N. A. VERTY<sup>a</sup>, I. S. MCGREGOR<sup>b</sup> and P. E. MALLET<sup>a</sup>

<sup>a</sup> School of Psychology, University of New England, Armidale, Australia <sup>b</sup> School of Psychology, Sydney University, Sydney, Australia

Previous research has established that the rewarding effects of morphine as assessed in the place conditioning task can be attenuated by co-administering the CB<sub>1</sub> cannabinoid receptor antagonist SR141716. Because it has not yet been determined if the brain's cannabinoid system is involved in the behavioural sensitising effects of opioids, the present study compared the effects of SR141716 on morphine-induced place conditioning (Experiment 1) to the effects on morphine-induced locomotor sensitisation (Experiment 2) in male albino Wistar rats. In Experiment 1, rats received either SR141716 (0.1, 0.5, or 3.0 mg/kg, IP) or its vehicle, followed 30-min later by either morphine (10 mg/kg, SC) or saline in an unbiased two compartment place-conditioning task. SR141716 (3.0 mg/kg) attenuated the place preference produced by morphine. In Experiment 2, rats received either SR141716 (0.1, 0.5 or 3.0 mg/kg, IP), naloxone (10 mg/kg, IP) or vehicle, followed 30-min later by either morphine (10 mg/kg, SC) or saline. Rats pretreated with morphine alone showed significantly higher locomotor activity compared to vehicle-pretreated rats. The development of morphine-induced locomotor sensitisation was blocked by naloxone, but not by SR141716. It was concluded that the brain's cannabinoid system is likely not involved in opioid-induced behavioural sensitisation. Results further support the notion that the neural mechanisms underlying the hedonic properties of opioids differ from those mediating their behavioural sensitising effects.



# Interactive Effects on Food Intake by Cannabinoid and Opioid Receptors in the Paraventricular Hypothalamic Nucleus

# A. N. A.VERTY<sup>a</sup>, M. E. SINGH<sup>a</sup>, I. S. MCGREGOR<sup>b</sup>, and P. E. MALLET<sup>a</sup>

# <sup>a</sup> School of Psychology, University of New England, Armidale, Australia. <sup>b</sup> School of Psychology, Sydney University, Australia.

The present study examined the interactive effects of opioid and cannabinoid systems in mediating food intake. In Experiment 1, male albino Wistar rats were injected with the  $CB_1$ cannabinoid receptor antagonist SR141716 (3 mg/kg, IP), morphine (2.5 mg/kg, SC), vehicle, or SR141716/morphine combined (n=8 per group). Rats were perfused 2 h later and brains were processed for Fos immunoreactivity (Fos-IR). Administration of morphine or SR141716 alone, increased Fos-IR in several regions including the medial shell of the nucleus accumbens (nAcc), bed nucleus of the stria terminalis, central amygdaloid nucleus (CeA), arcuate nucleus, as well as paraventricular (PVN) and dorsomedial (DMH) nuclei of the hypothalamus. Furthermore, SR141716 attenuated morphine induced Fos-IR in the CeA, PVN, and dorsal region of the nAcc. In Experiment 2, free-feeding rats (n=12) were injected with SR141716 (0.03, 0.3, 3.0 mg/kg or vehicle, IP) and given 30-min access to standard rat chow. Rats were then injected with morphine (2.5 mg/kg SC) or its vehicle and food intake measured for 120 min. Experiment 3 was similar to the first experiment, except that morphine was delivered via microinjection directly into either the nAcc (n=12) or the PVN (n=14). SR141716 attenuated hyperphagia produced by systemic and intra-PVN, but not by intra-nAcc morphine administration. Results provide strong evidence of an interactive role between cannabinoid and opioid systems in the PVN influencing food intake.

## Comparison of the Effects of MDMA, Amphetamine and Cocaine on Delayed Matching-to-Sample Performance in Rats

## D. N. HARPER, R. G. WISNEWSKI, M. HUNT, and S. SCHENK

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

Although there is concern about the long term effects of MDMA ('Ecstasy') on various aspects of behaviour, relatively little research has examined the acute effects of exposure to MDMA on memory function. The present study compared the effects of MDMA against two other drugs of abuse (amphetamine and cocaine) in terms of their effect on performance in an automated delayed matching-to-sample task using rats as subjects. All three drugs produced an overall delay-independent impairment to performance at the highest doses tested. At intermediate doses amphetamine and MDMA produced qualitatively similar delay-dependent changes in accuracy (i.e., they had a similar effect on the rate of forgetting). These two drugs also produced similar dose-dependent (but delay-independent) increases in overall response bias (i.e., a tendency to respond to one response option over the other). The present results suggest that MDMA and amphetamine share not only a similar profile in terms of their acute effects on memory-task performance.



# Increased Anxiety and Altered 5-HT Receptor and Transporter Density in Rats 3 Months After MDMA ("Ecstasy")

K. J. CLEMENS<sup>a</sup>, G. VAN DER PLASSE<sup>a</sup>, I. S. MCGREGOR<sup>a</sup>, A. J. LAWRENCE<sup>b</sup>, and F. CHEN<sup>b</sup>

<sup>a</sup> School of Psychology, University of Sydney, NSW 2006, Australia <sup>b</sup> Department of Pharmacology, Monash University, Clayton, VIC, Australia

Male Wistar rats were given either high dose 3.4-methylenedioxymethamphetamine (MDMA, "Ecstasy") (4 x 5 mg/kg), low dose MDMA (1 x 5 mg/kg) or vehicle over four hours on each of two consecutive days. The MDMA produced dose-dependent increases in body temperature and locomotor activity. Ten weeks later, rats were tested in behavioural measures of anxiety (social interaction and emergence tests). Rats previously given either low or high doses of MDMA displayed greater anxiety-like behaviour in both tests, with rats given high doses of MDMA showing the greatest anxiety. At the conclusion of behavioural testing, the rats were killed and their brains frozen for quantitative autoradiography. The selective ligands [<sup>125</sup>I] RTI-55, [<sup>125</sup>I] DOI and [<sup>125</sup>I] cvanopindolol were used to assess the 5-HT transporter, 5HT<sub>2A/2C</sub> and 5HT-1<sub>1A/1B</sub> receptors respectively. Many changes in receptor and transporter density were observed in cortical and limbic structures, dependent upon MDMA dose. High dose MDMA was associated with loss of 5-HT transporter and 5HT<sub>2A</sub>/<sub>2C</sub> receptor density in numerous sites, while low dose MDMA produced a smaller number of significant effects. These data suggest that even brief and modest MDMA exposure can produced significant long-term changes in 5-HT function and associated emotional behaviours.

8.5

## Acquisition and Maintenance of MDMA ("Ecstasy") Self-Administration

### S. SCHENK

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

The ability of drugs to reinforce operant responding in laboratory animals is a valid and reliable predictor of abuse potential. MDMA ("ecstasy") is self-administered by humans but there have been few reports of reliable self-administration by drug-naïve laboratory animals. MDMA was self-administered by laboratory rats that were experienced with self-administration of amphetamine as well as by rats that were initially drug-naïve. Self-administration persisted during a 24 hour session, was dose-dependent, extinguished when saline was substituted for MDMA and was reinstated when MDMA was reintroduced. The pattern suggested that MDMA was self-administered in "bursts". During short sessions (2 or 6 hrs) most responses were produced during the initial 30 min. With extended tests (24 hrs), a burst pattern was apparent and responding was maintained in bursts throughout the test period. These results indicate that MDMA has abuse liability that compares favorably to amphetamine and suggest that increased use of the drug should raise concern of growing and widespread potential for abuse.

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8.6

# The role of the D1 and D2 Receptors in the Maintenance of MDMA Self-Administration

## E. DANIELA, K. BRENNAN, L. HELY, D. GITTINGS and S. SCHENK

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

3.4 methylenedioxymethamphetamine (MDMA; "ecstasy") is a ring substituted amphetamine that has become an increasingly popular illicit recreational drug. Animal models have been particularly effective in determining the contribution of various neurochemical systems to drug self-administration. A significant contribution of central dopaminergic mechanisms has been demonstrated for self-administration of virtually all drugs of abuse. The present study sought to determine whether dopaminergic mechanisms also contribute to the reinforcing effects of MDMA. Rats were trained to self-administer MDMA during daily 2 hr sessions according to an FR-1 schedule of reinforcement. Once stable responding was produced, the effects of pretreatment with the dopaminergic D1-like antagonist, SCH 23390 (0.005-0.02 mg/kg) or the D2-like antagonist, eticlprode (0.03 - 0.3 mg/kg) were measured. During baseline conditions, responding maintained by MDMA was inversely related to dose; higher doses supported lower rates of responding. Following pretreatment with the dopamine antagonists, responding maintained by low doses of MDMA was decreased whereas responding maintained by high doses was increased. These data suggest that pretreatment shifted the dose-effect curve for MDMA self-administration to the right and are consistent with an attenuation of the reinforcing effects.

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# 8.7

## Demand Curve Analysis for the Self-Administration of Cocaine

### L. HELY, S. SCHENK, M. HUNT and D. N. HARPER

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

Drugs of abuse have the capacity to act as positive reinforcers that guide and direct behaviour. The reinforcing effects of different drugs can be measured using a behavioural economic framework. In this procedure, the rat is required to perform increasing fixed ratio requirements (e.g. 5, 10, 20 etc lever responses) in order to obtain an infusion of cocaine. Various manipulations can be used to produce changes in responding such as an increase or decrease in dose, or administration of various pharmacological agents (for example, agonists or antagonists for specific neurochemical systems). A function examining the relationship between responding and ratio requirement is produced and this function can be compared across drug groups and/or within drug doses. Drugs or drug doses that have greater reinforcing efficacy are expected to maintain responding when higher ratio demands are in place. In the present study, this function was examined for the reinforcing effects of cocaine (0.125 versus 0.5 mg/kg/infusion). Results indicated that the high and low doses of cocaine produced functionally different curves using a behavioural economic analysis. These data provide a framework for examining the effects of specific antagonists on cocaine, and other drug self-administration.



Instabilities During Anti-Phase Bimanual Movements: Are Ipsilateral Pathways Involved?

F. KAGERER<sup>a</sup>, J. SUMMERS<sup>a</sup> and A. SEMJEN<sup>b</sup>

 <sup>a</sup> Human Motor Control Laboratory, School of Psychology, University of Tasmania, Hobart, Tasmania, Australia
<sup>b</sup> Centre de Recherche en Neurosciences Cognitives, CNRS & Universite Mediterranee, Marseille, France

The spatial and temporal coupling of hands is known to be very robust during movements which use homologous muscles (in-phase movements). In contrast, movements using non-homologous muscles (anti-phase movements) are less stable and exhibit a tendency to undergo a phase transition to in-phase movements. The instability during anti-phase movements has been modeled in terms of signal interference mediated by the ipsilateral corticospinal pathways. In this study we report that subjects in whom distal ipsilateral motor evoked potentials could be elicited with transcranial magnetic stimulation (TMS), performed substantially more variably during a bimanual circling task than subjects whose ipsilateral pathways could not be transcranially activated. These results may help explain the large individual differences in the degree of interaction between the limbs during bimanual asymmetrical coordination.

## The Role of Interhemispheric Pathways in Bimanual Coordination

I. J. KIRK<sup>a</sup>, C. M. STINEAR<sup>b</sup>, S. WARBROOKE<sup>b</sup>, and W. D. BYBLOW<sup>b</sup>

 <sup>a</sup> Research Centre for Cognitive Neuroscience and Department of Psychology, University of Auckland, Auckland, New Zealand
<sup>b</sup> Human Motor Control Laboratory, Department of Sport & Exercise Science,

University of Auckland, Auckland, New Zealand

Two subjects with callosal agenesis (AC1 and AC2) and eight control subjects performed a bimanual circle-tracing task, paced with an auditory metronome while 128-channel EEG was recorded. Movements were either mirror-symmetric or asymmetric with respect to the midline. FFT power topographies were plotted onto an MRI- derived scull surface using a spherical Laplacian procedure and subsequently projected to the surface of the model cortex. The topography of FFT power relative to a control condition (auditory metronome alone) was calculated in the alpha (8-14 Hz) range. Decreases in alpha power were taken as indicators of activation in underlying neural networks. In controls, neural activation distributed bilaterally over the motor cortices during symmetric movements and over SMA during asymmetric patterns. Conversely, AC1 showed maximal activation at the midline during both symmetric and asymmetric patterns (The EEG and behavioural data collected from AC2 was highly variable). It is suggested that control subjects utilise functional coupling between primary motor cortices (via corpus callosum) during symmetric pattern production with little SMA involvement. SMA activation is required during asymmetric movements however. AC1 did not demonstrate functional coupling between the primary motor cortices during this task, and seemed to utilise SMA to coordinate both symmetric and asymmetric patterns.



## Central Cost and Stability of Interlimb Coordination

C. Y. HIRAGA and J. J. SUMMERS

## School of Psychology, University of Tasmania, Australia Human Motor Control Laboratory

Under the framework of dynamical system and information processing approach, the present study investigated the central cost associated with the dynamics of coordination patterns, and also the cost of intentionally stabilising those patterns. Eighteen participants performed a circle drawing task involving in- and anti-phase coordination modes under three limb combinations: homologous (both upper arms), contralateral (left arm and right leg), and ipsilateral (right arm and right leg). A dual-task procedure with probe RT was utilised to compare shared attention between tasks and attentional allocation prioritised to the motor task. Results indicated that coordination stability decreased linearly from homologous to contralateral with ipsilateral evidencing the lowest stability. Dual-task with shared attention was more unstable than single and dual-task prioritising the coordination task. In-phase was performed in a more stable fashion and required less central cost than anti-phase but only for homologous and ipsilateral combinations. Central cost measured by probe RT was fastest during homologous and slowest during ipsilateral conditions with the contralateral showing intermediate cost. RT was also significantly faster when sharing attention between tasks than when prioritising the coordination task. Overall, the results showed an inverse relationship between stability and probe RT suggesting that central attentional costs are associated with coordinating arm and leg movements as well as coordination mode (i.e., in-phase vs. antiphase). Furthermore, the results support previous research suggesting that attention plays an important role in sustaining the stability of coordination patterns.

# Phasic Modulation of Interhemispheric Inhibition During Passive Movement of the Upper Limb

#### S. A. WARBROOKE and W. D. BYBLOW

#### Human Motor Control Laboratory, University Of Auckland, Auckland, New Zealand

We investigated modulation of inhibition of motor evoked potentials (MEPs) in a forearm muscle during passive rhythmic movement of the contralateral limb. In the main experiment, eight healthy volunteers pre-activated their left flexor carpi radialis (FCR) in a simple isometric contraction (2.5-7.5% MVC) while their right hand underwent passive wrist flexion/extension. Transcranial magnetic (TMS) or electric (TES) stimulation was applied to the motor cortex contralateral to the test limb in eight phases of the wrist flexion/extension cycle of the passive limb. In half of the trials conditioning was applied to the motor cortex ipsilateral to the test hand at an optimum conditioning-test interval (12 ms) for examining interhemispheric inhibition (Ferbert et al., 1992). The conditioning pulse applied to the contralateral hemisphere significantly inhibited TMS-evoked responses in the test FCR muscle, whereas TES-evoked responses did not appear to be inhibited. For TMS-evoked responses only, inhibition in FCR responses was modulated such that inhibition was greater when the contralateral wrist was flexing, compared to extending. Suppression of the corticospinal pathway associated with forearm flexors during contralateral passive movement may release a tonic transcallosal inhibitory effect during extension. Conversely, during flexion a marked disinhibition of the corticospinal pathway associated with FCR may serve to increase the efficacy of a tonic interhemispheric inhibition effect passing transcallosally. Modulation of interhemispheric inhibition may be critical for unimanual movement as well as independent limb movements.



Decreases in Rat Motor Cortex Activity Precede Acute Parkinsonian Movement Deficits

#### L. C. PARR-BROWNLIE and B. I. HYLAND

## Department of Physiology and Neuroscience Research Centre, University of Otago, Dunedin, New Zealand

Bradykinesia is a prominent symptom of Parkinson's disease, but little is known of its physiological basis. We investigated changes in motor cortex activity in an acute model of Parkinson's disease (dopamine-2-like receptor blockade with haloperidol, 0.12 mg/kg i.p.). We previously reported (Parr-Brownlie, et al., 2001, Soc. Neurosci. Abstracts, 27, 750.8) that haloperidol-induced bradykinesia of forelimb reaches is associated with decreases in resting and movement-related firing rates in the motor cortex. The question that remains is whether the reduction in resting and movement-related firing rate causes the bradykinesia or is a consequence of the bradykinesia. To investigate this we took advantage of the fact that in some experiments haloperidol did not produce slowing that met our criterion for bradykinesia (increased movement time > 75%). In these non-bradykinetic haloperidol sessions, resting firing rate decreased compared to vehicle only sessions (-15  $\pm$  58%, p = 0.0001, n = 204). In addition, movement-related excitatory peaks decreased by  $11 \pm 76\%$ (p = 0.001, n = 53). There was a trend that larger decreases in movement-related firing rates occurred in bradykinetic sessions (-39  $\pm$  56%, n = 20). The results indicate that (1) acute reduction of dopaminergic activity decreases resting and movement-related activity of most neurons in the motor cortex and (2) significant bradykinesia occurs when the decrease in movement-related firing rate exceeds some critical value.

# Treatment Effects of N-Terminal of IGF-1 (GPE) in a Rat Model of Parkinson's Disease

# R. KRISHNAMURTHI<sup>a</sup>, H. WALVOGEL<sup>b</sup>, S. STOTT<sup>a</sup>, M. MAINGAY<sup>a</sup>, R. L. M. FAULL<sup>b</sup>, D. MCCARTHY<sup>c</sup>, P. GLUCKMAN and J. GUAN<sup>a</sup>

<sup>a</sup>NeuronZ, Liggins Institute, <sup>b</sup>Department of Anatomy with Radiology, <sup>c</sup>Department of Psychology, University of Auckland, Auckland, New Zealand

Parkinson's disease is a common neurodegenerative disease without a cure. The effect of administration of the N-terminal of IGF-1 (GPE) was examined in a rat model of Parkinson's disease. GPE, an endogenous peptide naturally cleaved from IGF-1, has previously been shown to be neuroprotective. GPE (3ug) or its vehicle was administered 2 hours after a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway. Tyrosine hydroxylase (TH) immunocytochemistry was examined 2 weeks post-lesion. GPE treatment significantly prevented the loss of TH immunopositive neurons in the SNc (n=9 per group, p < 0.001), and significantly increased the density of TH in both the SNc and the striatum compared with vehicle (p < 0.001). In a separate study, the long-term effect of peripheral administration of GPE on 6-OHDA lesion induced motor deficits was examined. At three days post-lesion rats were placed in pairs following rotation tests to receive either GPE (3mg/kg, i.p.) or vehicle. Rotations tests and step-tests (time to walk over a meter, step length, and number of adjusting steps) were carried out on weeks 1, 2, 3, 4, 6, 8, and 12 postlesion. At 12 weeks post-lesion, brains were processed for TH immunocytochemistry. There was a significant overall reduction in the number of rotations, stepping time and the number of adjusting steps in the GPE treated group compared to vehicle and an overall significant increase in step length in the GPE treated group (p < 0.01 in all cases). GPE treatment did not prevent the loss of TH immunoreactivity in the SNc, or the striatum. The results from both these studies suggest that GPE may have therapeutic potential in Parkinson's disease.



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## Altered Sensorimotor Integration in Parkinson's Disease

W. D. BYBLOW and G. N. LEWIS

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

Transcranial magnetic stimulation (TMS) was used to investigate sensorimotor integration in the upper limb of 10 patients with Parkinson's disease (Pd) and 10 age-matched controls. Non-conditioned and subthreshold conditioned (2 ms interstimulus interval) responses were recorded in the flexor- and extensor carpi radialis muscles (FCR, ECR) of the more impaired (non-dominant) limb. Stimuli were delivered while the wrist joint was positioned statically at various joint angles as well as during different phases of passive movement of the wrist joint (90° amplitude, 0.2 Hz). The FCR and ECR muscles remained relaxed during all stimulation. In both groups, responses in the static condition were larger when the target muscle was in a shortened position. Responses were also facilitated in the muscle shortening phases of passive movement. In both static and dynamic conditions, the extent of modulations in response amplitude was significantly reduced in the patient group. The level of intracortical inhibition (ICI) was also significantly less in the Pd patients in static conditions. During passive movement, control subjects demonstrated a clear reduction in ICI compared to the static trials, however the level of ICI was unchanged in the Pd group in the dynamic condition. The results suggest an abnormal influence of afference on corticomotor excitability in Pd. This may be related to abnormal sensory input, a defective integrative unit, or an inappropriate motor response.

# 10.1

## Exposure to an Enriched Environment Increases Cell Excitability but not Synaptic Efficacy in the Dentate Gyrus of Freely Moving Rats

G. I. IRVINE and W. C. ABRAHAM

## Department of Psychology and the Neuroscience Research Centre, University of Otago, Dunedin, New Zealand

Recurrent exposure to a stimulus-enriched environment (EE) has been reported to induce a long-term potentiation (LTP)-like effect in the dentate gyrus (DG) region of the rat hippocampus in some (Foster, Gagne & Massicotte, 1996, Brain Research, 736, 243-250) but not all experiments (Sharp, McNaughton & Barnes, 1985, Behavioral Neuroscience, 101(2), 170-178; Sharp, Barnes & McNaughton, 1987, Brain Research, **339**, 361-365). An explanation for these different effects could be a discrepancy in the living conditions or handling of rats between the two experimental protocols. In the present research, adult male Sprague-Dawley rats were chronically implanted with recording and stimulating electrodes in both CA1 and the DG, and housed singly in standard cages. After stable recordings of the field excitatory postsynaptic potentials (EPSPs) were established, the ability of EE exposure to modify evoked potentials was assessed. Comparisons were made between animals that were housed in groups or singly, and between animals that had handling or no handling prior to the EE. Neither type of housing nor prior handling appeared to influence the effect of EE on evoked potentials. For all conditions a transient increase in cell excitability was observed, but no LTP-like changes were found after EE exposure. These results suggest that exposure to an EE does not necessarily induce LTP and that neither type of housing, nor handling are key factors that explain the variability between experiments in the ability of EE exposure to induce LTP-like effects.



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# Regulation of the NMDA Receptor Complex Following LTP: A Biochemical Investigation

# J. T. T. KENNARD<sup>a</sup>, D. GUÉVREMONT<sup>a</sup>, S. E. MASON-PARKER<sup>b</sup>, W. C. ABRAHAM<sup>b</sup> and J. M. WILLIAMS<sup>a</sup>

# <sup>a</sup> Department of Anatomy and Structural Biology, University of Otago, Dunedin <sup>b</sup> Department of Psychology, University of Otago, Dunedin

The N-methyl-D-aspartate (NMDA) receptor is central to the induction of hippocampal longterm potentiation (LTP), a molecular model of learning and memory, and consists of core subunit proteins, as well as associated signal transduction and structural proteins. In this study, the expression of the NMDA receptor complex in dentate gyrus synaptic membrane fractions (synaptoneurosomes) was investigated following perforant path LTP. Western blot analysis showed significant increases in NMDA receptor subunits NR1 (30 ±7%, n=5; p<0.05, 2 tailed t-test) and NR2B ( $60 \pm 22\%$ , n=5; p<0.05, 1 tailed t-test) at 48 hours post LTP. Significant increases were also found in NMDA receptor associated proteins PSD-95 ( $33 \pm 13\%$ , n=7; p<0.05; 2-tailed t-test) nNOS ( $104 \pm 31\%$ , n=7; p<0.05, 2-tailed t-test) and  $\alpha$ CaMKII ( $11\pm4\%$ , n=6; p<0.05; 1 tailed t-test). These results suggest that LTP induction causes an increase in the total number of functional NMDA receptor complexes. This may occur at existing synaptic sites, or may reflect an increase in the number of synaptic connections.

## Long-Term Potentiation of Human Visual Evoked Responses

# W. CLAPP<sup>a</sup>; T. TEYLER<sup>b\*</sup>; J. HAMM<sup>a</sup>; B. JOHNSON<sup>a</sup>; M. CORBALLIS<sup>a</sup>; and I. KIRK<sup>a</sup>

# <sup>a</sup> Department Psychology, University of Auckland, Auckland, New Zealand <sup>b</sup> Department of Neurobiology & Pharmacology, NE Ohio Col Med, Rootstown, OH, USA

LTP is a candidate synaptic mechanism underlying learning and memory. It has been shown in many areas of the brain and is well-represented in hippocampus and neocortex. LTP has been documented in human cortical tissue obtained from surgical patients, where it displays properties identical to that seen in non-human preparations. Here we report cortical LTP recorded non-invasively from normal human subjects fitted with a multi-channel EEG electrode cap. Subjects fixated on a visual target while a checkerboard was presented to the Right or Left visual field at a low rate to obtain baseline evoked responses from 128 scalp electrodes. A subsequent high rate of "tetanic" presentation of either the Right or Left checkerboard leads to a significant post-tetanic potentiation of the "N1b" response (176ms latency component of N1 determined by Independent Component Analysis). The visually evoked responses P1, N1a, and P2 remained unchanged following the visual tetanus. The potentiated N1b response decayed back toward baseline over time.



# 10.4

Restoration of Simple Lower Limb Movements in the Chick using Functional Electrical Stimulation

#### J. M. JASIEWICZ

## School of Human Movement Studies, Queensland University of Technology, Kelvin Grove, Queensland, Australia

Advances in functional electrical stimulation (FES) technologies have made a significant impact on restoring important motor functions in spinal cord injured (SCI) individuals. Despite major advances all FES devices have the disadvantage that they cannot provide unassisted balance. That is, SCI individuals must use external support (handrails, crutches, etc) to be able to stand or walk. There has been some initial work related to restoring stance in one paraplegic (Matjacic & Badj, 1998) but the FES device did not directly control balance. Studies on humans to test such an approach using FES are difficult to perform because of its invasiveness. An alternative is to use an appropriate bipedal animal model (birds). In this study chicks were used to test the feasibility of using a multichannel FES device to restore simple coordinated lower limb movements. Anaesthetized chicks (n= 15) were implanted with fine wire electrodes near the motor points of ankle flexors and extensors, knee flexors and extensors and hip flexors and extensors. Using biphasic stimuli a variety of movements were successfully restored and resembled normal movement patterns. The results suggest that the FES can be used in the chick to restore complex movement patterns. The next phase of the project will attempt to restore independent weight support in "paraplegic" chicks.

# 11.1

## The Neural Representation of Context

## K. J. JEFFERY and M. I. ANDERSON

#### Department of Psychology, University College London, UK

The hippocampus is often implicated as the site of context representation, because lesions to this structure affect several context-dependent processes such as contextual fear conditioning. In support of this hypothesis, the spatially localised firing of place cells in the rat hippocampus is strongly influenced by non-spatial "context" aspects of the environment. We have been exploring the contextual modulation of place cell firing in order to find out whether the place cells receive a unitary context signal, and if so, whether this signal is "elemental" or "configural". We created compound contexts, consisting of an odour (vanilla or lemon) together with a "colour" (black or white) whose elements (the odour or the colour) were varied independently. We were interested to see (a) whether context-induced changes affected the whole population of place cells, and (b) whether place cells responded to the olfactory or visual components of the context change. We found that, surprisingly, fragmentary context changes produced fragmentary place cell responses - some cells responded to changes in colour only, some (rarely) to changes in odour only, and the majority to a combination. We propose that each place cell receives a partial, compound context signal that gates its spatial inputs, and that the ensemble of place cells together are needed to represent the whole context. These findings suggest that the hippocampus may be the place where a unitary context signal is first synthesized.



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# A Reduction in the Area of the Place Fields of Hippocampal Place Cells Correlates with Reduced Theta-Phase Variance Following Perirhinal Cortex Lesions

# X. LU and D. BILKEY

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

The hippocampal formation (HPC) is critically involved in spatial memory. The neighbouring perirhinal cortex (PRC) has a role in visual recognition memory. The present study investigates what information is provided by the PRC to the HPC by comparing the location- and theta-related firing properties of HPC place cells in PRC lesioned (n=7) and sham operated rats (n=7). Twenty-eight HPC CA1 or CA3 place cells were recorded from PRC lesioned rats and 18 from sham-operated rats as they foraged freely. A significant decrease (p<0.05) in the size of place fields in lesioned rats was observed without a change in mean firing rate. Place cells tend to fire at a particular phase of the theta EEG rhythm and normally display a systematic change in this phase of firing as the animal changes location (phase precession). In lesioned rats there was a significant reduction (p<0.01) in the variance in place cell firing phase and the place field size was positively correlated (p<0.01) with the amount of phase variance in theta-modulated lesion-group cells. These findings indicate that PRC lesions produce specific location-related alterations in the firing of HPC place cells and, therefore, that the PRC contributes location-relevant information to the HPC.

## Retrograde Amnesia: Entorhinal Cortex, Perirhinal Cortex and Anterior Thalamus

## J. P. MORAN and J. C. DALRYMPLE-ALFORD

# Christchurch Movement Disorders and Brain Research Group, Psychology Department, University of Canterbury, Christchurch, New Zealand

A summary of animal work on the neural basis of retrograde amnesia (RA) will be provided, together with evidence from work in progress. Hippocampal damage in classic cases of amnesia often produces temporally-graded RA. This pattern of impaired recent relative to remote memory has led to the view that the hippocampus, supported by structures with strong neural connections, is involved in initial acquisition and consolidation, but long-term memories eventually become independent of hippocampal function (Squire & Knowlton, 2000. In: The New Cognitive Neurosciences. ed, Gazzaniga). Human and animal evidence indicates that the parahippocampal region may influence RA. Alternatively, RA is prominent in Korsakoff's cases, who have diencephalic pathology. Work in progress is examining the comparative effects on RA of entorhinal cortex, perirhinal cortex, and anterior thalamic nuclei lesions. Rats were given initial training in an 8-arm maze and then trained on 4 successive left/right discrimination problems in a 12-arm maze, at 6, 4, 2, and 0.5 weeks before surgery. Each preoperative test is in a different maze environment. Retention is assessed using a counterbalanced design one week postoperatively. This new evidence will complement planned experiments on the neural substrates of RA on non-spatial tasks.



# Limbic Thalamus and Related Non-Specific Thalamic Nuclei: Differential Systems with Differential Involvement in Memory?

### A. S. MITCHELL, J. C. DALRYMPLE-ALFORD

## Christchurch Movement Disorders and Brain Research Group and Psychology Department, University of Canterbury, Christchurch, New Zealand

The relevant contributions to diencephalic amnesia of limbic thalamic and non-specific thalamic components is a contentious issue. Initial research focussed primarily on the mediodorsal thalamic nuclei. Recent lesion studies have implicated either the anterior or the intralaminar thalamic nuclei. We provide a visual summary of the main connections of limbic and non-specific anterior and dorsal thalamic regions in the rat, that suggest three partially segregated neural systems. One thalamic system has connections with the hippocampal system whereas the other two systems have differential connections with the prefrontal cortex. Based on their connections, and on findings from relevant behavioural studies, each thalamic system may be an integral component of functionally segregated circuits that may contribute to different aspects of learning and memory. If correct, variability in deficits across lesion studies could reflect variability in lesion site. Behavioural evidence is provided on these systems, that tests the following predictions: that anterior thalamic lesions to the anteroventral and rostral anteromedial nuclei impair spatial working memory; that lateral thalamic lesions to the paracentral and centrolateral nuclei and adjacent lateral and paralamellar mediodorsal nuclei impair memory for temporal order of events, and that posterior thalamic lesions centred on the intermediodorsal nucleus and adjacent regions of the mediodorsal and centre median nuclei impair working memory for food reward value. It may be inappropriate to focus exclusively on any one group of thalamic nuclei to explain the neural basis of diencephalic amnesia.

## Investigating the Modality-Specific Hypothesis of Semantic Memory

## C. ILSE<sup>a</sup>, L. TIPPETT<sup>a</sup> and L. MILLER<sup>b</sup>

# <sup>a</sup>Department of Psychology, Auckland University, Auckland, New Zealand <sup>b</sup>Neuropsychology Unit, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital and The University of Sydney, NSW, Australia

It has been proposed that semantic memory is organized according to modality, in that representations of living items depend to a greater extent on visual attributes and representations of nonliving items depend to a greater extent on functional attributes (Warrington & McCarthy, 1987, Brain, 111, 1273-1296). This hypothesis was tested using a picture-set, matched on picture complexity, familiarity and frequency, where pictures were divided into living and nonliving categories, and further into 'visual' and 'functional' items. Pictures were presented, using a paced picture-naming paradigm, to unilateral temporal lobectomy (TLE) participants and to normal controls, and error data were collected. Preliminary results suggest that the right TLE and control participants made a similar number of errors on naming visual and functional items. The left TLE participants however, made significantly more errors on functional items, relative to visual items, and relative to right TLE and control participants. Further, there was no significant difference between left and right TLE and controls in the number of errors made when items were divided into living and nonliving groups. These results support the modality specific hypothesis, because a relative impairment in naming was observed in response to modality (functional items for the left TLE group), but not in response to category (living or nonliving).



# 11.6

## Higher Language Competence and Working Memory in Older Adults

#### E. LOUKAVENKO and J. C. DALRYMPLE-ALFORD

# Christchurch Movement Disorders and Brain Research Group, Department of Psychology, University of Canterbury, Christchurch, New Zealand

As with other areas of cognition, three primary hypotheses are invoked to explain discourse functioning in the elderly: 1) reduced working memory, 2) inhibitory inefficiency and 3) cognitive slowing. Highly representative groups of young adults (20-34 years), young-old (65-74 years) and old-old adults (75-89 years) were assessed on the Test of Language Competence Expanded Edition (TCL-E, Wiig & Secord, 1989), a measure of discourse and higher language skills. Clear evidence of progressive age-related differences was obtained on the TLC-E. Age-related performance also decreased on several measures of working memory, processing speed, Stroop inhibition and long-term memory. Of particular theoretical relevance, path analyses indicated that the contribution of speed and long-term memory to age differences on the TLC-E was only indirect and was mediated by working memory, which itself also directly explained age-related differences on this language task. Stroop Inhibition was not associated with language performance. These findings provide new evidence on impaired discourse skills in the healthy elderly and extend our understanding of the relationship between aging and cognition by clarifying the important role of working memory in comparison to other cognitive processes as potential mediators of changes in these higher language skills. The evidence provided will establish provisional local norms for the TLC-E, and facilitate future work on higher language function in neurological conditions.

