LEABHARLANN CHOLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH | TRINITY COLLEGE LIBRARY DUBLIN
Ollscoil Átha Cliath | The University of Dublin

Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

Neural Mechanisms underlying Visuomotor Learning: Interacting Cortical Systems

by

Richard AP Roche

A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland.

This research was carried out in the Department of Psychology.

September 2002.

TRINITY COLLEGE
2 0 FEB 2003
LIBRARY DUBLIN
THESIS
7145

Declaration

I declare that this work has not been submitted previously as an exercise for a degree at this or any other university and that it is entirely my own work. The Trinity College Library may lend or copy this thesis without restriction.

Signed

Richard Roche

Richard Roche.

Acknowledgements

I would firstly like to thank my supervisor, Shane O'Mara, for his encouragement, trust and wise counsel during this thesis, and his seemingly endless supply of (only occasionally wacky) ideas; he has been everything a supervisor should be. Thanks also must go to the other members of Shane's lab group, both past and present, for creating an environment that was simultaneously warm and supportive as well as intellectually stimulating and challenging. Sean, Mike, Kendra, Dave, Maeve, Olivier, Thelma, Sinead, Jorge – thank you all. Thanks also to Hugh Garavan for letting us use his response inhibition task, which helped drag this thesis in more interesting directions.

Sincere thanks also to my friends/colleagues who also found themselves adrift with me in the sea of electrophysiology. Nicola, Michelle and Paul, I think between us we found dry land. And thanks to all the participants for enduring the things we put them through; I hope all the gel came out eventually. Thanks to Miguel Rodriguez at Medtech, also, for his advice and technical assistance over the past few years. Special thanks to my family, both those present and absent, and my friends from Trinity and from home, for making me who I am. Finally, my warmest and most heartfelt thanks must go to those I call my closest friends (Beth, Brendan, Kiera, my dear Michelle, others I have not named) for the love, companionship, patience, advice, support and all the other things you have given me; I could not have done this but for you.

List of Abbreviations

ACC Anterior cingulate cortex

ACh Acetylcholine

AChe Acetylcholine esterase

ADD Attention deficit disorder

ADHD Attention deficit hyperactivity disorder

ANOVA Analysis of variance

CA1 Cornu Ammonis 1

CA3 Cornu Ammonis 3

CBT Cognitive behavioural training

CFQ Cognitive failures questionnaire

ChAT Choline acetyltransferase

CNV Contingent negative variation

CPT Continuous performance task

DA Dopamine

EEG Electroencephalogram

EMG Electro-myogram

EPSP Excitatory post-synaptic potential

ERN Error-related negativity

ERP Event-related potential

fMRI Functional magnetic resonance imaging

HADS Hospital anxiety and depression scale

HEOG Horizontal electro-oculogram

IPSP Inhibitory post-synaptic potential

ISI Inter-stimulus interval

IT Infero-temporal

LTP Long-term potentiation

mAChR Muscarinic acetylcholine receptors

MANOVA Multivariate analysis of variance

MEG Magneto-encephalography

NA Noradrenalin

NART National adult reading test

Ne Error negativity

OCD Obsessive-compulsive disorder

Pe Error positivity

PET Positron emission tomography

PFC Prefrontal cortex

PMC Premotor cortex

rCBF Regional cerebral bloodflow

RI Response inhibition

RT Reaction/response time

RTA Response-triggered average

R-SAT Revised strategy application task

SA Sustained attention

SART Sustained attention to response task

SCD Scalp current density

SEM Standard error of the mean

SOA Stimulus onset asynchrony

S-R Stimulus-response

STA Stimulus-triggered average

TBI Traumatic brain injury

TEA Test of everyday attention

TMS Transcranial magnetic stimulation

VEOG Vertical electro-oculogram

WMS Wechsler memory scale

Publications resulting from the present work:

Articles:

Roche, R.A.P. & O'Mara, S.M. (2003) Behavioural and electrophysiological correlates of visuomotor learning in a visual search task. *Cognitive Brain Research,* **15**, 127-136.

Roche, R.A.P., Garavan, H. & O'Mara, S.M. (*under review*). Individual differences discriminate event-related potentials but not performance during response inhibition. Submitted to *the Journal of Cognitive Neuroscience.*

Roche, R.A.P., Commins, S., Agnew, F., Corapi, K., Leibbrand, S., Lipson, Z., Rickard, J., Sorohan, J. & O'Mara, S.M. (*under review*). Concurrent task performance enhances low-level visuomotor learning. Submitted to *the Journal of Experimental Psychology: Learning, Memory and Cognition.*

Reviewed Abstracts:

Roche, R.A.P. & O'Mara, S.M. (2000). Event-related potentials during low-level visual search: a task components analysis. Proceedings of the Forum of European Neuroscience (FENS), Brighton, UK.

Other Publications:

Connolly, J., Roche, R.A.P. & Robertson, I.H. (2000). Electrophysiological correlates in prism-induced spatial-remapping: pseudoneglect and differences in ERP waveforms. Conference on Action and Visuo-spatial Attention: Neurobiological Bases and Disorders, Konigswinter, Germany.

Garavan, H., Ross, T.J., Murphy, K., Roche, R.A.P., & Stein, E.A. (2002). Dissociable executive functions in the behavioural control: Inhibition, error detection and correction. *NeuroImage*, **17**, 1820-1829.

Chapter 1 ..... **5**

General Introduction **5**

1.1 Arbitrary Visuomotor Association Learning *6*

1.1.1 The Prefrontal Cortex 10

1.1.2 The Premotor Cortex 11

1.1.4 The Hippocampus 14

1.1.5 The Cerebellum 15

1.2 Behavioural Control, Response Inhibition and Sustained Attention *17*

1.2.1 The Race Model, Imaging and Electrophysiology of Response Inhibition 18

1.2.2 Response Inhibition and Sustained Attention 22

1.3 Visual Search *26*

1.4 Event-related Potentials (ERPs) *30*

1.5 Outline of the Thesis *31*

Chapter 2 ..... **33**

Methods **33**

2.1 Event-Related Potentials: Introduction *33*

2.1.1 Historical Background 34

2.1.2 Temporal and Spatial Resolution of ERPs 35

2.2 Physiological Basis of ERPs *38*

2.2.1 Electrical Activity in the Brain 38

2.2.2 Spatial Localisation of ERPs 44

2.2.3 The Reference Electrode 45

2.2.4 Neural Mechanisms of ERPs 46

2.3 Electrode Cap Application Procedures *51*

2.3.1 Applying the Cap, Ground and VEOG Electrodes 51

2.3.2 Applying Electro-conductive Gel to the Electrode Cups 52

2.3.3 Testing and Reducing Impedance 53

2.3.4 Removing and Washing the Cap after Testing 54

2.4 ERP Data Analysis and Processing *55*

2.4.1 Continuous to Epoch Data 55

2.4.2 Ocular Artifact Reduction and Artifact Rejection 56

2.4.3 Sorting Sweeps and Averaging 57

2.5 Time-Locked Averages: Issues *59*

2.5.1 Stimulus-Triggered Averages and Response-Triggered Averages: Merits 60

Chapter 3 ..... **61**

Behavioural and Electrophysiological Correlates of Visuomotor Learning in a Visual Search Task ***61***

3.1 Introduction *62*

3.2 Materials and Methods *64*

3.2.1 Participants: 64

3.2.2 Materials: 64

3.2.3 Procedure: 65

3.3. Results *69*

3.3.1 Behavioural Data: Training 69

3.3.2 Waveform Data: Training 71

3.3.3 Behavioural Data: Learning Effects 72

3.3.4 Waveform Data: Training Block 75

3.4 Discussion *76*

Chapter 4 ..... **80**

Concurrent Task Performance Enhances Low-level Visuomotor Learning ***80***

4.1 Introduction *81*

4.1.1 Experiments 1, 2 and 3 83

4.2 Experiment 1: Methods *84*

4.2.1 Participants: 84

4.2.2 Materials: 84

4.2.3 Procedure: 85

4.2.4 Experiment 1a: Dual-Task 86

4.2.5 Experiment 1b: Arousal 89

4.3 Experiment 1: Results *90*

4.4 Experiment 1: Short Discussion *98*

4.5 Experiment 2: Methods *99*

4.6 Experiment 2: Results *100*

4.7 Experiment 2: Short Discussion *102*

4.8 Experiment 3: Methods *102*

4.9 Experiment 3: Results *103*

4.10 Experiment 3: Short Discussion *104*

4.11 General Discussion *106*
4.11.1 Experiment 1 106
4.11.2 Experiment 2 109
4.11.3 Experiment 3 110
Chapter 5 ..... **112**
Individual Differences Discriminate Event-related Potentials but not Performance during Response Inhibition ***112***
5.1 Introduction *113*
5.2 Materials and Methods *120*
5.2.1 Participants: 120
5.2.2 Materials: 120
5.2.3 Procedure: 122
5.2.4 Data Analysis: 124
5.3 Results *126*
5.3.1 Response Inhibition: Behavioural Data: 126
5.3.2 Electrophysiological Data: 127
5.3.3 Cognitive Failures and Response Inhibition: Behavioural Data: 130
5.3.4 Electrophysiological Data: 130
5.4 Discussion *135*
Chapter 6 ..... **141**
Traumatic Brain Injury (TBI) produces Impaired Performance and Diminished ERP Waveforms during Response Inhibition ***141***
6.1 Introduction *142*
6.2 Materials and Methods *146*
6.2.1 Participants: 146
6.2.2 Materials: 149
6.2.3 Procedure: 150
6.2.4 Data Analysis: 151
6.3 Results *152*
6.3.1 Neuropsychological Battery 152
7.3.2 Behavioural Performance and Reaction Times 154
8.3.3 Event-related Potentials 154
6.4 Discussion *160*
Chapter 7 ..... **165**

Low-level Visuomotor Learning Disrupts Higher-order Behavioural Control ***165***

7.1 Introduction *166*

7.2 Materials and Methods *168*

7.2.1 Participants: 168

7.2.2 Materials: 169

7.2.3 Procedure: 171

7.3 Results *173*

7.4 Discussion *177*

Chapter 8 ..... **181**

General Discussion ***181***

8.1 Insights into Arbitrary Visuomotor Association Learning *182*

7.1.1 Attention and Learning 186

8.1.2 Arousal and Learning 188

8.2 Response Inhibition and Sustained Attention – Mechanisms and Individual Differences *189*

8.2.1 Individual Differences and Acetylcholine 189

8.2.2 Response Inhibition and Sustained Attention 194

7.2.3 Error Processing in Response Inhibition 199

7.3 Interaction of Cortical Systems – Learning Across Task Domains *200*

8.3.1 Disruption of Inhibitory Control through Training 201

8.3.2 Facilitation of Inhibitory Control through Training 203

8.4 Concluding Remarks *204*

Appendix I **205**

Psychological Tests **205**

References **206**

Chapter 1

General Introduction

"Learning, that cobweb of the brain,

Profane, erroneous, and vain."

(Samuel Butler (1612-1680), *Hudibras*, part 1, canto 3, line 1339)

"I have but one lamp by which my feet are guided, and that is the lamp of experience. I know no way of judging the future but by the past."

(Unknown author)

We are the products of our experiences. Every sight, sound and smell, every event, encounter and exchange, all leave their indelible mark on the way we act, think and feel. The things we learn from our experiences stay with us, they allow us to better

understand the nature of our world, to reveal connections that were once veiled. Learning arms us with the knowledge to make better choices, steers us to take one path over another, lights our way and helps us find solid ground for our footfalls. We can see a distance into the future because we stand, not on the shoulders of giants, but atop a mound of bones, the bones of experiences past. Through learning, how we react in different situations will be informed; one course among a multitude of possible actions will seem preferable. Learning occurs in the brain. Despite his harsh and disdainful view, Butler's conception of learning as a "cobweb of the brain" is startlingly apt. The complex web of learning that is spun by experience into ever more intricate patterns mirrors the intermingling branches of the brain's structure as it grows and connects, moulded and guided by experience. This thesis is concerned with learning: what happens in the brain when we learn, how this learning takes place and how what we have learned can be used to influence our complex behaviours.

1.1 Arbitrary Visuomotor Association Learning

In order to successfully carry out complex behaviours, navigate through elaborate environments and adapt to the differing demands of everyday challenges, we are equipped with a selection of highly flexible cognitive capacities including learning, memory and attention. One basic and important type of learning is the ability to form and internalise meaningful associations between particular visual objects in the environment and certain motor behaviours that they are intended to elicit. In this way we learn to press a foot on the brake pedal when confronted with a red traffic light or STOP sign when driving, to cross the street when we see a "green man", or to turn off the cooker when a pot boils over. The learning of such associations is vital for successful living, and is termed visuomotor association learning, though it has in the

past also been referred to as conditional visuomotor learning, conditional associative learning, or visuomotor mapping; these terms have been used less frequently, largely because the use of "conditional" creates misleading connotations of classical conditioning.

In many cases, the visual component of the association contains within it instructions as to what behavioural response is required; for example, the STOP sign on the road informs us that the appropriate motor response is to "stop". Alternatively the stimulus may provide visuospatial information regarding *where* an action is desired. In other instances, however, the visual stimulus contains no such clue as to the desired behaviour, the association must be learned and internalised, requiring a greater degree of cognitive flexibility. Such learning is referred to as arbitrary visuomotor association learning, because the stimulus contains no information as to the necessary response; the association is therefore arbitrary. This form of learning is exemplified by learning to "stop" in response to a red light; the association between the colour red and stopping has to be learned and internalised, especially due to the fact that other possible colours, amber or green, are associated with different behaviours. Because an internal representation of the association needs to be generated and maintained to ensure that the appropriate behaviour follows the right stimulus, it is said that this learning demands considerable cognitive flexibility, as a response must be selected on the basis of reward characteristics, and for this reason some have claimed that this form of learning represents an important aspect of intelligent behaviour (Wise & Murray, 2000). As such arbitrary visuomotor association learning has been the subject of experimental investigation in both animals and humans.

Converging evidence from single- and multiple-unit recordings and ablations in animals, and imaging and neuropsychological studies in humans has allowed a clearly defined cortical circuit subserving this form of learning to be identified. In addition to primary visual and motor areas, the key nodes in this distributed network are the prefrontal cortex (PFC), premotor cortex (PMC), hippocampal formation and the basal ganglia (Wise & Murray, 2000; See Figure 1.1). Others have suggested a role for the cerebellum in this circuit, though there is some debate about this point (discussed below). Ablation studies by Passingham and Petrides (reviewed in Wise & Murray, 2000) found that damage to dorsal premotor cortex, dorsolateral prefrontal cortex or the inferotemporal-PFC pathway all produced learning impairments on visuomotor tasks, while thalamic lesions severing the basal ganglia-frontal connections resulted in a profound disruption of learning. Bilateral removal of the hippocampus disrupted the learning of new associations, though existing stimulus-response (S-R) pairings remained intact. Single-cell recordings point to the same cortical structures, as evolution of neural firing has been found during learning in each of the areas cited above: by Rolls and colleagues in the hippocampus (Cahusac *et al.*, 1993), in the prefrontal cortex (Mitz *et al.*, 1991) and in the basal ganglia (Tremblay *et al.*, 1998). These experiments report either learning-dependent increases or learning-selective decreases in activation in these areas, strongly suggesting a role in learning for these areas. In addition, in a study of motor skill acquisition Staines *et al.* (2002) showed learning-related changes in fronto-parietal ERPs that they attributed to changes in the activity of motor preparation and sensorimotor integration systems.

In humans, Ghilardi *et al.* (2000) observed activity in primary motor and sensory areas, basal ganglia and cerebellum during the execution of prior learned motor actions, while learning new sequences activated dorsolateral prefrontal and anterior

cingulate areas. Using both positron emission tomography (PET) and functional magnetic resonance imaging (*f*MRI), Passingham *et al.* (1998) reported activations in the ventral visual system (prestriate areas, inferotemporal cortex and ventral PFC), the basal ganglia and the dorsal premotor cortex. Learning-related changes in activity were seen in the globus pallidus of the basal ganglia, leading the authors to suggest that the basal ganglia represent a flexible system whereby arbitrary associations between sensory cues and motor movements may be learned. Toni and Passingham

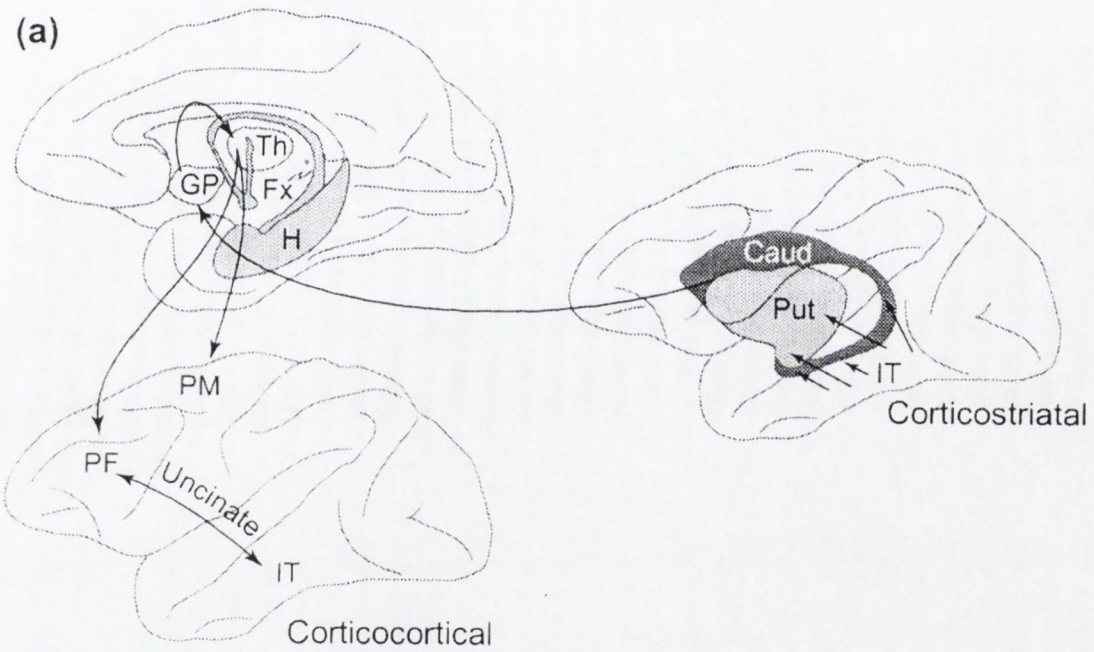

Figure 1.1: Lateral and medial views of a macaque monkey brain showing some pathways involved in arbitrary visuomotor mapping. Abbreviations: Caud, caudate nucleus; Fx, fornix; GP, globus pallidus; H, hippocampus; IT, inferior temporal cortex; PF, prefrontal cortex; PM, premotor cortex; Put, putamen; Th, thalamus. Adapted from Wise & Murray (2000).

(1999), using PET, again observed activity in the prefrontal cortex and basal ganglia, but also in the left parahippocampal gyrus. An *f*MRI study by Toni *et al.* (2001) to elaborate the timecourse of activity in visuomotor learning revealed early activity in

the hippocampal formation, with subsequent activation in the basal ganglia, while the inferotemporal and ventral PFC areas were also engaged.

1.1.1 The Prefrontal Cortex

Further support for the role of the prefrontal cortex has been provided by Petrides (1997), in an experiment in which patients with either frontal or temporal lesions were trained to make a series of hand postures in response to arbitrary visual stimuli (colours). The training consisted of both demonstration of postures by the experimenter and correction of patients' errors during a practice session. Patients with either left or right frontal damage were reliably impaired on the learning of the associations, while the temporal lobe patients' performance did not differ from controls (the only instances in which temporal patients showed a learning deficit were in cases where there was extensive damage of the left hippocampus). Importantly, the modified training regime controlled for the possibility that the deficit in these patients was due to problems with trial-and-error learning, rather than a specific learning deficit. Rather, the results suggest that frontal patients suffer from a more specific deficit in mapping particular motor sequences to arbitrary stimuli. In addition, Deiber *et al.* (1997) reported changes in regional cerebral blood flow in the prefrontal cortex in a PET study of this form of learning, while Bussey, Wise and Murray (2001; 2002) and Toni *et al.*, (2001) point to the ventral and orbital PFC interacting with area IT of the temporal lobes in rhesus monkeys and humans, respectively. A large number of inputs converge on the prefrontal cortex (from posterior parietal, superior temporal and cingulate cortices, superior colliculus and somatosensory areas, among others; Kolb & Whishaw, 1996), and the PFC projects back to every structure from which it receives afferents, as well as to some subcortical structures that provide no input

(most notably, the basal ganglia). Reciprocal connections also exist between the dorsolateral prefrontal area and the hippocampus. In addition, there is a cascade of projections from prefrontal to the premotor, cingulate and supplementary motor cortices that project on to the primary motor cortex (Duncan & Owen, 2000; Fuster, 1997). Given the richness of the connections between the prefrontal cortex and both sensory and motor/premotor areas, a role for the PFC in the mapping of sensory events to motor actions does not seem unlikely.

1.1.2 The Premotor Cortex

The premotor cortex (Brodmann's areas 6 and 8; Passingham, 1993) is thought to have a role in the selection of movements or sequences of movements based on the environmental context, as it can influence movement either via the primary motor cortex, or directly through its efferents to the spinal cord (Roland *et al.*, 1980, in Kolb & Whishaw, 1996; see Figure 1.2). It receives input from dorsolateral prefrontal cortex and posterior parietal areas that are responsible for egocentric representation of the body and limbs in three-dimensional space (Stein, 1991), suggesting that the premotor area acts to control and coordinate limb movements. Fuster (1997) notes that the premotor cortex forms the central node of a hierarchy with the prefrontal area at the top, projecting to PMC (including supplementary motor and cingulate cortex), and thence on to the primary motor area. Learning-dependent changes in premotor neurons of monkeys was observed by Mitz *et al.*, (1991) when the animals were engaged in visuomotor learning; over 50% of the cells they recorded from in the PMC showed changes in firing as the learning of associations took place. Furthermore, Halsband and Freund (1990) found that patients with lesions of the PMC were impaired on an association task that was arbitrary, whereas when the stimulus

appeared at the spatial location which was the target of the motor action, their performance was not disrupted. It seems possible that when the association is arbitrary, and thus is dependent on a learned rule stored in memory, the PMC is essential for successful expression of the learning, whereas when the stimulus itself contains all the necessary information for making the response, the PMC is not necessary and may even be bypassed (this latter case may involve the cerebellum; this is discussed below).

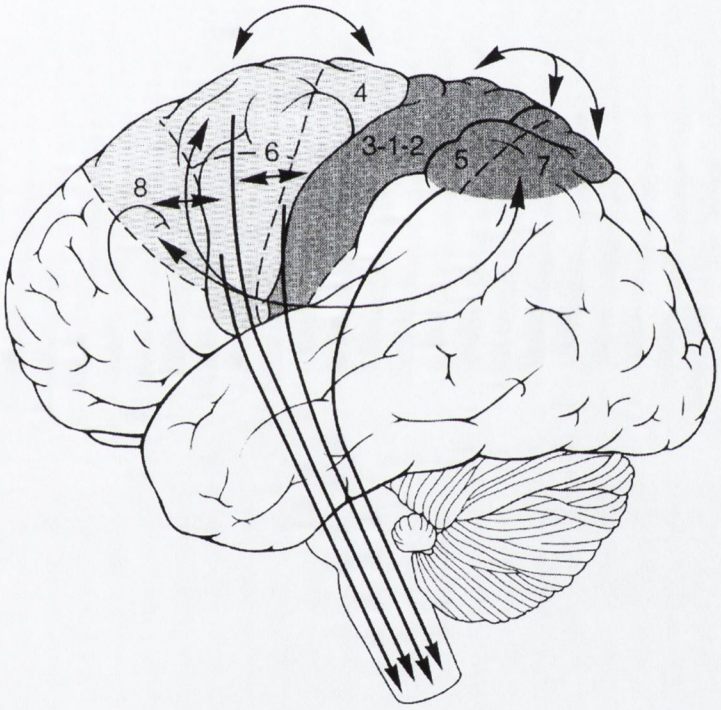

Figure 1.2: Emerging view of cortical motor systems. Note the many reciprocal connections between sensory (3-1-2, 5, 7) and motor (8, 6, 4) areas, and descending pathways to spinal cord. (From Kolb & Whishaw, 1996)

1.1.3 The Basal Ganglia

The basal ganglia are a collection of five large subcortical nuclei including the putamen, the globus pallidus, the caudate nucleus, the substantia nigra and the amygdala. The main input site for the basal ganglia is the caudate nucleus, which

receives afferents from all cortical areas, and then projects through the putamen and globus pallidus via the thalamus to prefrontal and motor areas (see Figure 1.3). Damage to the basal ganglia or depletion of its dopaminergic input from the substantia nigra results in motor disorders such as Parkinson's Disease, and has therefore implicated these structures in the coordination and smooth execution of motor sequences, as well as stimulus-response learning (Kolb & Whishaw, 1996). Doya (2000) proposes that the basal ganglia are specialised for learning based on reinforcement rather than trial-and-error learning, and that the reward signal for such learning is encoded within the dopaminergic inputs from the substantia nigra. Thus internally-generated movements that require the application of a stored rule detailing the reward value of different actions require an intact basal ganglia with dopaminergic inputs from the substantia nigra. Single-cell recordings from the globus pallidus show changes in firing rates during a delay period for a pre-learned association and greatly enhanced firing when a new association was being learned (Inase *et al.*, 2001). Furthermore, Laforce and Doyon (2002) showed that the striatum is critical for novel visuomotor association learning, but the cerebellum is not, as evidenced by the performance of Parkinson's Disease and Cerebellar Lesion patients.

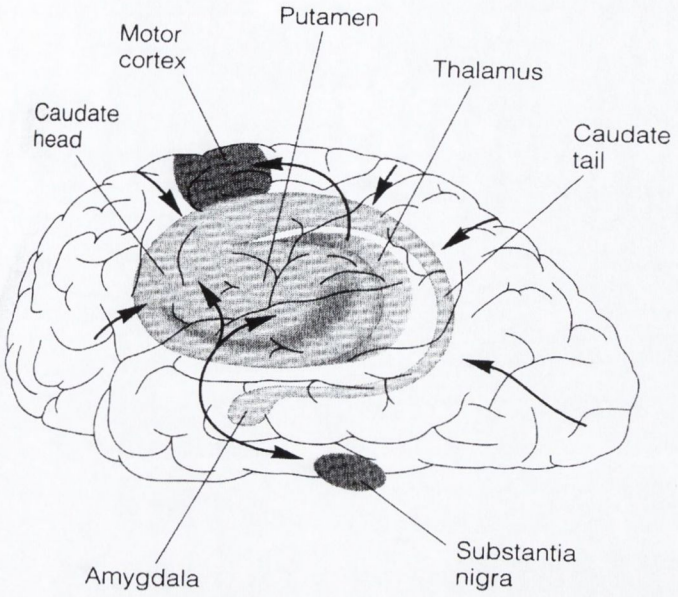

Figure 1.3: Relation between the basal ganglia and the cortex. Arrows indicate theoretical projections of the various areas into basal ganglia structures. (From Kolb & Whishaw, 1996).

1.1.4 The Hippocampus

The hippocampus is a limbic system structure located in each of the temporal lobes whose many proposed functions include learning, memory, allocentric spatial representation and spatial navigation (O'Mara, 1995; Squire, 1992). It receives converging inputs from sensory and association areas, as well as reciprocal connections with cortical (frontal, cingulate, parietal and temporal) and subcortical (including basal forebrain and thalamus) regions. The hippocampus is also the area in which the principle putative biological mechanism underlying learning and memory, long-term potentiation (LTP; Bliss & Collingridge, 1993), was discovered. The role of the hippocampal formation in arbitrary association learning has been investigated by Wise and Murray (1996, 1999, 2000). They have demonstrated that only lesions of the

hippocampus, and not the amygdala, retard learning of visuomotor mappings, and that the retention of old association was not disrupted in either case. They also argue that, since damage to the hippocampal formation in animals produces a pattern of deficits and preserved abilities similar to that of the human patient H.M. (Scoville & Milner, 1957), and since arbitrary visuomotor learning involves the learning and storage of an association rule, then this learning in animals might serve as a useful model for investigating declarative memory in animals. They propose that the hippocampal formation may serve a more general and fundamental role in this form of learning than is presently accepted.

1.1.5 The Cerebellum

The function of the cerebellum in arbitrary association learning remains controversial. Although activity has been found here in some imaging studies (e.g. Deiber *et al.*, 1997), it has not been consistently implicated and its role may be restricted to certain specific conditions. For example, Nixon and Passingham (2000) trained monkeys to make movements to arbitrary stimuli before lesioning the cerebellum. They concluded that the cerebellum was not essential for either the learning or recall of S-R associations, but that it was an important part of the process whereby motor sequences become automatic with extended practice. This may explain some of the cerebellar activation in imaging studies of visuomotor learning. Other studies (e.g. Timmann et al., 1996; Laforce & Doyon, 2002) bring the role of the cerebellum further into question, giving inconclusive results as to its involvement in visuomotor learning. Doya (2000) proposes that, while the basal ganglia may be specialised for reward-based learning (see above), the cerebellum may be more important for visually-guided (or non-arbitrary) movements that are learned in a trial-

and-error manner. This functional specialisation between the basal ganglia and the cerebellum is based on the differences in circuit architecture and synaptic mechanisms in the two. While both project to the prefrontal and premotor cortices via the thalamus, Doya proposes that the cerebellar-thalamo-frontal circuit is activated for externally-guided movements, while for internally- or memory-guided actions, the basal ganglia-thalamo-frontal pathway allows the appropriate response to be selected on the basis of the stored rule. Regardless of which theory of cerebellar involvement is more accurate, it can be concluded that the role of the cerebellum in visuomotor learning is more questionable than any of the other structures mentioned in this review and as such will not be considered further in this thesis.

Arbitrary visuomotor association learning is a type of learning that requires a complex rule to be learned, stored and retrieved in order that an appropriate motor action is made in response to a visual stimulus. This learning demands a high level of cognitive flexibility and may even be considered an example of the sort of functional system that underpins episodic memory (Wise & Murray, 1999) or even language acquisition (Perkel & Farries, 2000). The ability to learn such associations has even been shown to diminish with old age (Cole & Rotella, 2002). It is also subserved by a well-defined, distributed cortical/subcortical network, a network whose activity is amenable to experimental manipulation and may be observed using recording and imaging techniques in the performing animal and human.

1.2 Behavioural Control, Response Inhibition and Sustained Attention

A major feature of high-level executive function is the ability to exert top-down control over motor responses. The ability to suppress or inhibit a motor act is an important aspect of executive control; it is essential for the successful execution of complex behaviours, and is one of the defining deficits in dysexecutive syndrome following frontal brain injury (Fuster, 1997; Lezak, 1983). This capacity, termed response inhibition (RI) allows us to override habitual, automatic or routine behaviours and also facilitates error-correction and behavioural control (Garavan *et al.*, in review). In fact, a failure of this response inhibition capacity is suspected in disorders such as attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and schizophrenia (Carter *et al.*, 2001; Casey *et al.*, 1997; Curtis *et al.*, 2001; Enright *et al.*, 1993; Pliszka *et al.*, 2000).

RI is known to be resistant to training and practice effects from repeated exposure, making rehabilitation of deficits difficult (Chen *et al.*, 1998). Different strategies and training regimes have been used in the past to attempt to improve executive control over motor output. Banaschewski *et al.* (2001) trained children with ADHD with either sensorimotor practice or cognitive behavioural training (CBT), and found some improvements in motor coordination after sensorimotor training, with improved impulse control following CBT. They concluded that a combined treatment would be most effective. Dowsett and Livesey (2000) reported better inhibitory control on inhibition tasks including the Wisconsin Card Sorting Task in preschool children who had been given training on acquisition of complex rules.

1.2.1 The Race Model, Imaging and Electrophysiology of Response Inhibition

The most influential model of processing in RI is the "horse race" or "race model" of inhibition (see Logan *et al.*, 1984). When processing stimuli in an RI task, two sets of processes are pitted against each other in a race. Processes that will lead to a behavioural response are set in motion by the appearance of a "go-signal". Processes that will cause this response to be inhibited are initiated by a "stop-signal". In order for a response to be successfully withheld, the stop processes must win the race and be executed before the go processes. This model was developed mainly to explain inhibition processes during the stop-signal or STOP paradigm, in which standard stimuli (requiring a response) are infrequently followed by a signal that tells participants not to respond. In this way, it was possible to determine how much of a "head start" the go-processes could be allowed for an attempted inhibition to be successful. The application of the race model to other RI tasks, such as the Go/NoGo paradigm, raises other issues regarding the nature of the racing processes.

The Go/NoGo task is one of the most commonly used measures of response inhibition; it involves making a motor response (usually a button-press) to a designated stimulus type (targets), which may be presented visually and/or auditorially. The presentation of another particular stimulus type ("critical lures") requires the inhibition of the motor response. Targets and lures are presented in rapid random succession. Successful performance of the task requires the participant to press for targets and withhold the press for lures. A mistaken response to a lure is an *error of commission*, or "false alarm"; a mistaken non-response to a target, is an *error of omission*, or "miss". Application of the race model to this type of task adds a processing stage not necessary in the STOP paradigm. In the STOP task, response-demanding stimuli may or may not be followed by the signal to stop; this separate,

discrete event occurs after the response process has been initiated. In the Go/NoGo task, by contrast, the stimuli themselves are either go stimuli (targets) or no-go stimuli (lures). There is therefore an additional processing stage wherein the stimulus must be first identified and flagged if inhibitory processes are to be initiated in time to prevent a response. Adequate stimulus identification must take place if a lure is to be correctly flagged before response processes have gone beyond the "point of no return". It is likely that top-down attentional factors play a role in the modulation of sensory input; this is discussed below. Furthermore, in some inhibition tasks, termed *elemental RI tasks*, the lure is a unique stimulus, which aids identification (e.g. X is the lure; Y is the target); in other tasks (*configural RI tasks*), the lure is only identifiable through the application of a stored rule (e.g. an X is the lure *only* if it follows an X, but not if it follows a Y). In addition, in many RI tasks the lures are very infrequent, thereby creating a propensity to respond and making the inhibition more difficult. If "respond" is the default output to the majority of stimuli, then that process will have a clear advantage over the inhibit process; to continue the horse-race analogy, it will be faster out of the stalls. It is clear that, although the race model of inhibition is a useful way of conceptualising some of the processes that are at work in RI tasks, there are several factors (attention, task specifics, stimulus frequency) that can tip the balance of that race in one direction or the other.

Studies using functional imaging have allowed some of the anatomical substrates of response inhibition to be identified. An *f*MRI study using the X-Y response inhibition task (Garavan, Ross & Stein, 1999) reported activity in the right hemisphere, including inferior parietal lobule and dorsolateral prefrontal cortex. These regions may constitute a major part of the right parietal/prefrontal circuit suspected of involvement in tasks requiring sustained attention and response

inhibition. Anterior cingulate areas were also activated. Interestingly, in a subsequent investigation that compared correctly withheld responses (STOPS) and errors of commission (ERRORS), no regions showed greater activation for STOPS over ERRORS (Garavan *et al.*, *in press*). The authors suggested a temporal hypothesis to explain the differential processing of correct and error trials, which the poor temporal resolution of *f*MRI was unable to test; the present study attempts to address this question. Error-related processing, localised to the cingulate cortex, was also observed by Garavan *et al.* Thus the right hemisphere parietal/prefrontal circuit (see Figure 1.4) and the cingulate cortex seem to be strongly involved in separate response inhibition and error detection processes, and may be likely candidates for the generators of the NoGo-N2/NoGo-P3 and Ne components (see Chapter 2). Another *f*MRI study by de Zubicaray *et al.* (2000) using a visually based motor suppression task observed increases in rCBF in prefrontal, parietal and occipito-temporal cortices. The authors emphasised the importance of the right hemisphere, particularly the right prefrontal cortex, in motor suppression.

Event-related potential (ERP) studies of response inhibition reliably elicit amplitude and/or latency differences in the N2 and P3 components (Falkenstein *et al.*, 1999). NoGo stimuli produce a negative deflection in the 200-400 ms time window with a frontal maximum (the so-called "NoGo-N2") that is smaller or totally absent for Go stimuli. Amplitude and latency differences are also seen for the P3 elicited by NoGo stimuli (the "NoGo-P3") compared to stimuli requiring a button press (the "Go-

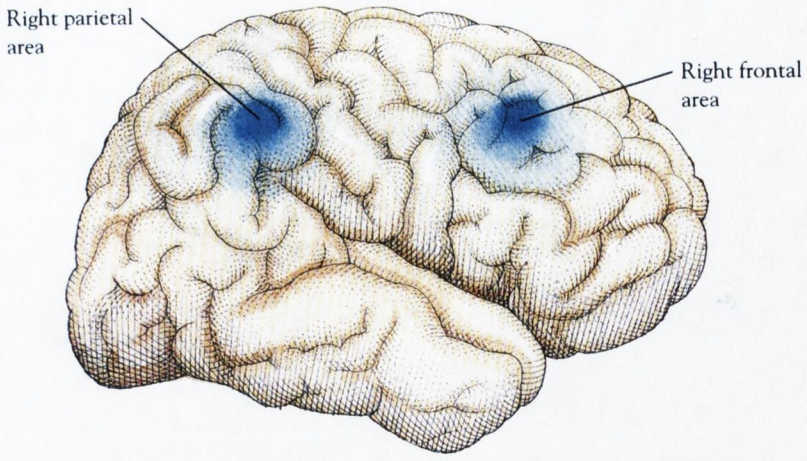

Figure 1.4: Right frontal and right parietal areas suspected of involvement in response inhibition and sustained attention. (From Posner & Raichle, 1994).

P3"). NoGo-P3 amplitude is larger at central leads, whereas Go-P3 amplitude tends to be maximal at parietal sites. In addition, a longer-latency negative component has also been observed over central electrodes following errors of commission (termed Error Negativity, Ne). However, Falkenstein *et al.* (1999) suggest that this component is unlikely to be a late version of the NoGo-N2, as the two components appear to have separate cortical generators, given their different scalp topographies. Despite general agreement that the N2 and P3 are the key electrophysiological indices of response inhibition (among other processes), there is much debate regarding which component is more important for successful inhibition of motor actions. This issue is discussed in detail in Chapter 5.

The neurochemical basis of response inhibition has not been delineated in any great detail. The main neurotransmitter substances in the prefrontal cortex are noradrenaline, acetylcholine, dopamine and serotonin (Fuster, 1997). Noradrenaline and acetylcholine projections originate mainly from structures in the ascending

reticular activating system, specifically the locus coeruleus and basal forebrain, respectively. They are likely to serve some role in general excitability and somatosensory information processing, as well as mediating sustained attention (discussed in the next section). The dopaminergic innervation comes from the substantia nigra, via the striatum, and is suspected of a specific role in motor control. Serotonin projects from the raphé nucleus to the limbic system and the cortex, and has the lowest concentration of these four chemicals in the prefrontal area. Dysfunction of this chemical system has been implicated in stress and depression. Experimental studies showing RI impairments and alterations in the brain activity of patients with schizophrenia and (non-psychotic) psychopathy allow us to infer that dopamine may have a major function in inhibition due to the dysfunction of that chemical in these disorders (Kiehl *et al.*, 2000; Weisbrod *et al.*, 2000). However, Nordahl *et al.* (2001) suggests a depletion of noradrenaline in the anterior cingulate system may underlie the performance deficits they observed from schizophrenic patients performing a Stroop task. In contrast, Robbins et al. (1998) lesioned portions of the raphé nucleus and concluded that while noradrenaline may be involved in attention, acetylcholine in stimulus detection and dopamine in response speed, serotonin systems are responsible for response inhibition. Thornton and Goudie had proposed this role for serotonin as far back as 1978. As can be seen, these four neurotransmitter substances all have strong claims on involvement in inhibitory processes; further investigation at a neurochemical level is required to settle this issue.

1.2.2 Response Inhibition and Sustained Attention

Although the topic is controversial, there seems to be a considerable cognitive and anatomical overlap between tasks requiring response inhibition and some of those

designed to investigate sustained attention (e.g. the sustained attention to response task, or SART; Robertson *et al.*, 1997). While it is beyond the scope of this thesis to decide the relative contributions of each of these capacities to the other, it is obvious that the standard RI Go/NoGo task does require sustained attention as the participant monitors stimuli for the appearance of an infrequent "lure". Therefore, the main theories of the neuroanatomical and neurochemical bases of sustained attention will be briefly reviewed.

Sustained attention is the ability to maintain a high level of alertness for a prolonged period of time, and has been extensively studied since the early radar-operator experiments of Broadbent in the 1950s (for a review of attention and arousal, see Coull, 1998). The imaging and lesion literature points to a right frontal-right parietal circuit that appears to be essential for successful performance on sustained attention tasks. Coull (1998) proposes a model of the neural basis of sustained attention that constitutes a compromise position between the two major theories of the past two decades, those of Mesulam (1981) and Posner and Petersen (1990). Coull's model posits that "arousal" occurs in the form of ascending projections from the reticular formation to multiple *sources of attentional modulation*; these include the anterior and posterior attentional networks thought to reside in frontal and parietal areas, respectively. From these sources, the same neurotransmitters project to specific *sites of attentional modulation*, namely sensory and association cortices whose activity is enhanced as a result. Sensory information then feeds forward to the attentional systems for evaluation of the filtered/enhanced input and subsequent response selection. In this model, three neurochemicals are thought to underpin the spread of activation in this system: noradrenaline, acetylcholine and dopamine. The key features of this model are the proposal that arousal takes the form of ascending

activation from the reticular formation to attentional areas, and that these attention centres influence stimulus perception through neurochemical modulation or facilitation.

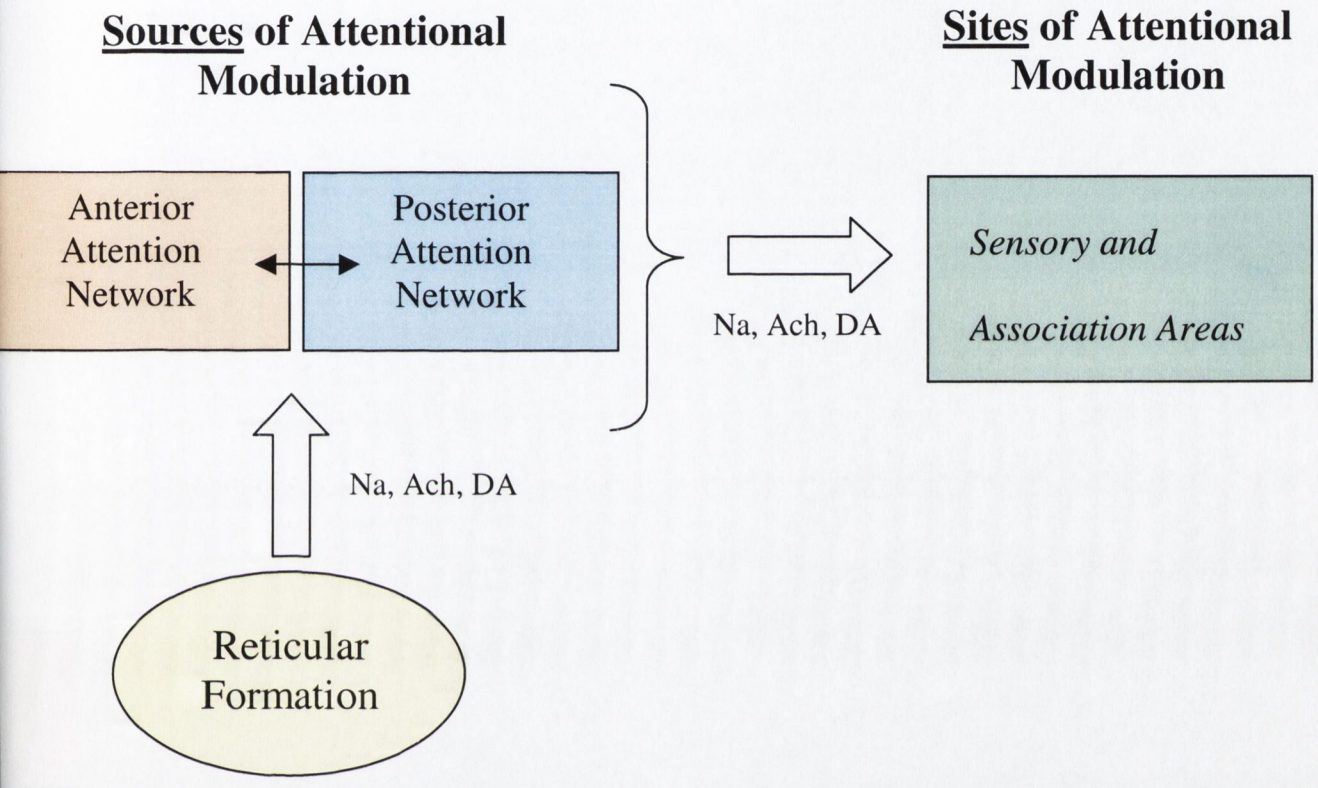

Figure 1.5: Coull's (1998) model of sustained attention, showing ascending noradrenergic (Na), cholinergic (Ach) and dopaminergic (DA) projections from the reticular formation innervate anterior and posterior attentional systems, leading to enhancement of processing in sensory and association cortices, achieved by the same neurochemicals.

Sarter and colleagues (2001) offer a variation on this idea which gives a major role to the basal forebrain. They suggest a mechanism that explains the operation of both internally-generated ("top-down") attention and attention elicited by alerting or interesting stimuli ("bottom-up"). In cases where attention is internally-generated, projections from the prefrontal cortex recruit the basal forebrain, a major source of

cortical acetylcholine; this serves as a "call-to-arms" for attentional resources. The basal forebrain then activates cholinergic projections to the posterior and anterior attentional networks (residing in right posterior parietal and right frontal cortices, respectively), and to sensory regions to facilitate stimulus detection. In the case of stimulus-driven attention, the "bottom-up" arousal element is provided by ascending noradrenergic projections from the locus coeruleus and thalamus to the basal forebrain, which again releases acetylcholine as described above. Thus distinct roles are given to the different neurochemicals, and the basal forebrain is seen as central in this model. As in the Coull model, the reticular system is seen as the source of arousal effects, and the idea of neurochemical modulation of sensory systems is again present (see Figure 1.6).

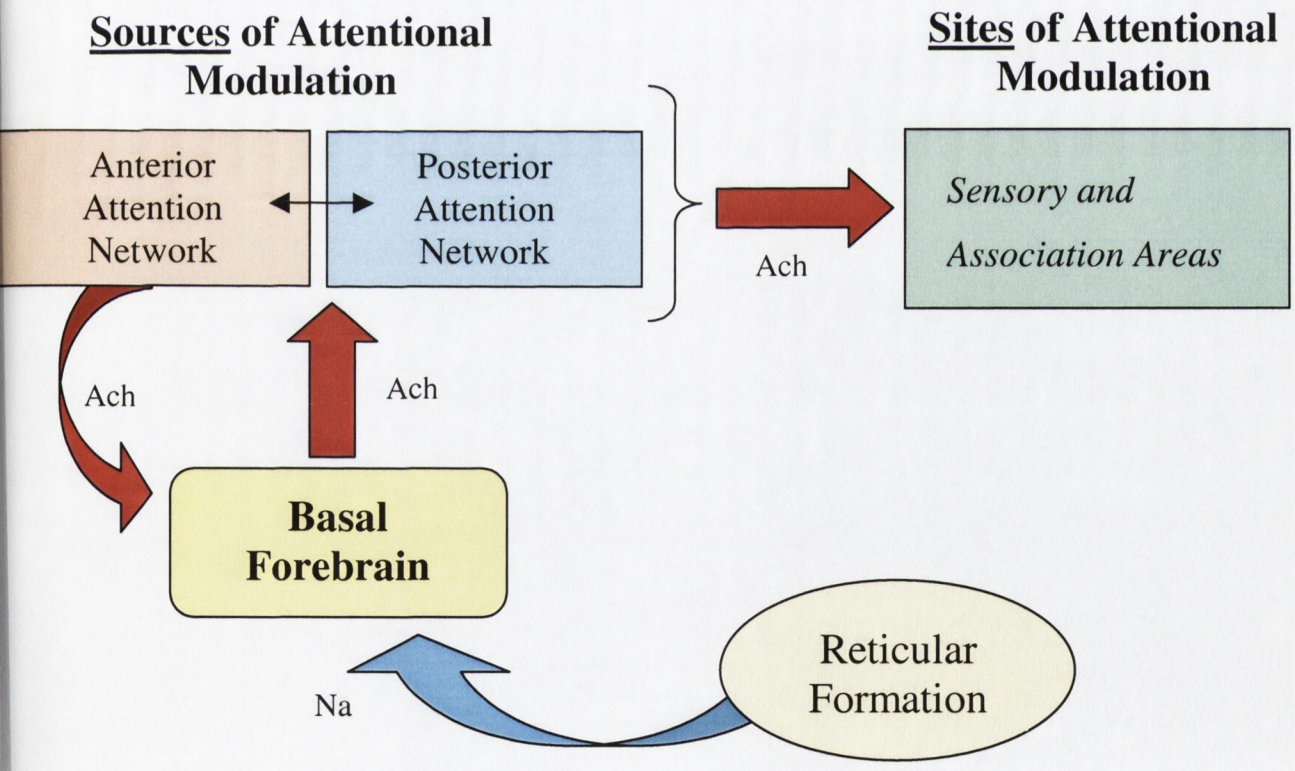

Figure 1.6: Sarter et al. (2001) model of sustained attention, showing that top-down attention is achieved by frontal-basal forebrain projections causing the release of Ach to anterior and posterior attentional systems, leading to perceptual enhancement. This release of Ach can also be induced bottom-up, by ascending Na input from the reticular formation.

Taken together, the experimental literature on response inhibition and the theoretical models of sustained attention allow us to conclude that the executive control of motor behaviour relies on a predominantly right-hemisphere circuit including frontal, parietal and cingulate areas, and is likely modulated by the activity of the neurochemicals acetylcholine (for selective enhancement of activity in specific cortical target sites) and noradrenaline (for more generalised activation of structures important for initiating the attentional modulation of these sites). The success of an attempt to withhold a prepotent response seems to be determined by the outcome of a race between processes leading to a response and competing inhibitory processes.

1.3 Visual Search

In a visual search task, a participant must visually inspect a stimulus array and make a forced-choice button-press response to indicate the presence or absence of a predefined target. This target differs in some way from the other stimuli in the array (distractors), and the participant must react as quickly as possible by making the present/absent response. This paradigm has been used extensively since the early 1980s to reveal important features of processing in the early stages of the visual system, including the role of attention. For example, it has been revealed that when a visual target is defined by a unique stimulus feature (its colour, shape, direction of motion or other unique feature), visual attention is drawn automatically to that stimulus, so it appears to "pop out" of the stimulus array (e.g. a green square among red squares; Figure 1.7). Such a search is termed "pre-attentive" or feature search, or alternatively parallel search because the stimuli are all processed in parallel.

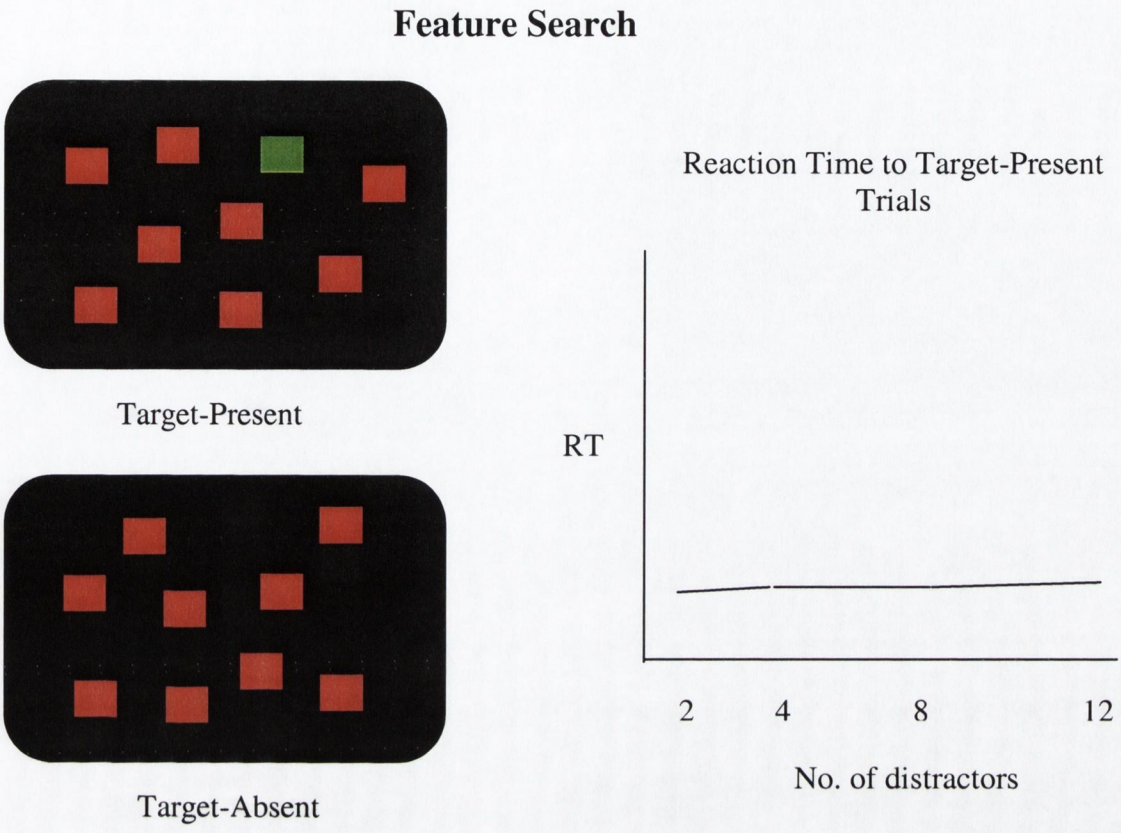

Figure 1.7: Target-present and target-absent trials in a feature visual search task. The target is the green square, which "pops out" of the array when present. Right hand panel shows invariance of RTs as number of distractors increases.

In other cases where the target is only distinguishable from the distractors due to the way its features are combined (e.g. a green square among red squares and green triangles), the target does not pop out and the scene must be scanned serially. The attentional spotlight must move from one stimulus to the next until the target is found, or else until all stimuli are scanned and the target is deemed absent. This type of search is known as conjunction search, because the target is defined by the conjunction of features, or also serial search due to the serial nature of processing involved. It has been found that reaction times tend to change very little as the array

size in increased in feature searches, whereas RT increases as the set size increases for conjunction search (Figure 1.8).

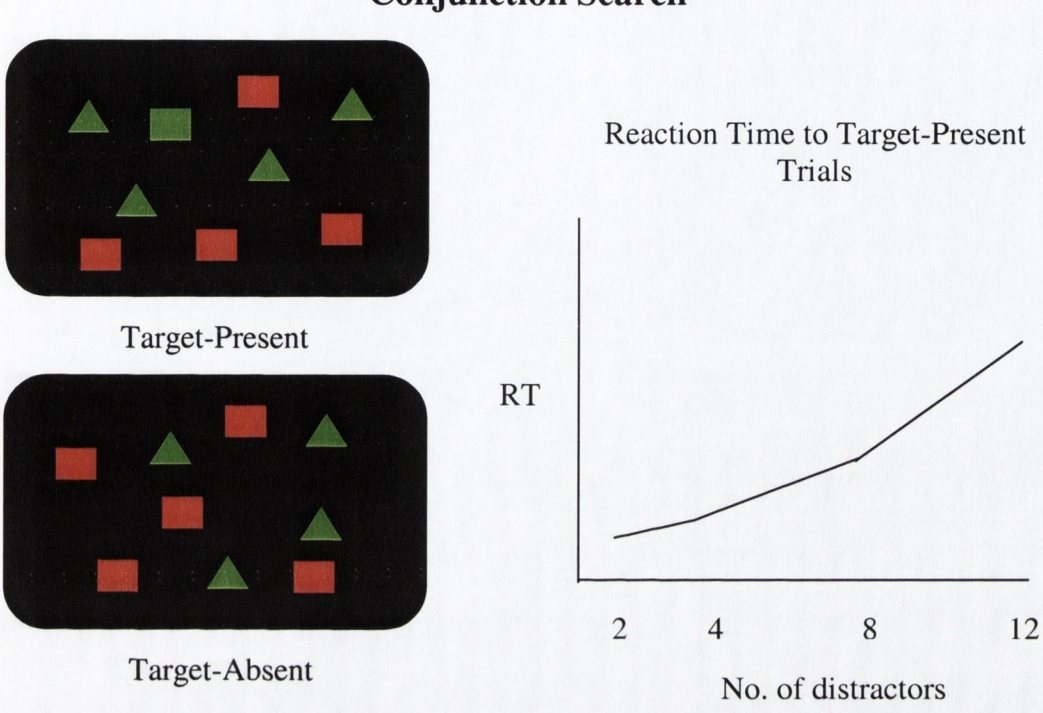

Figure 1.8: Target-present and target-absent trials in a conjunction visual search task. The target is again the green square. Right hand panel shows increase in RTs as number of distractors increases, emphasising the serial nature of processing.

The most influential model of stimulus processing in visual search is Anne Treisman's Feature Integration Theory (Treisman & Gelade, 1980), which posits that visual input is first deconstructed into its constituent features (colour, size, orientation etc.) in a series of modules. The presence of a unique feature here will be flagged and attention drawn automatically to its source (feature search). If this fails to happen, the features are then recombined in a feature map, and each stimulus is scanned by an attentional spotlight (conjunction search). If the target is found, the target-present response is made; if all the stimuli are deemed to be distractors, the target-absent response occurs. This theory has proved useful in explaining a large corpus of

experimental findings, and is noteworthy for its view of the differential operation of attention mechanisms in the two types of search task.

Visual search is a complex behaviour requiring multiple cognitive operations and is thought to be subserved by a distributed network involving frontal (dorsolateral prefrontal cortex and frontal eye fields), posterior parietal/temporo-parietal areas, the intra-parietal sulcus (IPS) and its junction with the transverse occipital sulcus, motor and extrastriate areas (Eglin, Robertson & Knight, 1991; Pollmann & von Cramon, 2000; Donner *et al.*, 2000, 2002; Wilkinson *et al.*, 2002; Leonarts *et al.*, 2000). The nature of visual search necessarily implies that an arbitrary visuomotor association must be made between a stimulus (the target) and response (pressing the "target-present" button) for its successful completion. This would suggest that there is some overlap in the neural substrates of visual search and the distributed network responsible for visuomotor learning (see Section 1.1). Based on the visual search imaging literature, the most likely sites of overlap are the prefrontal, premotor and motor areas, though some authors have also suggested a role for the basal ganglia in search (Miyashita *et al.*, 1995; Lawrence *et al.*, 2000; Fimm *et al.*, 2001; Huettel *et al.*, 2001). Because the use of an arbitrary visuomotor pairing is integral to the visual search task, it can therefore be considered a useful test measure by which the degree of learning of such visuomotor mapping can be assessed. Furthermore, the possibility also exists that repeated exposure to a visual search should promote the learning of the arbitrary association between the target stimulus and the "target-present" response; this latter claim has yet to receive experimental verification.

1.4 Event-related Potentials (ERPs)

The main methodological technique used in this thesis is the analysis of the event-related brain potentials of the electroencephalogram. This technique and the key issues pertaining to its use are described in detail in Chapter 2. This approach was chosen for several reasons: primarily, it provides an excellent index of the temporal sequence of neural events (to millisecond accuracy), along with sufficiently adequate spatial information to make broad estimates of the suspected sources of these events. Such temporal resolution is particularly useful for investigating, for example, the race model of inhibition (see above) in which the timing of processes is central. Moreover, the tasks under investigation here (repetition training, visual search, response inhibition) lend themselves well to investigation with ERPs. These tasks consist of large numbers of discrete events, and ERPs allow brain activity to be recorded on a trial-by-trial basis. In this way activity during correct responses can be compared with activity in erroneous trials, or targets may be compared to distractors. This type of analysis cannot be performed with block-design based imaging techniques such as PET or *f*MRI (although event-related *f*MRI is now also possible), in which activity during a trial block of one stimulus type is compared with a block of another type. Application of the recording apparatus and preparation times are also relatively speedy, with the entire experimental session rarely lasting longer than two hours. Also, participants are not required to lie in a large scanner, as is the case for imaging studies. In sum, event-related potentials represent a relatively discomfort-free, fast and flexible system for recording neural events in the performing human which provides an accurate picture of the timing of processing in the substrates of cognition.

1.5 Outline of the Thesis

This thesis presents an investigation of the neural and cognitive substrates of visuomotor learning. The technique for examining cortical activity during these tasks is analysis of the event-related potentials of the electroencephalogram; this technique is discussed in detail in Chapter 2. Chapter 3 demonstrates that repetition training of an S-R association produces behavioural enhancement on a subsequent test involving that pairing, thereby validating the paradigm as an adequate example of arbitrary visuomotor learning. Furthermore, it shows that electrophysiological changes, possibly due to activity in the neural substrates of this learning, can also be detected by scalp electrodes. Chapter 4 contains three experiments that examine the roles of attention and arousal in this learning paradigm. These experiments reveal that the addition of an attention-demanding dual-task during training produces facilitation of the learning and its expression, and that this effect is attentional rather than due to arousal. Also, it is shown that the S-R pairing can be trained by presenting it within the context of a visual search task.

Chapter 5 is an electrophysiological investigation of brain activity during a response inhibition task. Results show latency and amplitude differences in ERP components that may reflect activity in cingulate and prefrontal areas when successful inhibition is compared with unsuccessful. Also, individual differences in absentmindedness result in waveform but not performance differences, suggesting different levels of activity in these individuals. In Chapter 6, performance and brain activity during the same type of task is investigated in participants with traumatic brain injury (TBI) and normal controls. In Chapter 7 we attempt to influence performance on a response inhibition task by training with a visual search that incorporates the same S-R association as the RI task. Again, absentmindedness plays

a role in the success of this behavioural effect. The strength of the association seems to be key in determining this disruption. In the General Discussion, these findings are considered together. Issues surrounding training and general principles of learning are discussed, as well as possible chemical mechanisms underlying the observed ERP and behavioural effects. Also mentioned is the possible potential for rehabilitation strategies of higher cognitive functions using the basic principle of training low-level aspects of higher order cognition. Other issues relating to the nature of response inhibition and sustained attention are raised and considered.

Chapter 2

Methods

Event-Related Brain Potentials (ERPs): Electrophysiological Basis, Apparatus and Application Procedures

2.1 Event-Related Potentials: Introduction

The study of the event-related brain potentials (ERPs) of the electroencephalogram has, along with functional imaging and magnetic stimulation techniques, become one of the main research tools in the fields of cognitive neuroscience and neuropsychology. The method involves recording a participant's continuous EEG during a sensory, motor or cognitive task; any changes in EEG due to the demands of the task are amplified, averaged and extracted as ERP waveforms. The components of

the ERP waveforms are labelled according to their polarity (positive or negative) and latency (time of occurrence, in milliseconds) or temporal order (first positive, second negative, etc.). For example, the first positive peak appearing after about 100 ms. could be referred to as either P100 (polarity-latency) or P1 (polarity-order). Other notations have also been used in specific cases (see, for example, Hohnsbein *et al*, 1998). Some of the most extensively documented waveform components include the P100, N100, N200 and the P300, which has two sub-components, P3a and P3b. Each of these components has been associated with a different set of cognitive activities and processes. These are reviewed in section 2.2.4 below.

2.1.1 Historical Background

In 1875, the British physiologist Caton described the first sensory evoked electrical responses from the surface of the brains of rabbits and monkeys. This sparked interest in the relationship between electrical brain activity and sensory events. Fifteen years later, Beck studied the electrical brain responses of rabbits and dogs to presentation of sensory stimuli. Within the next 40 years, recordings of electrical brain potentials had moved from animals to humans, and in 1929 Hans Berger, the German psychiatrist today considered the father of modern electroencephalography, published on the scalp recordings of the human EEG, in which he coined the term "Elektenkephaolgram". In 1939, Davis published a paper in which he extracted the changes in EEG due to a sensory stimulus (Evoked Potential; EP). In the 1940s Renshaw proposed the possible relationship between the slow potentials of neurons and the oscillations of the EEG, and by the end of the decade the American EEG Society had been founded. By the end of the 1950s, a committee headed by Jasper had developed the international 10-20 placement system, devised to standardise the positions of EEG scalp recording

electrodes. Also around this time Dawson (1954) extended the extraction techniques introduced by Davis. He averaged large numbers of EPs to increase the signal to noise ratio, thereby giving birth to Event-related Potentials (ERPs) as we know them today. By the 1970s, ERPs were being widely applied to clinical diagnoses, while Dipole Source Modeling (see below) was introduced in the 1980s to improve the spatial resolution of ERPs. At present, ERPs are used to great effect in the investigation of sensory and cognitive processes such as attention, vision and memory. Most impressive insights can be gained from the coregistration of ERPs with other techniques like functional imaging (e.g. fMRI), magnetic stimulation (TMS) and magnetoencephalography (MEG).

2.1.2 Temporal and Spatial Resolution of ERPs

The utility of any investigative tool in cognitive neuropsychology is measured by its performance on two dimensions; *temporal resolution*, its ability to provide an accurate picture of the timing and sequence of occurrence of cognitive events, and *spatial resolution*, how well it identifies the different anatomical areas of the cortex that are involved in processing. Below is a brief comparison of ERPs with the other main research techniques in neuropsychology, along both of these dimensions.

ERPs consist of scalp recorded electrical brain activity. Because electrical potentials travel through the bone and skin of the skull and scalp at high speed, ERPs provide very high temporal resolution. The time-course of processing in the cortex may be seen with millisecond accuracy. Where ERPs suffer, however, is in terms of spatial resolution. Electrical fields are distorted significantly by skull and scalp tissue, so the pattern of activity recorded on the scalp may bear little resemblance to the regions of cortex responsible for such activity. It is therefore invalid to assert that a

potential recorded by a dorsolateral prefrontal electrode emanated from the dorsolateral prefrontal cortex. Methods have been implemented to improve the spatial resolution of ERPs (discussed below), but the problem may only be lessened rather than solved. In sum, ERPs provide excellent temporal resolution, with relatively poor spatial resolution.

Imaging techniques (PET, fMRI; see Orrison *et al.*, 1995 for a review) work on the basis that increased cognitive processing in an area of cortex requires increased regional cerebral blood flow (rCBF) to support the local energetic demands of the tissue for nutrients and oxygen. Such techniques allow for very high spatial resolution, because the anatomical structures receiving such increased blood flow can be represented in three dimensions. Also, because they do not rely on mere scalp recordings, activity in deep subcortical regions may also be seen. However, there is a significant time-lag involved in such approaches, due to the relatively slow speed at which blood flows through the brain (in comparison to electrical impulses). Also, a blocked design must be used in imaging studies, so a real-time record of processing cannot be obtained (although event-related functional MRI techniques are currently being developed). Therefore the unparalleled spatial resolution of functional imaging comes at the expense of coarse temporal resolution.

Another addition to the neuropsychologist's arsenal of tools is the technique of Transcranial Magnetic Stimulation (TMS; Orrison *et al.*, 1995). The method involves applying a powerful magnetic field to a location on the scalp, causing the neurons in the underlying cortical tissue to fire. This effectively precludes that area's involvement in any concurrent processing tasks while the stimulation continues. Thus the effect is akin to a virtual lesion of that region of cortex. The temporal resolution of TMS is high, allowing one to deduce at precisely what stage in a processing loop an

area is necessary (as indexed by disrupted performance on the task). The spatial resolution is also quite high, accurate to the centimetre, although structures at depths below the superficial layers of cortex are inaccessible to TMS. The most powerful feature of TMS, however, is its *functional resolution*, a property which none of the other techniques can boast. Functional resolution is the term used to describe the fact that TMS isolates the areas that are *required* or *necessary* for the successful completion of a task, rather than areas whose activity is merely correlated with such performance. When used in conjunction with the other techniques mentioned here, TMS should provide a significant contribution to our understanding of the neural bases of cognitive processing.

The newest technique to be developed is magnetoencephalography (MEG; Orrison et al., 1995). MEG involves the measurement of the tiny electromagnetic fields that are produced whenever a neuron fires. Magnetic fields pass through skin and bone at the same high speed as electric ones, giving MEG comparable temporal resolution to ERPs. But unlike electric potentials, magnetic fields are not distorted by the skull and scalp, so much better spatial resolution is possible. At present, the use of MEG is limited due to the massive expense involved.

To summarise, ERPs constitute one major strand of neuropsychology's methods for gaining an understanding of the processes and mechanisms of the human brain. By combining its high temporal resolution with the impressive spatial localisation power of imaging techniques and MEG, as well as the unique functional resolution of TMS, significant advances can be made into elucidating the anatomical bases of cognition.

2.2 Physiological Basis of ERPs

2.2.1 Electrical Activity in the Brain

Communication in the central nervous system takes place through the transmission of electrochemical signals between nerve cells, or neurons (Figure 2.1). Messages to either excite or inhibit activity in other neurons are passed via the release of neurotransmitter substances from the axon of the efferent (or pre-synaptic) cell to the dendritic tree or cell body of the afferent (or post-synaptic) neuron.

The neurotransmitters influence the activity of the neuron by binding to receptors which alter the electrical potential across the membrane of the cell. Due to the constant influx and outflow of both positively and negatively charged ions across this membrane, the equilibrium state, or resting potential, of a neuron is approximately –70 mV. Any deviation from this state will make the cell either more or less likely to generate an action potential, or fire. An excitatory signal from a presynaptic cell will cause certain ion channels to open or close, with the result that the membrane potential rises from –70 mV to 0 mV and possibly higher. Such excitatory impulses are termed EPSPs, or excitatory post-synaptic potentials. If the membrane potential rises above a particular threshold level, approximately +30 mV, then an action potential is generated in the neuron, and neurotransmitter is released onto another cell. The rise in membrane potential due to an EPSP is called depolarisation.

In contrast, inhibitory post-synaptic potentials (IPSPs) make cell firing less likely by lowering the membrane potential, thereby pushing it further from the threshold level for action potential propagation. This lowering of the potential across the

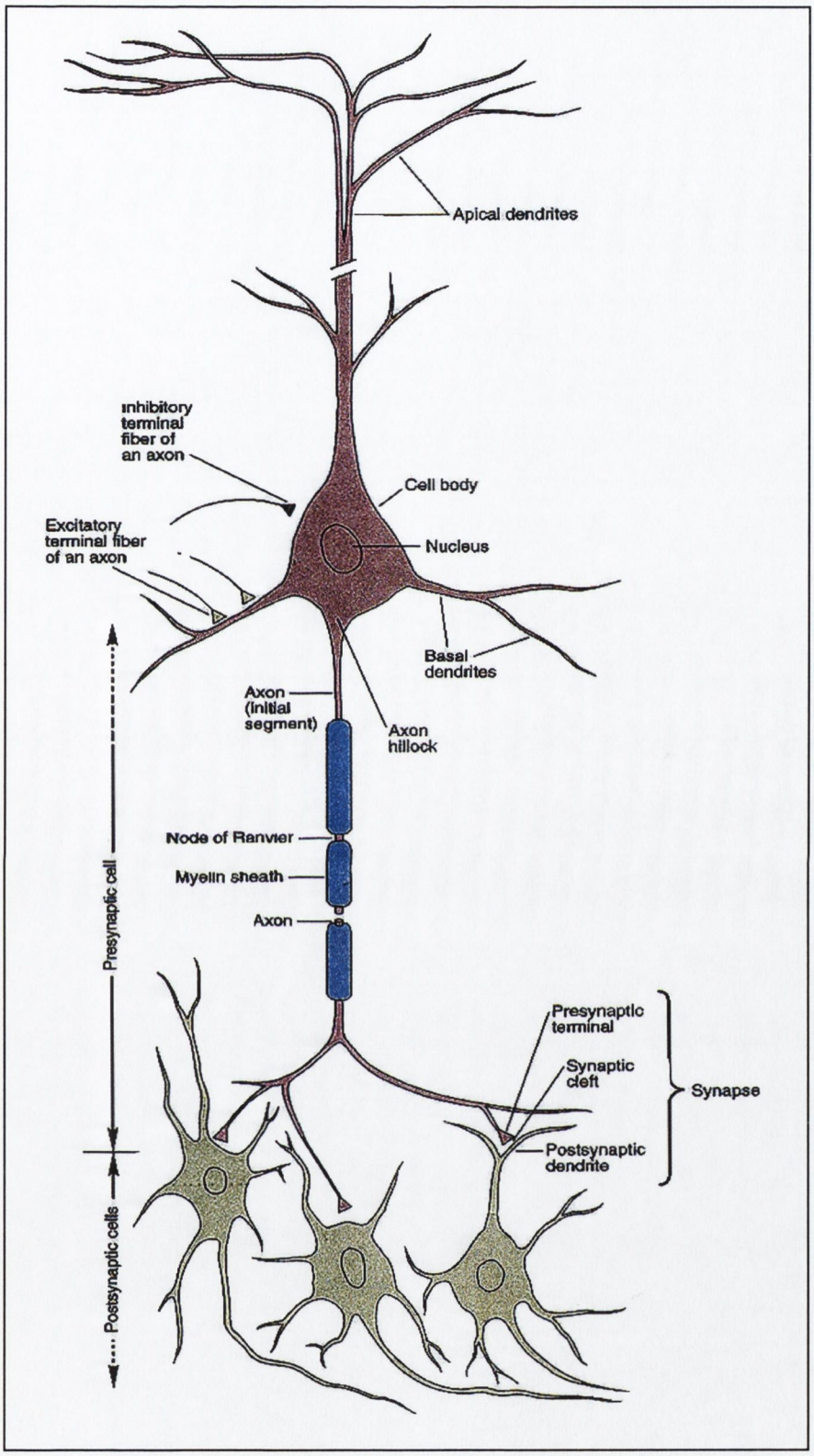

Figure 2.1: Neural communication in the central nervous system. The diagram depicts the anatomical structure and connectivity of neurons in the brain. (From Kandel, Schwartz & Jessell, 1995)

membrane is called hyperpolarisation. It is the summated effects of these depolarisations and hyperpolarisations (which may collectively be termed Neural Current Sources), rather than the action potentials themselves, that are recorded by EEG and ERPs.

As has been described above, Neural Current Sources originate at the cell membrane and represent a deviation from the equilibrium state or resting potential. During an EPSP, a local current Sink is produced, which sucks positive ions into the cell, thereby moving the potential closer to 0 mV. A sink may be thought of as a negative source. Local sinks are balanced by distant passive sources; as the sink draws ions into the cell, thus depolarising the membrane, these ions move through the neuron and are ejected at some other location, known as a (positive) Source. For example, if a sink existed at a branch of the cell's dentritic tree, the distant source might occur at the cell body, or near the axon hillock. The co-occurrence of the positive source at one location and the negative sink at another means that the cell may effectively be viewed as a dipole.

In an IPSP, the opposite situation occurs. A local source is produced, which emits positive ions, thereby lowering the membrane potential. This source is balanced by a distant sink, which takes in ions at another location on the cell. Again, this may be considered as a dipole. The EEG gives a macroscopic view of the activity of these sinks and sources. A detailed account of the workings of this technique is provided by Paul Nunez (1990); a general overview of this work is provided here.

EEG and ERPs record from the scalp the electrical activity (produced by sinks and sources) of populations of pyramidal cells which form the grey matter of the cortical surface. If a scalp potential recorded activity due to current sources over an area of

less than 1 cm^2, then the large number of sources may be considered as a *single dipole source*. Usually, however, scalp potentials are due to larger areas of activity. When a large number of dipoles fire with synchronous activity, and their polarities are the same (i.e. all their positive terminals or sources are adjacent to other positives), as can happen with the densely interconnected pyramidal neurons of the cortical surface, then the group could be considered to form a *homogenous dipole layer*. However, dipole layers rarely occur with completely homogenous polarities of sinks and sources. The more common occurrence is for the layer to consist of a mixture of polarities of dipoles, in which case the overall potential will reflect the majority of dipole polarities.

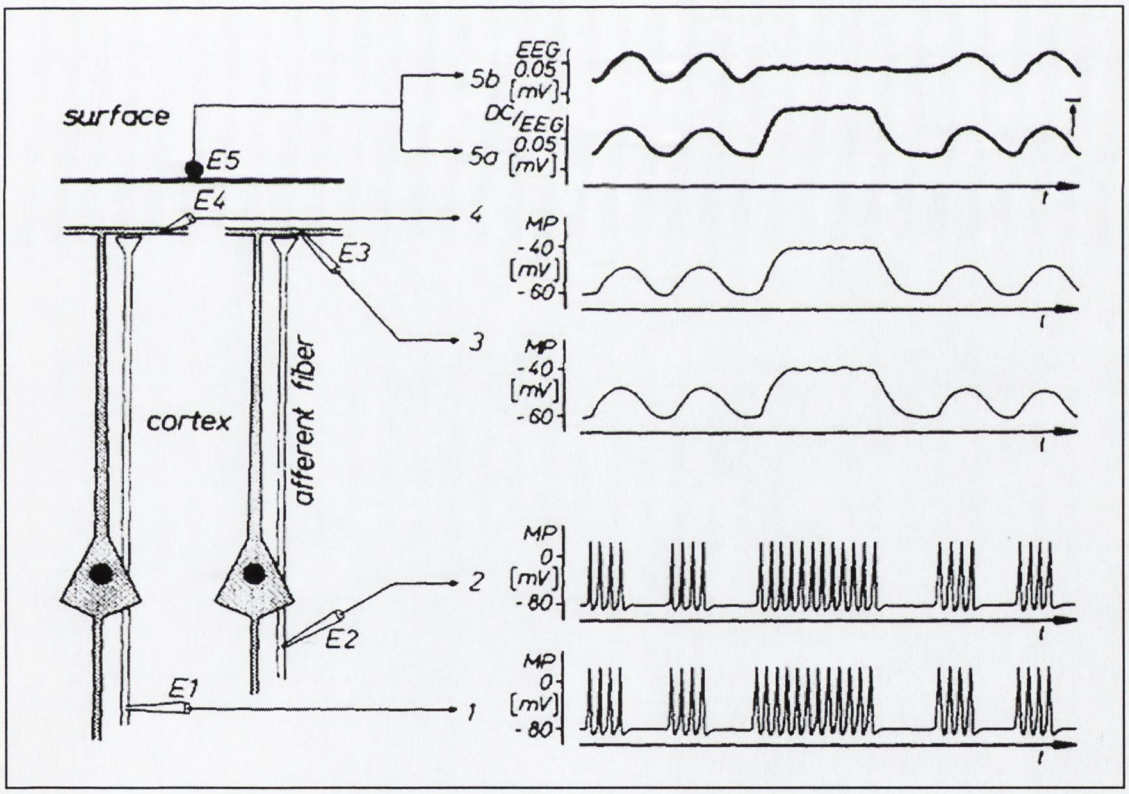

Figure 2.2: A model showing the principles of EEG wave generation. Note that the electrical potentials recorded from the two large pyramidal cells have the opposite polarity at the cortical surface (upper right waveforms) compared to those recorded at E1 and E2 (lower waveforms). (From Coenen, 1995)

It has been repeatedly demonstrated by correlating scalp recorded EEG with intracranial neuronal discharges in the monkey and the cat that the polarity of ERPs are related to either excitation or inhibition of cells. Comparison of evoked potentials and neuronal spiking activity reveals that neuronal discharges/firing in thalamocortical cells seem to result in negative ERP components, while cellular inhibition underlies positive potentials. Thus EPSPs/depolarisations appear responsible for negative ERP deflections, while IPSPs/hyperpolarisations are the cause of scalp-recorded positivities. Specifically, the scalp recorded negative shifts seem to be due to the depolarisation of pyramidal cell dendrites, which results in an extracellular surface current sink, with the opposite situation the case for scalp recorded positives. The relationship between neuronal activity and scalp-recorded potentials is shown in Figures 2.2 and 2.3, taken from Coenen (1995). Although this polarity reversal between intracranial and scalp recorded activity is true in most cases, the opposite relationship, where scalp positives are due to neuronal excitation and negatives to inhibition, has also been found on occasion.

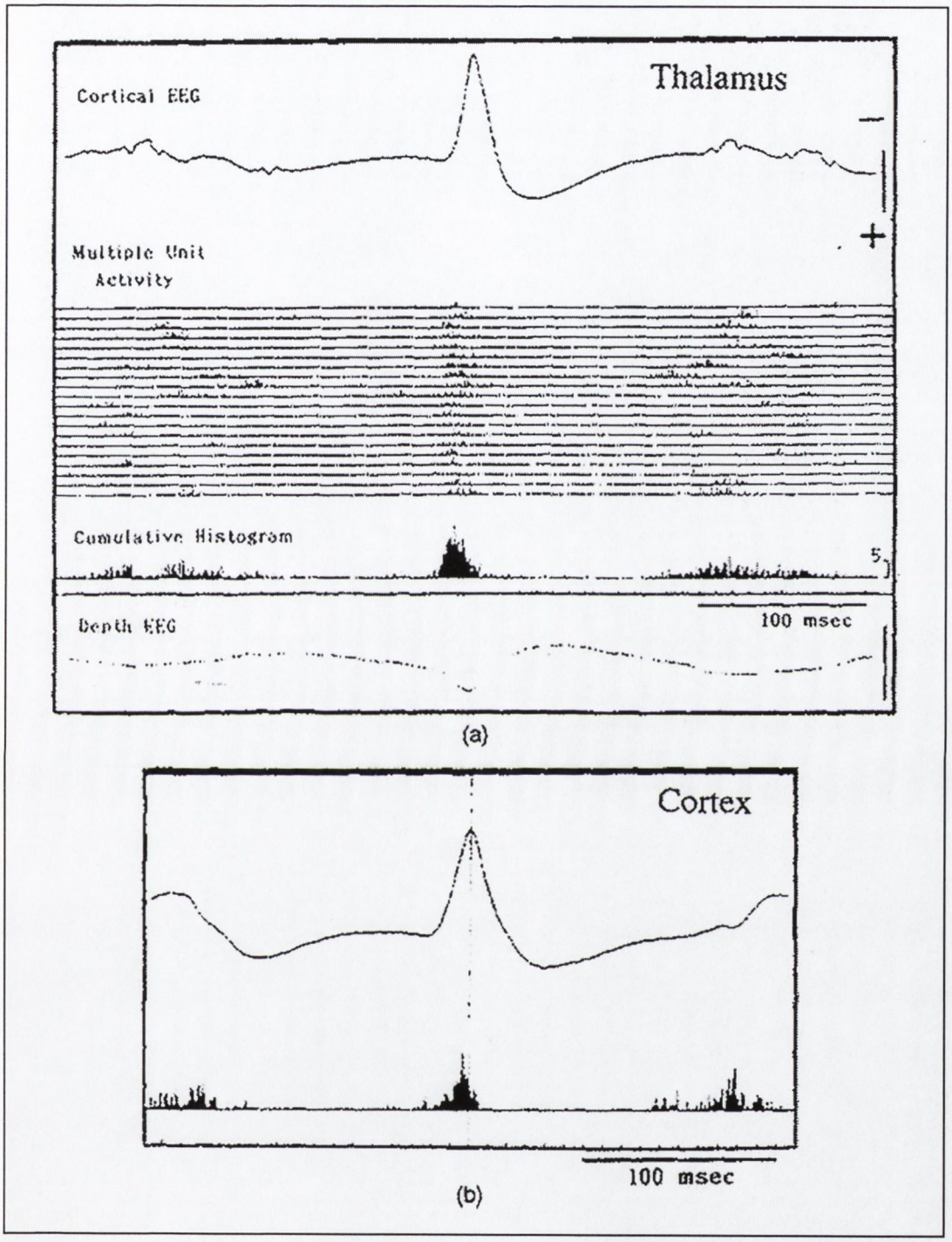

Figure 2.3: Correlation of cortically recorded spike-wave discharges with "multiple unit activity" of (a) thalamic and (b) cortical neurons. Note again the polarity reversal between depth and surface recorded potentials. (From Coenen, 1995)

2.2.2 Spatial Localisation of ERPs

The other key problem associated with ERPs is the Inverse Problem. This involves the attempt to infer the neural generators of potentials based on their scalp distribution. Because any number of individual or combined neural sources could produce the same pattern of scalp potentials, this problem is essentially insoluble. More information than mere scalp distribution is necessary to determine the locus of a pattern of activity. Judgements may be informed by evidence from functional imaging techniques such as magnetoencephalography (MEG), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), from virtual lesion techniques such as transcranial magnetic stimulation (TMS), or from behavioual and cognitive deficits reported by patients with brain injury.

Another method involves attempting to reproduce the observed pattern of scalp potentials by placing model dipoles at different locations in a computer model of the head consisting of three concentric spheres (to represent the brain, skull and scalp, and their different relative conductances). This technique of dipole modeling, also known as Spatial Deconvolution, can be used to make educated guesses about the potential neural generators of ERP waveform components. An additional method of improving the spatial resolution of scalp-recorded potentials is known as the scalp current density (SCD) or Laplacian method (Hjorth, 1975). The Laplacian is a spatial filter that emphasises local neural current sources while simultaneously reducing the contribution of distant sources. This function therefore dramatically improves he fit between the scalp topographies of brain potentials and their cortical generators. Two of the more widely used source localisation techniques are Curry and LORETA (low resolution electromagnetic tomographical analysis; e.g. Brandeis *et al.*, 1998).

2.2.3 The Reference Electrode

A key aspect of EEG and ERP recordings is the reference electrode. Ideally, the reference electrode is a recording location at which no electrical activity due to the source/sink or interest is detected. Such an idealised reference is termed a True Reference. This gives one a comparison recording site by which the scalp potentials may be extracted and their magnitudes quantified. There are, however, some fundamental problems to be considered in relation to the role of the reference electrode which are salient to the recording and interpretation of scalp potentials.

In intracranial micro-eeg recordings, the reference electrode is placed some distance from the area of interest from whence the recordings are taken. However, although this reference may be quiet (that is, no local sources exist in its vicinity), it may still not be a True Reference. Source activity may still be detected at the reference if, for example, the activity is of such a magnitude that its effects are felt in all areas of the head, or if a highly conductive current path, like cerebro-spinal fluid, connects the source region and the reference. These problems are exacerbated when considering extracranial scalp recorded EEG. Usually, the scalp electrodes are referenced to a distant location such as the earlobes, mastoids or the tip of the nose. These sites are popular because they overlie regions of thick bone or cartilage, where there should be little or no contribution of cortical sources. Problems arise because the recoding electrodes are usually at least one centimetre from the source, which further blurs the distinction between the recording and reference electrodes. The second problem is due to the fact that the skull is a very poor conductor in comparison to the cortex. Some estimates claim that the skull has a conductivity about $1/80^{th}$ that of brain tissue. Therefore potentials tend to spread out more and bear scant resemblance

to their neural generators. Furthermore, the holes in the skull at the ears, eye sockets and jaw mean that the distortion of the potentials is far from uniform. Thus any reference electrode placed on the head is unlikely to be free from a contribution of distant generators, and as a result all scalp-recorded potentials should be regarded as a mixture of both local and global sources.

The reference electrode also plays an important role in the interpretation of the isopotential lines produced by patterns of scalp potentials. It is important to remember that the *pattern* of isopotential lines is determined by the sources and the volume conduction properties of the skull, whereas the *magnitudes* attributed to these lines are due entirely to the choice of reference electrode. This is because the line of zero potential must always pass through the reference electrode. Thus, although the same pattern of isopotentials would be observed whether a nose or central scalp reference was used in recording, the magnitudes assigned to each of these lines would be very different in each case.

The experiments reported here utilised a linked-ear/mastoid form of reference. This type of system brings with it two new difficulties. If the contact resistances are too small, then current may flow between the ears, which could alter the pattern of current flow and potentials recorded. Secondly, even if these resistances are large, unless they are equal the ear whose wire is of the lesser resistance effectively becomes the lone reference.

2.2.4 Neural Mechanisms of ERPs

A clearer understanding of the mechanisms and processes underlying ERPs can be gained by the study of humans with syndromes, implanted intracranial electrodes and

focal brain lesions. The main insights are reviewed comprehensively by Knight (1990), the key points of which will be covered briefly here.

Neurodegenerative disorders such as Alzheimer's and Parkinson's Disease can provide further clues to both the anatomical generators and the anatomical loci of certain waveform components. The coincident occurrence of amplitude and latency changes in the P300 component with the reported decrement of acetylcholine (Ach) in hippocampal areas in Alzheimer's patients has led to suggestions of a relationship between the two phenomena, particularly given previous claims that the hippocampus may be at least a partial generator of the P300. Scopolamine, a potent Ach blocker, induces both memory deficits and a reduction in scalp P300 in normals, further supporting this claim. Similarly, the loss of dopamine from the substantia nigra in Parkinson's patients has been tenuously associated with the parietal P3b and the anticipatory contingent negative variation (CNV) waveform.

Intracranial recordings from the mesial temporal lobe have reported P300 like activity from this region, which concurs with the hippocampal P300 hypothesis. Of the two subcomponents of the P300, the posterior P3b seems more likely to be influenced by this hippocampal generator, while the anterior P3a may have multiple and distinct sources in other areas, possibly including dorsolateral prefrontal cortex.

The study of patients with focal brain lesions has furthered our understanding of the N200-P300 complex. A dissociation was found which implies a superior parietal source for the N2, and a temporoparietal locus for P300. This is in agreement with data suggesting a role in sensorimotor integration for the N2, and attention, orientation and memory for P300. It has also been proposed that the prefrontal region may modulate the generators of N2 and P3a residing in subcortical or posterior

association areas. Table 2.1 contains a brief and selective review of key characteristics and some cognitive functions associated with the P1, N1, N2 and P3 components.

Table 2.1: Brief review of key ERP waveform components P1, N1, N2 and P3 and suspected associated functions of each.

P100/ P1 Component

- Latency between 80 and 120 ms. Largest over **Posterior** and **Occipital** sites.
- May reflect automatic, as opposed to controlled, processing.
- Elicited by visual stimuli, and modulated by attention (Coull, 1998)
- Possibly generated by the ventral stream. Symbolic Cues modulate P1 amplitude; Peripheral Cues do not (Mangun, 1995)
- Modulated by spatial cueing (Luck, Fan & Hillyard, 1993)
- Focused attention to one side of a bilateral array enhances contralateral P1 (Lange *et al*, 1999)
- Larger P1 amplitude for Active, compared to Passive, task conditions (Paz-Caballero & Garcia-Austt, 1992)
- P1 has a role in the spatial attention that is vital for conjunction search, as opposed to pop out. Generator of P1 may be in lateral prestriate areas 18 and 19, not striate cortex (Luck & Hillyard, 1995)
- Possibly elicited by priming paradigms, aka c110. Shows larger amplitude to primed compared to unprimed visual stimuli. (Zhang *et al*. 1997)

N100/N1 Component

- Latency 80-120 ms.
- TWO components: **Anterior/Frontal N1** and **Posterior/Occipito-Parietal N1**
- Both are enhanced by spatial cueing of target in visual search (Luck, Fan & Hillyard, 1993)
- Elicited by auditory and visual stimuli and is modulated by attention (Coull, 1998)
- Symbolic Cues modulate posterior N1. Cue validity influences Occipital N1 amplitude, which may be generated by the Ventral stream. Dorsal stream may generate the parietal part of the posterior N1 (Mangun, 1995)
- N1 may be a search-related negativity, and may be involved in object recognition in the ventral stream (Lange *et al*, 1999)
- Elicited in Passive task conditions; may reflect sensory analysis of simple visual features (Paz-Caballero & Garcia-Austt, 1992)
- Evident for both target and non-target stimuli. May reflect precategorical spatial filtering
- Larger in amplitude to slanted than to vertical line segments (O'Donnell, Swearer *et al*, 1997)

N200/N2 Component

- Latency 120-300ms. **Posterior/Occipital** locus
- A negative potential at OZ electrode. Reflects discrimination and classification. Modulated by variation of set size in serial, but not conjunction search (Sugita, 1995)
- Effected by cue validity (Mangun, 1995)
- N2 is a collection of negatives that may reflect processes of detection and discrimination. An early subcomponent is the Mismatch Negativity (MMN), but this is seen for auditory stimuli only. The latter subcomponent is sensitive to deviation form a centrally maintained expectancy (Hoffman, 1990)
- Long latency N2 is observed in Active task conditions due to the additional processes required in discrimination. Differences in N2 amplitudes are seen for

target and non-target stimuli (Paz-Caballero & Garcia-Austt, 1992)

- Posterior N2 elicited by low probability stimuli. May reflect operations on a representation of the stimulus
- Anterior N2 is larger in amplitude to vertical than to slanted line segments, especially along the midline (O'Donnell, Swearer *et al*, 1997)

P300/P3 Component

- Latency 250 – 600 ms.
- TWO components: **Frontal/Central** P3 (**P3a**) and **Parietal** P3 (**P3b**)
- P3a involved in orienting, arousal and response to novelty; P3b reflects controlled processes such as response selection or choice (Hohnbein, Falkenstein & Hoorman, 1998)
- Although prefrontal area may not generate P3a, it does seem to modulate its activity (Kertesz, 1994)
- P3 amplitude is sensitive to probability of response, stimulus modality, speed/accuracy tradeoffs, task difficulty. The typical P300 study is a visual oddball task (Acosta & Nasman, 1992)
- In an Easy discrimination task, parietal P3b is larger for target than non-target. In a Difficult discrimination task, fronto-central P3a was larger for non-targets, and P3b was larger for targets. Difficulty of discrimination determines P3a generation (Comerchero & Polich, 1999)
- Modulation of P300 due to attention, task difficulty and subjective probability of the target (Hoffman, 1990)
- Infrequent or oddball stimuli lead to P3 generation. It may index the on-line updating of working memory (Coull, 1998)
- P3 amplitude is larger for Invalidly cued trials in a Symbolic Cue situation (Mangun, 1995)
- P300 is an index of the attentional resources allocated to each task in a Dual Task paradigm. P3 amplitude is related to stimulus evaluation and the target representation system, while latency is an index of the response system (Hoffman *et al*, 1985)
- In Active tasks,. P300 habituated when short inter-block intervals were used. In Passive conditions, P3 amplitude declined with repeated stimulus presentation, unless discrimination or attention to stimuli was required (Ravden & Polich, 1998)
- P3 amplitude is smaller for visual compared to auditory stimuli. The Active task produced P3b (central-parietal), while the Active resulted in P3a (fronto-central) (Bennington & Polich, 1999)
- In the Active task, the P3 showed differences in amplitude for target and non-target stimuli (Paz-Caballero & Garcia-Austt, 1992)
- Elicited to low probability stimuli. May reflect context updating or STM reset.
- Larger amplitude to slanted than vertical line segments, especially at occipital sites. May have multiple distributed generators (O'Donnell, Swearer *et al*, 1997)

2.3 Electrode Cap Application Procedures

2.3.1 Applying the Cap, Ground and VEOG Electrodes

Prior to testing, participants were seated in a prepping chair and their clothes covered with a hairdresser's cape or gown. The electrode cap was placed loosely over the head, ensuring that the midline electrodes (AFz, Fz, FCz, Cz, CPz, Pz, Oz) were straight along the saggital axis of the head. The cap's earflaps were left up so that the ears were exposed. The tail of the cap (i.e. the cable carrying the 32 recording channels) was then affixed to the participant's neck or left shoulder using surgical tape, to prevent tugging or strain on the delicate VEOG and earlobe/mastoid ground electrodes.

The cap was next pulled into position, making sure that the frontal ground electrode (AFz) was 4 inches from the naison (this corresponds to locating a central frontal pole electrode FPz 4 cm from naison). The two horizontal electro-oculograms (HEOGs) were then pulled as near to the outer canthus/corner of each eye as possible.

Using Omni-prep or NuPrep solution, the skin on each earlobe and above and below the left eye was gently rubbed with a cotton ball (if the participant had no ear lobes, the mastoid/bony protrusion behind the ears was used). The skin was allowed to dry. When the skin had dried, a small amount of Ten-20 electro-conductive paste was smeared onto each ear lobe, and above and below the eye. A small amount of the paste was also placed on the two earlobe ground electrodes (marked 1 and 2) and these were then pressed onto the ear lobes, with the paste holding them in place. The ear flaps were pulled down and the chin-strap attached to the cap, thus pressing and holding the electrodes in position.

A small amount of paste was placed onto the two VEOGs and they were pressed onto the face above and below the eye. Again, the paste held them in place. They were secured in position with two v-shaped sticky electrode pads. At this point, it was again important to ensure that the AFz was still 4" from the naison.

2.3.2 Applying Electro-conductive Gel to the Electrode Cups

An elastic bandage was pulled over the entire cap, to press the electrode cups against the head. A generous amount of Quikgel was then poured into a polystyrene cup, and stirred until the mixture was smooth.

Five 10 ml syringes were filled with QuikGel and a blunt needle (16 x ¾ or 14 x ¾) was placed on each. The blunt needle was inserted into an electrode cup until the participant reported feeling it against the scalp. The needle was then gently swirled in a circular movement to remove any hair that might be in the way, and to allow a clear path from scalp to electrode. While lifting the needle out, up to 1ml of gel was injected into the electrode cup, until a small amount of gel came out the hole at the top of the electrode. The cup was pressed lightly against the head so that more gel (and any air bubbles) was forced out. Excess gel was wiped away with paper towel.

This procedure was repeated for the other 32 electrodes, the AFz and the HEOGs. Particular care was taken with the AFz electrode. If it was deemed necessary (e.g. when some electrode cups were standing out from the head), a second elastic bandage was applied to the head. A large piece of paper towel was then pressed gently on the head, to press the electrodes against the scalp and to absorb any excess gel. The gel was then left to dry for 10-15 minutes.

2.3.3 Testing and Reducing Impedance

Testing the impedance of the array allows one to see how well the electrodes are conducting electrical activity from the scalp. The Scan 4 software shows a colour-coded measure of impedance quality at each electrode. The scale ranges from pink/red, signifying poor impedance, through green to dark blue/black, indicating excellent impedance (5 kOhms or less). The procedure for testing and optimising impedance was as follows.

The cap's tail was first plugged into the electrode board. The calibration and impedance were checked, making sure to switch the SynAmps amplifier on before switching the computer on. A coloured box representing the quality of impedance at each electrode position, including VEOGs, was presented on the screen.

If the impedance showed all pink, all the connections from the cap to the amplifier were first checked. If they remained pink, the needle was re-inserted back into AFz and swirled around to remove hair and/or bubbles. If there was still no change, the ear ground electrodes were checked to ensure that they were still attached. These steps usually reduced impedance on most channels to green or blue.

If the impedance was green/light blue, the needle was inserted into each cup, swirled to remove hair or bubbles, and more gel was added if needed. Changes in colour were monitored on the screen. When the majority (preferably all) electrodes were blue, the participant was moved to the testing chair (a large armchair) and testing began.

Participants were informed of the problems of artifacts induced by blinks, other eye movements, head/neck movements, muscle bursts, facial movements and other twitches. They were asked to try to keep such movements to a minimum. A pillow or cushion was placed behind their head and they were allowed to find a

comfortable position, ensuring that they could reach the mouse or whatever device was being used to make the response. They were asked to, if possible, restrict blinks to between trials; i.e. after the response to one trial and before the next commenced. The testing session then began.

2.3.4 Removing and Washing the Cap after Testing

After testing was completed the participant was seated back in the prepping chair, after first unplugging them from the electrode board. Any stretchy bandages were first removed from the head. The chinstrap was removed and the earflaps were lifted up. The ground electrodes were carefully removed from the ears. This was done by pulling the plastic/rubber cover near the electrode only, never the wire itself (these were prone to detaching). The paste was cleaned off the electrodes using paper towel and Q-tips. The VEOGs were removed in the same way, taking equal care. They were cleaned in the same manner using paper towel and Q-tips.

The participant's face and ear lobes were cleaned off using paper towel and alcoholic prep pads. The surgical tape was removed from the neck/shoulder, and the electrode cap was gently lifted off and hung on a coat hook. The participants were allowed to wash their hair in a sink fitted with a showerhead attachment. It was suggested they place some shampoo directly onto the hair before wetting it, as some found this helpful in removing the gel.

When the participant had left, the cap was placed in the sink and turned inside out. At all times great care was taken with the loose ground and VEOG electrodes. The inside of the cap was washed out using the showerhead on full power. It had to be ensured that all traces of the gel were removed; if left, the gel can harden and block the electrode cup. The inside was washed for 2-3 minutes.

The cap was then turned the right way out to wash the outside. Particular care was taken with the areas near the hole at the top of each cup – there are small grooves and crevices in this area where gel can be hard to wash out. The outside was also washed for 2-3 minutes. The cap was removed from the sink and placed on a mannequin head to dry. It was secured to the head with the chinstrap.

The 5 syringes were washed out and the needles were discarded. New syringes were used after 5-6 participants, as they started to become clogged if they were used for longer periods. The cap was sterilised using 70% alcohol solution.

2.4 ERP Data Analysis and Processing

2.4.1 Continuous to Epoch Data

Offline processing of the ERP data consisted of several procedures which are detailed here. The raw electrophysiological data recorded from participants is in the form of unprocessed EEG signals, termed a continuous file. Such a file contains the raw scalp-recorded EEG from each of the 32 channels. Also present in this file are voltage triggers or markers, sent from the stimulus-presentation computer at the time of stimulus presentation. These triggers are vital in allowing the extracted ERPs to be time-locked, or effectively "anchored", to the presentation of the stimulus. The first stage of analysis is the extraction of the ERP signal from the ongoing EEG, and is referred to as "epoching" because the continuous file is divided into individual time epochs or sweeps, with each sweep corresponding to a trial. The stimulus presentation trigger represents the zero ms time point on the x-axis, and the epoch duration is

selected to extend a designated period prior to stimulus presentation (the pre-stimulus interval; usually 100 to 200 ms), and a designated duration post-stimulus (anything from 500 to 1300 ms, depending on the ISIs and SOAs of the task being used). Thus a continuous file recorded from a participant doing a block of 100 trials yields a total of 100 sweeps, with each sweep extending from 100 or 200 ms prestimulus (i.e. –100 or –200 ms) through 0 ms (stimulus presentation) and ending some time poststimulus (e.g. 1000 ms for a task with trials of 1 second duration).

2.4.2 Ocular Artifact Reduction and Artifact Rejection

Because ERPs record electrical activity from the scalp, the technique is highly sensitive to two main sources of interference: eye-movements and muscle bursts. These sources of contamination must be removed or reduced in order to obtain reliable and artifact-free ERPs. Two procedures exist to this end.

The influence of ocular artifacts on epoched sweeps is reduced first. All vertical and horizontal eye movements and blinks are recorded by the VEOG and HEOG electrodes, respectively. As can be observed in unprocessed epoch files or sweeps, the impact of an eye movement /blink on the other electrodes is not uniform: there is usually greater contamination at frontal leads as the ripple of electrical activity due to the blink travels back across the scalp from the eyes, diminishing as it travels. Thus the amount of contamination at frontal electrodes is much greater than that at occipital. To combat this, a specially designed ocular artifact reduction algorithm cam be applied to the data. The algorithm searches all the sweeps in the file and detects the largest blink (the largest potential in the VEOG channel). It then calculates the average impact of such a blink on each of the scalp electrodes, applying the appropriate weights to anterior compared to posterior leads. Then this average

degree of contamination is subtracted from all sweeps containing blinks, thereby reducing the impact of the ocular artifact.

Other artifacts due to horizontal eye movements or muscle bursts are dealt with by a second function, termed Artifact Rejection. This allows for the selection of specific voltage thresholds (e.g. ±70 μV). The file is then searched, and any epochs in which the waveform exceeds the designated threshold are automatically rejected and excluded from further analysis. The thresholds can be applied to selected (e.g. only VEOG and HEOG) or all channels; it is recommended to apply the thresholds to all channels in case a muscle artifact is evident on the scalp but not in the EOG channels.

These two methods ensure that the influence of artifactual potentials due to sources of interference are minimized or eliminated, thus leaving only "clean" sweeps for further analysis.

2.4.3 Sorting Sweeps and Averaging

In order to generate average files corresponding to activity for different types of stimuli or response, sweeps must be sorted when in epoch mode before averaging procedures are carried out. The sorting of sweeps can be done a number of ways.

Sorting by Stimulus Trigger: if different types of voltage trigger/TTL pulse were sent to the continuous file for the different stimulus types (e.g. a pulse of 50 for a target, 60 for a non-target), the sweeps can be separated on this basis. Separate averages will be generated for trials containing a 50 pulse and those with a 60 pulse.

Sorting by Response Trigger: in the same way, if voltage triggers were sent when the response was made, different pulses for correct and incorrect responses (or for some

experiments, no response), the sweeps can be divided up according to these triggers, and individual averages can be generated. As with the stimulus triggers, it is necessary for the response triggers to be built into the stimulus presentation program for such grouping to be possible.

Sorting by Sweep Number: even if it was not possible to send different types of stimulus trigger (i.e. the same pulse type was sent for all stimuli), it is still possible to separate sweeps into different stimulus types. All that is required is some record of the order of stimuli presented, such as a data file stating that trial 1 was a target, trail 2 a non-target and so on. It is then possible to select sweeps based on trial number. In the same way, if a record of responses exists, it is possible to divide sweeps into correct and incorrect trials, even if no response trigger was sent.

Selecting Random Sweeps: it is generally accepted as good practice to ensure that there are roughly comparable numbers of sweeps in any average files that are going to be compared with each other. Therefore in cases where there is a large disparity between the numbers of sweeps in two files, it may be necessary to pick out a random selection of sweeps from the larger file to ensure equal numbers. For example, if targets were infrequent in a task, resulting in 20 targets and 80 non-targets from a block of 100 trials, it is necessary to select 20 non-target sweeps at random from the 80 to give equal numbers of trials. This can be done by simply stating the number of trials one wishes to select at random.

2.5 Time-Locked Averages: Issues

It is essential in ERP research that a trigger pulse is sent to the amplifier so that the sweeps can be time-locked to some event, usually either the onset of a stimulus or of a button press response. Such averages are said to be "stimulus-locked" or "response-locked" because the sweeps are locked or centred around the stimulus or response trigger, respectively. Unfortunately, this terminology has led to some nomenclature problems in the literature, as some authors use a slightly different meaning for the term. Below is a brief description of the issue, and how it is reconciled in this thesis.

A number of authors treat the term "response/stimulus locked" as implying that a separate grand average waveform was generated for each type of stimulus/response. Thus the waveform is "locked" or *defined* by the type of stimulus (e.g. distractor or target) that was presented, or the type of response (correct or incorrect) that was made. Although the term "locked" is used incorrectly here, since there is no *time-locking* element to the process, this is the meaning that is adopted in this thesis for the phrase "response/stimulus locked". To prevent possible confusion, however, the term is used infrequently, and where it is used, it is made explicit in the text which meaning is implied.

Others treat the phrase (more correctly) as indicating that the epochs and subsequent averages were created around the stimulus/response trigger or TTL pulse; i.e. the zero latency point on the x-axis represents when the stimulus/response trigger was sent. However, to avoid confusion some authors (e.g. Falkenstein *et al.*, 1999) refer to such grand means as Stimulus *Triggered* Averages (STAs) and Response *Triggered* Averages (RTAs). In this thesis, in order to avoid a nomenclature problem, sweeps that are epoched around a stimulus trigger are referred to as STAs and those epoched around a response trigger are called RTAs.

2.5.1 Stimulus-Triggered Averages and Response-Triggered Averages: Merits

STAs and RTAs are each useful for investigating different aspects of cognitive processing. STAs are particularly relevant when the research question concerns the perception of stimuli, and possible modulations or influences on these perceptual processes. Observing the electrophysiological changes following stimulus-presentation allows, for example, the top-down modulation of visual processing by attention to be examined. RTAs are more useful when post-response processes are under scrutiny. Equally interesting processing can occur after the response to a trial is made; these include error monitoring and feedback processes, preparation for the next trial and anticipation. Thus each of these types of average is equally important in the investigation of electrical brain activity in demanding cognitive tasks.

Chapter 3

Behavioural and Electrophysiological Correlates of Visuomotor Learning in a Visual Search Task

Abstract

Visuomotor association learning involves learning specific motor responses to arbitrary cues, and is dependent on a distributed and highly flexible network in the brain. I investigated here the behavioural and electrophysiological correlates of arbitrary visuomotor learning in twenty normal participants. An experimental group learned an arbitrary association between a visual stimulus and a motor response during a training block. Their performance was compared with that of untrained controls on a subsequent visual discrimination task in which the learned association was a crucial element. Event-related brain potentials (ERPs) were recorded from the scalp of each participant during learning and discrimination blocks. Reaction times to stimuli in the discrimination task were significantly faster in the trained group compared to controls. There was a corresponding difference in the ERP waveforms recorded during the task, with larger P3b amplitude for the trained group over midline

and centroparietal scalp areas. A latency difference in P3b was also observed for trained targets compared to distractors. RTs during the training block decreased in a manner consistent with learning effects. I conclude that training of a visuomotor association facilitates subsequent performance on a related task, and that the waveform correlates found here may reflect the involvement of parts of the network underlying arbitrary association mapping.

3.1 Introduction

Visuomotor learning involves learning a motor response to a specific stimulus. The learning is "arbitrary" when there is no information provided by the perceptual characteristics of a stimulus regarding the motor response required to that stimulus (Wise & Murray, 2000). The relationship between stimulus and response necessarily has to be learned. Such learning requires more substantive processing capabilities than the simple perception of stimulus features, which makes this paradigm a useful tool for examining aspects of higher cognitive processing (Wise & Murray, 1999). Visual search tasks require participants to make a Go/Go response to indicate the presence or absence of a target from a visual stimulus array (Treisman & Gelade, 1980). Because the correct response is defined by perceptual characteristics of the stimuli, visual search relies on arbitrary learning as described above. Search tasks have been used extensively to investigate processing and learning in the visual modality (Ellison & Walsh, 1998; Walsh, Ashbridge & Cowey, 1998; Walsh, Ellison, Ashbridge & Cowey, 1998; Walsh, Ellison, Batelli & Cowey, 1998).

Wise and Murray (2000) suggest that key brain areas underlying arbitrary visuomotor learning are the prefrontal cortex, the hippocampal formation and the basal ganglia. Ablations of monkey dorsal premotor cortex, dorsolateral prefrontal

cortex, basal ganglia and hippocampal formation, as well as transection of the pathway between inferior temporal and prefrontal cortex, all result in serious deficits on arbitrary visuomotor mapping tasks (Murray & Wise, 1996; Toni & Passingham, 1999). Furthermore, in each of these areas, learning-related increases or decreases in reward discharge have been observed with single-unit recordings (Cahusac *et al.*, 1993; Mitz *et al.*, 1991; Tremblay *et al.*, 1998). Human studies suggest a similar network in arbitrary visuomotor mapping. Petrides (1997) found that patients with right or left frontal excisions were severely impaired on learning arbitrary associations between coloured stimuli and hand postures. Ghilardi *et al.* (2000) found activity of primary motor and primary sensory cortices, basal ganglia and cerebellum during the execution of learned responses, whereas the learning of new sequences activated the dorsolateral prefrontal and anterior cingulate cortices.

In the present experiment, participants were required to learn a motor response (button press) to a specific stimulus during a training block. In order to investigate if this learning was evident in a subsequent visual discrimination task, featuring the same learned stimulus-response pairing, trained experimentals and untrained controls both engaged in a visual search task in which the same S-R association was an element. A number of studies have linked the P300 (P3) component of the scalp-recorded ERP with a possible hippocampal generator (Halgren *et al.*, 1998; Picton, 1992). Studies using intracranial depth electrodes in the hippocampal formation report P3-like activity in hippocampal cells (Brazdil *et al.*, 1999; Halgren *et al.*, 1995 (a,b), 1998). Dipole modelling studies of the scalp P3 imply generators in the hippocampal region (Nakajima *et al.*, 1994; Tarkka *et al.*, 1996; Yamazaki *et al.*, 2001); in addition, reduced amplitude P3 components have been found in patients suffering from temporal lobe/hippocampal abnormalities such as epilepsy (Psatta & Matei,

1995) and after bilateral hippocampal lesions, in which case the P3 was absent (Nakajima *et al.*, 1995). The P300 component of the ERP is therefore thought to be at least partially generated by the hippocampus, and as such can be viewed as a broad index of hippocampal involvement in a task. Ipredict that the learning will be manifested as shortened reaction times and increased P3 amplitudes, reflecting activity changes in some of the structures subserving this form of learning.

3.2 Materials and Methods

3.2.1 Participants:

Twenty participants (9 male and 11 female) were divided randomly into control (n=10) and experimental groups (n=10) (age range: 19-35 years; mean = 23.2). All were right-handed with normal or corrected-to-normal vision. Each participant was fully briefed before each task commenced, and given additional feedback after its completion. Each wore a Quikcap 32-channel EEG recording cap connected to the Neuroscan Synamps (Scan 4.1) ERP recording system (Medtech Systems Ltd., Horsham, UK) for the duration of the tasks, and EEG activity was recorded. Participants were seated 100 cm from the computer monitor throughout the testing sessions.

3.2.2 Materials:

Visual Stimuli:

The stimuli (see Ellison & Walsh, 1998; Walsh, Ashbridge & Cowey, 1998; Walsh, Ellison, Ashbridge & Cowey, 1998; Walsh, Ellison, Batelli & Cowey, 1998) were white line segments (0.93 degrees long, 0.13 degrees wide) presented horizontally,

vertically or diagonally at a 45-degree angle (forward slash or backslash) at the centre of a black monitor screen. Each trial was preceded by an auditory tone of duration 500 ms, and a central fixation point which remained on screen for 500 ms. The fixation point disappeared and the stimulus was presented. Visual stimuli remained on screen until a button press response was made. The screen then remained blank for a further 1,000 ms before the next trial commenced. Fig. 1 displays the stimulus presentation sequence. Stimuli were generated using a DOS-based TurboPascal programme (version 7) on a DELL PC. A colour monitor was used to display the stimuli, and the participants used a standard PC computer mouse to make their responses.

Event-Related Potentials

Electrophysiological EEG data were recorded in AC mode (gain: 500; band pass: 0.15-30 Hz); the A/D conversion rate was 500 Hz, and the range was 11 mV. Scalp potentials were obtained using a 32-channel Quikcap using linked ear reference electrodes and an anterior scalp reference site (AFz). The electrode array consisted of 12 frontal, 15 central/temporal/parietal and 3 occipital electrodes conforming to the International 10-20 System (American Encephalographic Society, 1994). Vertical and horizontal eye movements were recorded with two VEOG and HEOG electrodes placed above and below the left eye, and at the outer canthus of each eye, respectively. Recording commenced when electrical impedance had been reduced to less than 15 kOhms by Quikgel application combined with light abrasion of the scalp.

3.2.3 Procedure:

Control Group: Visual Discrimination

In the Control condition, horizontal, vertical, forward slash and backslash were

presented on the screen within the central window for 100 trials (Fig. 3.1). Participants monitored the stimuli for a pre-defined target (present on 50% of trials), the forward slash, to which they responded by pressing the left mouse button with the index finger of the right hand. The right mouse button was to be pressed with the middle finger in the event of any of the other stimuli being presented. Participants were instructed to give equal emphasis to speed and accuracy of response. Stimuli remained on the screen until the participant made one of the two overt behavioural responses.

Experimental Group: Training Block followed by Visual Discrimination (Trained Condition)

The training block required the participant to respond to a block of 70 presentations of the stimulus (forward slash) later designated the target. After a 3-5 minute break,

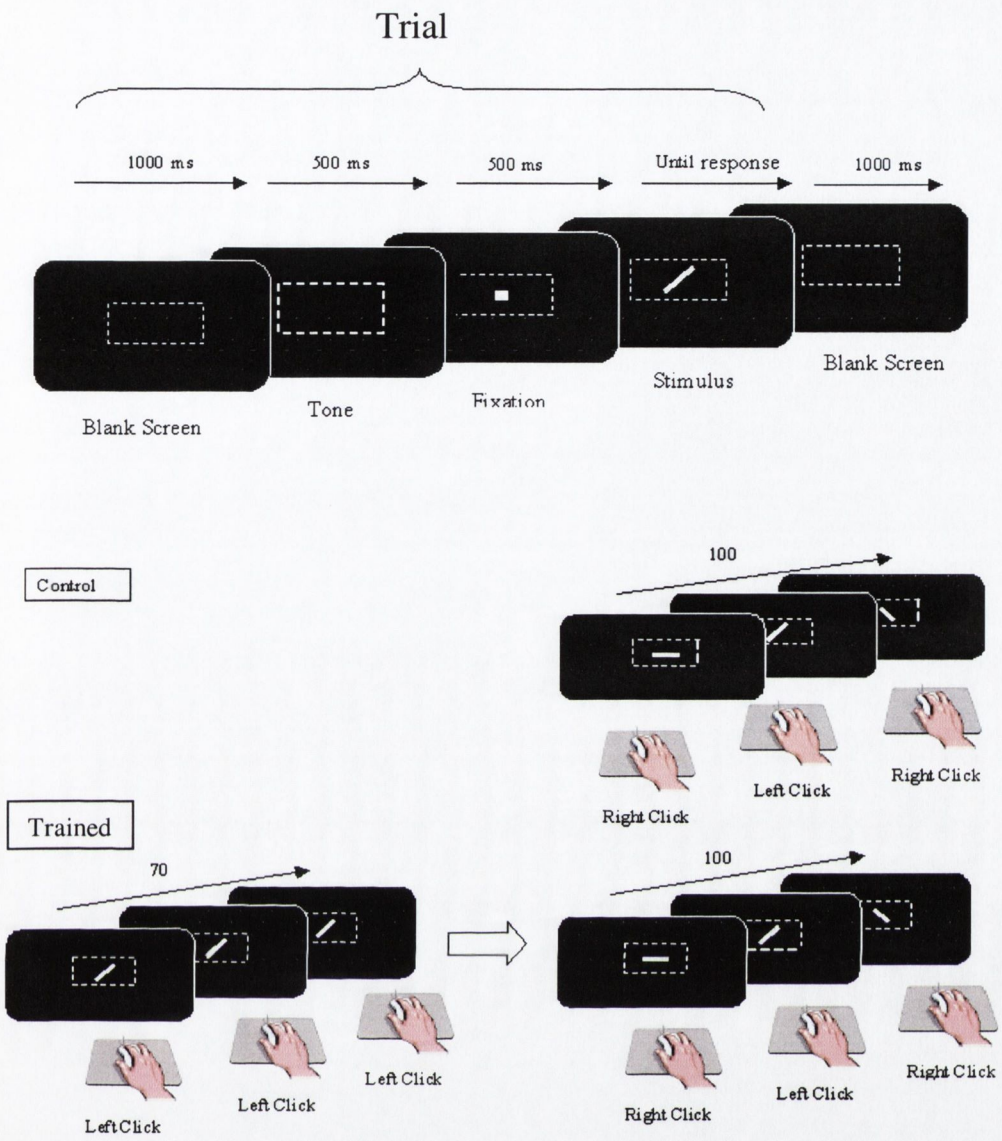

Figure 3.1: Presentation sequence for visual stimuli in all conditions, showing order and duration of blank screen, auditory tone, fixation point and visual stimulus. The interval between blank screen onset and stimulus offset represents one trial (top). Experimental design for control and trained conditions, with blank screens, tones and fixation points omitted (bottom two panels).

experimental participants completed the same visual discrimination task as the Control group, with random presentation of the four stimulus types for 100 trials. Again, the index finger/left button response was required for the target (forward slash) and the middle finger/right button response was to be made for any of the other three stimuli (Fig. 3.1). EEG activity was recorded during each trial block in both control and experimental conditions.

3.2.4 Data Analysis:

Behavioural Data

Reaction times (RTs) for the different conditions were averaged for each participant, and for all participants in each condition; RTs for incorrect responses and outliers (over 3000 ms) were removed before analysis. RTs were analysed using two-way analysis of variance (ANOVA), with factors Stimulus (target vs. distractor) and Group (control vs. trained); significant main effects subjected to Tukey's multiple comparisons.

Electrophysiological Data

The continuous EEG recordings were subjected to ocular artifact reduction to remove artifactual scalp potentials caused by eye-blinks; recordings from each participant were combined for all trials within each condition.

Data were epoched into single sweep recordings: 100 ms prestimulus to 500 ms poststimulus for the training blocks, and to 800 ms poststimulus for the visual discrimination task (due to the longer reaction times associated with this task). Sweeps for trials where participants made incorrect responses were rejected, as were blocks of aberrant waveform activity (caused by EMG activity or other forms of interference). All sweeps were baseline corrected using the 100 ms prestimulus interval as the baseline interval. Ocular artifacts were reduced using blink-averaging algorithms, and still contaminated trials were then rejected by selecting cutoff thresholds, usually ± 50 μV, yielding 15-20% rejected epochs per participant. Remaining epochs were averaged for each participant, and these averages were combined to produce a grand average for each condition.

Epochs were separated into target trials and distractor trials. Separate stimulus-triggered grand average (STA) waveforms were calculated for target stimuli and distractor stimuli. Peak amplitude and latency values for P1, N2 and P3 components were recorded in designated time windows (P1: 80-120 ms; N2: 170-220 ms; P3 250-600 ms). These values were analysed using MANOVAs with factors Group (control, trained), Stimulus (target, distractor) and Group x Stimulus (control target, control distractor, trained target, trained distractor). Tukey multiple comparisons were used when variances were equal; otherwise Games-Howell tests were employed. The alpha level was set at 0.06 or below to compensate for the highly conservative bandpass frequency used.

3.3. Results

3.3.1 Behavioural Data: Training

Response accuracy was high in both groups for the visual discrimination task, with a total error rate less than 5% (3.6% for control group, 2.8% for trained; $t = -0.554$, $df = 18$, $p = 0.587$). Overall mean response time to all stimuli in the control group was 535 ms (± 4.9 SEM); this was broken down into 504 ms (± 7.1 SEM) for responses to targets (forward slash), and 567 ms (± 6.6 SEM) for non-targets or distractors (Fig. 2). Overall mean RT in the experimental group was 503 ms (± 4.3 SEM), with an average RT of 468 ms (± 6.2 SEM) for targets and 536 ms (± 5.6 SEM) for non-targets. An ANOVA revealed significant differences between targets and distractors in both conditions ($F(1,16)=10.63$, $p < 0.01$). The differences between targets and distractors ($p < 0.01$), trained and control targets ($p < 0.01$), and trained and control distractors ($p = 0.008$) were significant. Average RT to the forward slash stimulus in the training

block was 263 ms (± 4.3 SEM; Fig. 3.2). No significant interaction of Stimulus x Group was found ($F(1,16)=0.002$, $p=0.96$)

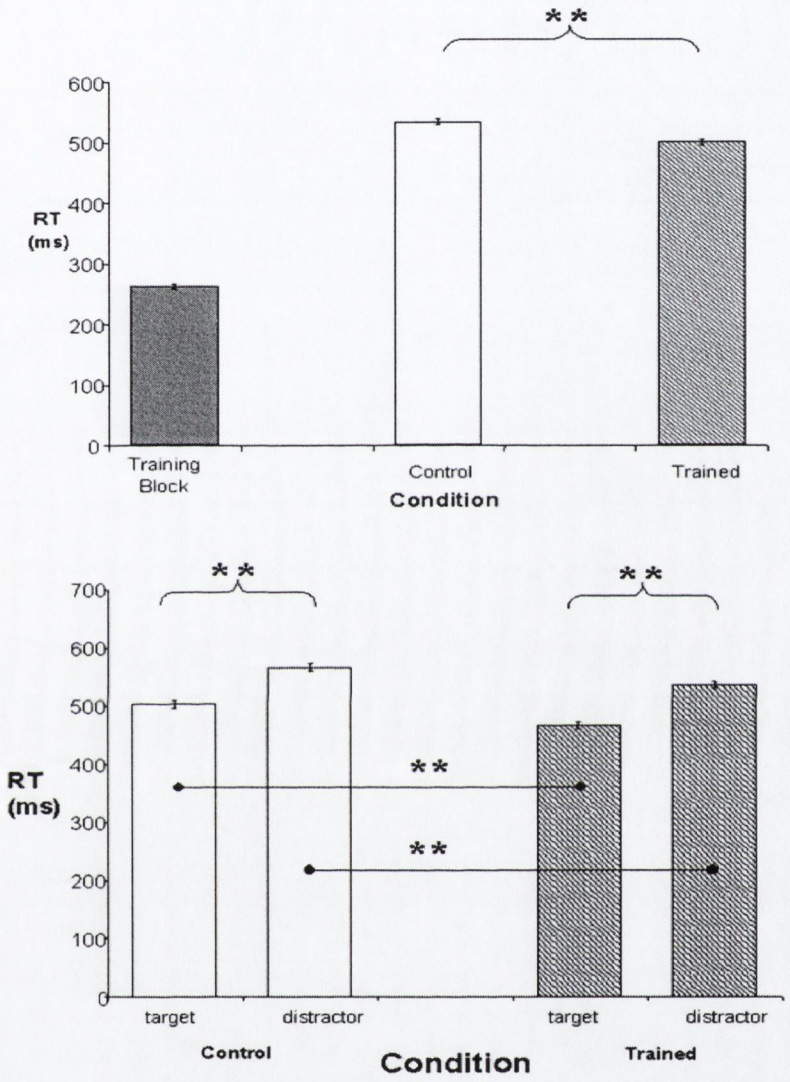

Figure 3.2: Bar graphs depicting mean overall reaction times to stimuli in training block, and control and trained visual discrimination tasks (top), and mean reaction times for target and distractor stimuli in control and trained conditions (bottom). ** indicates significance at $p < 0.05$. Significant differences are marked ⌐¬ or ●——● .

3.3.2 Waveform Data: Training

Visual Discrimination Task: Control and Trained Conditions

A bipeaked P3a component was evident at frontal and fronto-central electrode sites (Fig. 3.3), with maximal amplitude at fronto-central electrodes; the component was markedly larger in the trained condition at all electrode sites (only midline electrodes are reported here). The frontal P3a was larger for trained relative to control ($F(1,18) = 4.28$, $p = 0.05$), as was the centro-parietal P3b (Cz: $F(1,18) = 20.99$, $p < 0.0001$; Pz: $F(1,18) = 8.45$, $p < 0.009$). The posterior P1 and N2 waveforms were also larger for trained (P1: $F(1,18) = 4.92$, $p = 0.04$; N2: $F(1,18) = 4.48$, $p = 0.049$). The only latency difference was evident in the N2 centrally, which was earlier for trained ($F(1,18) = 6.16$, $p = 0.023$).

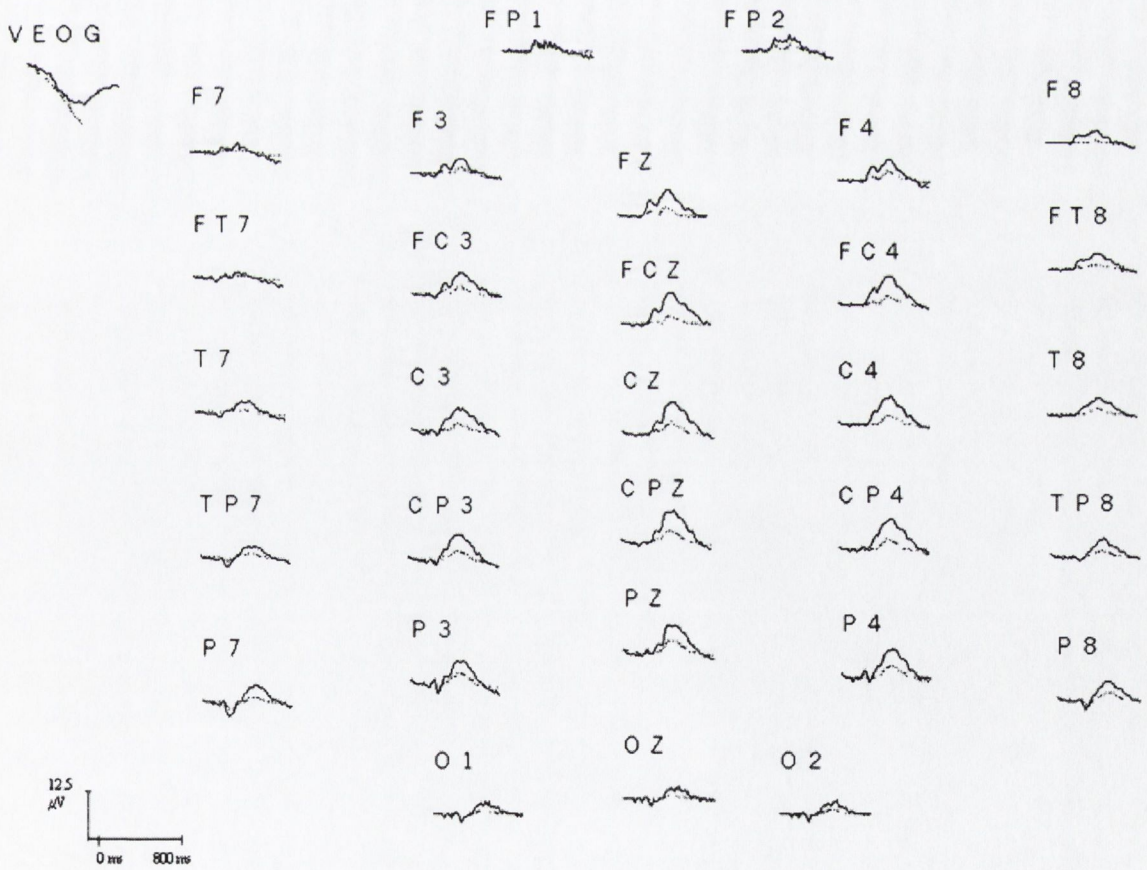

Figure 3.3: Overall grand mean waveforms for trained (solid line) and control (dotted line) groups on visual discrimination task for all 32 electrodes. Amplitude differences between trained and control (untrained) P3 components are evident at all leads.

Visual Discrimination Task: Target vs. Distractor Waveforms

For the grand mean waveforms for targets and distractors in the control and experimental groups, the pattern of components was identical to that of the overall waveform (Figure 3.4). Overall differences were observed between targets and distractors in P3 amplitude frontally ($F(3,36) = 3.15$, $p = 0.037$), centrally ($F(3,36) = 11.08$, $p < 0.0001$) and parietally ($F(3,36) = 5.7$, $p = 0.003$), with more positive components for trained. Further, the only latency difference was central for P3 ($F(3,36) = 3.12$, $p = 0.038$), where the target P3s (control: 391 ms; trained: 371 ms) peaked earlier than distractor (control: 400 ms; trained: 422 ms).

Multiple comparisons showed no differences between target and distractor stimuli in the control group. For the trained group, there was a significant P3 latency difference ($p = 0.024$) over central leads, with target P3 peaking earlier (371.4 ms) than distractor P3 (422.3 ms). Trained targets had larger P3b amplitudes than control targets centrally ($p = 0.002$) and parietally ($p = 0.042$). The same pattern was visible for trained distractors compared to control distractors, with larger amplitude for trained (central: $p = 0.001$; parietal: $p = 0.02$).

3.3.3 Behavioural Data: Learning Effects

The 70 training trials were divided in three to test for learning effects: early (trials 1 to 23), middle (trials 24 to 46) and late (trials 47 to 70). Individual mean reaction times for each phase are shown in Fig. 3.5 (top left). An ANOVA revealed a main effect for phase ($F(1,18)=5.077$, $p < 0.006$), while post hoc tests showed that Phase 1 RTs (284 ms ±

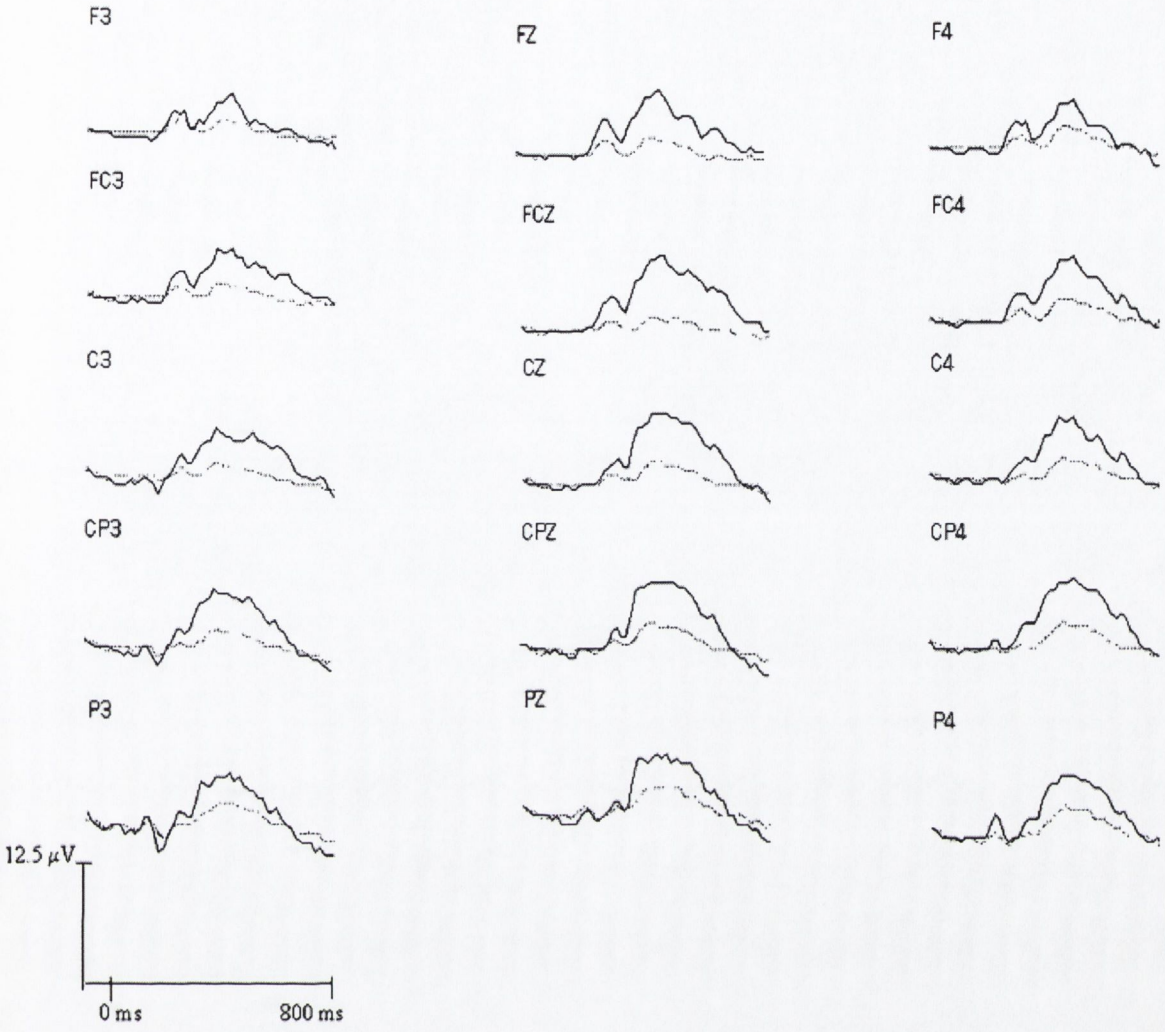

Figure 3.4: Overall grand mean waveforms for control (dotted line) and trained (solid line) conditions over frontal, central and parietal electrodes, showing the trained-untrained P3 difference.

9.0 SEM) differed significantly from both Phases 2 (RT = 255 ms ± 7.0 SEM) and 3 (RT = 254 ms ± 6.7 SEM). The difference between the two latter phases was not statistically significant. An average RT was obtained from the ten participants for each of the 70 trials (Fig. 3.5, bottom left). The greatest reduction in reaction times occurred between the first 30 trials and the remainder of the block.

This procedure was repeated for the control and experimental visual discrimination blocks. Fig. 3.5 (top right) depicts RTs to target stimuli in the control

condition. The plot shows a generally similar pattern to that in the training block, with longer RTs evident in the earlier portion of the block, and shorter response latencies occurring later.

The scatter plot of RTs to trained target stimuli is shown in the bottom right of Fig. 3.5. All RTs in this condition are in the 300-600 ms range; there is no evidence of a progressive decrease in RT over the duration of the block in this condition. Trend lines represent a two-factor power function.

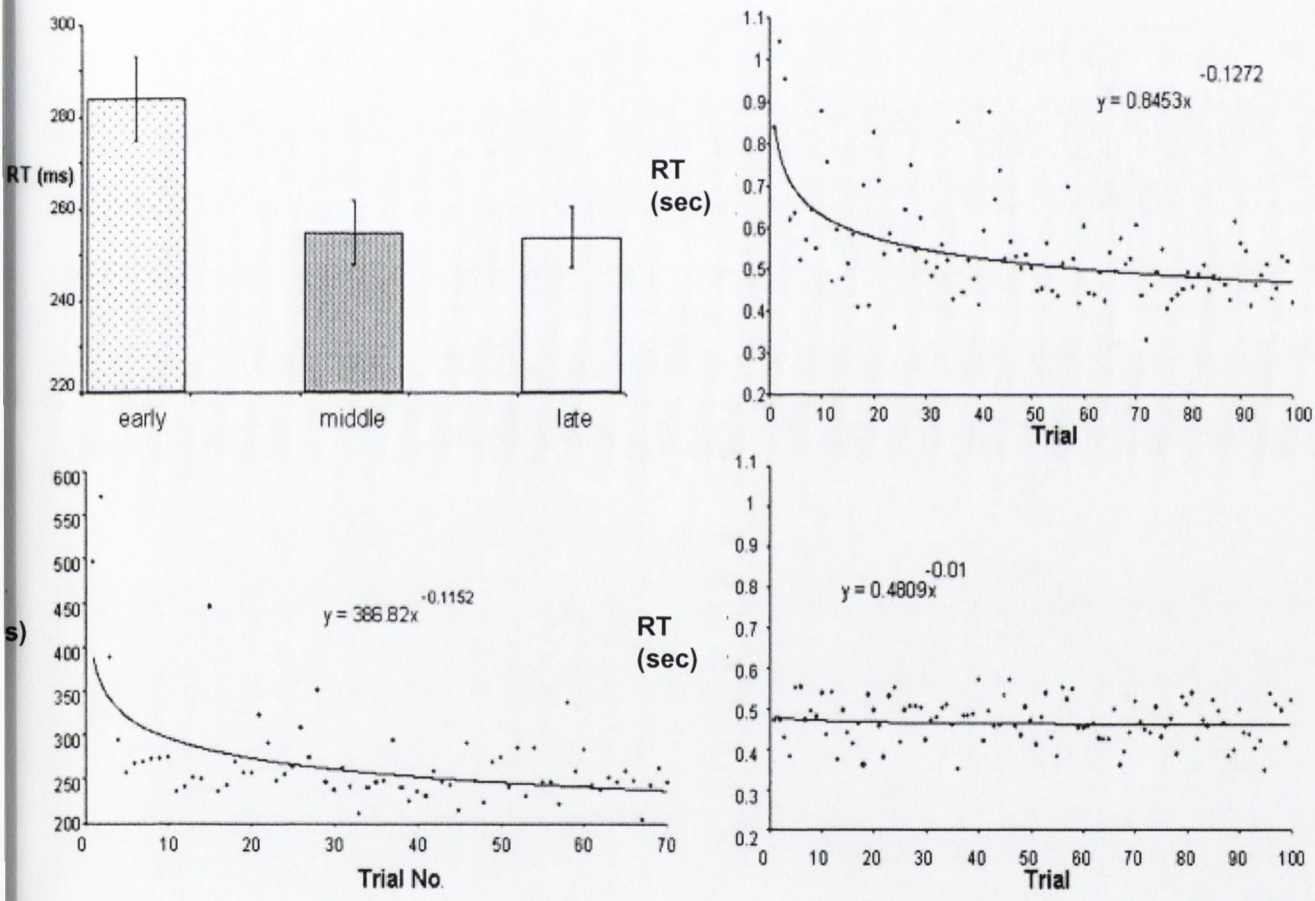

Figure 3.5: Bar graph representing mean RTs to each phase of the training block (top left), with scatter plots of mean RTs to each target trial in control (top right), experimental training (bottom left) and experimental visual discrimination blocks (bottom right). Trend lines represent two-factor power functions.

3.3.4 Waveform Data: Training Block

ERPs recorded during the training block revealed a similar pattern to those found in the discrimination tasks; an anterior P3a was present, with a posterior P1-N2-P3b complex (Fig. 3.6)

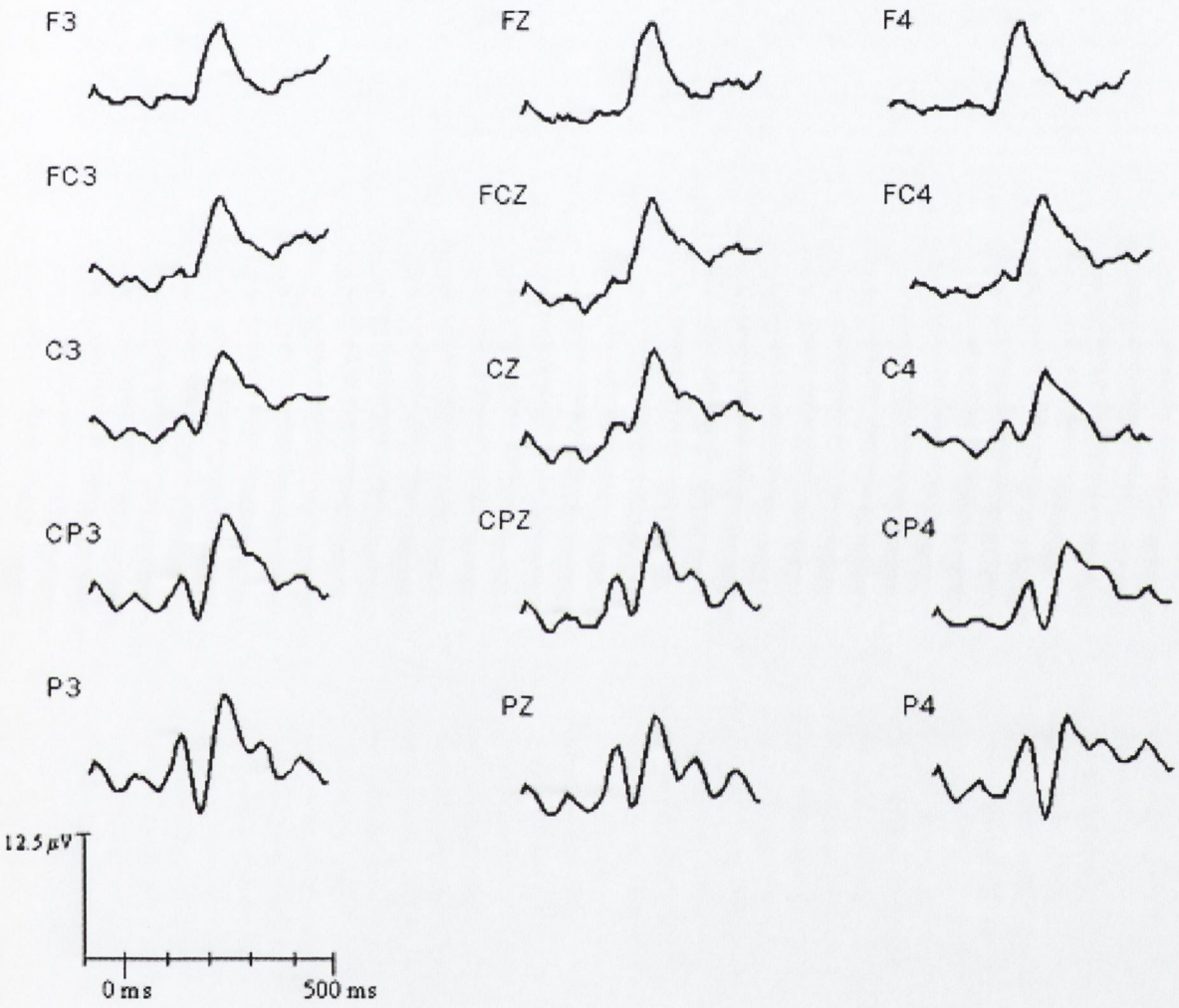

Figure 3.6: Grand mean waveforms recorded during training block, showing anterior P3a and posterior P1-N2-P3b complex. These components may reflect the activity of parts of the arbitrary visuomotor association network.

3.4 Discussion

Prior learning of the arbitrary association between a visual stimulus and a motor response resulted in behavioural and electrophysiological changes in a subsequent related task. The learning itself produced changes within the training block which were also evident behaviourally. The response speed advantage conferred to trained participants was not confined to reactions involving the trained association; RTs were shorter for distractors as well as targets. The learning of the crucial association between target stimulus and left button-press response may have facilitated the visual discrimination process in general, or alternatively the absence of the onset of the learned association may serve as a signal to instigate the rapid selection of the alternative response.

There was also evidence of electrophysiological correlates of this advantageous training effect. Grand mean waveforms for control and experimental conditions revealed significant amplitude differences over midline and central areas (Fig. 3.3 and 3.4). This suggests the presence of some additional cortical activity in response to trained over untrained stimuli, and may be an indication of the visuomotor training that this group received. Alternatively, this effect could represent the recruitment of additional cortical areas. Further, there was a significant difference in P3 latency for trained targets compared to trained distractors, with earlier P3 peaks for trained. A corresponding latency difference was not found for untrained stimuli (targets and distractors had similar latencies), implying that this difference resulted from task-specific learning, rather than non-specific learning effects. The latency of the P3 is believed to be an index of the speed of processing/evaluation time (Gratton *et al.*, 1992; Magliero *et al.*, 1984; McCarthy & Donchin, 1981) so the earlier P3 latency for trained targets may be a reflection of more rapid processing when the S-R

association has been trained. It is also thought that the P3b component is at least partially generated by the hippocampal formation (Halgren *et al.*, 1998; Picton, 1992); observed amplitude increases and latency decreases might be an index of learning-related hippocampal involvement in the task.

The training block showed a rapid decrease in RTs during the first 30 trials, followed by an asymptote, following the traditional power learning curve j-shape (Stevens, 1951). The majority of the learning therefore appears to take place within the first 30 exposures to the trained association. In the scatter plots, the learning curve observed during the training block for experimentals was absent from their subsequent discrimination block; in contrast, the discrimination block for controls showed a similar learning curve. One may therefore conclude that, in this task, the learning that occurred during the training block was the learning of a specific association between stimulus and response, and that evidence of this learning was also evident in the subsequent visual discrimination task, relative to untrained controls.

Waveforms elicited by the stimulus in the training block revealed a posterior P3b component, as well as earlier P1 and N2 (Fig. 3.6). The differences in amplitudes and latencies observed in the subsequent discrimination task may be related to the repeated activation of the visuomotor association system, as indexed by these components. Future studies might examine if amplitude and latency differences occur throughout the duration of the training block; that is, if the components change from the early training trials to the later trials, thereby supporting the assertion that the effects observed here reflect neural changes due to association learning.

The network hypothesised to mediate arbitrary visuomotor associations includes the prefrontal cortex, hippocampus and basal ganglia (Wise & Murray, 2000). The role of the hippocampus in the present study may possibly be indicated by

the P3b component. Intracranial ERP recordings show task-related changes in activity in the basal ganglia-thalamic circuits during the N2-P3 complex latency (Kropotov *et al.*, 2000); the N2 observed during the training and discrimination blocks might reflect the activation of the basal ganglia. There were amplitude and latency differences for N2 when trained was compared with control, further supporting this contention. However, the absence of N2 differences between trained targets and distractors would seem to suggest that the contribution of the basal ganglia is relatively unspecific and not confined to the trained association. Rather, they may be activated when any S-R association, be it trained or novel, is made. Single-unit and intra-cranial recording experiments will be required to test these speculative claims.

In addition to the involvement of the baso-hippocampal-prefrontal network, the observed amplitude differences could be partially due to activity in the occipito-parietal-frontal - the dorsal "action" stream (Goodale, 1993). Neurons in this stream respond to the behaviour of an animal with respect to a visual stimulus. Feed-forward projections from parietal perceptual areas to frontal, premotor or supplementary motor areas may contribute to the scalp-recorded P3a (frontal), P3b (parietal) or both. This dorsal stream may contribute to the selection of an appropriate response to a visual stimulus.

In conclusion, this experiment demonstrated behavioural and electrophysiological correlates of the acquisition and expression of arbitrary visuomotor learning, with a posterior scalp locus for the learning of the S-R association. The observed waveform modulations may be indicative of the involvement of the hippocampus and basal ganglia, in the learning and utilisation of visuomotor associations. The results suggest that the neuronal activity of the hippocampal-basal ganglia-prefrontal circuit thought to mediate this type of learning

is detectable by scalp electrodes, and allow us to speculate on the different contributions of components of the circuit.

Chapter 4

Concurrent Task Performance Enhances Low-level Visuomotor Learning

Abstract

Visuomotor association learning involves learning to make a motor response to an arbitrary visual stimulus. I investigated the possible role of attentional processes during such learning using dual-task interference. In Experiment 1, a motor, verbal or perceptual concurrent task, each with one of two levels of attentional engagement, was performed during the learning/training block of visual search training. Contrary to expectation, the dual-task groups showed improved learning and learning-dependent performance relative to untrained control and non-dual-task trained groups. This effect did not appear to be due to increased arousal. In Experiment 2 the visuomotor association was trained within the context of one of two visual search tasks, again varying attentional engagement. Training of the S-R association in the search tasks resulted in comparable performance to the explicitly trained group. Experiment 3 showed that training the motor and perceptual aspects of the association

alone resulted in comparable training effects to normal training, confirming that the observed effects are not due to simple motor preparedness to respond. Taken together, the findings suggest that engagement of attention, but not arousal, during the acquisition of a visuomotor association can facilitate this learning and its expression. Possible neural substrates for this effect are also discussed.

4.1 Introduction

Learning to make a specific action in response to a stimulus that does not specify the required response is termed arbitrary visuomotor association learning. This learning requires substantial cognitive flexibility, as the meaningful relationship between stimulus and response must be learned (Wise & Murray, 1999). Such learning is subserved by a brain network, including prefrontal cortex, hippocampal formation, basal ganglia and premotor regions (Wise & Murray, 2000), in addition to the cortices. We have previously found (Roche & O'Mara, 2002) that this learning follows the traditional power curve, and that its effects can be detected in a subsequent task that depends on the learning. Exposure to a training block in which the S-R association was learned led to faster response times compared to that of untrained controls in a visual discrimination block which followed. These behavioural effects were mirrored by event-related potential (ERP) component changes, particularly larger P300 amplitudes after training; P300 amplitude is thought to reflect attention, memory and other cortical functions (for a review, see Knight, 1990). I hypothesised that attention to the stimulus during training was at least partially involved in determining the strength of the learning. Here I investigate the effects of manipulating this level of attention on learning and performance.

Dual-task paradigms reveal the limitations of human information-processing systems by combining two concurrent tasks to produce performance deficits (Hampson, 1989). The degree of impairment is dependent on the combined attentional demands of the two tasks: a concurrent task requiring greater attention should produce more severe disruption than one low in attentional demands. Some theorists (e.g. Baddeley, 1986; Eysenck, 1982) explain dual-task disruption in terms of a central attention processor which deploys limited resources to subordinate processing mechanisms that execute the tasks. The locus of this executive is likely to be frontal, as Moscovitch (1994) noted, after observing dual-task deficits on tasks that are frontally dependent, but not on tasks that draw on the hippocampus/medial temporal lobe. If visuomotor learning recruits the central executive, then withdrawing attention from association learning because of a dual-task will impair acquisition and expression of the learning; the greater the attentional demands of the concurrent task, the greater the disruption will be. Corr (*in press*) showed that procedural learning was disrupted to differing degrees by two types of dual-task (mental arithmetic or nonsense syllable counting), while Frensch *et al.* (1999) also found dual-task disruption when the concurrent task was performed during training. However, Jimenez and Mendez (1999) found no effect of a concurrent counting task on learning, suggesting the nature of the secondary task may be of vital significance in determining the effects on performance. For this reason, a number of different dual-tasks are used in the following experiments. Importantly, Schubert *et al.*(1998) either of two motor dual-tasks resulted in impaired performance on an auditory classification task, which was accompanied by reduced P3b amplitude, a component known to be affected by dual-task conditions. The finding from Chapter 3 that the

present task seems to be indexed by the P3b component suggests that the inclusion of a concurrent task is likely to have an effect on this learning.

Visual search tasks require participants to make a motor response to the presence or absence of a target stimulus in a visual array (Treisman & Gelade, 1980). Successful performance of the task depends on learning the arbitrary association between target stimulus and button-press response. There are two types of visual search task (Treisman, 1986): feature or "pop-out" search, hypothesised to be low in attentional demands because the target is defined by a unique perceptual feature (e.g. colour, size, shape etc.), and conjunction search, which requires greater attentional engagement because the target is only defined by a combination of features (e.g. shape and colour). Thus the amount of attentional resources deployed to learning an S-R association is greater during the latter rather than the former of these two search tasks.

4.1.1 Experiments 1, 2 and 3

Here I attempt to affect visuomotor response acquisition and expression by manipulating attention and arousal during S-R pair learning. In Experiment 1, I manipulated attentional deployment to the association using a concurrent task, with the goal of disrupting the learning and its subsequent expression. The degree of attentional engagement in the concurrent task was also varied. The role of arousal level was addressed by including two conditions in which arousal was increased by an auditory tone during training. The tone was either continuous or occurred at random intervals during the training block. In Experiment 2, I investigated whether experience of the S-R association exposed participants to the same visuomotor association within

the context of a visual search task, again varying the degree of attentional deployment to this S-R association. The goal was again to investigate the effects of manipulating the attentional resources directed to the association learning. In Experiment 3, I attempted to separate perceptual and motor aspects of this form of learning, and to evaluate which is more important for association learning. I predict that, within motor, perceptual and verbal dual-task conditions, high attentional deployment tasks will produce more profound disruption than low attentional tasks. I also expect that increasing arousal during training will facilitate acquisition and expression of learning, and that exposure to a target stimulus within a conjunction search task will lead to greater or swifter acquisition than exposure during pop-out search.

4.2 Experiment 1: Methods

4.2.1 Participants:

The participants were 128 Trinity College undergraduate students, with an age range of 18 to 23 (mean = 20.3) years. All were right-handed, had normal or corrected-to-normal vision, and were randomly assigned to one of 16 experimental conditions, each containing 8 participants.

4.2.2 Materials:

Visual Stimuli:

The stimuli (see Roche & O'Mara, 2002) were line segments presented in white (except the conjunction visual search condition; see below) on a black screen; each was 0.93 degrees of arc long and 0.13 degrees of arc wide, and was presented either horizontally, vertically or diagonally at a 45-degree angle (forward slash or backslash)

at the centre of the monitor screen. Each trial was preceded by an auditory tone of 500 ms duration, and a central fixation point which remained on screen for 500 ms. The fixation point disappeared and the stimulus was presented. Visual stimuli remained on screen until a button press response was made. The screen remained blank for a further 1,000 ms before the next trial commenced. Figure 4.1 displays the stimulus presentation sequence. Stimuli were generated using a DOS-based TurboPascal programme (version 7) on a DELL PC, which automatically recorded reaction times and error rates. A colour monitor was used to display the stimuli, and the participants used a standard PC computer mouse to make their responses.

4.2.3 Procedure:

Participants were seated 100 cm from the screen in a slightly darkened room with the computer mouse placed in their right hand on a table in front of them. Three types of concurrent task were used: motor, perceptual and articulatory/verbal. These were selected to tax different aspects of attentional resources by sharing or competing with stimulus modality (visual), motor output and working memory capacity, respectively (Wickens, 1984). Each of these tasks could also be manipulated to require relatively high or low levels of attentional deployment, by varying task demands.

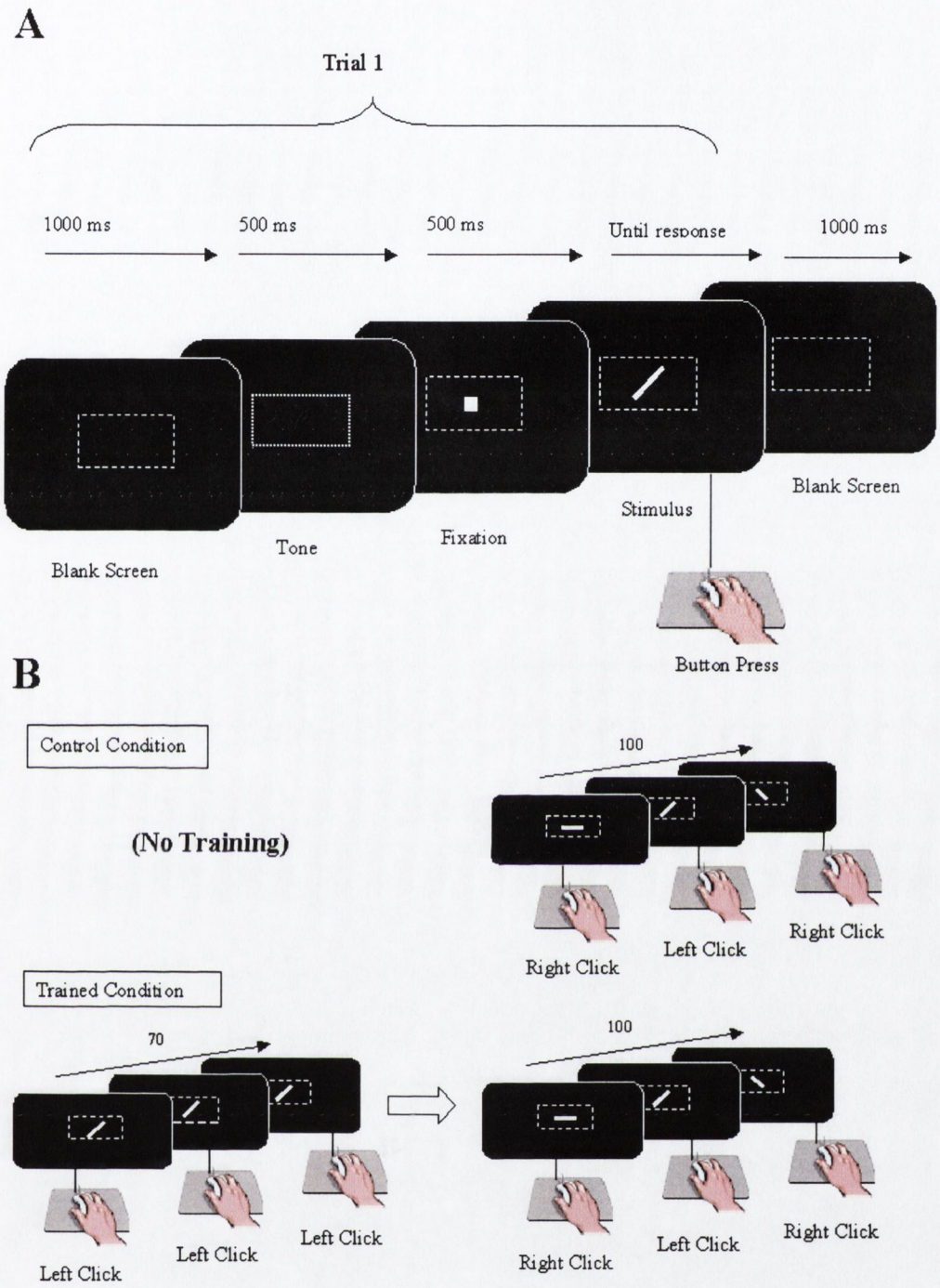

Figure 4.1: A) Stimulus presentation sequence and durations for one experimental trial. B) Experimental design for control and normally trained conditions (blank screens, tones and fixation points are omitted). Dual-task manipulations were employed during the training blocks.

4.2.4 Experiment 1a: Dual-Task

Control Group (Untrained)

In the control condition a mixture of stimuli (horizontal, vertical, forward slash and backslash) was presented on the screen within the central window. Participants monitored the stimuli for a pre-defined target (forward slash) and responded by pressing the left mouse button with the right hand index finger. The right mouse button was to be pressed with the middle finger to any of the other stimuli. Participants were instructed to give equal emphasis to speed and accuracy of response. The target was present on 50% of trials, and stimuli remained on the screen until the participant responded. A trial block consisted of 100 trials.

Normally Trained Group

This group received a training block prior to completion of the same visual discrimination task as the control group. During the training block, the participant responded to a block of 70 presentations of the forward slash stimulus (later designated the target), using right index finger press to the left mouse button. This was followed by a short rest period (3 to 5 minutes), which was followed by the visual discrimination task.

Motor Dual-task 1: Slow Tapping

All dual-task participants were presented with the training and visual discrimination blocks, as per the control and normally trained groups, with an additional task added during the training block. Participants were instructed to give equal emphasis to both tasks in all dual-task groups. Motor dual-task participants were required to tap their right foot in time with a metronome while they completed the training block. The low attentional demand group were required to tap at a rate of 60 beats per minute ("largetto"). Performance was monitored by the experimenter, who instructed the

participant to correct their behaviour if their tapping was not in time with the metronome.

Motor Dual-task 2: Fast Tapping

The high attentional demand motor group were required to tap their foot at a faster rate of 160 beats per minute ("vivace") during the training block, and then completed the visual discrimination task.

Verbal Dual-task 1: Nonsense Syllable Production

The low attentional demand group repeated the nonsense word "blah" at a rate of once per second while they engaged in the training block. The experimenter instructed the participant to adjust their rate if it deviated from one per second.

Verbal Dual-task 2: Random Number Generation

The high attentional demand group for the verbal dual-task had to generate random numbers (from 1 to 9) at a rate of one per second during the training block. The experimenter monitored and corrected for participants' speech rates.

Perceptual (and Working Memory) Dual-task 1: Asynchronous Flashes

The perceptual dual-task conditions required the participant to divide attention between responding to the stimulus on screen during the training block and counting the number of times a light flashed distal to the stimulus, giving this condition an additional working memory aspect. The light was placed near the periphery of vision, 200cm from the participant in the upper left quadrant of vision (elevated at a 45 degree angle to the horizontal) such that an eye-movement was necessary to identify a

flash. In the low attentional engagement group, the flashes occurred while the training stimulus was not on screen (i.e. during the blank screen, tone or fixation point). These were termed asynchronous flashes. At the end of the training block, participants were asked to report how many flashes (n = 50) they had observed.

Perceptual (and Working Memory) Dual-task 2: Synchronous Flashes

In the high attention condition, the light flashes occurred in synchrony with the appearance of the training stimulus on the screen. It was therefore necessary to divide attention between the location of the light flash and the stimulus on screen at the same time in this condition. Participants were also asked to report how many flashes (n = 50) they had observed at the end of the block.

4.2.5 Experiment 1b: Arousal

Increased Arousal Group 1: Tonic Alerting

This group completed the training block as per the normally trained condition, with the addition of a sustained alerting tone that was presented when the training block began and lasted for the duration of the block. The tone was a persistent ringing tone of 11kbps, 88Hz and was presented from a tape recorder placed 80cm from the participant at a volume level of 78dB. The visual discrimination block was then presented in the absence of any alerting tones.

Increased Arousal Group 2: Phasic Alerting

The phasic alerting group was identical to the tonic, except that the tone used was discrete, of 300ms duration, and occurred randomly 18 times (approximately 25% of trials) during the 70 trial block. The same tone, volume level and method of

presentation were used as in the tonic condition. Again, the discrimination block followed.

4.3 Experiment 1: Results

All tasks (Experiments 1-3) were performed with a high level of accuracy (mean absolute errors=4.03±0.41 SEM), as were concurrent tasks (>80% accuracy).

4.3.1 Experiment 1a: Dual-Task

Training Blocks

Figure 4.2 (top) shows mean RTs to the forward slash stimulus during the training block for the normally trained group and each of the experimental groups. In general, significantly longer RTs were obtained for fast versus slow tapping, asynchronous versus synchronous flashes and random numbers versus nonsense syllables.

Shortest RT was recorded for normal training (264±4.6 ms). A series of ANOVAs revealed significant overall RT differences for each of the groups. In the Motor dual-task, RTs were shorter to slow (273±5.6 ms) than to fast tapping (391±1.2 ms; $F(1,14)=6.15$, $p<0.05$). The Perceptual dual-task produced shorter RTs to synchronous (330±2.6 ms) compared to asynchronous flashes; this difference was non-significant (350±9.5; $F(1,14)=0.84$, $p=0.38$). For Verbal, shorter (though non-significant) RTs were found for nonsense/"blah" (347±6.1 ms) versus random number generation (422±12.3 ms; $F(1,14)=2.43$, $p=0.14$). Post hoc tests showed all groups to differ significantly from each other with two exceptions: the normal training and slow

tapping groups in the Motor condition, and the synchronous and asynchronous groups in the Perceptual condition did not differ.

Visual Discrimination Blocks

RTs during the visual discrimination blocks are shown in Figure 4.2. Normally-trained participants had shorter RTs than controls, as did all dual task groups. Fast tapping had shorter RTs than slow, asynchronous flashes (which were shorter than synchronous) and random numbers (which were shorter than nonsense syllables). With the exception of synchronous flashes, all dual task RTs were shorter than normal training.

The control condition had a longer overall RT (508±5.6 ms) than the normally-trained condition (487±4.5 ms). In the Motor group, slow tapping (463±5.4 ms) produced a longer mean RT than fast (410±3.5 ms; $F(1,14)=37.58$, $p<0.001$). Both of these were shorter than normal training trials. For Perceptual, synchronous flashes (496±1.2 ms) resulted in a mean RT that did not differ significantly from asynchronous flashes (458±6.5 ms; $F(1,14)=2.08$, $p=0.17$). The Verbal group gave longer RTs for nonsense utterances (471±4.2 ms) compared to random number production (451±4.3 ms); again, both were shorter than normally-trained ($F(1,14)=25.96$, $p<0.01$). Tukey post hoc tests showed the differences between all groups within these comparisons to be significant, with the exceptions of the synchronous group, which did not differ from the control or trained. No interactions achieved significance.

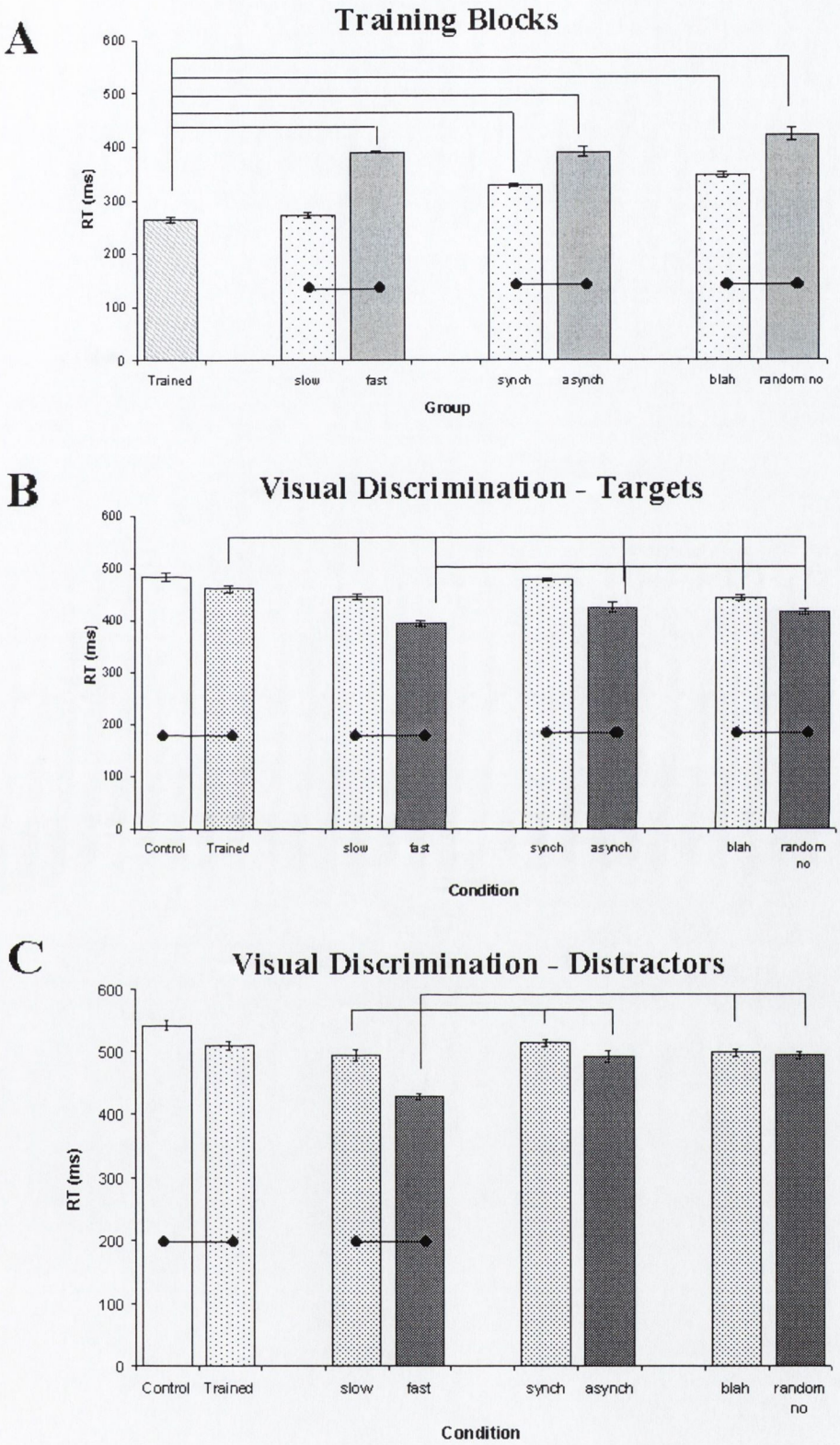

Figure 4.2: A) Mean RTs to target stimuli during training blocks for normally-trained and dual-task conditions. B) Mean RTs to target stimuli during visual discrimination blocks in control (untrained), normally-trained and dual-task conditions. C) Mean RTs to distractor stimuli during visual discrimination blocks in control (untrained), normally-trained and dual-task conditions.

These patterns were maintained when the responses were separated into RTs for target present and distractor/target absent trials (Fig. 4.2, bottom panel). In all cases, RTs to target-present trials were shorter compared to target-absent trials. All dual-task target RTs were significantly shorter than the normally trained target RTs (Motor: $F(11, 31)=31.26$, $p<0.01$; Perceptual: $F(11, 31)=6.34$, $p<0.01$; Verbal: $F(11, 31)=30.74$, $p<0.01$). Distractor RTs in the dual-task groups tended not to differ from those of normally trained or from each other; there was one exception to this, fast motor tapping, which was shorter than the others. All other differences were significant at the 0.05 level, as revealed by Tukey post hoc tests.

Learning Effects

For every trial in the training and visual discrimination blocks, an average RT was obtained across the eight participants in each condition. These are represented on the scatter plots in Figures 4.3 and 4.4. Figure 4.3 shows these data for the control and normally trained conditions. The training block of the trained condition (bottom) displays a learning curve fitted by a power trend line with a coefficient of 0.36. The subsequent visual discrimination block showed no such acquisition curve (coefficient = 0.17). In the untrained control condition (top), an acquisition curve was evident in the visual discrimination block (coefficient = 0.32).

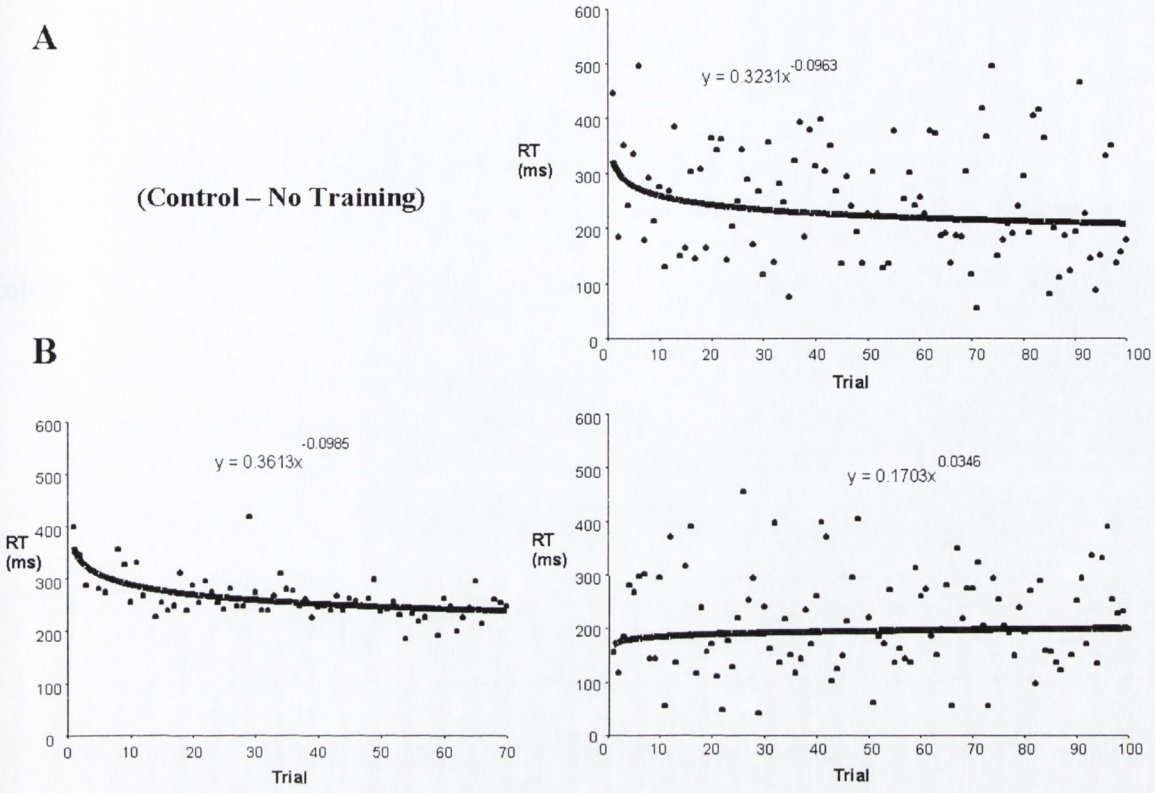

Figure 4.3: Scatter plots depicting A) mean RT to target stimuli during control visual discrimination and B) normally trained training and visual discrimination blocks. Each data point represents the mean RT to target stimuli for that specific trial, in sequence from 1-70 for the training block (left panels) and 1-100 for the discrimination blocks (right panels). Initial exposure to the visuo-motor association shows a j-shaped learning curve, be it in the training block, or as part of the discrimination task.

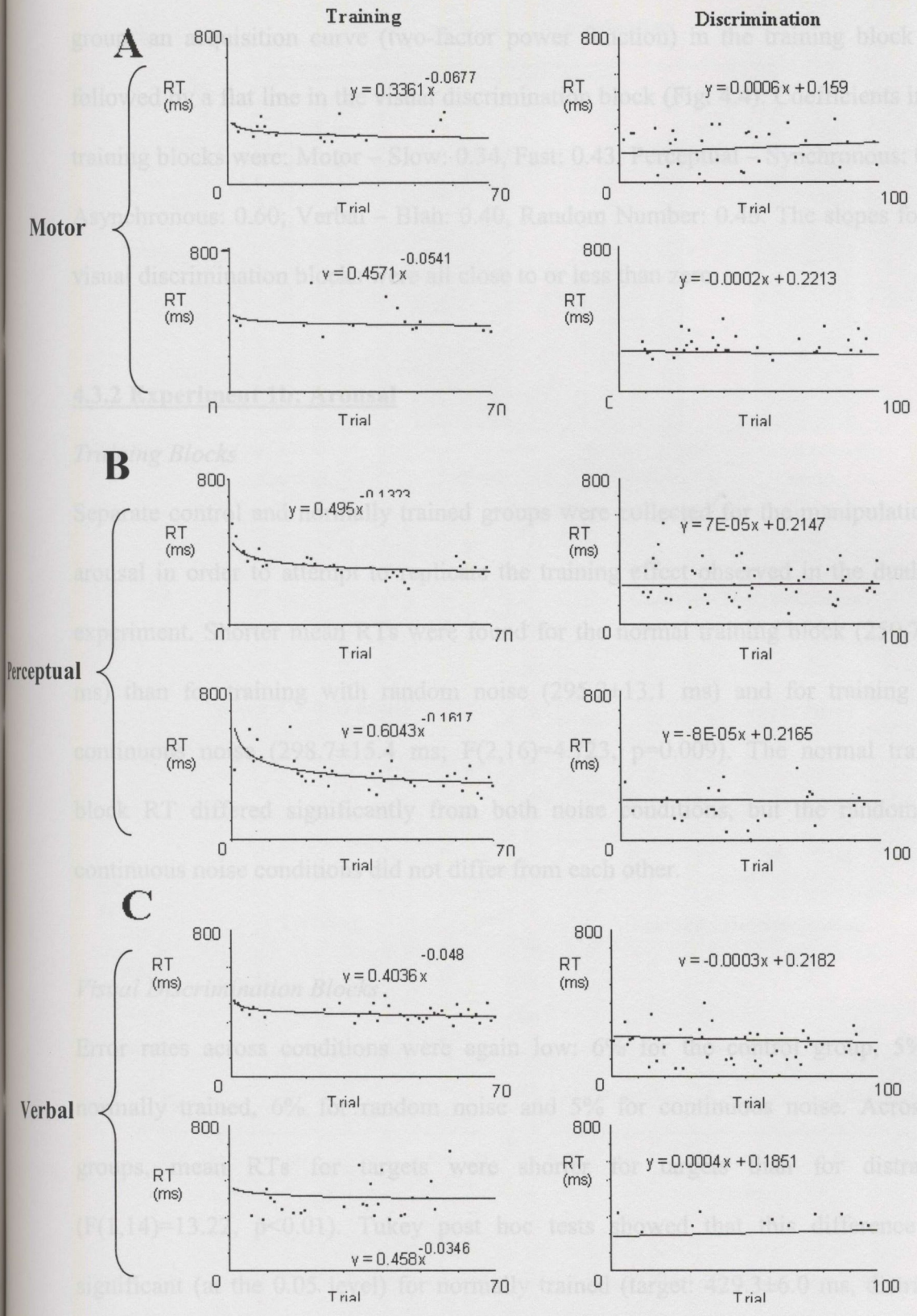

Figure 4.4: Scatter plots (data points omitted) and trend lines for training (left panels) and visual discrimination blocks (right panels) in motor (top), perceptual (middle) and verbal (bottom) dual-task conditions.

All dual-task conditions revealed a similar pattern to the normally trained group; an acquisition curve (two-factor power function) in the training block was followed by a flat line in the visual discrimination block (Fig. 4.4). Coefficients in the training blocks were: Motor – Slow: 0.34, Fast: 0.43; Perceptual – Synchronous: 0.45, Asynchronous: 0.60; Verbal – Blah: 0.40, Random Number: 0.46. The slopes for the visual discrimination blocks were all close to or less than zero.

4.3.2 Experiment 1b: Arousal

Training Blocks

Separate control and normally trained groups were collected for the manipulation of arousal in order to attempt to replicate the training effect observed in the dual-task experiment. Shorter mean RTs were found for the normal training block (250.7±7.3 ms) than for training with random noise (295.2±13.1 ms) and for training with continuous noise (298.7±15.4 ms; $F(2,16)=4.723$, $p=0.009$). The normal training block RT differed significantly from both noise conditions, but the random and continuous noise conditions did not differ from each other.

Visual Discrimination Blocks

Error rates across conditions were again low: 6% for the control group, 5% for normally trained, 6% for random noise and 5% for continuous noise. Across all groups, mean RTs for targets were shorter for targets than for distractors ($F(1,14)=13.22$, $p<0.01$). Tukey post hoc tests showed that this difference was significant (at the 0.05 level) for normally trained (target: 429.3±6.0 ms, distractor: 492.4±7.7 ms), random noise (target: 437.2±6.5 ms, distractor: 492.3±6.4 ms) and continuous noise (target: 441.2±6.1 ms, distractor: 513.5±6.5 ms), but not for the

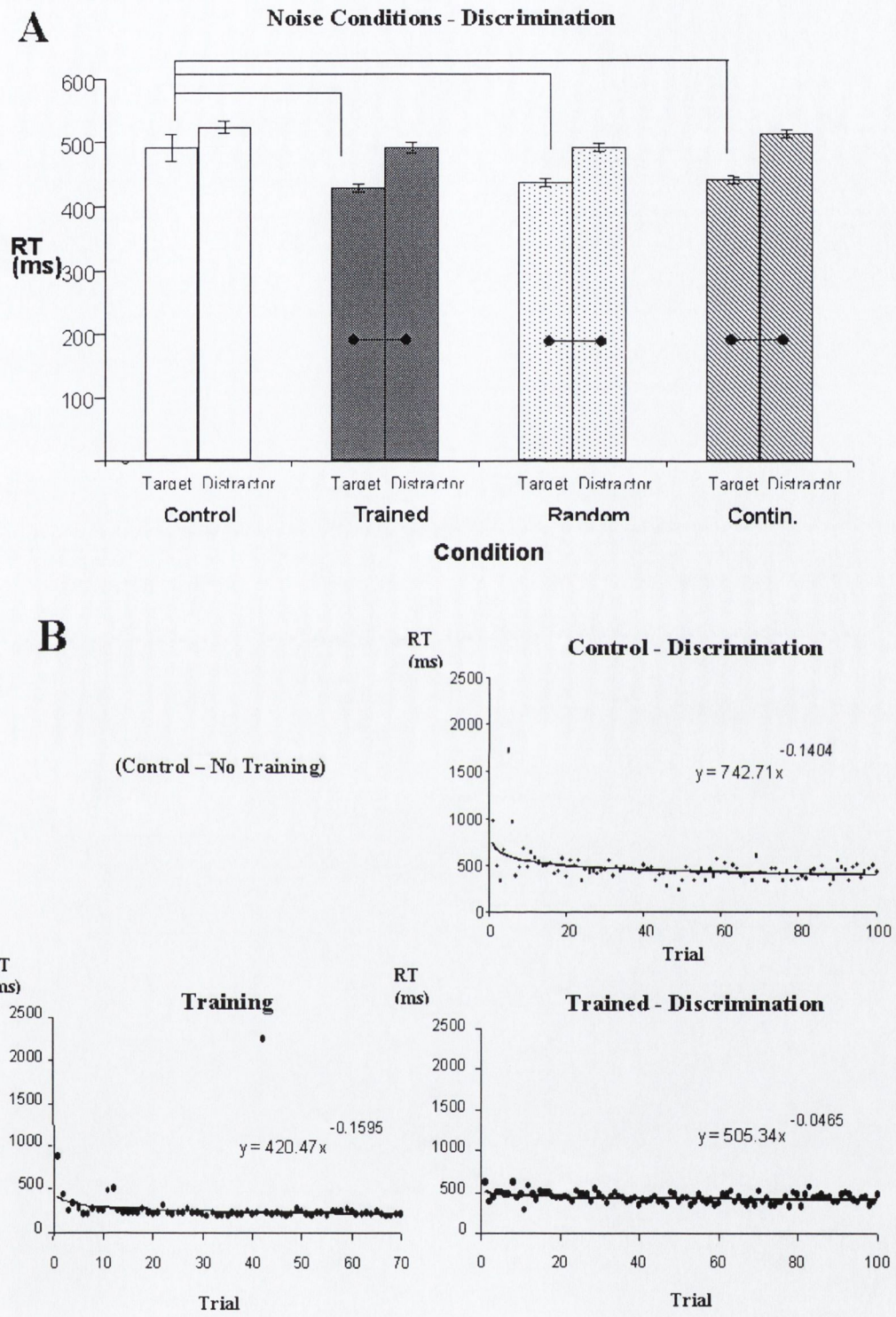

Figure 4.5: A) Mean RTs to target and distractor stimuli during visual discrimination blocks in control, normally trained and alerting noise (random and continuous) conditions. B) Scatter plots and trend lines for mean RT to target stimuli during control visual discrimination (upper panel) and normally trained training and visual discrimination blocks (lower panel).

control group (target: 492.6±21.7 ms, distractor: 524.7±9.7 ms). RTs to distractors did not differ between any groups. RTs to targets in the three trained conditions were all significantly shorter than target RTs in the control group (Fig. 4.5). Interactions were non-significant.

Learning Effects

Scatter plots of RTs to individual trials (control and normal training are shown in Figure 4.5; data not shown for noise conditions) revealed the same pattern as in the dual-task conditions – all training blocks showed a j-shaped acquisition curve (coefficients: normal training=0.42, random noise=0.57, continuous noise=0.48), with the subsequent discrimination blocks showing a flat trend line. The control condition again showed a j-shaped curve during the discrimination block (coefficient=0.74).

4.4 Experiment 1: Short Discussion

Our goal in Experiment 1 was to induce disruption of arbitrary visuomotor learning by means of dual-task interference. This attempt was unsuccessful. Instead, manipulation of the level of attention allocated during the learning of an association produced changes in the learning of that association, and facilitation of performance of a subsequent related task. It appears, therefore, that rather than reducing the attentional deployment to the target stimulus, the concurrent task *increased* the amount of attentional resources directed toward the stimulus. This appears to have resulted in improved learning of the S-R association, compared to those who were normally trained. These effects do not appear to be due to differences in arousal level. It seems more likely that the critical variable in determining the strength of association learning is the level of attention deployed during training.

4.5 Experiment 2: Methods

4.5.1 Visual Search Training

Visual Search Training 1: Pop-out Search

I investigated if exposure to a stimulus within a visual search task facilitates subsequent recognition of that stimulus, by giving one of two visual search tasks in place of the training block. In the low attention condition, a block of feature or "pop-out" search trials was given to the participant prior to the visual discrimination task. In this pop-out task, an array of eight stimuli was presented: either eight distractors (white backslashes) or seven distractors and a target (forward slash). Target presence required a left button-press, and target absence required a right press. Participants completed 70 trials in which the stimulus was present on 70% of trials.

Visual Search Training 2: Conjunction Search

In the high attention condition, a serial or conjunction search was used in place of the training block. The target was a white forward slash; target absent trials consisted of eight distractors (four white backslashes and four bright turquoise forward slashes) and required a right button-press, whereas target present trials contained the target (white forward slash) and seven distractors (three white backslashes and four bright turquoise forward slashes) and again required a left press on the mouse. Again, 70 trials were given with the target present on 70% of trials.

In both visual search conditions, the target stimulus was the forward white slash, as in the normal training condition, and the response was a left button-press, again as in normal training.

4.6 Experiment 2: Results

4.6.1 Visual Search Training

Training Blocks

In the visual search training condition (not shown), RTs were longer for conjunction (1,385±21 ms) compared to pop-out search (657±18 ms) in the training block (top). An ANOVA showed an overall significant effect ($F(1,14)=53.48$, $p<0.01$) and multiple comparisons revealed that each condition differed from the others at the 0.05 level.

Visual Discrimination Blocks

For the search trained groups, pop-out and conjunction training both produced mean RTs that were slightly longer than normal trained, but shorter than control (pop-out: 491±5.7 ms; conjunction: 489±5.2 ms; $F(1,14)=3.56$, $p<0.01$). Post hoc tests revealed that both search trained groups differed significantly from the controls, but not from each other or from the normally trained group ($F(1,14)=0.66$, $p=0.43$). The overall effect retained significance when the responses were separated into target and distractor/target absent trials. Target RTs did not differ for pop-out and conjunction conditions; nor did distractor RTs differ across pop-out and conjunction. Interactions were non-significant.

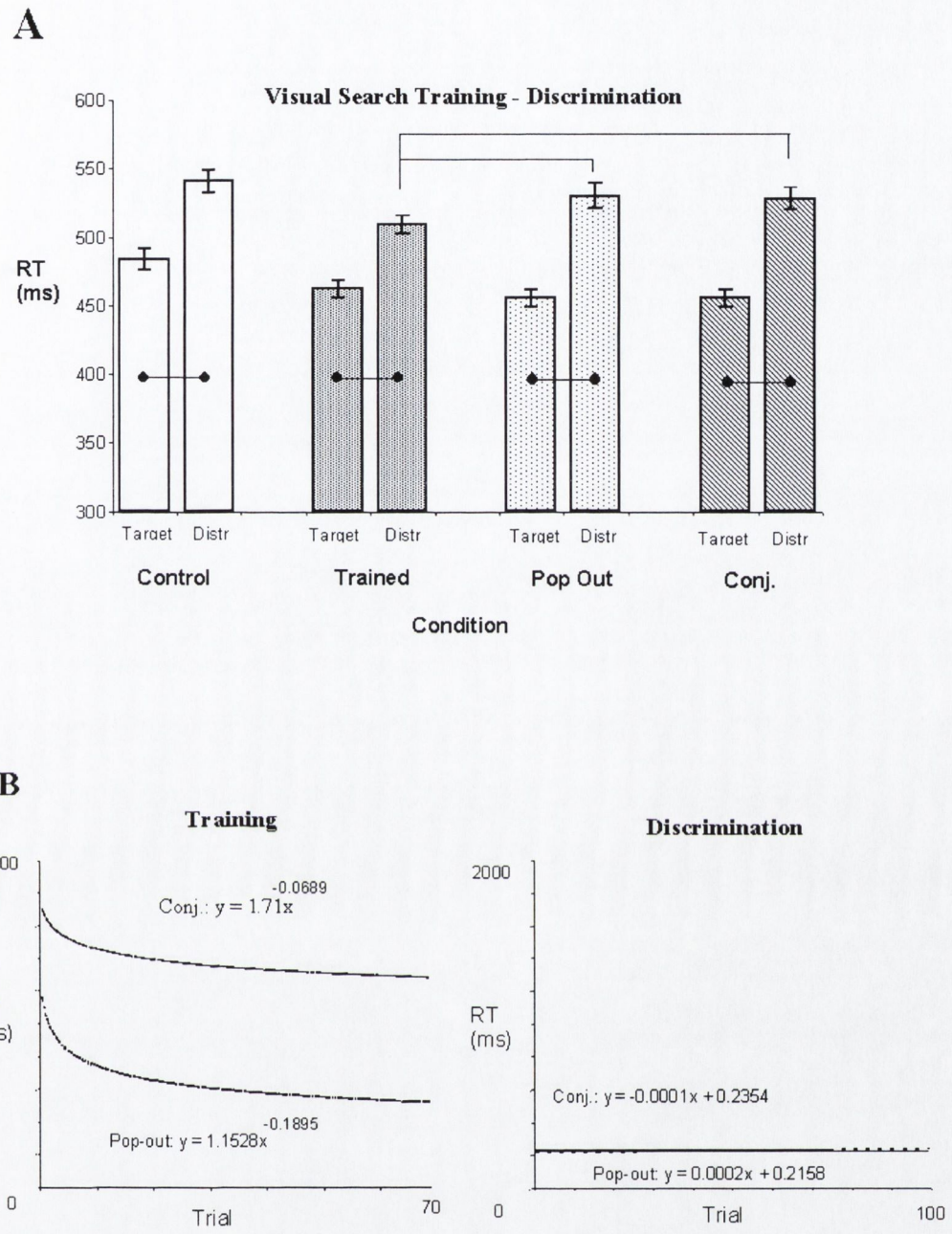

Figure 4.6: A) Mean RTs to target and distractor stimuli during visual discrimination blocks in control, normally trained and visual search trained (pop-out and conjunction) conditions. B) Scatter plots (data points omitted) and trend lines for training (left panel) and visual discrimination blocks (right panel) in pop-out and conjunction trained conditions.

Learning Effects

Scatter plots for the search groups (Fig. 4.6, bottom) adhered to the pattern observed for the dual-task conditions. The coefficient for the pop-out training block was 1.38, while that for conjunction was 1.81. Slope coefficients for both visual discrimination blocks were again both close to or less than zero.

4.7 Experiment 2: Short Discussion

In Experiment 2, I found that exposure to a target stimulus within the context of a visual search task facilitated subsequent performance of that task. Contrary to predictions, however, the level of attention required for these search tasks did not affect visual discrimination performance; RTs for both pop-out-trained and conjunction-trained groups were remarkably similar. This may be explained by the idea that the level of attention necessary for the learning of the S-R association may be very low. If so, the attentional demands required may have been easily met by the pop-out task, which required less attention than the conjunction task. The additional demands of conjunction search may have thus been surplus to task demands.

4.8 Experiment 3: Methods

4.8.1 Motor and Perceptual Aspects of Learning

Partial Training Group 1: Perceptual Training

The partially trained groups were exposed to only one aspect of the visuomotor association; the perceptually trained group was required to look at the 70 presentations of the target stimulus during the training block, but they were not

required to make the button-press response to it. This was followed by the discrimination block, which was completed as normal.

Partial Training Group 2: Motor Training

The motor training group were deprived of visual stimulation (both the viewing of the fixation dot and the target) during the training block, and were instructed to respond to the initial warning tone by pressing the left mouse button. The stipulation to respond to the warning tone ensured a comparable press rate to other (visually based) conditions. As in a normally trained condition, there were 70 repetitions. This was again followed by the discrimination block.

4.9 Experiment 3: Results

4.9.1 Motor and Perceptual Aspects of Learning

Training Blocks

The same control and normally trained groups used for Experiment 1b were used for Experiment 3. Mean RT to stimuli in the normal training block was 250.7±7.3 ms. No RTs were recorded in the visual only training condition, and RTs in the motor only condition were not elicited by a visual stimulus and are therefore not reported.

Discrimination Blocks

As in Experiment 1b, control RTs were 492.6±21.7 ms for targets and 524.7±9.7 ms for distractors, while normally trained RTs were 429.3±6.0 ms for targets and 492.4±7.7 ms for distractors. In the visual only condition, mean target RT was 473.4±7.4 ms, while distractor RT was 532.0±10.6 ms. For motor training only, mean target RT was 504.0±8.6 ms, and distractor RT was 588.6±11.5 ms (Overall main

effect: $F(3,30)=18.4$, $p<0.01$). Tukey multiple comparisons revealed significant differences at the 0.05 level between targets and distractors in all conditions except control, with shorter RTs evident for targets in each. Target RT was also significantly shorter for the normally trained group than for targets in control and motor only, but not visual only. Interactions were non-significant.

Learning Effects

Scatter plots for the visual discrimination blocks in the motor only and perceptual only conditions are shown in Figure 4.7. For both groups, comparable j-shaped acquisition curves were observed, with x-coefficients of 605.16 (visual only) and 839.87 (motor only).

4.10 Experiment 3: Short Discussion

The level of facilitation on a discrimination task produced by normal training was achieved here by exposure to separate elements of that training individually. Participants who were exposed to a training block of S-R association between the forward slash and the left button-press response showed statistically equivalent facilitation to those who only practiced viewing the slash, and those who only practiced the left button-press. Thus the benefits of learning to associate a particular stimulus with a specific response were replicated by merely exposing participants to the appropriate stimulus or response in isolation.

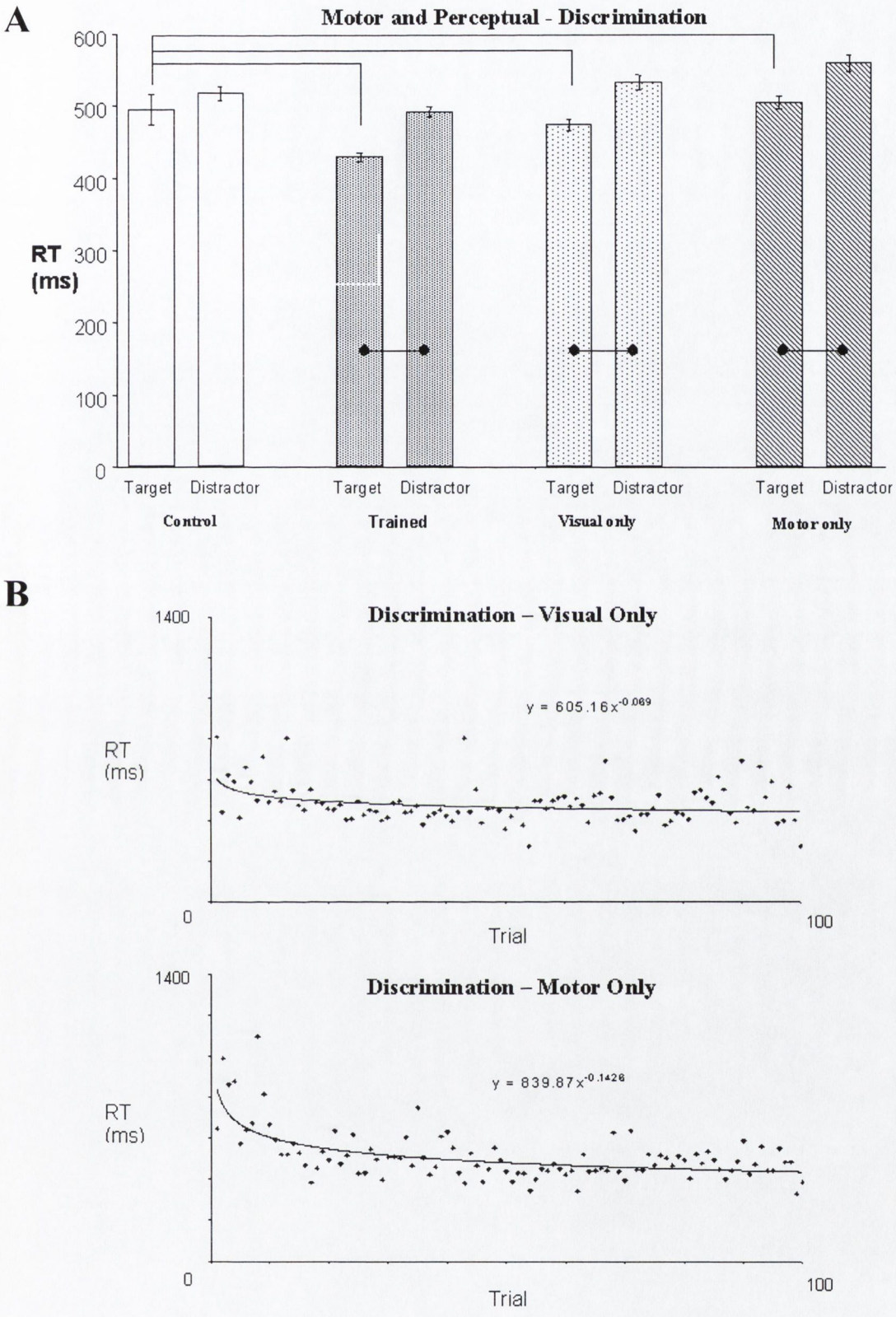

Figure 4.7: A) Mean RTs to target and distractor stimuli during visual discrimination blocks in control, normally trained, visual training only and motor training only conditions. B) Scatter plots and trend lines for mean RT to target stimuli during visual discrimination for visual training only (upper panel) and motor training only (lower panel).

4.11 General Discussion

The three experiments reported here investigated the putative mechanisms underlying simple arbitrary visuomotor association learning, particularly the roles of attention and arousal and the contributions of motor and perceptual systems in such learning. Experiment 1 showed that the addition of a dual task facilitated learning acquisition and expression, and that this effect was not arousal-cased. Experiment 2 demonstrated that visuomotor associations can be trained when presented in a visual search task. Experiment 3 showed that motor and perceptual aspects of learning are equally important.

4.11.1 Experiment 1

In Experiment 1, a simple task, largely devoid of cognitive evaluation, was used so minimal attentional engagement may be all that is required to perform adequately. If so, the dual-task may have raised the level of attention devoted to *both* tasks, rather than redirecting resources from one task to another. This suggestion is supported by the fact that in both the motor and verbal conditions, the concurrent task intended to elicit greater attention (fast tapping and random number generation, respectively) led to shorter RTs than did low attention dual-tasks (slow tapping and nonsense utterance). The addition of a dual-task increased attentional allocation to both ongoing tasks, and that this increase was uniform for both tasks. Alternatively, it is possible that the presence of the concurrent task helps to maintain some basal level of attention necessary for such a simple task. The exception to the above was the Perceptual dual-task condition. Counting asynchronously presented flashes appeared to have the same effect as the other dual-tasks. However, counting synchronous

flashes produced no facilitation. Furthermore, the lack of dual-task disruption in any condition strongly suggests that the central executive is not involved in this type of learning: acquisition of a simple S-R association through repetition may be primarily implicit and independent of the need for a (frontal) central processor. The enforced recruitment of this executive by the addition of a concurrent task may have had the effect of allocating attention to all ongoing tasks, but this level may have been greater than the normal level applied to the S-R learning, thereby facilitating its acquisition.

Learning a simple visuomotor association can be affected by a concurrent task during learning. A concurrent task requiring greater attentional demands appears to have a greater facilitatory effect than tasks with lesser attentional demands. This agrees with the finding of Kramer *et al.* (1995), who observed more rapid and superior learning when the training block of a task was variable (or dual) as opposed to fixed priority. How this facilitation takes place is not yet clear, although arousal and sustained attention may play important roles. It is possible that heightened arousal (mediated by brainstem structures) or sustained attention (emanating from right frontal areas) due to the introduction of a second task facilitates the structures suspected to be responsible for arbitrary S-R learning. Experiment 1b showed that this effect was not caused by increased arousal, favouring an attentional explanation, assuming that the auditory tones increased arousal.

In terms of learning theory, it is also possible that the effects observed here are relevant to learning phenomena such as the massed/spaced effect (see, e.g. Benjamin & Bjork, 2000; Benjamin *et al.*, 1998; Simon & Bjork, 2001), in which material learned *en bloc* and rapidly (as in this task) is more accessible in the short-term, but proves harder to retrieve in the longer-term. A follow-up testing session perhaps a week later would prove revealing for the present task, to see if this pattern is present.

The rapid and repetitive nature of the training in the present task is similar to rote learning in many ways, which suggests the possibility that other rote-related phenomena might also apply to this task. It has been shown, for instance, that rote-learned material does not suffer in speeded recognition conditions as elaboratively-learned material does (Benjamin & Bjork, 2000), which may explain the pattern of short RTs to test items in these studies. However, the data do not support the regularly observed pattern that good performance at training (i.e. rote over elaborative) leads to poorer performance at test (elaborative over rote); the considerable ease of this task may explain this anomaly.

The most robust facilitation of performance occurred when the concurrent task was a motor task (fast and slow tapping). This suggests that the direction of additional resources to motor or premotor areas has a more direct effect on the network subserving S-R learning because these areas comprise part of that network. By this reasoning, it could be predicted that a dual-task which engaged another part of the network - prefrontal cortex, basal ganglia or hippocampus – should also result in facilitation of learning. This prediction should be qualified, however, by stating that this may only hold for simple association learning of the sort used in these experiments. Such low-engagement conditions may benefit from the addition of a concurrent task by increasing attentional deployment to all ongoing behaviours. However, more complex learning may suffer detrimental effects if an additional task demand is added, due to the limited attentional resources available at any given time. If this claim, that dual-tasks facilitate simple but disrupt complex learning, can be demonstrated experimentally, our understanding of the interaction between learning and attention will be greatly advanced.

4.11.2 Experiment 2

The results of Experiment 2 further support the claim from Experiment 1 that repetition learning of an S-R association involves minimal attentional resources, being perhaps more implicit or procedural. Thus, exposure to the same S-R pairing within the context of an attention-demanding task, such as search, facilitates the acquisition of that learning, just as it did when the central executive was engaged in the dual-task conditions. In addition, these results provide further evidence that it is the allocation of attention, and not arousal, that is important for such facilitation.

As visual search appears capable of comparable training benefits to repetition training, it is perhaps likely that there is some overlap in the neural substrates of both search and arbitrary visuomotor learning. Of the hippocampal-prefrontal-basal ganglia network thought to underpin visuomotor learning, it is the basal ganglia that are suspected to be vital for storing the association. Visual search is thought to be subserved by a network involving frontal (dorsolateral prefrontal cortex and frontal eye fields), posterior parietal/temporo-parietal areas, the intra-parietal sulcus (IPS) and its junction with the transverse occipital sulcus, motor and extrastriate areas (Eglin, Robertson & Knight, 1991; Pollmann & von Cramon, 2000; Donner *et al.*, 2000, 2002; Wilkinson *et al.*, 2002; Leonarts *et al.*, 2000). Thus the only likely sites of overlap are the prefrontal cortex and motor/premotor areas. An alternative possibility is that different forms of learning take place in visual search and visuomotor learning, subserved by different cortical/subcortical structures, but their expression is the same. It is possible that the learning achieved by repeated exposure to the S-R is mainly implicit, as suggested above, implicating structures like the basal ganglia (Phillips & Carr, 1987). The form of the learning due to a visual search task may be far more explicit or declarative, and therefore more dependent on higher-order

processing structures such as the prefrontal cortex, and complex multisensory areas like the hippocampus and/or the intra-parietal sulcus of the posterior parietal cortex.

I have shown that the learning of an arbitrary S-R association can take place during the execution of another task. Although the rate of learning was influenced by the attentional demands of the search task, as evidenced by the larger coefficient for conjunction compared to pop-out search, the degree of facilitation resulting from the learning was not affected. In fact, for both groups it was comparable to normal repetition training. A more challenging task may be needed to make the effects of differential attentional deployment visible. This again will require further study. One final issue that requires clarification is whether the effects observed in these experiments could be due to mere motor preparedness to respond created by the provision of a preceding task.

4.11.3 Experiment 3

Experiment 3 suggests that the effects of visuomotor training observed in these studies and others (Roche & O'Mara, 2002) cannot be attributed to mere motor practice; rather they consist of changes in both perceptual recognition systems and motor pathways that underpin the expression of this learning. These claims must be qualified, however, given that the visuomotor learning in these tasks is extremely simple – the pairing of a single, low-level stimulus with a simple and singular motor response. These claims may not hold true in situations that involve more complex/less distinctive stimuli and/or sequences of action in response to the stimuli. In such cases, it is perhaps unlikely that the same degree of benefit could be accrued from the perceptual or motor aspects alone as could from repeating the appropriate motor sequence in response to the contingent stimulus. This claim will require further study

to verify, but the result may have important implications for our understanding of the nature of learning.

Aside from the fact that, in all trained conditions, the response time to target stimuli was significantly shorter than that for distractors, the most interesting phenomenon observed was the significantly longer distractor RTs for motor-trained participants compared to all other groups. It appears that repetitive motor activation of one response in the absence of any contingent visual input acts to suppress or inhibit alternative motor responses when they must be made in reaction to a stimulus. It is possible that the potentiation of one motor circuit through repeated activation may suppress the activity in neighbouring or competing circuits.

In conclusion, the experiments reported here reveal aspects of the relationship between learning and attention. During the learning of a simple visuomotor association, the provision of a second task to be performed simultaneously facilitates the acquisition of this learning and its subsequent expression in a related task. The mechanism by which this operates appears to involve increased deployment of attentional resources. Manipulation of arousal levels does not produce such facilitation, supporting the attentional explanation. In addition, both motor practice and perceptual familiarity are equally important in the acquisition of arbitrary visuomotor association learning.

Chapter 5

Individual Differences Discriminate Event-related Potentials but not Performance during Response Inhibition

Abstract

Event-related brain potentials (ERPs) were recorded from 20 normal participants while they completed a Go/NoGo response inhibition task. Previous ERP studies have implicated the N2 and P3 waveforms as the main indices of processing in this task, and functional brain imaging has shown parietal, prefrontal and anterior cingulate cortices to be involved in response inhibition. 32-channel ERP analysis revealed latency differences in the N2/P3 when targets were compared to lures, and in P2 and P3 when correct withholds (STOPS) to lures were compared to commission errors (ERRORS). Further differences in the P2, the N2/P3 complex and error-related components emerged when participants were grouped in terms of a measure of absentmindedness/impulsivity (the Cognitive Failures Questionnaire; CFQ). Larger

and earlier components were found for high CFQ respondents. I conclude that the latency and amplitude of the P2 may be the critical indicator of active inhibitory processes for this task, while error negativity (Ne), error positivity (Pe) and P3 are involved in post-response processes such as error-detection and behavioural correction. Inhibitory processes may manifest themselves in waveform components of different latency, depending on the complexity and stimulus characteristics of the task. Highly absentminded participants may be more responsive to errors, and require greater activity in the neural substrates of response inhibition in order to accomplish this task at the same level of performance as less absentminded participants.

5.1 Introduction

The ability to inhibit the execution of a motor behaviour in response to a stimulus is termed response inhibition. This capacity appears to be closely related to attentional performance, and tasks measuring response inhibition are thought to indicate impairments such as Attention Deficit Disorder (ADD; Brandeis *et al.*, 1998). Everyday lapses of attention, as measured by a questionnaire index of absentmindedness, the Cognitive Failures Questionnaire (CFQ; Broadbent *et al.*, 1982) have been shown to be related to performance on the SART Go/NoGo task (Robertson & Porter, 2002). The Go/NoGo task is one of the most commonly used measures of response inhibition; it involves making a motor response (usually a button-press) to a designated stimulus type (targets), which may be presented visually and/or auditorially. The presentation of another particular stimulus type ("critical lures") requires the inhibition of the motor response. Targets and lures are presented in rapid random succession. Successful performance of the task requires the

participant to press for targets and withhold the press for lures. A mistaken response to a lure is an *error of commission*, or "false alarm"; a mistaken non-response to a target, is an *error of omission*, or "miss". Response inhibition tasks effectively constitute a form of contingent visuomotor mapping involving serial visual search; successive stimuli must be detected and identified, and an appropriate response (press or withhold) made based on an arbitrary stored rule. Investigation of successful performance and errors using neuroimaging and electrophysiological methods provide useful insights into the mechanisms of response inhibition and their cortical substrates.

Event-related potential studies of response inhibition reliably elicit amplitude and/or latency differences in the N2 and P3 components (Falkenstein *et al.*, 1999). NoGo stimuli produce a negative deflection in the 200-400 ms time window with a frontal maximum (the so-called "NoGo-N2") that is smaller or totally absent for Go stimuli. Amplitude and latency differences are also seen for the P3 elicited by NoGo stimuli (the "NoGo-P3") compared to stimuli requiring a button press (the "Go-P3"). NoGo-P3 amplitude is larger at central leads, whereas Go-P3 amplitude tends to be maximal at parietal sites. In addition, a longer-latency negative component has also been observed over central electrodes following errors of commission (termed Error Negativity, Ne). However, Falkenstein *et al.* (1999) suggest that this component is unlikely to be a late version of the NoGo-N2, as the two components appear to have separate cortical generators, given their different scalp topographies.

Despite general agreement that the N2 and P3 are the key electrophysiological indices of response inhibition, there is much debate regarding which component is more indicative of successful inhibition of motor actions. Falkenstein *et al.* (1995) concluded that the absence of the NoGo-N2 enhancement to auditorially presented

stimuli is evidence that this component is not a true index of inhibitory processes. However, only one frontal electrode (Fz) was used in that study; the N2 may not have been detected. However, in a subsequent study Falkenstein *et al.* (1999) observed earlier (by approximately 30 ms) and larger N2 components for good inhibitors compared to poor, while the P3 component was not affected by performance differences, supporting the claim that the N2 is a valid index of inhibitory processing.

A different view is proposed by Fox *et al.* (2000). They compared ERPs in a task where NoGo stimuli were defined by unique features (elemental) and one in which NoGo stimuli were defined by the conjunction of two features which individually necessitated a Go response (configural). They found the traditional NoGo-N2 and NoGo-P3 enhancements in the elemental condition, but the configural task produced enhanced late frontal negative and positive parietal slow wave. This result cast further doubt on the proposal that the N2 enhancement reflects inhibition processes *per se*, due to its absence in the configural condition. The authors suggested that when the NoGo stimulus is elemental, inhibition depends on the automatic detection of a novel feature, whereas configural tasks require the application of a rule, rather than detection of superficial stimulus characteristics. Thus the NoGo-N2 might be an indicator of perceptual orienting processes to novel stimulus features, rather than an index of inhibition-related processing. The NoGo-P3 may therefore be the better reflection of the cognitive operations that underlie response inhibition. However, the mean P3 peak in this study occurred *after* the mean RT for errors of commission; the claim that the P3 is a better reflection of inhibitory operations must be qualified by stating that this may be true for the *post-response* phase of such tasks only. It seems reasonable that any component that follows the RT for an error of commission or normal target by a substantial period is unlikely to reflect processes

that determine the trial outcome and are most probably involved in post-inhibition processes. Bruin *et al.* (2001) share the view that the P3 is a more accurate correlate of response inhibition. In a response priming experiment, they found that priming modulated the P3, but not the N2; they concluded the N2 reflects response activation, while the P3 is a superior indicator of inhibition.

In contrast to the focus on the N2-P3 complex, some authors have suggested that earlier ERP components during the latency of the P1-N1-P2 complex are more important for the decision to inhibit a response. Filipović *et al.* (2000) identified an early negative component corresponding to the N1 that preceded the onset of an EMG signal during an S1-S2 task. They concluded that components occurring at earlier latencies, up to 200 ms, provide a better window into the decision to inhibit behaviour. Brandeis *et al.* (1998) recorded ERPs from children with attention deficit disorder (ADD) and normal controls during a delayed GO task and a STOP task, both of which require inhibition of motor acts. In the STOP task, LORETA analysis indicated that successful stops produced strong frontal activation in later components, and that prefrontal generators underlay this centroparietal scalp potential. For both tasks, the ADD children had altered P2/N2 and N1 components; the authors concluded that the primary deficit in ADD children on this task lay in the early orienting to the stimulus and not in response-related processes. In contrast to this, Bokura *et al.* (2002) noted no differences in the early latency N1 and P1 components. This apparent contradiction may be due to the specific demands of the tasks used: in the Filipović and Brandeis tasks, participants were inactive between S1 and S2, whereas for the Bokura task (as with most of the cued RI tasks reported here) the interval was filled with targets that required a motor response. It is possible that during the period of inactivity in the Filipović and Brandeis tasks, inhibitory

processes were given time to prepare for engagement, allowing their impact to be seen in earlier components relative to tasks in which no such preparation was allowed. The complexity of the stimuli may also play a large role in how early the correlates of inhibition can be observed. In the Fox *et al.* (2000) experiment, modulations of N2 and P3 were seen for the elemental stimuli (where lures were defined by unique stimulus features), but only later components were affected for the configural condition (where the lures were defined by the conjunction of stimulus features).

Studies using functional imaging have allowed some of the anatomical substrates of response inhibition to be identified. An fMRI study using the XY response inhibition task (Garavan, Ross & Stein, 1999) reported activity in the right hemisphere, including inferior parietal lobule and dorsolateral prefrontal cortex. These regions may constitute a major part of the right parietal/prefrontal circuit suspected of involvement in tasks requiring sustained attention and response inhibition. Anterior cingulate areas were also activated. Interestingly, in a subsequent investigation that compared correctly withheld responses (STOPS) and errors of commission (ERRORS), no regions showed greater activation for STOPS over ERRORS (Garavan *et al.*, *under review*). The authors suggested a temporal hypothesis to explain the differential processing of correct and error trials, which the poor temporal resolution of fMRI was unable to test; the present study attempts to address this question. Error-related processing, localised to the cingulate cortex, was also observed by Garavan *et al.* (*in press*). Thus the right hemisphere parietal/prefrontal circuit and the cingulate cortex seem to be strongly involved in separate response inhibition and error detection processes, and may be likely candidates for the generators of the NoGo-N2/NoGo-P3 and Ne components. Another fMRI study by de Zubicaray *et al.* (2000) using a visually based motor suppression

task observed increases in rCBF in prefrontal, parietal and occipito-temporal cortices. The authors emphasised the importance of the right hemisphere, particularly the right prefrontal cortex, in motor suppression.

Using a cued continuous performance task (CPT), Strik *et al.* (1998) found that different generators are responsible for the NoGo-P3 and the Go-P3. Analysis with the LORETA three-dimensional source localisation method (See Chapter 2) indicated that right frontal sources were responsible for the NoGo-P3. The authors suggest that phasic activation of these right frontal areas was necessary for the inhibition of a prepared motor action, and that this activity was time-locked to the moment of motor inhibition. Bokura *et al.* (2002), also using LORETA, attributed right lateral orbitofrontal and cingulate generators to the NoGo-N2, while left lateral orbitofrontal sources were found for the NoGo-P3. They concluded that both hemispheres, and both the N2 and P3, were vital for response inhibition processes. Interestingly, Rieger and Gauggel (2002) found no performance differences on a response inhibition task between a group of brain-injured patients (with either focal or diffuse damage) relative to a normal control group. Although areas such as right parietal, right prefrontal and cingulate cortex are involved in inhibition, they may be sufficient rather than necessary regions and that the same behaviour can be achieved when one or more of these areas have been damaged.

Nieuwenhuis *et al.* (2001) studied error detection processes in an antisaccade task in which participants made errors of which they were either aware or unaware (as indexed by a post-response key press). They found that the error negativity (Ne; also known as Error Related Negativity, ERN) was associated with errors irrespective of whether they were consciously registered, whereas the subsequent error positivity (Pe) was elicited only for errors of which the participants were consciously aware.

Furthermore, only perceived errors were followed by behavioural correction manifested in posterror slowing, suggesting a link between the Pe and behavioural correction. Both the Ne and Pe are subtraction phenomena, and as such result from increased activity in an area for errors relative to corrects. The fMRI findings of Garavan *et al.* (*in press*) suggest that the source of this additional activation for errors may be the cingulate cortex.

The present study examines ERP correlates of response inhibition using the same XY task as the fMRI study of Garavan *et al.* (*in press*). Based on the complexity of the rule relative to other studies, I predicted that response inhibition processes should be manifested in the medium latency markers (N2/P3) rather than the early (P1/N1/P2) or late (frontal negativity or posterior slow wave) components. The study was designed to identify waveform components that determine the success or failure of an attempt to inhibit a motor action by comparing correct withholds with errors of commission. I predicted that the component immediately preceding the mean reaction time for a commission error would be affected by the success of the attempted inhibition. Further, as this was a task of inhibitory control, I investigated whether highly absentminded participants would show different patterns of activation to less absentminded participants, in their waveforms to corrects and errors, and for error-related components Ne and Pe. Previous work has shown the Go-NoGo task to be a valid index of absentmindedness/sustained attention in both normals and brain-injured samples (e.g. Robertson *et al.*, 1997). Absentmindedness was measured by a self-report questionnaire (the Cognitive Failures Questionnaire; Broadbent *et al.*, 1982) which is correlated with attentional functions (Strik *et al.*, 1998) distractibility/impulsivity and everyday accidents (Larson *et al.* 1997). Because impulsive people are presumably by definition poor at inhibitory control, I predicted

that more absentminded participants would process events differently and thus elicit altered ERP waveforms, and that, due to the complexity of the rule in this task, the affected ERPs would be the later N2 and P3 components.

5.2 Materials and Methods

5.2.1 Participants:

Twenty participants were tested (3 male), with an age range of 17 to 31 years (mean = 21.5). All were right handed with normal or corrected-to-normal vision and no history of mental illness. Each was briefed before the tasks commenced, and given additional feedback after its completion. Each wore a Quikcap 32-channel EEG recording cap connected to the Neuroscan Synamps (Scan 4.1) ERP recording system (Medtech Systems Ltd., Horsham, UK) for the duration of the tasks, and EEG activity was recorded. Participants were seated 100 cm from the computer monitor throughout the testing sessions, and had all given signed consent to partake in the study.

5.2.2 Materials:

X-Y Task

The task used was the XY response inhibition task, modified from one used previously by Garavan, Ross and Stein (1999). A stream of visual stimuli was presented at a rate of one per second, in black on a white background. The stimuli consisted of capital letters X or Y which were presented in alternating order. Participants were instructed to click the left mouse button (the right button was

unused for the entire task) for every stimulus *when it followed a different stimulus* (i.e. when an X followed a Y, or when a Y followed an X). When two identical stimuli followed each other (an X following an X, or a Y following a Y), participants were instructed to *withhold their response* (see Fig. 5.1). A trial block consisted of 315 trials, of which 20 trials were "critical lures", or trials which required a withhold. The durations of stimulus and inter-stimulus interval (ISI) varied (see Procedure) but always summed to 1,000 ms.

Event-Related Potentials

Electrophysiological data were recorded in AC mode with a gain of 500 and a band pass of 0.15-30 Hz. The A/D conversion rate was 1000 Hz, and the voltage range was 11 mV. Scalp potentials were obtained using a 32-channel Quikcap using linked ear reference electrodes (the conductive gel used was Quikgel). The electrode array conformed to the International 10-20 System (American Encephalographic Association, 1994b). Vertical eye movements were recorded with two VEOG electrodes placed above and below the left eye, while HEOG electrodes at the outer canthus of each eye recorded horizontal movements. Silver/silver-chloride (Ag/AgCl) electrodes were used at all sites. Participants were tested while seated in an armchair, with a pillow behind the head to reduce contamination of the ERPs due to head/neck movements or muscle spindles (Roche & O'Mara, 2002). Recording commenced when electrical impedance had been reduced to less than 10 kOhms by light abrasion of the scalp. Impedance was also checked at the end of the testing session to ensure it was still acceptably low.

5.2.3 Procedure:

Practice Blocks

Participants were first presented with a practice ("pre-training") block of the task, during which ERPs were not recorded. The primary analysis of interest was to compare successful withholds with errors of commission (or false presses, e.g. to an X that followed an X). It was therefore necessary to obtain approximately equal numbers of such trials. This was achieved by manipulating the relative durations of stimulus and blank screen (ISI; our previous testing has shown that commission errors increase as stimulus duration decreases). Thus the practice session consisted of four blocks: a block of 315 trials at which the stimulus/ISI rate was 900-100 ms, a block at 800-200 ms, a block at 700-300 ms and a block at 600-400 ms (see Fig. 5.1). A "warm-up" block at 800-200 ms preceded these four blocks and was not included in the analysis. Each block contained 20 lures. Performance on these blocks was then examined to determine at which duration rate approximately equal numbers of correct withholds and errors of commission occurred. This rate was then used for the ERP-recorded testing session.

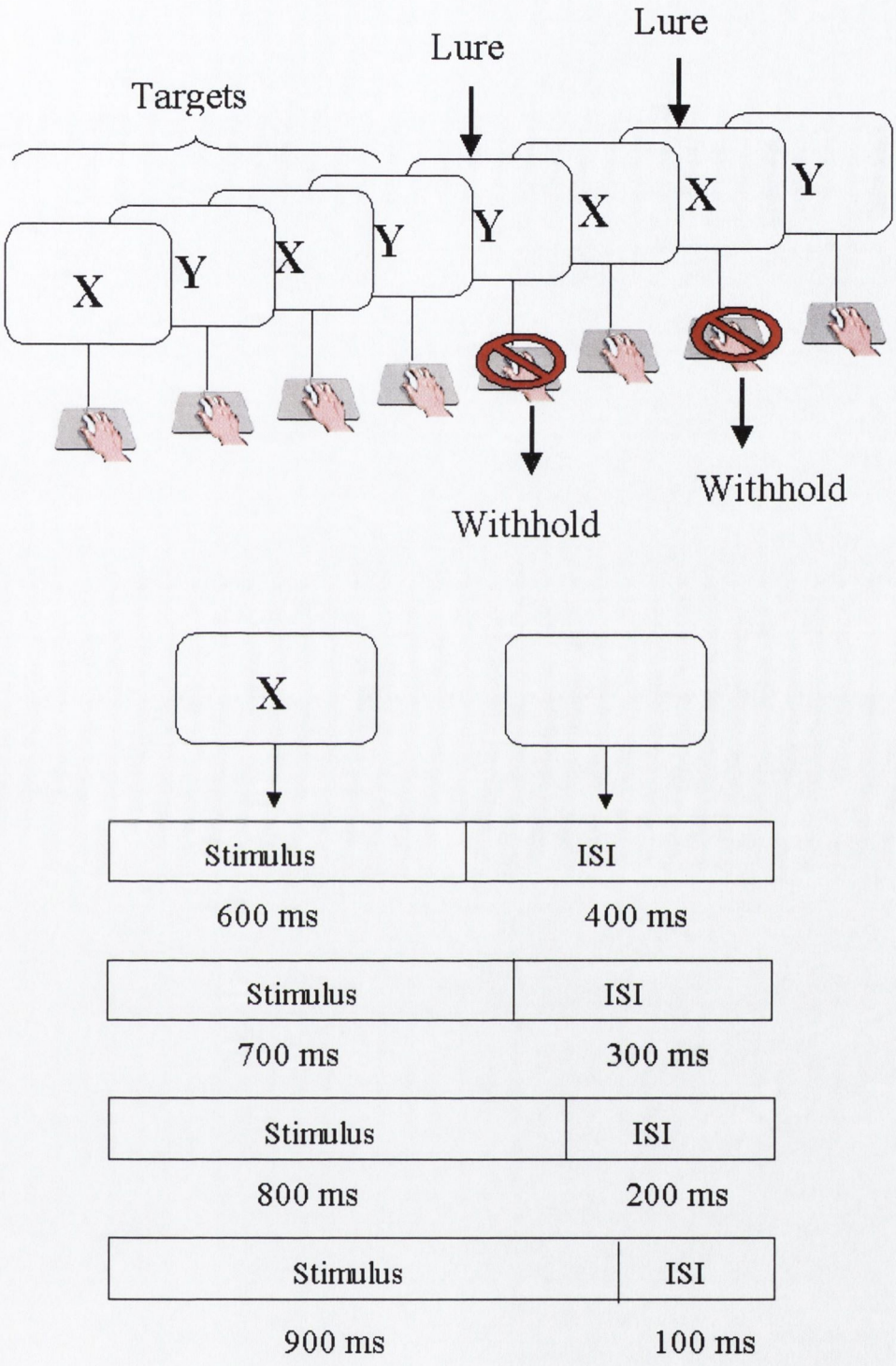

Figure 5.1: (upper panel): Experimental design displaying normal target and critical lure stimuli, with the appropriate response to each: target = button press; lure = withhold response. (lower panel): Description of how the interstimulus-interval (ISI) and stimulus on-screen duration was varied to manipulate difficulty during pre-screening block. The four ISI-duration pairings used are depicted.

Testing Session

ERPs were recorded during the testing session. Participants were given the same instructions as for the practice block. They were then presented with four trial blocks of 315 stimuli at the predetermined optimal stimulus/ISI rate; each block again contained 20 lures. Each block was followed by a brief rest period (3-5 min), after which the next block at the same stimulus/ISI rate was presented. After the fourth block, participants were thanked for their cooperation and the ERP apparatus was removed.

Cognitive Failures Questionnaire (CFQ)

At the time of testing, participants were also administered the Cognitive Failures Questionnaire (CFQ; Broadbent *et al.*, 1982). This 25-item questionnaire gives an index of how prone a person is to lapses of attention, cognitive failures and minor mistakes, and is considered an indicator of the degree of absentmindedness of the respondent. It has been shown elsewhere (Fassbender *et al.*, *unpublished data*) that CFQ scores correlate positively with the Barratt Impulsivity Scale and the Dickman Dysfunctional Impulsivity Scale. Each item is rated for frequency in the last 6 months, from 4 ("very often") to 0 ("never"). A maximum score of 100 is possible, indicating a high frequency of cognitive failures, while the minimum possible score is 0.

5.2.4 Data Analysis:

Electrophysiological Data

The continuous EEG recordings were subjected to ocular artifact reduction to remove

artifactual scalp potentials caused by eye blinks; an "average" blink was generated for each participant based on a sample of not less than 30 blinks recorded at VEOG. The average impact of this blink on each scalp electrode was also generated and subsequently subtracted from each waveform at each electrode for every epoch (Neuroscan software, Medtech Systems Ltd., Horsham, UK). Blocks of EEG contaminated by muscle bursts were manually selected and excluded from the subsequent analyses. The data were epoched into single sweep recordings, from 100 ms prestimulus to 1,000 ms poststimulus. All sweeps were baseline corrected using the 100 ms prestimulus interval as the baseline interval. Ocular artifacts were reduced using blink-averaging algorithms, and sweeps in which amplitudes exceeded ± 70 μV at VEOG, HEOG or Cz were automatically rejected. The proportion of rejected epochs varied from 15 to 20% per participant. The remaining epochs were averaged for each participant, and these averages were combined to produce grand average waveforms.

Further analysis consisted of separating the epochs into those corresponding to normal target trials and lures. Separate stimulus-locked grand average waveforms were thus calculated for lures and targets (non-lures). Epochs were further separated on the basis of response characteristics: separate response-locked averages were thus obtained for correct withholds (to lures), correct presses (to targets) and errors of commission (incorrect presses to lures). Due to the much larger proportion of sweeps corresponding to target trials compared to lures (1,180 compared to 80), sweeps were randomly selected from the target trials to ensure equal numbers for comparison. An insufficient number of errors of omission (incorrect withholds to targets) occurred to generate an average waveform; this analysis was not conducted.

Peak amplitudes for the P2, N2 and P3 components were recorded within three time windows: 150-300 ms poststimulus for the P2, 130-320 ms poststimulus for the N2, 300-650 ms poststimulus for the P3. These windows were chosen after visual inspection of the component latencies in grand mean waveforms for each condition. The latencies at which these peak amplitudes occurred were also recorded. Statistical analyses of amplitudes and latencies consisted of repeated measures within-subjects oneway ANOVAs for each component with factor CHANNEL (all 30 scalp electrodes were used). Amplitude and latency values for each component were also analysed using MANOVAs with the factors STIMULUS (Target, Lure) or RESPONSE (Correct Withhold, Error of Commission). In cases where no distinct components were evident, amplitude and latency values from the time windows were discarded and no statistical analyses were performed.

Cognitive Failures Questionnaire (CFQ)

Behavioural and ERP data were analysed separately based on a median-split of CFQ scores.

5.3 Results

5.3.1 Response Inhibition: Behavioural Data:

Error Rates

During pre-training, the manipulation of stimulus duration produced differences in the number of errors of commission made, with significantly more errors found for shorter stimulus durations ($F(3,19) = 7.08$, $p = 0.0004$). A chi-squared test revealed no

significant differences in the optimal stimulus duration between high and low CFQ groups during pre-training. In the testing session, the mean number of errors of commission was 29.6 (± 2.5) from each set of 80 lures, corresponding to a rate of 37.0%. Mean number of errors of omission was 7.7 (± 1.7) out of each set of 1,180 normal targets, giving a rate of 0.65%.

Reaction Times

Mean RTs to targets and errors of commission are shown in Figure 5.2 (left panel). Correct presses to normal targets had a mean RT of 328.13 (± 6.90) ms. Mean RT for errors of commission was 280.6 (± 4.63) ms. RTs for corrects and errors differed significantly (Mann-Whitney U = 987, $p = 0.0001$).

5.3.2 Electrophysiological Data:

Normal Targets Vs. Critical Lures

Stimulus triggered average (STA) grand mean waveforms for normal targets and critical lures are shown in Figure 5.2 (middle panel; midline electrodes are depicted). At fronto-central, central and centro-parietal leads, the NoGo-N2 and NoGo-P3 components were evident in the lures waveform. These NoGo components were more clearly defined and of larger amplitude than the GO waveform (which elicited no distinct components) at the majority of the 30 scalp leads (N2 latency: 27 leads; N2 amplitude: 21; P3 latency: 28; P3 amplitude: 22).

Lures: Correct Withholds Vs. Errors of Commission

A MANOVA was carried out on the peak amplitude and latency values for the averaged waveform for each participant. Differences in P2 latency were observed at the right hemisphere leads P4, CP4, TP8, and FT8, where the component peaked earlier for correct withholds compared to errors (all $F(3,18) > 5.07$, $p < 0.031$). No differences were found in N2 latency or amplitude at any electrode. The latency of the P3 was earlier for correct trials at six leads: these were mainly centro-parietal (C3, CP3, CPz, P3, Pz and FCz; all $F(3,18) > 3.19$, $p < 0.036$), possibly representing P3b. Electrodes FCz, CP3 and Pz for corrects and errors are shown in Figure 5.2 (right panel).

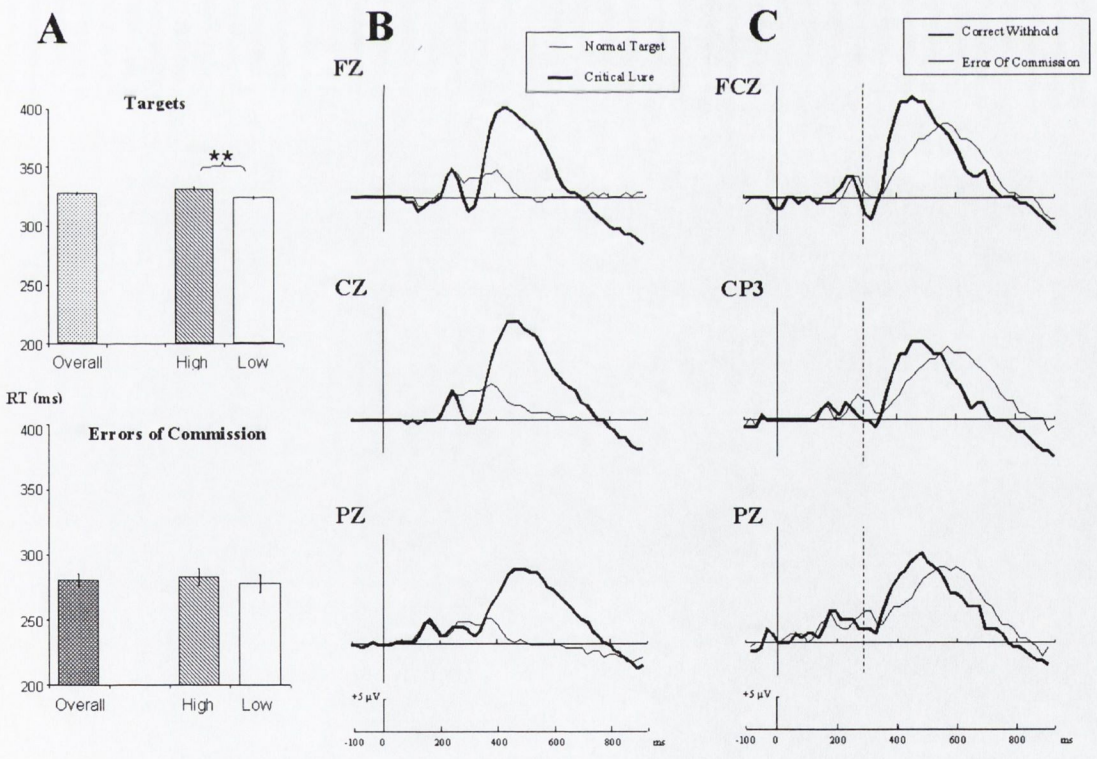

Figure 5.2: A: Bar graphs representing mean RTs for normal targets (upper panel) and errors of commission (critical lures mistakenly pressed). Overall RT is shown on the left, and divided into high and low CFQ group RTs on the right of each graph (** signifies statistically significant differences at $p < 0.05$ level).
B: Grand mean ERP waveforms (three midline electrodes) evoked by normal targets (thin line) and critical lures (thick line) during a 1000 ms epoch, from 100 ms prestimulus to 900 ms poststimulus.
C: Grand mean ERP waveforms (three electrodes) for correct withholds to lures (thick line) and errors of commission (thin line). Dashed line represents latency of mean RT to errors of commission (280.6 ms).

Significant interactions of Group x Accuracy were found for N2 amplitude ($F(1,38)=41.41$, $p<0.001$), P3 latency ($F(1,38)=30.86$, $p<0.001$) and P3 amplitude ($F(1,38)=65.5$, $p<0.001$), but not for N2 latency.

Error Negativity and Error Positivity

The subtraction of the correct withholds waveform from that for errors of commission (Error-Correct) was performed, and is shown in Figure 5.3. A large error negativity (Ne) was evident at several leads (Fz, FCz, FC4, FC3, C3, CP3, Pz and P4); the effect was largest at Fz and FCz. A post-Ne positive deflection was visible at the same electrodes as the Ne, with the addition of Cz. This Pe was of smaller magnitude than the Ne.

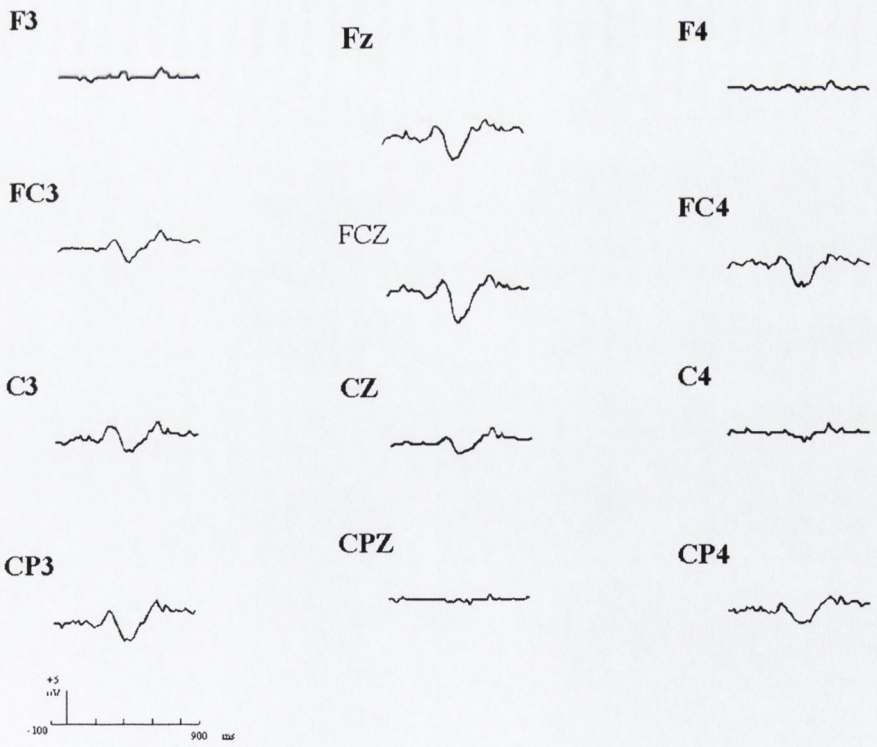

Figure 5.3: Grand mean ERP waveforms (12 frontal-central-parietal electrodes) for the subtraction of Error-Correct waveforms (0 ms represents stimulus onset). Greater magnitude deflections reflect extra activity in the Errors waveform. A large negative deflection (error negativity, Ne) is

5.3.3 Cognitive Failures and Response Inhibition: Behavioural Data:

Errors and Reaction Times

A median split was carried out based on CFQ scores (median = 41.0). Those scoring above the median were termed "high CFQ", indicating a higher rate of cognitive failures, and scorers below the median, "low CFQ", had a lower rate of cognitive lapses. This sample evidenced a clear attenuation of range (minimum CFQ score was 28; maximum was 59) relative to the general population, particularly at the higher end of the scale; effects obtained with this sample may be expected to be amplified with samples representative of the population at large.

There were no significant differences in the number of errors produced by the two groups (commission: $t = 0.31$, $df = 18$, $p = 0.76$; omission: $t = 0.72$, $df = 18$, $p = 0.48$); this was intended by the experimental design (see Procedure). RTs for errors of commission did not differ significantly between high (283.0 ± 6.39 ms) and low (278.0 ± 6.71 ms) CFQ groups ($t = 0.54$, $df = 424$, $p < 0.59$). For responses to normal targets, RTs for high CFQs were longer than those for low CFQs (332.02 ± 1.02 vs. 324.24 ± 0.93 ms); this difference was significant (Mann-Whitney $U = 372$, $p < 0.01$). These data are shown in Figure 5.2 (left panel).

5.3.4 Electrophysiological Data:

ERP grand mean waveforms were recomputed according to the CFQ median split. Main effects for both Group (high and low CFQ) and Trial (STOP and ERROR) were evident for P2, N2 and P3 latencies and amplitudes at widespread leads across the scalp. This was most pronounced for N2 amplitude (21 leads). The following differences were significant at the $p < 0.05$ level with Tukey's multiple comparisons.

High CFQ: Correct vs. Error

Stimulus-triggered averages (STAs) were generated for both correct withholds and errors of commission for high and low CFQ responders (Fig. 5.4, left panels). In the high CFQ group, corrects and errors only differed at 6 electrode sites: these were mostly isolated effects at single electrodes (e.g. P2 latency at F3, N2 amplitude at FP2) except for P3 latency, which differed at fronto-central sites Cz and FCz, possibly indicating P3a. At these sites, earlier components were elicited by correct withholds (Cz: $F(3,18) = 4.38$, $p < 0.005$; FCz: $F(3,18) = 5.63$, $p < 0.001$).

Low CFQ: Correct vs. Error

For the low CFQ comparison (Fig. 5.4, right panels), components for correct withholds were larger and peaked earlier relative to error waveforms. P3 amplitude differences were evident at frontal (FP2 and F8) and parietal/centroparietal sites (P3 and CP3). Larger P3 amplitudes were found for correct withholds at these locations (FP2: $F(3,18) = 13.51$, $p < 0.0001$; F8: $F(3,18) = 4.88$, $p < 0.002$; P3: $F(3,18) = 4.29$, $p < 0.005$; CP3: $F(3,18) = 4.64$, $p < 0.003$), which may indicate P3a and P3b, respectively.

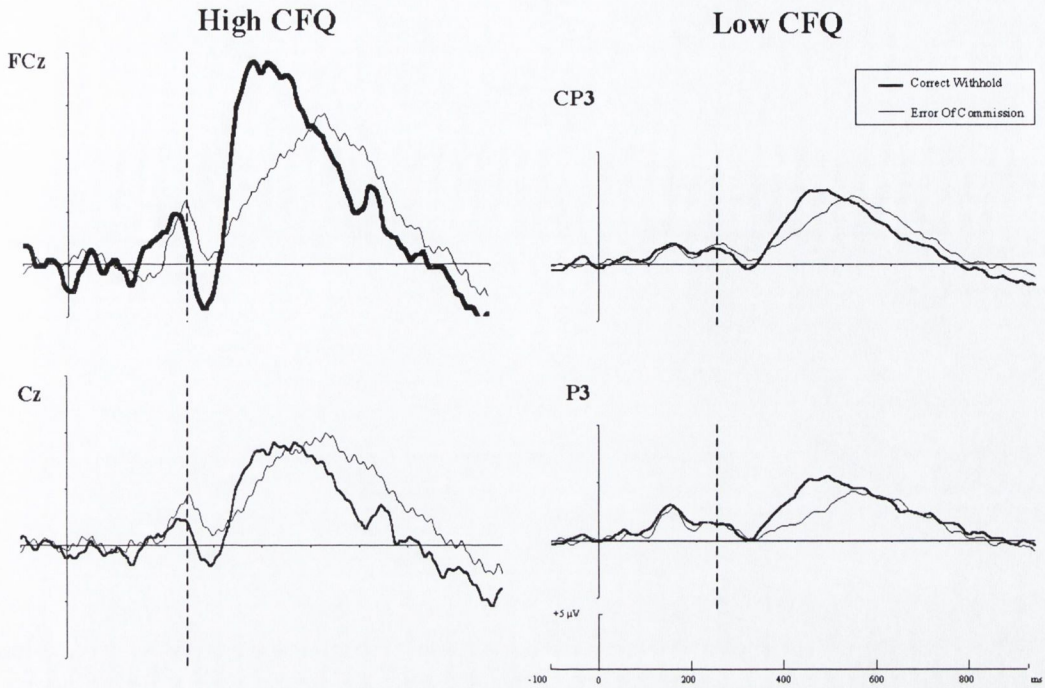

Figure 5.4: Grand mean ERP waveforms (three midline electrodes) for correct withholds (thick line) and errors of commission (thin line) for high CFQ (left panels) and low CFQ (right panels) respondents. Dashed line represents latency of mean RT to errors of commission (high CFQ = 283 ms; low CFQ = 278 ms).

Correct Withholds: High vs. Low CFQ

The most robust waveform differences were found for the comparison of high versus low CFQ scorers for correct withholds (Fig. 5.5, left panels). At 19 channels, N2 latency was earlier for high CFQs than for low (all $F(3,18) > 2.73$, $p < 0.044$). These sites were predominantly central and parietal, with some frontal. P3 latency was earlier for high CFQ at 9 frontal and central channels (all $F(3,18) > 2.75$, $p < 0.043$), while P3 amplitude was larger for high CFQ at 7 frontal and central leads, again suggesting the P3a subcomponent (all $F(3,18) > 2.70$, $p < 0.045$).

Errors of Commission: High vs. Low CFQ

No consistent pattern of differences emerged for the comparison of error waveforms (Fig. 5.5, right panels).

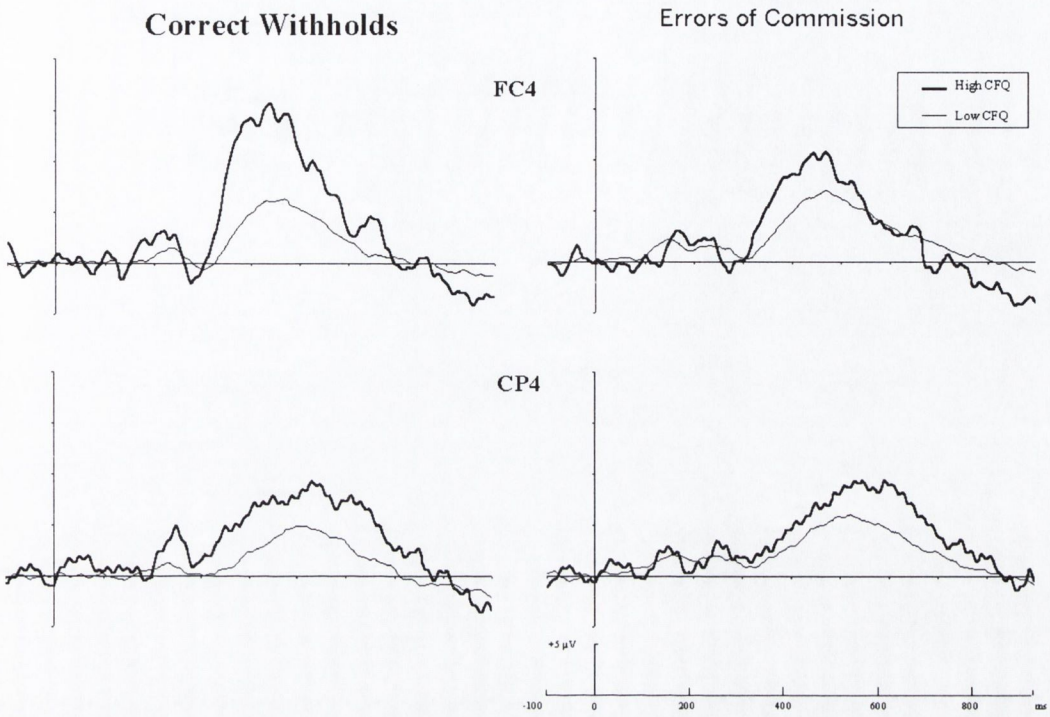

Figure 5.5: Grand mean ERP waveforms at FC4 and CP4 for High CFQ (thick line) and low CFQ (thin line) evoked by correct withholds (left panels) and errors of commission (right panels).

Error Negativity and Error Positivity

Error negativity and positivity waveforms were generated for each CFQ group by performing the error-correct subtraction (Fig. 5.6). Both groups resulted in a fronto-central negative-going potential between 300 and 400 ms, and a subsequent positive-going potential between 400 and 600 ms. The amplitude of this error negativity was larger for the high CFQ group, particularly at fronto-central leads (high: -2.75 μV; low: -1.16 μV). This difference was statistically significant ($F(1,62) = 5.55$, $p = 0.022$). The Pe was also significantly larger for the high CFQ group, with mean amplitude of 5.28 μV for high, compared to 2.5 μV for low ($F(1,62) = 23.4$, $p =$

0.0001). The largest differences between high and low CFQ were observed over left hemisphere central and fronto-central leads.

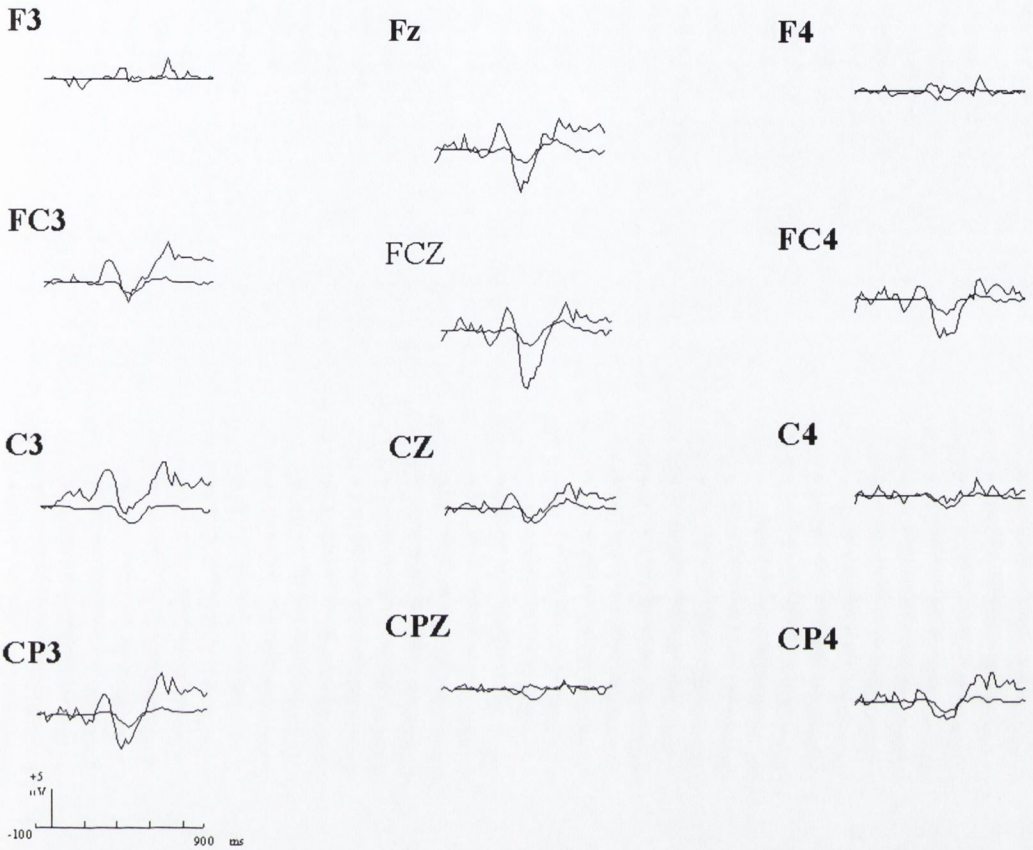

Figure 5.6: Grand mean ERP waveforms (12 frontal-central-parietal electrodes) for the subtraction of Error-Correct waveforms for high CFQ (thick line) and low CFQ (thin line). An larger error negativity (Ne) is visible for high CFQ at fronto-central sites, while a larger error positivity (Pe) can be seen over left frontal leads.

Summary:

- A significant "Go/NoGo Effect" of large N2 and P3 components for lures compared to targets was observed.
- When correctly withheld and erroneously responded lures were compared, the main significant differences were in the P2 and P3 latency.
- The subtraction of Error-Correct resulted in error negativity (Ne) and error positivity (Pe) waveforms which were maximal fronto-centrally.

- When split by CFQ scores, significant differences were evident between high and low CFQs and between correct withhold and error of commission waveforms. The most dramatic differences were between high and low CFQs for correct withholds, where earlier N2 and P3 were found for high CFQ. Behavioural accuracy did not differ between these groups.
- The error negativity and error positivity were both significantly more pronounced for the high CFQ group than for the low.
- Task performance did not differ between high and low CFQ groups on error rates or RTs to errors of commission, but high CFQs were significantly slower to respond to normal targets than low CFQs.

5.4 Discussion

Here I have demonstrated a clear dissociation between behavioural performance and electrophysiological brain state in this task: high and low CFQ scorers operating at comparable performance levels show significantly different patterns of brain activity. This suggests that relatively highly absentminded participants completed this inhibition task with a higher level of brain activity compared to relatively less absentminded participants. The implications of this dissociation are discussed below. The selection of an optimal stimulus duration for giving close to 50% errors in the task was largely successful, producing an acceptable 37% errors of commission. Electrophysiological differences between normal targets and lures were observed in the form of the "Go/NoGo Effect" – larger N2 and P3 components elicited by lures. Further differences were observed in the processing of the lures themselves based on performance accuracy: correct withholds had earlier latency P2 and P3 components

than erroneous presses to lures. Error-related processing was also evident, manifested in a post-response error negativity (Ne). Distinct patterns of differences between correct and error trials emerged when the groups were divided based on a self-report measure of absentmindedness. Further differences on error-related components Ne and Pe were also found. In summary, these data strongly suggest that the same behavioural performance can be achieved by different levels of cortical activity.

This study successfully replicated the frequently observed "Go/NoGo Effect" in which the amplitudes of the N2 and P3 components for lures are larger (or simply present) relative to the waveform elicited by normal targets. This finding has been taken to indicate that the processing of NoGo stimuli (lures) is qualitatively and/or quantitatively different to that of Go stimuli (targets).

The electrophysiological changes that occurred in this response inhibition task reflect both pre-response and post-response processing. The role of the P2 component lies primarily in the pre-response phase, since this component peaked before the latency of mean RT to errors of commission and targets. By contrast, the P3 may be more indicative of post-response processes, as it peaked over 100 ms after the erroneous response had been made. These data suggest that, for this task, the P2 component is crucial for determining whether the attempt to inhibit a response will be successful. The topographical distribution of the P2 suggests that it may be the scalp-recorded potential produced by activity in the right parietal/right dorsolateral prefrontal circuit that has been shown to be involved in response inhibition tasks (Garavan, Ross & Stein, 1999). Four of the six channels manifesting P2 latency differences were right hemisphere; thus, the P2 is a better candidate than the (mainly frontal) P3 for being the possible scalp-recorded manifestation of the right parietal/prefrontal circuit.

The main difference in post-response processing was evident in the latency of the P3. Peak amplitude occurred significantly later for lures compared to targets (Fig. 5.2, middle), and for commission errors relative to successful inhibitions (Fig. 5.2, right). Since this component occurred after the mean response latency in all conditions, it is likely that these latency shifts are due to processes dealing with evaluating the previous trial. They may represent an assessment of performance on the trial (successful or unsuccessful), or possibly processes involved with evaluating stimulus probability, one of the main functions associated with the P300 complex (Hoffman, 1990). Participants anecdotally reported using strategies whereby they try to predict when a lure is "due" to appear; such conscious probability assessment may be reflected in P3 latency – the longer the task went without the appearance of a lure, the more participants may have expected one. The critical rule in this task required participants to remember what the preceding trial was; therefore, the P3 could also be indicative of memory load, or some form of context updating, as has been suggested by others (Ravden & Polich, 1998). The possibility also exists that the P3 in this task represents an aggregate of post-response evaluative activity and preparatory processes before the forthcoming trial. An experiment in which the inter-stimulus interval was increased considerably (4 to 5 seconds, for example) should allow these pre-and post-trial processes to be separated. It may be concluded that for this specific task, the P2 is the most valid index of active inhibitory processes that determine the success of an attempted withhold of motor action. The P3 seems to be more involved in post-response processing, the nature of which will require further experimentation to confirm. The most likely explanation for these data may be that the P3 indexes evaluative processing in the aftermath of an action, and that it is not directly involved in determining the success of an attempted inhibition of response. The current

findings can be reconciled with previous research by consideration of the specifics of the tasks used. The XY task may be more comparable to the tasks used by Filipović *et al.* (2000), Brandeis *et al.* (1998) and Falkenstein *et al.* (1995; 1999) than those of Fox *et al.* (2000) and Bruin *et al.* (2001). As a result, I observed inhibition-related differences in earlier rather than late components (P2); perhaps the complexity of the task and/or task stimuli is the main determinant of the ERP components in which inhibitory processes are manifested.

Those participants who scored low on the CFQ, indicating that they were not prone to lapses of attention, did not differ from high CFQs on error rates or reaction times to errors of commission, only on RTs to normal targets (high CFQs were slower to respond). Despite this lack of behavioural difference in error performance, a clear pattern of electrophysiological differences emerged. For both high and low CFQ groups, there were differences in waveform components for correct compared to error waveforms; earlier and larger peaks were elicited by correct withholds. A larger number of channels showed this pattern for low CFQ than for high. When correct withholds were compared, the N2 and P3 were earlier and larger for high CFQ at a large number of channels. In contrast, no differences were found when error waveforms were compared. This implies that error processing may have been identical for high and low CFQ, whereas correct performance was executed in different ways. Given that no performance difference resulted from these electrophysiological differences, this also suggests that the two groups were either using the same brain areas at different levels of activation or else employing different strategies, possibly underpinned by different neural mechanisms, to accomplish the same task, and also to do so to comparable levels of success. The latency of the P3 has been found to correlate with the extent of processing, with longer latency thought

to be indicative of more deliberative or "deeper" evaluation. The high CFQ group show amplitude differences, perhaps suggesting that their level of cortical activity is strongly dependent on the success of the previous trial. Errors are followed by an increased P3 amplitude, possibly a cortical "wake-up call" to pay more attention. It may be the case that highly absentminded participants are more perturbed by their errors, and react to them with greater magnitude. If so, then the scalp-recorded cortical activity reported here may reflect the different approaches to the same task of more or less forgetful participants.

The subtraction of the correct withhold from the error waveform revealed a fronto-central error negativity (Ne) and error positivity (Pe). The error negativity may represent the cortical record of an unsuccessful attempt to prevent the motor act. In an fMRI study with an identical task, Garavan *et al.* (*in press*) reported bilateral anterior cingulate activity associated with commission errors which they attributed to error detection processes. The error negativities also differed for high and low CFQ groups, with significantly larger amplitude Ne for high CFQs. Examination of the correct and error waveforms for this group suggests that the Ne may be a result of the latency difference in the P3 peak, rather than an amplitude difference as is usually the case in subtraction positivities/negativities. By contrast, the amplitude difference in P3 observed in the high CFQ group is manifested in the positivity that follows the Ne in that waveform. This Pe was also larger for high CFQs, with this effect most pronounced over left fronto-central electrodes. In the light of the finding by Nieuwenhuis *et al.* (2001) that the Ne appears to be an endogenous reaction to errors while the Pe is correlated with conscious registration of mistakes and is followed by posterror slowing, it could be postulated that the Ne is a reflection of an automatic error-detection mechanism in cingulate cortex, while the Pe is an index of a left

frontal behavioural correction process, as postulated by Garavan *et al.* (*in press*). Behavioural correction would be dependent on awareness of performance; it would be worthwhile, therefore, to correlate the activity of the Pe with some self-report measure of error awareness. The subtraction effects also suggest that the disparity between correct and error waveforms is larger for high CFQs than it is for low CFQs; this may imply that the subtraction differences result from the larger response of high CFQs for correct withholds; there appears to be little difference between high and low CFQs on errors (Fig. 5.4).

In conclusion, these data suggest that the P2 component is implicated in the success of attempted response inhibition in this task, and may be generated at least partially by the right hemisphere parietal/prefrontal sustained attention network. The P3 has a major role in the post-response phase of the task, and may be involved in performance evaluation, error detection and preparation for future trials. However, it may be the case that the specifics of the task determine which ERP components will serve as adequate indices of inhibitory processes. Electrophysiological differences were found between groups divided by a self-report measure of absentmindedness, but in the absence of performance differences. This suggests that absentminded people require greater activity in the neural substrates of response inhibition in order to perform this task at the same level as less absentminded people. Further, forgetful people may be more responsive to errors, as manifested in the activity of error-detection and behavioural correction mechanisms.

Chapter 6

Traumatic Brain Injury (TBI) produces Impaired Performance and Diminished ERP Waveforms during Response Inhibition

Abstract

Damage to the brain as a result of traumatic brain injury (TBI) has been associated with deficits in executive functions and the dynamic control of behaviour. Here, I recorded event-related brain potentials (ERPs) from 11 participants who had sustained traumatic brain injury, and 11 matched controls while they completed a response inhibition task. Previous research in normals implicates the N2 and P3 ERP waveform components as indices of inhibitory control in tasks requiring response inhibition. The task required participants to withhold a prepotent motor response whenever a rare stimulus condition occurred during a rapidly-presented stimulus stream. The TBI group was found to be significantly impaired at the task compared to controls, and

exhibited diminished waveform components in response to lures and for successful inhibitions, relative to controls. The Go/NoGo effect was disrupted for patients, suggesting a lack of adequate processing of lures. Controls also showed a larger P3 amplitude for correct withholds than the TBI group, implying a specific dysfunction of the cortical structures necessary to produce effective inhibitory control. The brain-injured group also had a diminished error negativity, which may indicate a failure of error monitoring that may be related to their poorer performance. I also conclude that abnormal activity in the structures damaged in this sample may play a role in normal absentmindedness.

6.1 Introduction

Traumatic brain injury is known to particularly affect the frontal lobes, which when damaged may result in a number of cognitive and behavioural sequelae that are collectively termed dysexecutive syndrome (Stuss & Gow, 1992; Varney *et al.*, 1995). The main deficits in this syndrome pertain to the dynamic control of behaviour, the top-down executive processes whereby people can initiate, maintain, monitor, evaluate and (if necessary) correct their ongoing activities. Damage to this system as a result of brain injury can lead to behavioural problems such as perseveration, disorganised behaviour, disinhibition, akinetic mutism and problems with planning and task completion (Fuster, 1997). These functions are therefore vital for the successful negotiation of complex environmental demands and are an example of cognitive flexibility in the human brain.

A key capacity that is often compromised after frontal injury is response inhibition (RI), the ability to exert inhibitory control over motor output by withholding routine or reflexive behaviours. This capacity serves an important adaptive function, and may be deficient in such disorders as schizophrenia, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD; Carter *et al.*, 2001; Casey *et al.*, 1997; Curtis *et al.*, 2001; Enright *et al.*, 1993; Pliszka *et al.*, 2000). Considerable imaging research has been carried out to determine the brain areas that underpin RI, and it is currently hypothesised that a circuit involving the cingulate cortex and dorsolateral areas of the prefrontal cortex are implicated in successful inhibitory control (Carter *et al.*, 1998; de Zubicaray *et al.*, 2000; Garavan *et al.*, 1999; in review). Garavan *et al.* (in review) suggested that these areas may be used to differing extents in normal participants, depending on their self-rated level of absentmindedness (cognitive failures questionnaire, CFQ; Broadbent *et al.*, 1982); those more prone to cognitive failures seemed to rely on a rapid, "last-gasp" anterior cingulate mechanism to perform the same RI task that the less absentminded used a more conservative, "slow-and-steady" prefrontal generator to accomplish. In the same experiment, strong activation related to error detection was observed over the cingulate cortex.

While imaging has revealed the cortical substrates of RI, analysis of event-related potentials (ERPs) has allowed some of the temporal aspects of this process to be elucidated. RI tasks reliably produce changes in the amplitude and/or latency of the N2 and P3 components of the ERP (often termed "NoGo-N2" and "NoGo-P3" because NoGo stimuli tend to elicit larger amplitudes; Falkenstein *et al.*, 1995, 1999; Fox *et al.*, 2000; Bruin *et al.*, 2001), although Ihave proposed elsewhere (Roche, Garavan & O'Mara, *in review*) that the components that index inhibitory processes

may be at least partially determined by the specifics of the RI task used. In that study, successful inhibition was associated with earlier peaks for the P2 and P3 components, implying that the success of the attempted withhold was dependent on certain cortical generators being activated within a finite time window. Error related processing has also been reported in RI tasks, manifested in an Error Negativity (Ne, also known as Error-related Negativity, or ERN), a post-response negative deflection resulting from the subtraction of the correct response waveform from the error waveform (Falkenstein *et al.*, 1999). An error positivity (Pe) has also been observed following the Ne, leading some authors to propose that the Ne reflects automatic registration of the error while the Pe is a marker of the conscious awareness of the mistake (Nieuwenhuis, *et al.*, 2001). Source localisation studies (e.g. Bokura *et al.*, 2002; Strik *et al.*, 1998) have proposed that the generators of the N2 and P3 components may reside in the right prefrontal cortex and cingulate gyrus, among other areas. Taken with the functional imaging literature, this lends strong support to the claim of prefrontal and cingulate involvement in RI, and to the prediction that performance and electrophysiological deficits should be evident among those with frontal damage on an RI task. However, Rieger and Gauggel (2002) found no performance differences between matched normals and brain injured patients on such a task, perhaps suggesting that damage to these key areas may not be sufficient to impair performance, particularly if some cortical reorganisation has occurred in the post-injury period.

Damage to frontal brain areas as a result of TBI produces significant deficits on tasks that require sustained attention and response inhibition. Whyte *et al.* (2000) found TBI patients to be less attentive and more prone to distraction, and that the effects of distraction did not wane over time as they did for normals. Rueckert &

Grafman (1996; 1998) observed that frontal lobe lesion patients performed worse on tasks that required remaining alert for a long time-period, while posterior lesions produced performance decrements when the stimulus presentation rate was rapid. Wilkins *et al.* (1987) also found that at slow presentation rates, or when a task was boring, frontal patients were the most impaired. The nature of many response inhibition tasks involves waiting for variable time-windows for infrequent events to occur, so it is intuitive that frontal injury would result in deficits on RI tasks as well as tasks of sustained attention. The literature supports this. Anderson *et al.* (1998) and Fenwick and Anderson (1999) report that patients with moderate-to-severe TBI are significantly impaired on a selection of attentional tasks, including response inhibition. In addition, Konrad *et al.* (2000a,b) noted deficits in inhibitory control among TBIs, as well as a general slowing of information processing. Furthermore, TBIs were less amenable to improvement on RI performance than controls and ADHD children, leading the authors to conclude that the deficit in ADHD is primarily motivational, while that in TBI is due to structural damage to key brain structures.

In the present experiment, I investigate the behavioural performance and electrophysiological activity of a group of patients with traumatic brain injury (TBI) relative to normal controls on an RI task. I used the same task as in Roche, Garavan & O'Mara (in review) in which I observed P2 and P3 latency differences for correct versus error trails, as well as enhanced error-related components Ne and Pe for the highly absentminded, based on CFQ score. If we assume that the highly absentminded suffer from a mild dysfunction in the structures damaged in TBI, we can predict that the patients' behavioural accuracy will be poorer, and waveform components P2 and P3 will be diminished and later relative to controls. Error negativities and positivities may also be diminished in this group.

6.2 Materials and Methods

6.2.1 Participants:

There were twenty-two participants. Eleven (2 female; mean age=35.9) had sustained traumatic brain injury (TBI), while the control group consisted of eleven normal participants matched to the TBI group for age (mean age=40), sex and performance intelligence (as measured by the National Adult Reading Test; NART). All were right-handed and had normal or corrected-to-normal vision, and participated only after informed consent had been obtained. Each wore a Quikcap 32-channel EEG recording cap connected to the Neuroscan Synamps (Scan 4.1) ERP recording system (Medtech Systems Ltd., Horsham, UK) for the duration of the tasks, and EEG activity was recorded. Participants were seated 80 cm from the computer monitor throughout the testing sessions.

TBI patients were recruited from Headway Ireland, Dublin, and the National Rehabilitation Hospital, Dun Laoighre, Co. Dublin. All had sustained the injury within the last 6.6 years; mean time since the injury was 5.1 years. Two patients reported with "moderate" Post-Traumatic Amnesia, 6 were classed as "very severe", and 4 scored "extremely severe". Exclusion criteria for participants were: any history of epilepsy or other neurological condition prior to injury; history of drug or alcohol problems; history of major psychiatric disorder.

To control for potentially confounding effects of age and general intelligence I recruited age and IQ-matched control participants from the Psychology department participant panel and from members of the local community in Dublin. The participant details displayed in Table 6.1 indicate that the two groups of participants

are appropriately matched. In order to obtain a profile of cognitive and emotional functioning that pertain to everyday events the Hospital Anxiety Depression (HAD) scale and the Cognitive Failures Questionnaire (CFQ) were administered to all participants. The HAD scale is comprised of 14 statements, seven of which reflect anxiety levels and seven correspond to depression levels. Participants choose one of four responses that reflect how they have been feeling in the past week (Zigmond & Snaith, 1983). The CFQ comprises 25 questions whereby participants rate the frequency (on a 5 point Likert scale) with which they make cognitive errors in everyday scenarios. For example, "do you start doing one thing at home and get distracted into doing something else (unintentionally)?" (Broadbent *et al.,* 1982).

Table 6.1: TBI and control participant characteristics including gender (M = male; F = female), age, performance IQ (NART score) and time since injury ([a] Years from date of injury to the time of testing).

Characteristics	TBIs	Controls
Gender		
M	8	8
F	2	2
Age (years)		
M	37.20	38.70
SD	7.61	11.10
Predicted Performance IQ (NART)		
M	112.65	116.68
SD	6.57	4.14
Time Since Injury[a]		
M	6.5	
SD	6.6	

In addition, all participants undertook neuropsychological tests that indexed attention, memory and planning/strategy performance. The Telephone Search and the Telephone Search While Counting subtests of the Test of Everyday Attention (TEA) (Robertson *et al.*, 1996) were administered. The former requires participants to look for key symbols while searching through the pages of a simulated telephone directory and the latter requires participants to search for symbols while simultaneously

counting strings of tones presented on audio-cassette. To assess memory performance the subtests Logical Memory I and II were administered form the Wechsler Memory Scale (WMS-III^{uk}) (1998). In the first subtest two short stories are orally presented and the participant is asked to retell the stories from memory. In the second subtest participants are asked to retell both stories again after a 25-minute delay. Moreover, the participant is asked yes/no questions about both stories. Finally, to measure planning/strategy the revised Strategy Application Test (R-SAT) (Levine *et al.*, 2000) was administered. This task presents an unstructured environment in a laboratory setting whereby the most efficient strategy is challenged by salient external cues and internal habits. The best strategy involves completing the briefest items in three separate activities: figure tracing, sentence coping, and object numbering. The primary score reflecting strategy application is the proportion of items that are classified as brief.

6.2.2 Materials:

X-Y Task

The task used was the X-Y response inhibition task used previously by Roche, Garavan & O'Mara (*in review*). A stream of visual stimuli was presented at a rate of one per second, in black on a white background. The stimuli consisted of capital letters X or Y which were presented in alternating order. Stimuli remained on-screen for 700 ms, and were followed by a blank screen for 300 ms, giving an interstimulus interval of 1,000 ms. Previous testing has shown this stimulus duration to result in a

moderate difficulty level for the task. The task was written in the E-Prime stimulus presentation package. A Cedrus RB-620 response box was used for responses.

Event-Related Potentials

Electrophysiological data were recorded in AC mode with a gain of 500 and a band pass of 0.15-30 Hz. The A/D conversion rate was 500 Hz, and the range was 11 mV. Scalp potentials were obtained using a 32-channel Quikcap using linked ear reference electrodes and an anterior scalp reference site (AFz). The electrode array conformed to the International 10-20 System (American Encephalographic Association, 1994b). Vertical eye movements were recorded with two VEOG electrodes placed above and below the left eye, while HEOG electrodes at the outer canthus of each eye recorded horizontal movements. Silver/silver-chloride (Ag/AgCl) electrodes were used at all sites. Participants were tested while seated in an armchair, with a pillow behind the head to reduce contamination of the ERPs due to head/neck movements or muscle spindles. Recording commenced when electrical impedance had been reduced to less than 10 kOhms by light abrasion of the scalp.

6.2.3 Procedure:

Testing Session

Participants were instructed to click the response box key with the index finger of the right hand for every stimulus *when it followed a different stimulus* (i.e. when an X followed a Y, or when a Y followed an X). When two identical stimuli followed each other (an X following an X, or a Y following a Y), participants were instructed to *withhold their response* (see Fig. 6.1A). A trial block consisted of 315 trials, of which

20 trials were "critical lures", or trials which required a withhold. Two trial blocks were presented, with a short rest period (3 minutes) between the blocks.

6.2.4 Data Analysis:

Electrophysiological Data

The continuous EEG recordings were subjected to ocular artifact reduction to remove artifactual scalp potentials caused by eye blinks. Blocks of EEG contaminated by muscle bursts were manually selected and excluded from the subsequent analyses. The data were epoched into single sweep recordings, from 100 ms prestimulus to 900 ms poststimulus. All sweeps were baseline corrected using the 100 ms prestimulus interval as the baseline interval. Ocular artifacts were reduced using blink-averaging algorithms, and sweeps in which amplitudes exceeded ± 70 μV at VEOG, HEOG or any scalp electrode were automatically rejected. The proportion of rejected epochs varied from 15 to 20% per participant. The remaining epochs were averaged for each participant, and these averages were combined to produce grand average waveforms. Further analysis consisted of separating the epochs into those corresponding to normal target trials and lures. Separate stimulus-locked grand average waveforms were thus calculated for lures and targets (non-lures). Epochs were further separated on the basis of response characteristics: separate response-locked averages were thus obtained for correct withholds (to lures), correct presses (to targets) and errors of commission (incorrect presses to lures). Due to the much larger proportion of sweeps corresponding to target trials compared to lures (590 compared to 40), sweeps were randomly selected from the target trials to ensure equal numbers for comparison. An

insufficient number of errors of omission (incorrect withholds to targets) occurred to generate an average waveform; this analysis was not conducted.

Peak amplitudes for the P2, N2 and P3 components were recorded within three time windows: 170-290 ms poststimulus for the P2, 250-330 ms poststimulus for the N2, 300-650 ms poststimulus for the P3. These windows were chosen after visual inspection of the component latencies in grand mean waveforms for each condition. The latencies at which these peak amplitudes occurred were also recorded. Amplitude and latency values for each component were analysed using MANOVAs with the following factors: for within groups analyses, factors STIMULUS (Target, Lure) and RESPONSE (Correct Withhold, Error of Commission) were used; for between groups analyses, factors were GROUPSTIM (TBI-Target, TBI-Lure, Control-Target, Control-Lure) and GROUPRESP (TBI-Correct, TBI-Error, Control-Correct, Control-Error). ANOVAs were also conducted on the Error Negativity and Error Positivity waveforms.

6.3 Results

6.3.1 Neuropsychological Battery

No significant differences were found between the TBI and control groups for age ($F(1,17)=0.03$, $p<0.86$), NART score ($F(1,17)=3.38$, $p<0.08$) or HADS anxiety/depression scores (HAD-anxiety: $F(1,17)=1.49$, $p<0.24$; HAD-depression: $F(1,17)=0.096$, $p<0.34$). Significant differences were found for CFQ score (lower score for controls; $F(1,17)=7.66$, $p<0.013$), Logical Memory II – delayed recall (superior performance for controls; $F(1,17)=11.32$, $p<0.004$) and R-SAT score

Table 6.2: TBI and control participant scores on self-report measures and neuropsychological test battery results (*=0.05, **=0.01 significance levels).

	TBIs	Controls	*p*
SELF-REPORT MEASURES			
Hospital Anxiety Depression Scale			
HAD - anxiety			
M	9.30	6.30	< 0.24
SD	3.83	5.23	
HAD – depression			
M	6.90	4.30	< 0.34
SD	4.70	4.11	
Cogntive Failures Questionnaire			
M	54.40	36.70	< 0.013*
SD	14.10	11.84	
NEUROPSYCHOLOGICAL TESTS			
Test of Everyday Attention (Dual Task Decrement score)			
M	2.78	0.79	< 0.11
SD	3.73	0.44	
Logical Memory I (immediate recall)			
M	40.78	49.30	< 0.06
SD	9.82	8.81	
Logical Memory II (delayed recall)			
M	21.67	31.90	< 0.004**
SD	6.78	6.47	
Logical Memory II (recognition)			
M	25.22	26.50	< 0.31
SD	2.77	2.59	
Revised Strategy Application Task			
M	0.67	0.93	< 0.001**
SD	0.16	0.07	

(superior performance for controls; $F(1,17)=19.29$, $p<0.001$), but not for Logical Memory I – recall ($F(1,17)=3.98$, $p<0.06$), Logical Memory II – recognition ($F(1,17)=1.08$, $p<0.31$) and the TEA ($F(1,17)=2.84$, $p<0.11$) (Table 6.2).

7.3.2 Behavioural Performance and Reaction Times

The mean number of commission errors was 23.3 (±2.8) out of 40 lures for the TBI group (54.55% errors), compared to 14.7 (±2.8) out of 40 for controls (39.1% errors). This difference was significant ($F(1,18)=4.84$, $p<0.041$; Figure 6.1B). For the TBI patients, the mean reaction time to normal target stimuli was 366.99 ms (±18.9), while for controls it was 348.38 ms (±18.9). This was not significant ($F(1,20)=1.338$, $p<0.261$). Reaction times to errors of commission did not differ significantly (TBI: 336.12±18.5 ms; control: 313.22±18.5; $F(1,20)=1.747$, $p<0.201$; Figure 6.1C).

8.3.3 Event-related Potentials

Within Groups Analyses: Targets versus Lures – TBI Group

A within groups analysis revealed a partial Go/NoGo effect in the TBI group, with significant differences in N2 and P3 amplitudes at six electrodes (C4, CP3, CP4, P4, P8, TP8; all $F(1,20)>4.99$, all $p<0.037$). However, while the N2 adhered to the Go/NoGo pattern of larger amplitudes for lures, the P3 showed the reverse pattern, with larger amplitudes for targets (Figure 6.2A, left).

Control Group

The control group exhibited a standard Go/NoGo effect (Figure 6.2A, right). The main differences occurred in N2 amplitude (4 channels) and P3 latency (23 channels).

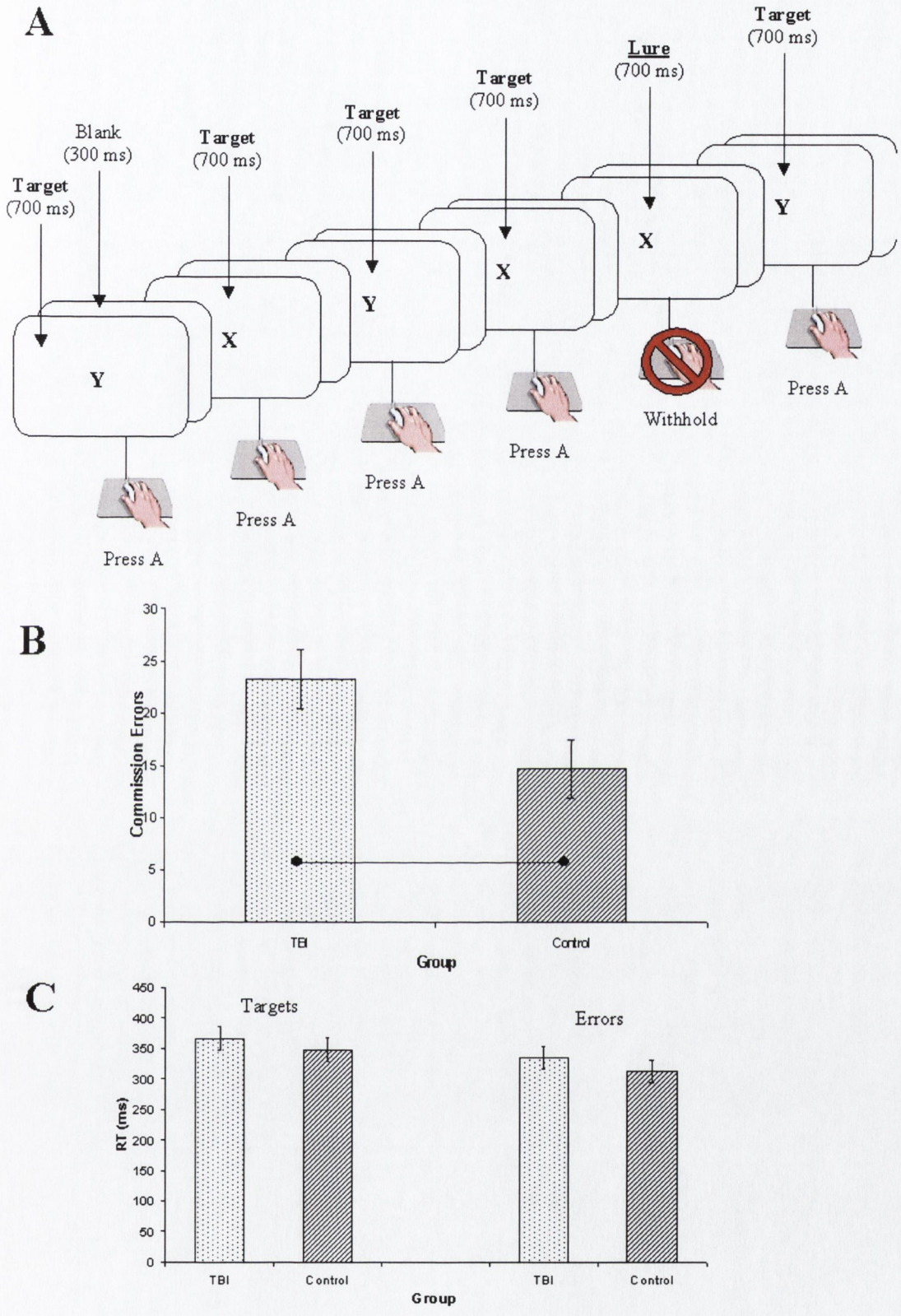

Figure 6.1: A) Presentation sequence and response demands for stimuli in XY response inhibition task; a lure is defined as a stimulus that follows an identical stimulus (e.g. an X following and X, a Y following a Y). B) Bar graph showing mean number of errors of commission in the TBI and control groups. C) Bar graphs showing mean RTs to targets (left) and falsely pressed lures (errors; right) for TBI and control groups.

N2 amplitude was larger for lures at C4, F4, FC4 and FCz ($F(1,22)>4.362$, all $p<0.049$). Later P3 lure peaks were widely distributed across the scalp ($F(1,22)>4.68$, all $p<0.042$).

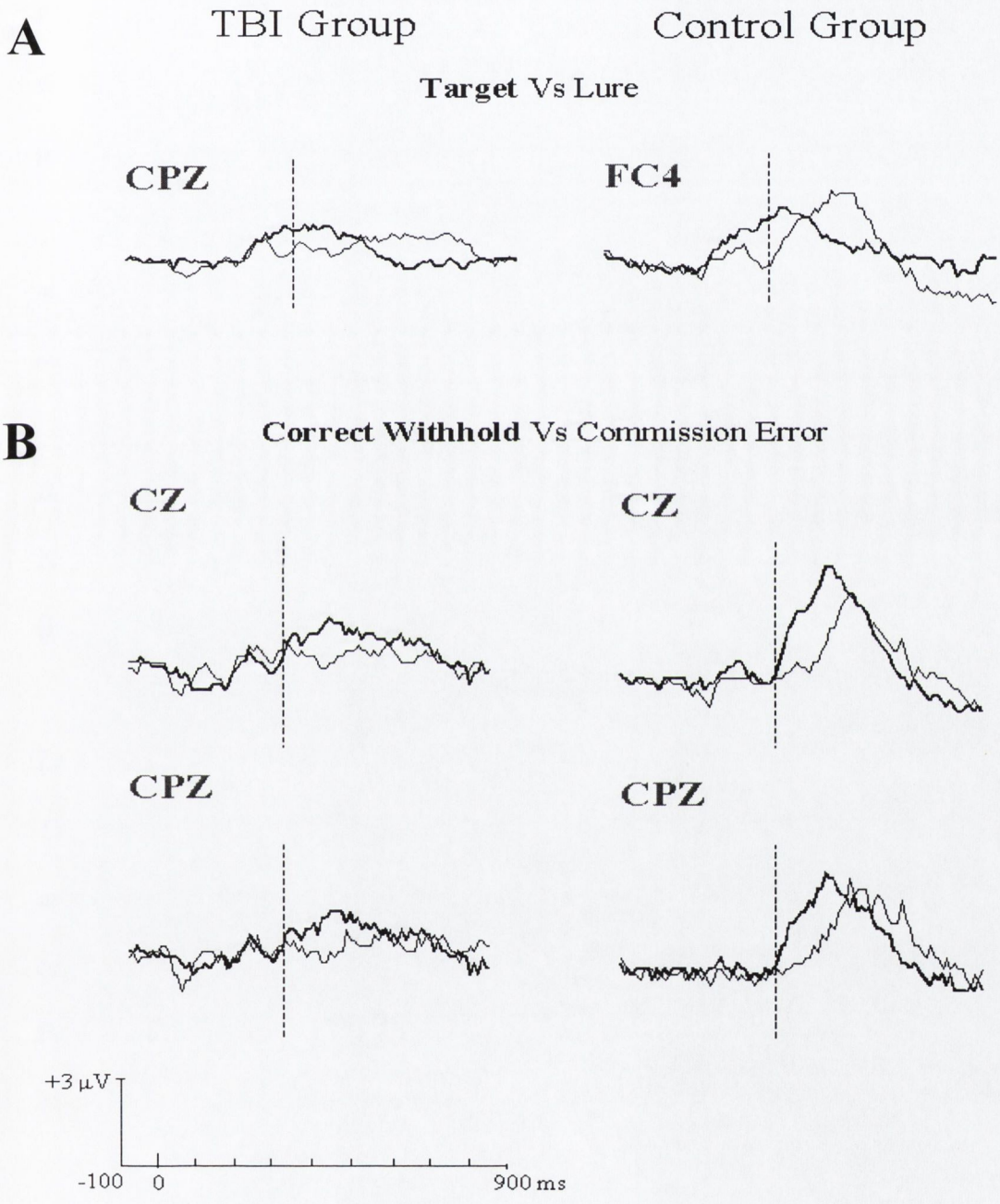

Figure 6.2: A) Stimulus-triggered average ERP waveforms (STAs) for target (heavy line) and lure (thin line) stimuli at CPz for the TBI group and FC4 for the control group (dotted line represents mean target RT). B) STAs for correct withhold (heavy line) and commission error (thin line) responses at Cz and CPz for TBI and control groups (dotted line represents mean error RT).

When correct withholds and errors of commission were compared in the TBI group, no significant differences were evident (Figure 6.2B, left).

Control Group

P3 latency differences occurred at four leads in the control group (Figure 6.2B, right), with later P3 peaks for errors at CP3 ($F(1,20)=4.34$, $p<0.05$), CPz ($F(1,18)=4.44$, $p<0.048$), Cz ($F(1,20)=5.61$, $p<0.028$), and Fz ($F(1,20)=6.00$, $p<0.024$).

Significant interactions between Group and Stimulus were found in the N2 amplitude ($F(1,46)=8.62$, $p=0.003$), P3 latency ($F(1,46)=12.49$, $p<0.001$) and P3 amplitude ($F(1,46)=6.30$, $p=0.012$), but not for N2 latency or P2 amplitude or latency.

Between Groups Analyses: TBI versus Control – Targets

No differences emerged across groups for waveforms elicited by normal targets (Figure 6.3, left).

Lures

The most robust difference when lures were compared across groups was in P3 amplitude, with significantly larger amplitude for controls at nine electrodes; three central (C3, C4, CP4 and Cz; $F(3,41)>4.6$, all $p<0.044$), three frontal (FC3, FCz, Fz; $F(3,41)>6.22$, all $p<0.021$) and two parietal (P3 and P8; $F(3,41)>5.45$, all $p<0.029$; Figure 6.3, right).

Correct Withholds

Correct withholds had earlier N2 components for the control group at four electrodes, C4, CP4, FC4 and T8 ($F(3,41)>4.3$, all $p<0.047$).

Errors of Commission

The comparison of errors across the groups showed no differences between TBI participants and controls.

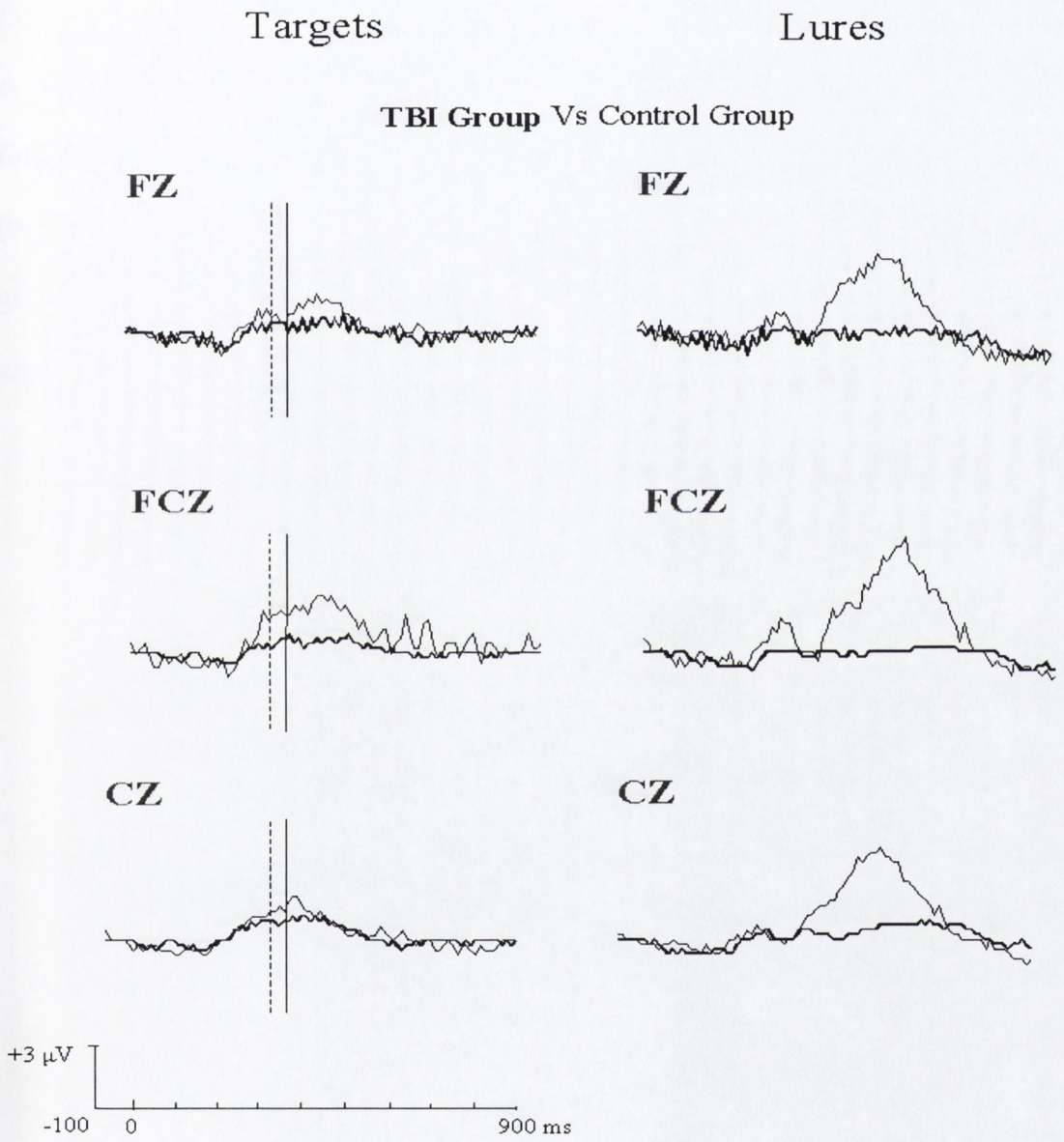

Figure 6.3: STAs for the TBI (heavy line) and control (thin line) groups for targets and lures at Fz, FCz and Cz. Dotted vertical line represents mean control target RT; solid vertical line represents mean TBI target RT.

Significant interactions of Group x Accuracy (correct vs. error) were found for N2 latency ($F(1,54)=3.86$, $p=0.05$) and N2 amplitude ($F(1,54)=7.19$, $p=0.007$), but not for the latency or amplitude of the P2 or P3 components.

Error Processing: Error Negativity and Error Positivity

A fronto-central error negativity was observed in both the TBI and control groups following the Error-Correct subtraction. This Ne was found to be larger for controls ($t=7.28$, $df=62$, $p<0.001$; Figure 6.4). No clear error positivity was evident in the TBI group, though a small positive deflection was evident at some sites in the control group.

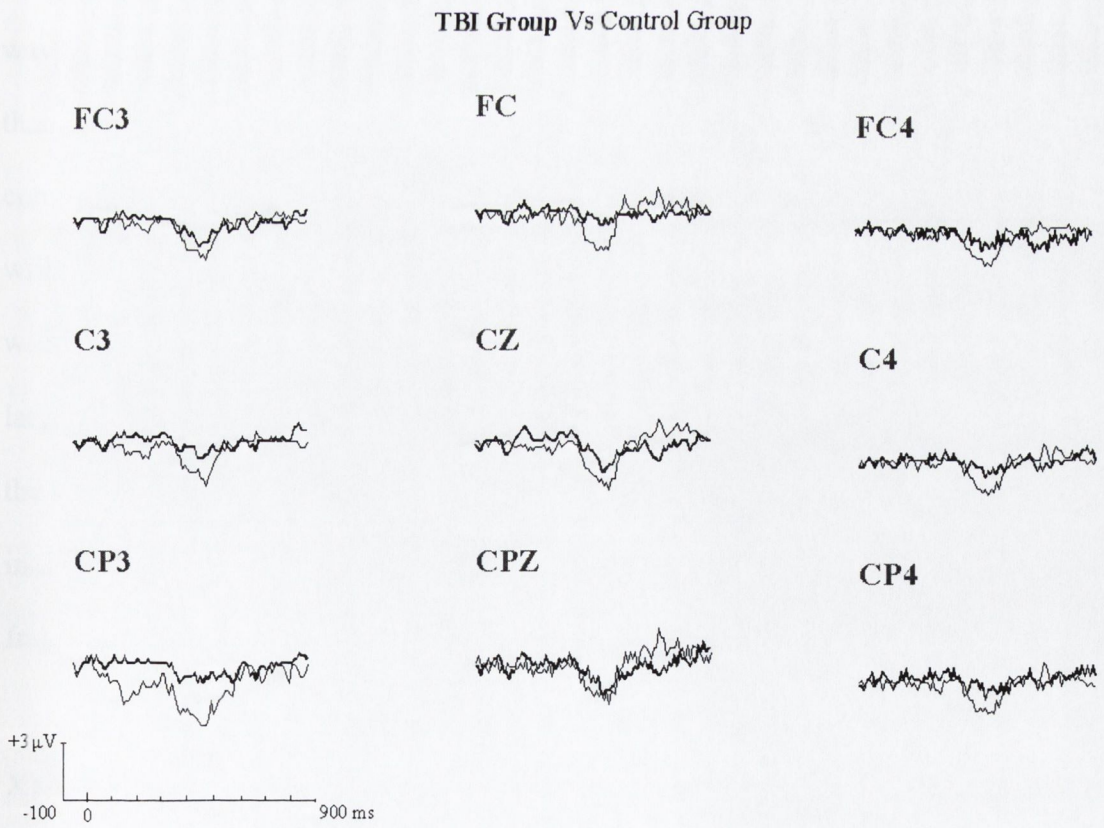

Figure 6.4: Subtraction waveforms (Error-Correct) showing error-related components Ne and Pe for the TBI (heavy line) and control (thin line) groups.

6.4 Discussion

In this experiment, I compared the performance and brain activity of a group of brain-injured patients with that of matched controls during a response inhibition task. The brain-injured group made comparatively more errors on the task, and this performance decrement was accompanied by electrophysiological differences from the controls. Specifically, the TBIs made significantly more errors of commission (false presses) than controls, but did not differ in their reaction times to targets or erroneously pressed lures. Both groups showed waveform differences between normal targets and critical lures, representing a partial Go/NoGo effect. TBIs and controls did not show waveform differences for targets, but for lures controls had significantly larger P3 than TBIs. Controls had earlier P3 latency for correct withholds compared to commission errors, whereas TBIs showed no difference in any component for correct withholds. The N2 peaked earlier for controls compared to TBIs when they correctly withheld a response, but the groups did not differ for error waveforms. Finally, a larger error negativity (Ne) was found in the control group. These data again suggest the importance of the N2 and P3 components for the successful execution of response inhibition, and point to a likely dysfunction of their neural generators in those with frontal brain injury, resulting in poorer performance.

The behavioural performance data show that the TBI group was impaired at the XY task, and also that this decrement was not due to a speed-accuracy trade-off; there were no differences in reaction times to lures or errors between the TBI and control groups. This strongly suggests that the areas damaged in these TBI participants are

necessary for the successful execution of the sort of top-down behavioural control required for response inhibition, and agrees with previous studies reporting impaired performance on sustained attention/RI tasks (Ruekert & Grafman, 1996; Anderson *et al.*, 1998; Fenwick & Anderson, 1999; Konrad *et al.*, 2000a,b). Given the hypothesised prefrontal-cingulate circuit suspected of involvement in RI, one may infer that the locus of damage in this group encompassed the cingulate and/or prefrontal cortices. This assertion is further supported by the results of the neuropsychological test battery, which showed impairments on frontally-dependent capacities such as strategy application and delayed memory recall. One may therefore conclude that the impairments in the TBI group tested here included frontal dysfunction, and this was associated with disrupted response inhibition performance.

ERP waveform components also discriminated the TBI and control groups in their responses to stimuli. In the control group, a standard Go/NoGo effect consisting of enlarged N2 and P3 components was observed for lures over targets. This effect was only partially evident in the TBI group; the N2 enlargement was visible, but no substantial P3 component was present (Figure 6.2A). This suggests that while the stimulus identification processes necessary for lure detection may be largely intact in TBIs (as indexed by the NoGo-N2), the subsequent behavioural control processes (perhaps manifested in the P3) could be compromised. When lure waveforms were compared across the groups (Figure 6.3, right), enlarged P3 amplitude was also seen for the control group; this was in contrast to the targets waveform, in which the groups did not differ. The implication is that, although lures may have been correctly identified (which is possible, given that TBIs were unimpaired on recognition memory in the Logical Memory Test), the resultant cortical activation was insufficient in the TBI group to allow the response to be withheld. Although the P3 peaked *after*

the mean response latency occurred for errors of commission, it is possible that the onset of this component might signal some active response inhibition processes, and that if this onset does not occur within a certain latency window, the attempted inhibition will fail.

Comparison of correct and error waveforms also revealed differences between the groups. While no differences were found for the TBI group, the P3 component was significantly earlier for correct withholds in the control group (Figure 6.2B). This again suggests that it may be the onset of the P3 that determines the success of an attempt to inhibit the response in this study, and is in support of race models of response inhibition (Logan *et al.*, 1984). This finding is also consistent with Roche *et al.*, (*in review*), in which P3 latency differences were also associated with successful performance, though differences in P2 latency were also observed in that study. In addition, the waveforms elicited by errors of commission did not differ across the groups; error waveforms were comparable for controls and TBIs. It appears that similar processing took place for both controls and TBIs in the case of an error, whereas successful performance was associated with greater activation in normals. If it is the case (as suggested above) that lures were correctly identified by the TBIs, then these participants' failure to adjust their behaviour according to the task rule might be indicative of perseveration, as would be expected if frontal structures were damaged (Fuster, 1997). This perseveration would be very likely if the overt response was prepotent, as was the design in this experiment. If this can be verified, it is possible that response inhibition tasks may represent an additional method of assessing perseveration in frontal-injury patients, along with the Stroop and Wisconsin Card Sort Test.

There were also indications of error processing in the waveforms elicited. A larger error negativity (Ne) was visible for controls in the subtraction waveform of Error-Correct. There was also a small error positivity (Pe) in the control waveform that was absent in the TBI group. These results could indicate a lack of error detection/awareness in the brain-injured group. This capacity has been associated with an anterior cingulate locus, and may be essential for appropriate behavioural correction in the aftermath of an error. Such diminished performance monitoring could be predicted to result in the poorer task accuracy observed for the TBI group in this experiment. It has been reported elsewhere that brain injury frequently results in a lack of awareness of errors (Hart *et al.*, 1998).

Finally, there was a significant difference between the groups on the CFQ measure of absentmindedness, with the TBI group scoring significantly higher (more cognitive failures) than controls. It is therefore possible that the higher frequency of cognitive slips in TBIs is a result of the damage to the same capacity that was measured by the XY task – a central inability to inhibit distracting or irrelevant stimuli, be they external or internal. Whyte *et al.* (2000) reported higher distractibility in TBI patients while they completed a task that mimicked everyday activities, suggesting that this capacity affects daily tasks as well as laboratory measures of inhibition. Furthermore, in a previous study (Roche *et al.*, *in review*), a high CFQ group of normals showed ERP differences in the absence of a behavioural difference relative to normals; however, in that experiment the high CFQs showed larger components than the low CFQs. It could be that the high CFQ-scoring normals exhibited over-activity in the structures important for RI, leading to exaggerated amplitudes, while damage to these same structures in the TBIs produced diminished amplitudes. The fact that the differences (irrespective of direction) were observed in

the same components (N2 and P3) suggests that those suffering from traumatic brain injury have sustained damage to structures that may be dysfunctional in normals that are particularly prone to cognitive failures.

In conclusion, I found that a group of brain-injured patients were significantly impaired on a response inhibition task relative to matched controls, with this behavioural difference mirrored by electrophysiological abnormalities. Disruption of the P3 component appears to be central in the poorer inhibitory control exhibited by this patient group, and its onset may predict the success or failure of an attempt to withhold a response. Error detection was also compromised, as indexed by diminished error-related markers. I conclude that cortical damage as a result of traumatic brain injury affects key brain structures necessary for effective inhibitory control of behaviour, and that this damage is manifested in abnormal P3 waveform components.

Chapter 7

Low-level Visuomotor Learning Disrupts Higher-order Behavioural Control

Abstract

I attempted, based on the functional and anatomical overlap between response inhibition and visuomotor learning systems, to induce a performance decrement in a high-level cognitive process (executive control of motor output) through the training of the lower-level visuomotor association system explored in previous chapters. Thirty normal participants (n=10 per condition) completed a configural response inhibition task in which a motor key-press response was required to rapidly presented visual stimuli; for infrequent "lures" this response was to be withheld. Controls received no training, an "anti-training" group was trained on a task that promoted a conflicting stimulus-response association (a motor press to the lure stimulus), and a third group was trained with a comparable task that used irrelevant stimuli. I predicted

that anti-training would induce a behavioural decrement due to the conflicting S-R association. This was not supported. A significant impairment was observed for the irrelevant training condition among highly absentminded participants, possibly due to more robust learning of the S-R association in that training task. This suggests that learning of any strong S-R association may prove disruptive for this group. Possible implications for rehabilitative interventions are discussed in the light of this finding.

7.1 Introduction

A key aspect of executive function in humans is the top-down dynamic control of behaviour. A high degree of cognitive flexibility is required to maintain, monitor, correct or suppress ongoing behaviours being executed at any given time. One of the main paradigms used for assessing such behavioural control is the response inhibition (RI) task, in which a participant must attempt to withhold a prepotent motor response when a specific cue is presented. Deficits in this ability to exert inhibitory control have been noted in disorders such as schizophrenia, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD; Carter *et al.*, 2001; Casey *et al.*, 1997; Curtis *et al.*, 2001; Enright *et al.*, 1993; Pliszka *et al.*, 2000). This particular cognitive capacity is thought to be subserved by a cortical network incorporating the anterior cingulate cortex (ACC) and the dorsolateral prefrontal area (Garavan *et al.* 1999, de Zubicaray *et al.* 2000). Garavan et al. (*in press*) propose that these areas may be implicated to differing degrees, depending on individual differences in absentmindedness/impulsivity; the highly impulsive may rely on a "last-gasp" cingulate mechanism to attempt to exert control, while the less absentminded/impulsive use a "slow-and-steady" prefrontal system. Ihave also observed individual differences in ERP waveform components relating to

inhibition and error detection based on the same self-report measure of absentmindedness (Roche, Garavan & O'Mara, in review). These effects were not accompanied by behavioural differences, suggesting that the same performance was produced by these participants using different levels of activity in the neural substrates of response inhibition.

RI is resistant to training and practice effects from repeated exposure to RI tasks, making rehabilitation of deficits difficult (practice effects are found in only 20-33% of schizophrenia sufferers; Chen *et al.*, 1998). Different strategies and training regimes have been used in the past to attempt to improve executive control over motor output. Banaschewski *et al.* (2001) trained children with ADHD with either sensorimotor practice or cognitive behavioural training (CBT), and found some improvements in motor coordination after sensorimotor training, with improved impulse control following CBT. They concluded that a combined treatment would be most effective. Dowsett and Livesey (2000) reported better inhibitory control on the Wisconsin Card Sorting Task and change paradigm in preschool children who had been given training on acquisition of complex rules. The present study attempts to influence RI task performance through training. Response inhibition tasks usually require a participant to follow a rule whereby one (frequent) stimulus or stimulus category is followed by a response while a different (infrequent) stimulus, or critical lure, necessitates withholding the response. Thus an association between an arbitrary stimulus and a behavioural response (either a press or a withhold) must be learned to successfully perform the task. Arbitrary visuomotor association learning represents a lower-level manifestation of cognitive flexibility and has been studied extensively in rats (Murray & Wise, 1996; Wise & Murray, 1999; 2000) and humans (Roche & O'Mara, 2002; Petrides, 1997). Through single- and multiple-cell recording, lesion

analysis and ERP studies, a distinct cortical network consisting of prefrontal cortex, hippocampal formation and basal ganglia (as well as visual and motor areas) has been proposed as the neural substrate of this form of learning. I have previously shown that through repeated exposure to the to-be-learned association, both behavioural and electrophysiological differences occurred, manifested in faster reaction times to the learned association in a subsequent task, and enhanced P300 amplitude, possibly reflecting hippocampal excitation (Roche & O'Mara, 2002). I subsequently demonstrated that the stimulus-response (S-R) association could also be trained if it was repeatedly presented within the context of a demanding cognitive task, specifically visual search (Roche *et al.*, in review). The association between the target stimulus in the search task and the appropriate response was again facilitated in the subsequent test of that association relative to controls, as revealed by reaction times.

Here I attempt to influence the performance of participants on a response inhibition task through training of this visuomotor association network. I predict that training a conflicting S-R association prior to the response inhibition task will result in a significant decrement in performance (more errors) relative to untrained controls and controls trained with an association that has no bearing on the RI task. Furthermore, I predict that different patterns of effects may be evident for those who score high on a self-report measure of absentmindedness.

7.2 Materials and Methods

7.2.1 Participants:

Participants were 30 Trinity College undergraduate and postgraduate students (6 male; mean age=23.4 years, range=18-35); undergraduates participated for course credit. All gave informed consent, were right-handed with normal or corrected-to-

normal vision and had no history of mental illness. Participants were assigned randomly to one of three experimental conditions (each of n=10).

7.2.2 Materials:

The visual stimuli used were upper case letters (X, Y, O, Q) presented in either green or red, against a white background (see Fig. 7.1). Presentation sequence and stimulus durations were dependent on experimental condition. The visual search and response inhibition tasks were written in the E-Prime stimulus presentation package; visual search stimulus arrays were generated using the Visearch program (see acknowledgements). A Cedrus RB-620 response box was used for responses.

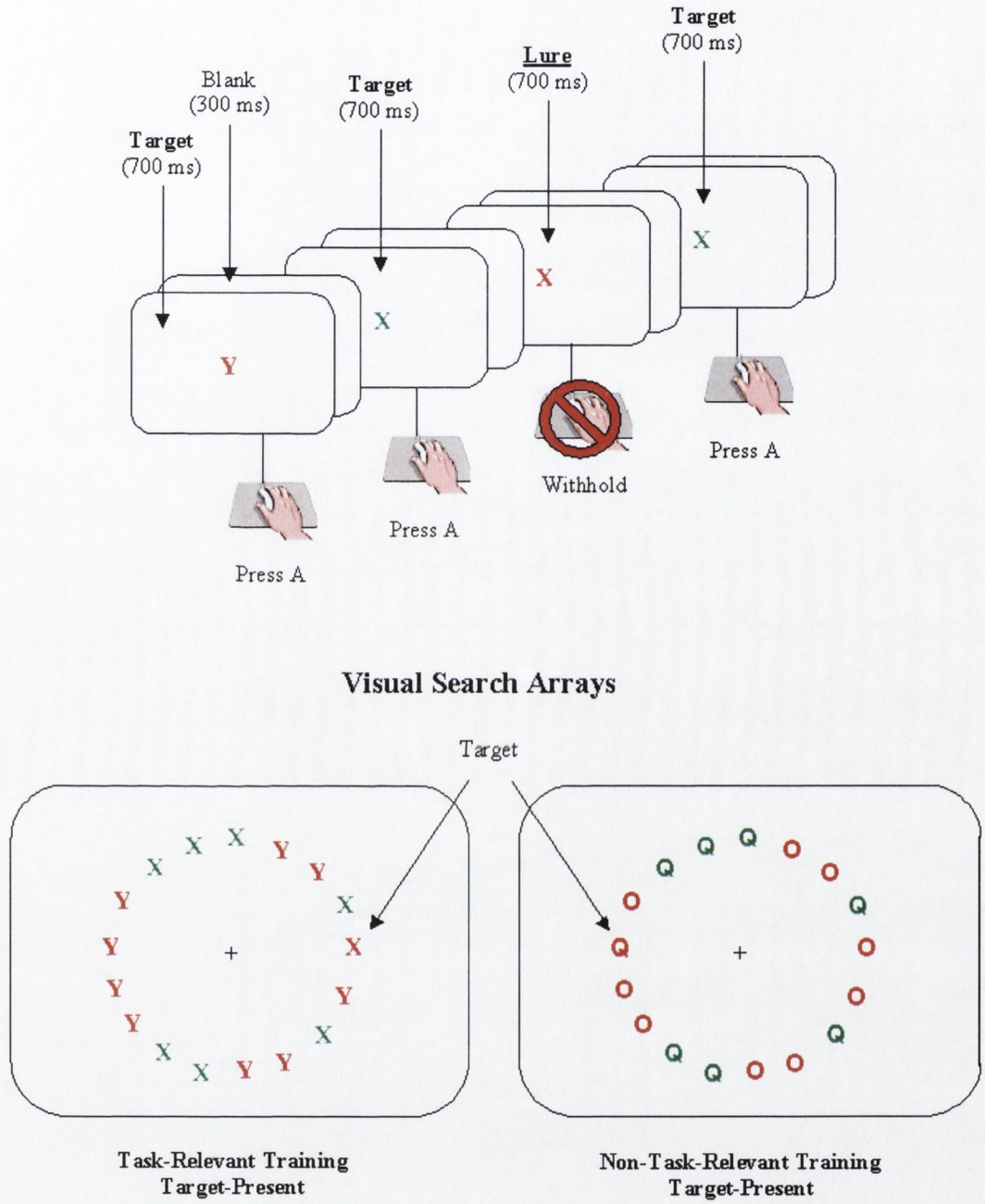

Figure 7.1: (Upper Panel) Stimulus presentation sequence for configural response inhibition task, displaying stimulus durations and response requirements. "Press A" refers to index-finger press on response box. (Lower Panel) Example stimulus arrays for anti-training (left) and irrelevant training (right) visual search tasks; a target present trial of each is shown.

Participants were also administered the 25-item Cognitive Failures Questionnaire (CFQ; Broadbent *et al.*, 1982). This questionnaire gives an index of how prone a person is to lapses of attention, cognitive failures and minor mistakes,

and is considered an indicator of the degree of absentmindedness of the respondent. Each item is rated for frequency in the last 6 months, from 4 ("very often") to 0 ("never"). A maximum score of 100 is possible, indicating a high frequency of cognitive failures, while the minimum possible score is 0.

7.2.3 Procedure:

Control Group: Configural X-Y Task

The control group was presented with a configural response inhibition task based on a task that we have used previously (Roche, Garavan & O'Mara, 2002); the task consisted of rapid sequential presentation of letters X and Y, in either green or red, in random order at the centre of the screen. Letters remained on-screen for 700 ms, and were followed by a blank screen of 300 ms duration; this gave a trial duration of 1,000 ms. The trial block consisted of 660 stimuli.

Participants were instructed to press a key on a response box with the index finger of the right hand in response to a green X or red Y (normal targets). However, upon presentation of a red X (designated a critical lure), the button-press response was to be withheld. The block of 660 stimuli contained 60 randomly presented lures, giving a frequency of 10%.

Experimental Group 1: Task-relevant ("Anti-") Training

Both experimental groups were presented with a block of visual search prior to completing the configural X-Y task. In the task-relevant training group, the search task involved the same green and red X and Y letters as in the X-Y task. For the non-task-relevant group, the search task consisted of red and green Os and Qs.

The task-relevant group were presented with 300 trials of a conjunction visual search task (set size 16). Stimulus arrays were circular, arranged around a central fixation-cross, and each stimulus subtended an angle of 0.7 degrees of arc vertically, and 0.5 degrees in width. The arrays consisted of one target (red X) and fifteen distractors (7 red Ys and 8 green Xs) for a target-present trial, or else sixteen distractors (8 red Ys and 8 green Xs) for target-absent. Stimulus arrays remained on-screen until participants pressed either the first key with the index finger (for target present), or the second key with the middle finger (for target absent), giving equal emphasis to speed and accuracy. After response, the fixation-cross remained on-screen for 500 ms, after which another stimulus array was presented. Of the 300 trials, 150 were target-present. Target-presence/absence was determined randomly, as were the positions of the stimuli in the circular array.

After the visual search block, participants were given a three-minute break, after which they completed the same configural X-Y response inhibition task as the controls. The key to be pressed in response to targets (green X and red Y) and withheld to lures (red X) was the same as the one to be pressed for target-present (i.e. red X present) trials in the visual search block.

Experimental Group 2: Non-task-relevant ("Irrelevant") Training

The group trained with stimuli that were not relevant to the X-Y task received a search block that was identical except for the stimuli used. The target was a red Q, while distractors were green Qs and red Os. The same key-press responses were required, and the instructions were the same. After a three-minute break, participants completed the same configural X-Y task as the other groups.

7.3 Results

Training: Visual Search Tasks

Participants completed both search tasks with a high degree of accuracy. In the anti-training task the mean number of errors was 75.9 (±2.31), while for irrelevant training it was 8.5 (±1.66). There were significantly more correct responses than errors in both conditions, both when the target was present and when it was absent (main effect of Trial: $F(2,32)=1920.05$, $p=0.001$; Greenhouse-Geisser corrected). For anti-training there were 112.25 (±1.96) present corrects compared to 37.7 (±1.93) present errors and 111.8 (±2.44) absent corrects compared to 38.2 (±2.44) absent errors (Bonferroni: present - $t=19.17$, $df=9$, $p=0.001$, absent - $t=15.06$, $df=9$, $p=0.001$). The disparity between correct and error was larger in the irrelevant training group: there were 143.3 (±1.66) present corrects versus 6.7 (±1.66) present errors, and 148.2 (±1.66) absent corrects compared to 1.8 (±1.66) absent errors (Bonferroni: present - $t=46.02$, $df=9$, $p=0.001$, absent - $t=127.6$, $df=9$, $p=0.001$). There were significantly more correct responses (both present and absent) in the irrelevant training group compared to anti-training (present: $t=12.8$, $df=18$, $p=0.001$, absent: $t=14.5$, $df=18$, $p=0.001$).

In the anti-training group, reaction times (RTs) to present corrects were shorter than those to present errors (733.74 ± 34.1 vs. 867.61 ± 90.5 ms), while RTs to absent corrects were longer than those for absent errors (853.35 ± 60.8 vs. 726.35 ± 96.3 ms; $F(2,29)=4.36$, $p=0.029$; Bonferroni: present – $t=4.281$, $df=9$, $p=0.002$, absent – $t=15.06$, $df=9$, $p=0.001$). In the irrelevant training condition, there was no significant difference in response time between corrects and errors for target present trials, whereas correct target-absent RTs were longer than error RTs (correct = 1064.58 ±

60.8, error = 696.97 ± 96.3 ms; t=127.64, df=9, p=0.001). These results are shown in Figure 7.2.

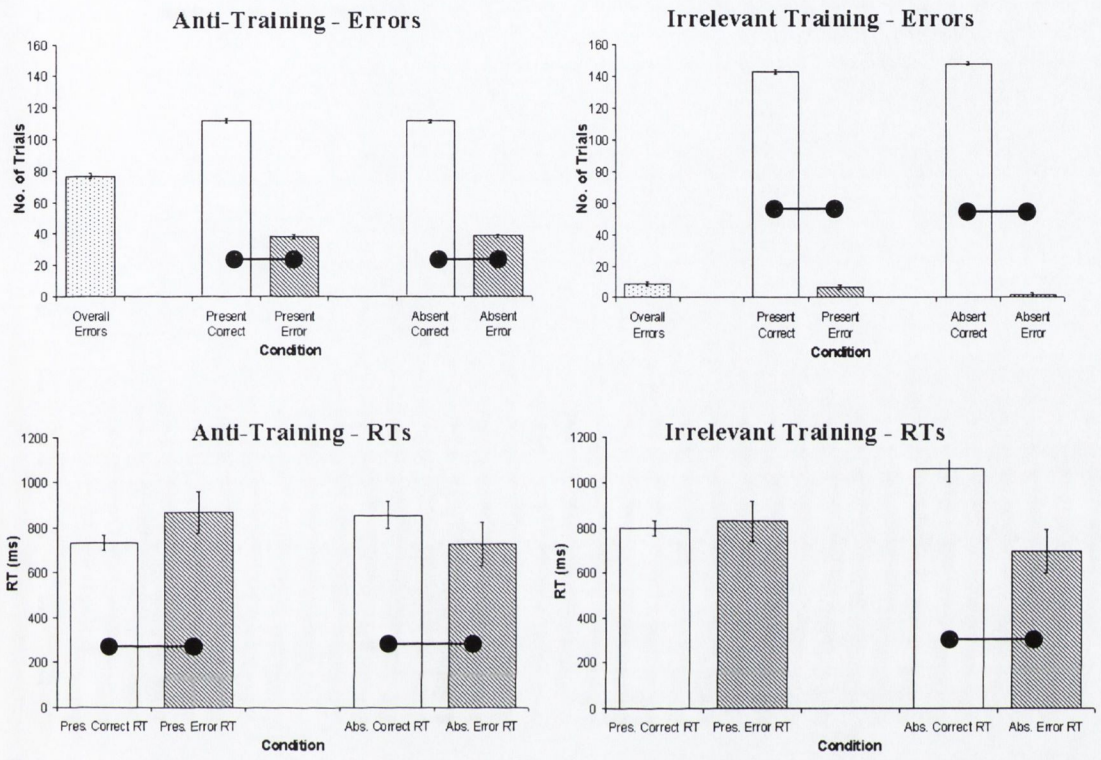

Figure 7.2: (Upper Panels) Mean correct and error responses (± SEM) for anti-training (left) and irrelevant training (right) visual search training tasks. Significant differences at $p<0.05$ are marked. (Lower Panels) Mean reaction times (RTs; ms, ± SEM) to stimuli for anti-training (left) and irrelevant training (right) visual search tasks.

Response Inhibition

There was no difference between the three groups in CFQ score (control = 42.6, anti-training = 39.6, irrelevant training = 41.2; F(2,29)=0.11, p=0.896). On the response inhibition task, the mean number of errors of commission did not differ between the groups; for controls, mean errors was 13.6, for anti-training 19.1 and for irrelevant training 16.7 (F(1,16)=0.112, p=0.743). When response times to the stimuli were examined, no inter-group differences were found. For normal targets ("go trials"), RTs were 323.79 ms for control, 287.08 ms for anti-training and 313.48 ms for irrelevant training (F(1,16)=3.72, p=0.072; multiple comparisons revealed a significant difference between anti-training and irrelevant training; p=0.045). The same was true of RTs to commission errors (control: 281.56 ms, anti-training: 244.89 ms, irrelevant training: 263.3 ms; F(1,16)=1.44, p=0.248; see Figure 7.3).

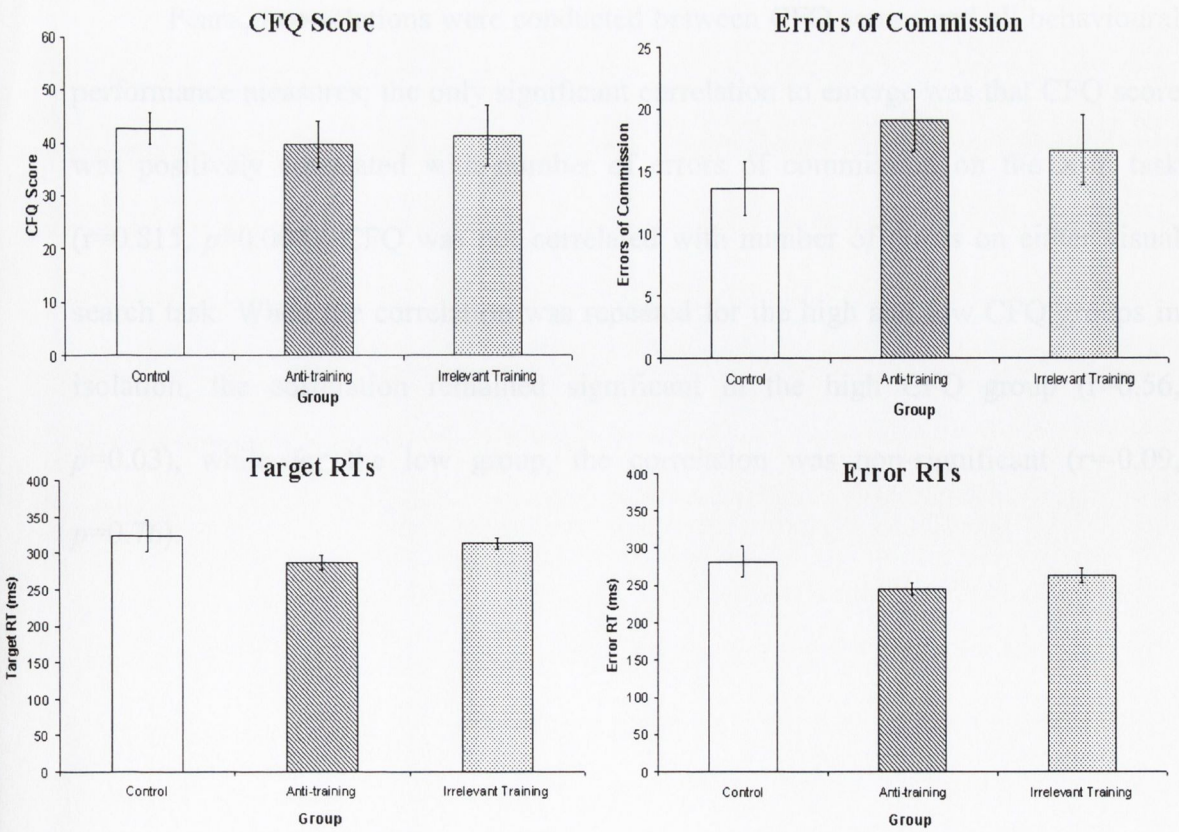

Figure 7.3: (Upper Panels) Mean CFQ questionnaire scores (± SEM) for control, anti-training and irrelevant training groups (left) and mean number of errors of commission (± SEM) for each group on the response inhibition task. (Lower Panels) Mean RTs (ms ± SEM) to normal target stimuli (left) and erroneously pressed lures (right) in the response inhibition task.

A median split was performed based on CFQ scores (median=42.5) and the sample was divided into high CFQ (i.e. high rate of cognitive failures) and low CFQ (low rate of failures) participants for each group. A significant interaction emerged between CFQ group and experimental condition on the number of commission errors made ($F(2,24)=5.33$, $p=0.035$; Figure 7.4, upper panels). In the low CFQ group, there was little difference between control and irrelevant training errors (13.25 vs. 11.5), while performance in the anti-training group was slightly worse (20.2 errors), though this difference was not significant. For high CFQ participants, however, the pattern was different. Again a slight decrement in performance was found between control (13.8) and anti-training (18.0), but the worst performance was found in the irrelevant training group (24.5 errors; $t=2.53$, $df=8$, $p=0.021$). As was found when analysed overall, no differences were evident in RTs to targets or errors of commission between experimental conditions, or between CFQ groups (lower panels).

Pearson correlations were conducted between CFQ scores and all behavioural performance measures; the only significant correlation to emerge was that CFQ score was positively correlated with number of errors of commission on the X-Y task ($r=0.815$, $p=0.004$). CFQ was not correlated with number of errors on either visual search task. When the correlation was repeated for the high and low CFQ groups in isolation, the correlation remained significant in the high CFQ group ($r=0.56$, $p=0.03$), while for the low group, the correlation was non-significant ($r=-0.09$, $p=0.76$).

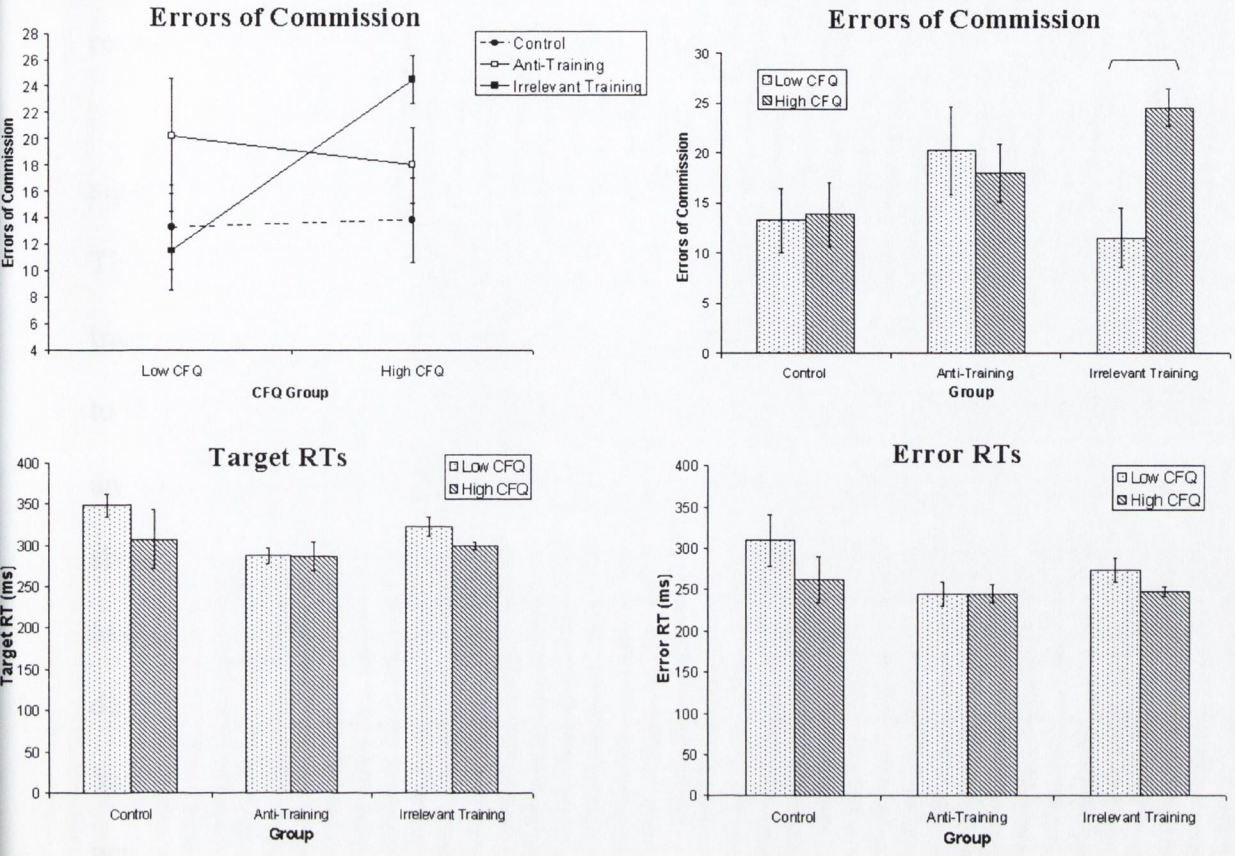

Figure 7.4: (Upper Panels) Interaction effect between CFQ group (high vs. low, based on median split of sample) and experimental condition for number of errors of commission (right), and mean errors for each group depicted on a bar graph (right). (Lower Panels) Mean RTs (ms ± SEM) to targets (left) and commission errors (right) split by CFQ group.

7.4 Discussion

This experiment successfully induced a behavioural decrement in performance of a high-level cognitive capacity through the manipulation of low-level association learning. This effect was mediated, however, by the degree of absentmindedness of participants as measured by CFQ score; high CFQ participants were more disrupted than low, and by a different training task. Ibelieve this finding represents a potentially

useful mechanism by which an important higher-order cognitive function that is resistant to training/practice effects can be influenced.

A block of training on an irrelevant stimulus-response association produced a significant impairment in performance among those who were highly absentminded. This result was contrary to our predictions; it was expected that a block of anti-training would result in performance decrements on the response inhibition task due to the conflicting nature of the S-R pairing that was trained. Intuitively, strengthening an association between stimulus and response that subsequently had to be suppressed should have resulted in poorer performance, while the training of an irrelevant association should have no effect. In fact, there was a (non-significant) trend in this direction for the low CFQ respondents (Figure 7.4). The pattern for high CFQs, however, was anomalous; while anti-training again resulted in slightly poorer performance than controls, the largest (and only significant) decrement was observed after irrelevant training.

This finding may be explained by consideration of the accuracy data on the training blocks themselves (Figure 7.2). There were significantly more correct target-present responses made in the irrelevant training group than in the anti-training. The irrelevant training task may have been more preattentive than the anti-training, resulting in target "pop out" and hence more correct target-present trials. The anti-training task may have been closer to the classic conjunction task. This implies that the association between the red Q (irrelevant stimulus) and the index-finger press (response) was trained more robustly than that between the red X (relevant stimulus) and the index-finger press (response). Therefore, it may be the strength of an S-R association (*any* S-R association) that exerts an influence on the performance of high CFQ respondents, while for low CFQs it is the nature of the association that

determines the level of disruption. Low absentminded participants may be more sensitive to S-R conflict between tasks, where the initial learned pairing must be subsequently inhibited. For high CFQs, it is possible that any strongly learned association that involves the to-be-suppressed response would prove disruptive, regardless of the stimulus used. This proposal, that high and low CFQ respondents process this type of task differently and may even use distinct brain areas to do so, has been supported in the past. We have previously observed electrophysiological differences in the absence of behavioural effects between high and low CFQ groups (Roche, Garavan & O'Mara, 2002), while others postulate that high CFQs may rely on an anterior cingulate system while low CFQs use a right prefrontal circuit to accomplish response inhibition (Garavan *et al.*, 2002). The present results could be interpreted as further support for this claim.

More generally, this experiment demonstrates that a high-level cognitive capacity that is known to be resistant to practice effects can, in fact, be modulated through training of a vital low-level component thereof. Given that the capacity in question here is suspected to underpin such problems as Attention Deficit Disorder (ADD), there are potentially important implications for rehabilitation. It is conceivable that through a different manipulation of the arbitrary visuomotor association system, improvements, rather than decrements, in performance could be achieved. Improved performance on a response inhibition task would require the S-R association between the lure stimulus (red X) and the response (index-finger button press) to be dampened or suppressed. This could potentially be achieved in a number of ways. Participants could be trained on a task that strengthens an association between the lure stimulus (red X) and a *different response* (e.g. middle-finger press). Alternatively, an association could be trained between a *different stimulus* (e.g. red Q)

and the normal response (index-finger press). A third option is that these two approaches could be combined, so that the stimulus and the response bore no relation to the response inhibition task. Furthermore, the observed differences between high and low CFQ groups suggest that one type of intervention may prove more effective for one group than for the other. In fact, based on the present data, one could tentatively predict that the first strategy would prove more effective for high CFQ participants (given their disruption when the task-relevant response was used), while the second strategy might be more successful for low CFQs (based on their apparently greater sensitivity to the content of the S-R association, and a small though non-significant trend towards improved performance in the irrelevant training condition). These predictions, while speculative, are worthy of pursuit, though it must be added that even if the proposed performance improvements were supported experimentally, it remains questionable whether these benefits would generalise to any other behavioural domains. Nevertheless, these claims are worthy of experimental investigation. It would also be of interest to investigate whether other cognitive capacities are susceptible to manipulation through training of specific subcomponents.

These data demonstrate that robust training of an irrelevant S-R association can induce impaired performance on a response inhibition task among the highly absentminded. If replicated, this finding may reveal a useful principle of cortical organisation while could allow certain higher cortical functions to be facilitated or improved through training, and could potentially offer a basis for novel rehabilitation strategies.

Chapter 8

General Discussion

"The more we learn about the nature of learning,

the farther we seem to get from being able to give firm answers."

(Donald O. Hebb (1904-1985), address to the Ciba Medical Horizons conference, Nebraska, 1976)

The series of experiments reported in this thesis, their results and the interpretations thereof, provide some insight into the nature of three key areas in neuropsychology: learning, inhibitory control of behaviour and dynamic interaction between brain subsystems. Chapters 3 and 4 deal with the learning of pairings between visual objects and arbitrary actions, how this learning may take place and some of the factors that may influence its acquisition and expression. Chapter 5 and Chapter 6 investigate the nature of response inhibition in tasks that require the suppression of a prepotent motor response, in normal participants and patients with brain injury, allowing the neural

substrates of RI to be revealed. Chapter 7 attempts to use intervention in one cortical system to influence the activity of another system that may share neural structures or chemical mechanisms. Through consideration of the results presented here and their implications, we may give some tentative suggestions rather than firm answers to questions regarding learning, attention, inhibition and cortical systems in general.

8.1 Insights into Arbitrary Visuomotor Association Learning

The pairing of a motor action to an arbitrary visual cue involves a distributed network including hippocampus, basal ganglia, prefrontal and premotor areas (Wise & Murray, 2000). In Chapter 3, I found that learning-related changes in the activity of this system can be detected by scalp-electrodes and manifested as changes in the waveform components of the ERP. Larger amplitudes and earlier latencies of the P300 component were found for trained participants compared to untrained controls on a subsequent test of the learning. This may be interpreted as evidence for the activity of the hippocampal formation, among other possible generators, in the learning and its expression. Based on the reaction time data, it seems that the greatest learning (for this task at least) occurs during the first thirty exposures to the S-R pairing. After this point, RTs tend to asymptote at between 300 and 600 ms. One may only speculate on the neural events that occur during this repetition training. In order to internalise a mapping of a response onto a visual stimulus, it is likely that the early stages of acquisition rely on a conscious decision to make the response before, through exposure, some element of automaticity takes effect. Therefore, in the early stages of training (the first thirty trials for this task), visual input is processed to high levels of the ventral object-recognition stream, from occipital cortex to inferotemporal areas (IT), depending on stimulus complexity. Once the object is identified, the

decision of what response to make will depend on referring back to a stored rule, most likely being maintained in short-term or working memory at this point; the suspected involvement of the prefrontal cortex in working memory and decision making (Fuster, 1997) make it the most likely candidate site for this function. Once the appropriate response has been selected, activation spreads to the basal ganglia and premotor areas to execute the behaviour, with the basal ganglia likely playing a role in the storage of the pairing (Figure 8.1).

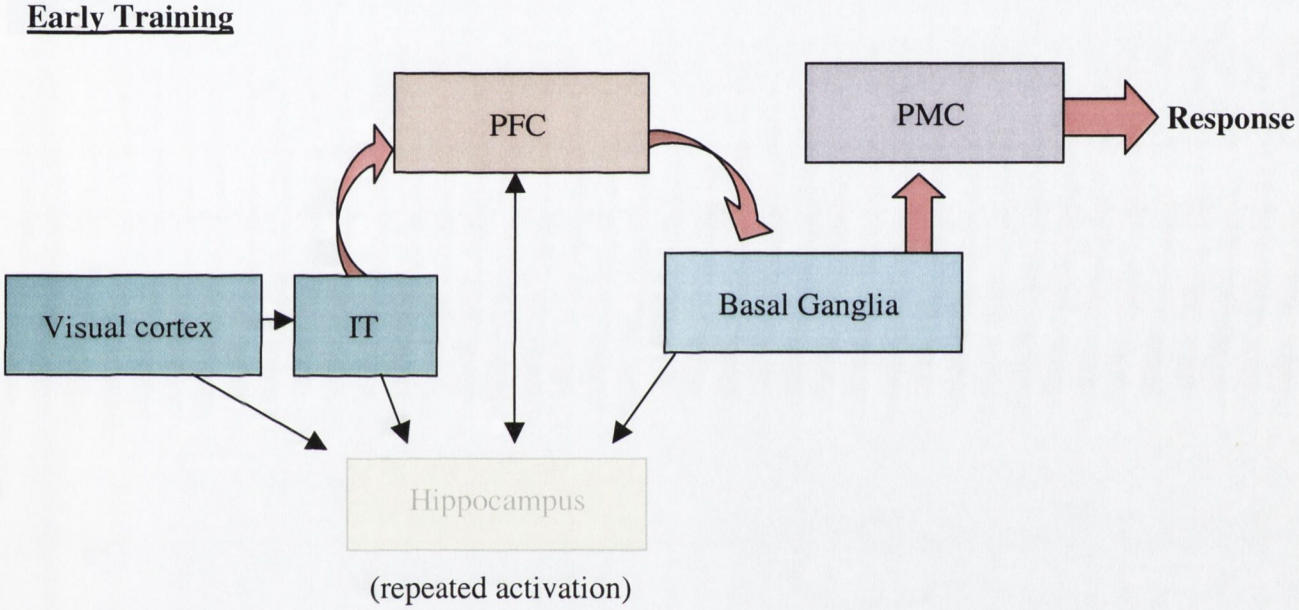

Figure 8.1: representation of hypothesised operation of arbitrary visuomotor association learning system, during the early phase of learning. Red arrows indicate primary processing pathway.

As training progresses from early to late stages, however, the system should, by definition, rely less on the conscious selection of the response, as the pairing becomes "learned". It may be in this phase of learning that the hippocampal formation has its major role. Decreases in (left) hippocampal metabolism have been observed in humans after they have engaged in a rote learning regime (Robertson *et al.*,

pers.comm.), leading to the suggestion that repetitive stimulation of hippocampal input may mimic the effects of low-frequency stimulation of hippocampal cells in animals, resulting in effects similar

Late Training

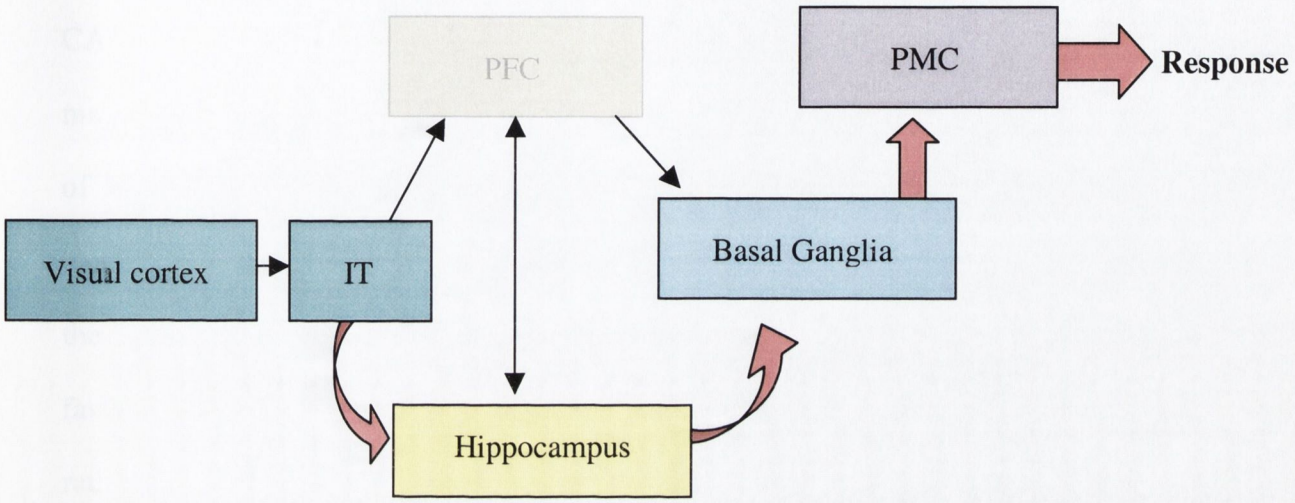

Figure 8.2: representation of hypothesised operation of arbitrary visuomotor association learning system, during the late phase of learning. Red arrows indicate primary processing pathway.

to long-term depression (LTD; Bliss & Collingridge, 1993). Perhaps the repeated activation of the IT-prefrontal-motor area system in the early phase of training leads (via back projections from these areas) to activation in the hippocampus. Repeated coincident activity in the same visual input and motor output pathways may lead the S-R pairing to be somehow represented in the hippocampus; this structure is well known for having a major role in memory (Squire, 1992). Such activity-dependent facilitation is the underlying principle of LTP, which remains the most convincing cellular model for learning and memory in the brain, and which is most easily induced in the hippocampus (Bliss & Collingridge, 1993; O'Mara, 1995), though it can be induced in other parts of the cortex. Petit *et al.* (1989) found that repeated activation

of CA1 and CA3 neurons led to changes in the number and morphology of synapses in these areas, suggesting that such changes following exposure to repeated activity may have a role in activity-dependent phenomena such as information storage. Tancredi and Dichter (1990) also demonstrated similar increases in conductance of CA1 pyramidal cells following repetitive activation. Alternatively, the hippocampus may oversee the storage of this association in the basal ganglia through modification of synaptic strength in the caudate and putamen. The implication, which remains tentative, is that the hippocampus takes over the mantle from the prefrontal cortex in the latter stages of learning, removing the necessity to make a conscious decision in favour of falling back on a "learned" stimulus-response set. Thus, the hippocampus rather than the prefrontal cortex, co-ordinates this visuomotor mapping in the basal ganglia in this later stage of learning (Figure 8.2). This might explain the findings of evolution of cell firing in the hippocampus during such learning (Cahusac *et al.*, 1993), as well as Ghilardi *et al.*'s observation of prefrontal activity only when new associations were being learned (2000). Furthermore, the impairments on such learning found with frontal patients may be due to their inability to successfully complete the early, frontal-dependent phase of learning (e.g. Petrides, 1997, in which frontals were impaired while the only temporal lobectomy patients to show learning deficits were those with hippocampal damage). This claim can easily be tested by imaging experiments: the prediction is that prefrontal activation will be greater than hippocampal in the early stages of a training session, while this pattern will be reversed in the later stages, with greater hippocampal activation. While this model remains highly speculative until further study can verify these claims, it represents a first attempt at delineating the differing roles of the cortical and subcortical structures involved in this form of learning.

Alternatively, the above model may hold only in cases where the to-be-learned visuomotor association is complex; the tasks used in the experiments reported here involved very simple associations between low-level and easily distinguishable stimuli (forward slash) and a very basic motor response (button-press with the index finger). It is possible that, given such simplicity, this form of learning could be accomplished without recourse to the prefrontal cortex or hippocampus, and could perhaps be achieved in striatal structures alone. Further experimentation comparing the sort of low-level mapping used here with associations between complex stimuli and more elaborate responses (as in Petrides, 1997, for example) would be instructive. Imaging or event-related potentials analysis may reveal whether this claim is valid.

7.1.1 Attention and Learning

The addition of an attention-demanding dual task during training (Chapter 4) facilitated the acquisition of the S-R pairing, as manifested in the rate of acquisition of the association and its subsequent expression. These effects did not appear attributable to a general increase in arousal, as the addition of phasic or continuous alerting tones produced no such facilitation. The mechanism by which attention modulates learning is as yet unknown, but the model of sustained attention proposed by Sarter *et al.* (2001) offers one possible explanation. The standard training session in these experiments is low in cognitive demands and requires minimal attention – all that is needed is to press the button when the stimulus appears. The addition of a concurrent task may act as a "call to arms" for greater attention to be deployed to all ongoing activities; this may be manifested cortically as the top-down recruitment of the basal forebrain by the prefrontal cortex. The resultant release of acetylcholine into anterior and posterior attentional networks and sensory cortices would therefore facilitate the

performance of the dual task (through innervation of the attentional systems) and the acquisition of the learning (through cholinergic input to prefrontal cortex and hippocampus). In fact, the cholinergic innervation of the hippocampus may possibly facilitate the learning of the S-R association by strengthening the activity-dependent facilitation effects suggested above; the basal forebrain does send a direct cholinergic input to the hippocampal formation (Mesulam *et al.*, 1983). Both acetylcholine and the hippocampus have been suggested as likely contributors to the generation of the scalp P300 waveform (Knight, 1990), and larger P300 was observed for trained over control groups during the expression of the learning in Chapter 3. Further support for a major role of Ach in the generation or modulation of the P300 comes from studies of the effects of acetylcholine agonists and antagonists. Scopolamine, an Ach blocker, has been found to reduce or abolish the frontal P3a (also known as the "novelty P3") in humans (Potter *et al.*, 2000; Wang *et al.*, 1999), while lesions of key acetylcholine production nuclei such as the nucleus basalis magnocellularis in experimental animals increased the latency and reduced the amplitude of the P3 (Wang et al., 1999). Further, these effects were partially reversed by activation of muscarinic Ach receptors (mAChR) and infusion of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE). The authors suggest that Ach may have an important role in regulating the scalp P300, but add that the generation of any scalp potential is likely to be the product of complex interactions between different neurotransmitter systems, particularly the noradrenergic system. In keeping with this, the above proposals (and those that follow below) regarding acetylcholine assume that such interactions are a given factor of cortical organisation, and focus on the role of Ach within this interactive framework.

8.1.2 Arousal and Learning

The lack of learning facilitation due to arousal suggests that the effects of the dual task are indeed truly attentional in nature, but also calls into question the nature of this "bottom-up" arousal mechanism proposed by Sarter *et al.* (2001). In that model, the presence of an arousing stimulus leads to the noradrenergic recruitment of the basal forebrain activating system by the locus coeruleus and thalamus, resulting in enhancement of attention and facilitating stimulus processing. That this did not occur in our experiment gives rise to several possibilities. It could be the case that the chosen method of arousal was ineffective – the presence of random or continuous ringing tones simply did not bring these participants to a heightened state of arousal. This is unlikely, as alerting tones have been used in the past (Robertson *et al.*, 1998) to produce increases in arousal level, and the volume of tones used here was high – the tones were audible from neighbouring testing rooms. A second possibility is that the tones were arousing and succeeded in activating the basal forebrain acetylcholine cascade to its target sites, but that only certain selected areas were facilitated by the cholinergic efferents. Perhaps the enhancement of sensory cortices is modality-specific, and the alerting influence of an auditory tone resulted in a heightening of processing of auditory input only. This is also unlikely, as the studies of arousal-based task facilitation (Robertson *et al.*, 1998) involved tasks in different modalities. Furthermore, in adaptive terms, an arousal system that only heightened sensitivity in the sensory domain that caused its activation would be extremely ineffective, particularly in survival situations. This explanation may therefore also be rejected. Perhaps the most likely possibility involves the idea of a threshold of activation in the locus coeruleus and thalamus. Only if this threshold of activation is exceeded will

these structures innervate the basal forebrain and lead to attentional enhancement. In our case, the tones may have been arousing, but not sufficiently arousing to trigger this sequence. If this proposition is supported experimentally, future studies could attempt to determine the exact stimulus characteristics that lead to supra-threshold activation and those that result in sub-threshold. Should this be the case, it presents an additional dimension to the "bottom-up" aspect of the Sarter model of attention.

8.2 Response Inhibition and Sustained Attention – Mechanisms and Individual Differences

8.2.1 Individual Differences and Acetylcholine

The primary finding of interest from Chapter 5 was that two groups (one very prone to cognitive lapses, the other less so inclined) performing at statistically comparable levels showed marked and significant differences in brain activity while doing the task. This result is of interest for a number of reasons. As was discussed in Chapter 5, it is possible that the larger amplitudes for the highly absent-minded group reflect the fact that these participants were forced to expend more neural resources on the task in order to achieve the same performance level as those to whom the task came relatively easy. However, there may be an alternative or perhaps complementary explanation based on individual differences in neurochemistry. The X-Y response inhibition task requires the participant to monitor for novelty, specifically the novel occurrence of two like stimuli in a row. It has been shown in animals using in vivo microdialysis that exposure to novelty led to increases in hippocampal levels of acetylcholine which paralleled increases in behavioural exploration in the animals (Thiel *et al.*, 1998). Further, the authors found that, when the animals were divided

into "superior" and "inferior" learners, the "superior" animals had higher levels of extracellular hippocampal acetylcholine, and showed stronger neurochemical responses both in the novel and familiar environments. The authors suggest that this higher cholinergic reactivity in the hippocampus is the reason for the greater response to novelty in these "sensation-seeking" animals.

It could then be possible that a similar phenomenon is present in humans; that varying levels of cholinergic reactivity in key brain structures might result in their being absent-minded, or impulsive, or sensation-seekers. The CFQ has been found to correlate with measures of impulsivity in the past (Fassbender et al., *unpublished data*), while others have proposed a genetic link between impulsivity and sensation-seeking (Hur & Bouchard, 1997). Furthermore, both impulsivity and sensation-seeking in humans have been identified as predictors of adolescent psychopathy (Vitacco & Rogers, 2001; Blackburn, 1969) and have been associated with adult psychopathy and schizophrenia (Kaliski & Zabow, 1995). Both schizophrenics and psychopaths produce impaired performance and abnormal ERP activity during response inhibition tasks and are associated with disruption of the cholinergic and noradrenergic systems in the brain (Terry *et al.*, 2002; Nordahl *et al.*, 2001; Weisbrod *et al.*, 2000; Kiehl *et al.*, 2000; Friedman *et al.*, 1999). Sensation-seeking and impulsivity have also been associated with a range of behaviour patterns, many of which are known to entail poor inhibitory control; these include aggression (Patkar *et al.*, 2002; Stanley *et al.*, 2000), alcohol addiction and dependence (Lejoyeux *et al.*, 1998; Weijers *et al.*, 1997; Castellani & Rugle, 1995; Cherpitel, 1993), emotional reaction to alcohol (Nagoshi *et al.*, 1991), addiction in general (Sarramon *et al.*, 1999), cocaine addiction (Castellani & Rugle, 1995), cigarette smoking (Mitchell, 1999), pathological gambling (Petry, 2001; Blanco *et al.*, 1996; Castellani & Rugle,

1995), substance abuse (Petry, 2001) and violence (Kaliski & Zabow, 1995). In addition to acetylcholine and noradrenaline, monoamine oxidase (MAO), serotonin and dopamine are suspected to mediate these effects (Petry, 2001; Stanley *et al.*, 2000; Weijers *et al.*, 1997; Blanco *et al.*, 1996). Sensation-seeking individuals have also been found to have greater cortical responses to stimuli (Zuckerman, 1993), in keeping with the experimental animals of Thiel *et al.* (1998).

If it is the case that increased acetylcholine levels might be present in some individuals, their performance on a Go/NoGo task that is dependent on detection of novelty might be expected to produce enlarged ERP amplitudes in response to lures, though not necessarily to be associated with a performance decrement. Indeed, there was a considerable attenuation of range in the CFQ scores of this sample relative to the population at large – no CFQ scores in any of our samples exceeded 70, so the median split effectively placed those with scores from about 45 to 70 in the "high CFQ" category. The inclusion of a "truly" high CFQ group might be predicted to manifest similarly enlarged P300 amplitudes but accompanied by a behavioural performance decrement. In fact, this effect has been observed using the SART, a Go/NoGo test of sustained attention; Porter & Robertson (2002) observed larger P300 amplitudes and poorer performance in a group of high CFQ scorers whose scores ranged as high as 87. For such very high CFQ scorers, elevated resting levels of acetylcholine may have a disruptive rather than facilitative effect. Instead of enhancing processing in sensory areas to allow for the more efficient detection of targets (as outlined in the Sarter model of sustained attention), the overabundance of Ach may serve to make such sensory pathways hypersensitive, leaving these people prone to distraction. This might explain the larger P300 amplitude in both this and

our own experiments, as Ach is thought to be one of the main determinants of the amplitude of this component.

These speculative suggestions, if supported, point towards the possibility of an inverted-u function describing the relationship between Ach level/P300 amplitude and Go/NoGo task performance (Figure 8.3). Very low levels of Ach (as in the case of brain injury, for example) with associated small P300 amplitudes result in poor task performance (A). Moderate Ach levels (low to medium CFQ scorers) have larger P3 amplitudes and perform the task well (B). High CFQ scores, with elevated Ach levels and greater responsiveness to novelty have very large P3 amplitudes and are poor at the task (C). This proposal is, of course, a gross simplification, as many other factors and generators are likely to contribute to the amplitude of the P300 component, but it is presented as merely an attempt to elucidate the relationship between P300, its neurochemical basis and overt behaviour in a way that explains the present data. The model owes much to a conception of the interaction of "cue function" of sensory stimulation and arousal level proposed by Hebb in 1955.

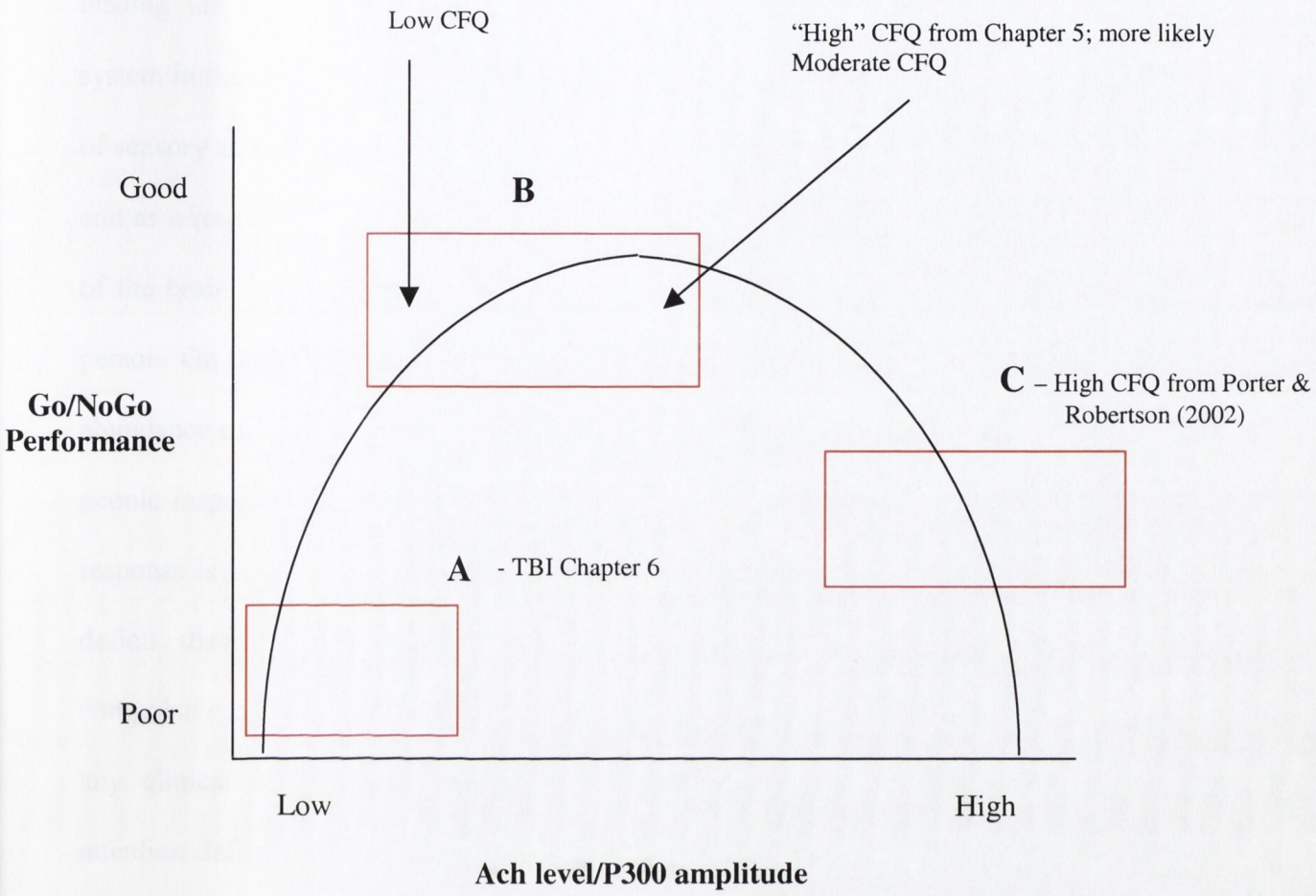

Figure 8.3: proposed model of the relationship between acetylcholine level with resultant P300 amplitude and performance on Go/NoGo tasks. Red squares represent positions at which data from specific experiments may lie.

A major implication of this model is that there are two distinct groups who may be poor at response inhibition/sustained attention, or rather at Go/NoGo tasks that purport to measure these capacities; one which falls on the left side of the curve, who are deficient in resting levels of acetylcholine, or perhaps in whom this cholinergic activating system is somehow dysfunctional, and another falling on the far right, in whom acetylcholine levels are high, or the cholinergic system is hyperactive (in fact, Nordahl *et al.* (2001) reported increased metabolic activity in anterior

cingulate cortex in schizophrenic patients who were poor at a response inhibition task, leading the authors to propose a hyperactive cholinergic/noradrenergic activating system in these participants). Those low in Ach do not receive sufficient enhancement of sensory and attentional networks to allow efficient detection of the NoGo stimulus, and as a result they appear to "forget" to withhold the response. This is characteristic of the brain-injured patient, or the absent-minded individual, or perhaps the elderly person. On the other end of the scale we find the highly impulsive person, with an abundance of Ach, who is hypersensitive to stimulation and highly distractible. Such people respond too fast to allow NoGo stimuli to be properly identified before their response is made. This end of the scale may contain those who suffer from attention-deficit disorders ADD and ADHD, those with schizophrenia and obsessive-compulsive disorder (OCD) as well as highly impulsive normals not suffering from any clinical disorder. Indeed, intuitively, the absent-minded academic and the attention-deficient child are qualitatively very different, yet both perform poorly on the Go/NoGo task. They seem more like polar opposites in their behaviour than two individuals both deficient in the same core capacity. The model proposed here might provide an explanation for this apparent paradox. It is again stated at this point that these proposals are made in reference to the role of acetylcholine within the context of its interaction with other neurotransmitters in generating ERP components and behaviour.

8.2.2 Response Inhibition and Sustained Attention

While the most famous and frequently used definition of attention comes from William James (1890) in which he states that attention is

"...the taking possession by the mind, in clear and vivid form, of one out of what seems several simultaneously possible objects or trains of thought"

a more useful definition in terms of current approaches to the topic comes from Donald Hebb (1976) in an address to a conference on minimal brain dysfunction:

"What does attention mean.....? .....Clearly, it means that one cortical-cognitive set of activities is able to maintain itself in spite of "noise" from irrelevant sensory stimulation and from the spontaneous activity of neurons, in the brain, that are not part of that cortical-cognitive process."

The former quote by James emphasises the idea of selection or enhancement, "taking possession", while Hebb's conception places a greater emphasis on inhibition of competing or irrelevant processes, be they driven by sensory input or internally generated. While both represent the same basic principle, the facilitation of one process over a number of others, either through enhancement of the central or suppression of the peripheral "cortical-cognitive sets", from a neuroanatomical point of view, it is likely that neurochemically-mediated strengthening of some circuits and damping of others takes place in the brain. This is an aspect neglected in the Sarter model of attention, which focuses purely on cholinergic facilitation of processing in attentional and sensory areas. In the specific case of response inhibition, a behaviour requiring both sustained attention and the ability to withhold an action, facilitatory and inhibitory processes are both clearly at play. What follows is an attempt, based on

data reported in this thesis and current theory, to provide a model of response inhibition in Go/NoGo tasks.

In addition to the individual differences between high and low CFQ scorers, the key finding of Chapter 5 was that successful withholding of a motor response was associated with earlier latency P2 and P3 components, implying support for a "horse race model" of inhibition (Logan *et al.*, 1984), with racing cognitive processes competing for completion. The P2 then, with its early peak latency, was considered (in this task, at least) to be an index of active inhibitory processes, with a P2 peak (or onset) occurring prior to a certain cut-off latency being necessary for successful inhibition. However, in Chapter 6 I concluded that it was the onset latency of the P3 component that seemed to determine the success of an inhibition attempt. No differences in P2 were found between the brain-injured and control groups. Perhaps the P2 reflects processes such as stimulus detection or classification necessary for effective inhibition, while it is the P3 onset that indexes inhibitory control *per se*. Irrespective of exactly what each of these components represents, it can be concluded that the latency of key ERP components is an indicator of speed of processing that may correspond to the "racing processes" posited in the race model of inhibition.

The success or failure of an attempt to withhold a response in a Go/NoGo task is dependent on the efficiency of top-down control of executive systems over motor pathways in the brain. This may be the site of the "race" between the competing processes of "respond" and "withhold". As was suggested in the Chapter 1, several factors may come into play to influence the outcome of this race, and primary amongst these is sustained attention. The decision to withhold must be made before a certain "point of no return" at which response-inducing processes have progressed to a point where overriding the command is impossible. This decision can only be made

if the lure stimulus is correctly and quickly identified, and the most significant influencing factor on this identification process is sustained attention. Through acetylcholine-mediated facilitation of sensory and attentional areas, the incoming stimulus will be identified as a target or a lure, and the appropriate response made to each. Thus, sustained attention may constitute the first stage of a two-stage process that determines the success or failure of an attempt to inhibit a response. The efficiency of stimulus identification processes will be a major determinant of the outcome of the race between inhibitory and action processes. The second stage of this two-stage model involves the "race" itself, or top-down control over motor pathways. This race is most likely run between frontal and cingulate executive sites and the striatum where the visuomotor association between target and response are probably stored. If sustained attention levels are low, respond processes will be given an effective "head start" over withhold processes. Furthermore, if the occurrence of lures is rare, and a propensity to respond has been established, respond processes will have a further advantage. Only in cases where attention is engaged will there be a possibility of detecting the lure stimulus early enough to allow inhibit processes to be initiated and overcome the advantage conferred upon respond processes by the infrequency of lures. In effect, for successful inhibition to occur, withhold processes have to come from the back of the field to win the race.

This model of response inhibition can be accommodated by the theory (discussed above) of the role of acetylcholine/P300 in attention. Very low levels of acetylcholine or disruption of cholinergic projections may result in ineffective attentional processes leading to failure to identify the lure stimulus in time to prevent the response. Abnormally high cholinergic reactivity may result in indiscriminate facilitation of all sensory input, leading to rapid responding to any visual stimulation.

In addition, it is possible that the exaggerated acetylcholine cascade may also innervate motor pathways, making them "potentiated", or more apt to fire in response to stimulation. This would predict faster reaction times to stimuli among the very high CFQ groups, as well as a higher rate of false presses. Clearly, the same groups who are poor at sustained attention measures based on Go/NoGo tasks would, under this model, also be predicted to be poor at Go/NoGo response inhibition tasks. There appears to be some support for this in the experimental literature, with disorders associated with poor response inhibition overlapping with those containing attentional deficits (Carter *et al.*, 2001; Casey *et al.*, 1997; Curtis *et al.*, 2001; Enright *et al.*, 1993; Liu *et al.*, 2002; Mataix-Cols *et al.*, 1997; Pliszka *et al.*, 2000).

The clear implication of this model, if it is to be believed, is that the standard Go/NoGo task in which the NoGo stimulus is infrequently presented is an inadequate index of sustained attention or response inhibition processes alone, and rather represents a picture of how these two cognitive capacities interact. Any task that purports to measure one of these capacities in isolation should give careful consideration to the other. Perhaps the best guideline for designing laboratory measures of sustained attention or response inhibition comes from real-life expressions of these capacities. Sustaining attention in reality often involves watching an object for long periods of inactivity; response inhibition is the ability to prevent oneself from scratching that itchy hive. The radar operator who fails to notice the appearance of an enemy aircraft is poor at sustaining attention. The sprinter who makes a false start is the one with poor inhibitory control, as is the pathological gambler who cannot stop pulling the lever on the slot machine. None of these situations involve making repeated motor actions and then trying to prevent them. The suggestion is made that an adequate measure of sustained attention will not

incorporate a response inhibition element, and a good inhibition measure will not be dependent on stimulus detection processes that can be influenced by attention.

7.2.3 Error Processing in Response Inhibition

A key feature of adaptive behavioural control is the ability to correct our own behaviour in the light of errors. Two of the experiments reported here investigated electrophysiological correlates of error-related processing. In Chapter 5, the error negativity (Ne) and error positivity (Pe) were both enlarged for high CFQ participants compared to low. It was proposed that this highly absentminded/impulsive group may have been hyper-responsive to errors, but also that since their behavioural performance did not suffer relative to low CFQs, this heightened level of responsiveness was not detrimental to performance; rather, it may lie near the threshold for effective execution of this task. Again the argument is put forward that this group was not a "truly" high CFQ group, and that such a group might show ever larger Ne and Pe, which would be associated with poorer performance. This proposal is again consistent with the cholinergic hypothesis, that increased levels of neurochemical (possible in the anterior cingulate area) may result in enlarged ERP amplitudes.

The data from the TBI group (Chapter 6) also supports the model. Like the amplitudes of the normal components (e.g. P3), the error-related waveforms had reduced amplitudes for the TBI group relative to matched controls. This suggests that errors may not be processed to a sufficient level in those suffering from brain injury, possibly leading to lack of awareness of errors, resultant failure to correct behaviour and ultimately producing poorer behavioural performance. This pattern of results also

gives further credence to the proposal of two distinct groups at opposite ends of a continuum who both are impaired on RI/SA tasks.

7.3 Interaction of Cortical Systems – Learning Across Task Domains

Understanding the way in which different cortical systems interact and cooperate, particularly in the context of learning, remains one of the most difficult tasks facing neuroscientists. As far back as 1949, Donald Hebb referred to three ways in which such systems could interact, and the differing effects of each way. Using the term "phase sequence" to refer to cortical pathways, he proposed that such interactions could be *conflicting*, wherein a stimulus or sensory event elicits a learned reaction that is incompatible with the current phase sequence. This can be achieved by disruption of any link in the sequence, which results in disruption of the whole. The second form of interaction could be *facilitatory*, where the input produces active support for, or direction of, the current phase sequence and leads to enhancement of that sequence. The third type of interaction involved *independent* phase sequences, where the sensory information is neither conflicting nor facilitatory, so independent phase sequences (pathways) are established. This third type of interaction mainly concerns situations in which one phase sequence is almost automatic, and so will receive no further attention here.

Taking the term "phase sequence" as roughly equivalent to a cortical pathway underpinning learned associations, I attempted to test the idea of conflicting interaction between cortical systems using the two cortical networks investigated in

Chapters 3-7, namely arbitrary visuomotor association learning and response inhibition. It is likely that these two processes share at least some neural apparatus, given that both require response evaluation and selection prior to execution. A successful demonstration of disruptive interaction between systems would make the possibility of facilitatory interactions very likely.

8.3.1 Disruption of Inhibitory Control through Training

In Chapter 7, I attempted to affect the performance of a higher order task (response inhibition) through the training of a low-level element of that task (a conflicting visuomotor association). This attempt proved largely unsuccessful until consideration of CFQ score was taken into account. It then emerged that, for high CFQ scorers, the association that had been most strongly learned (which was, in fact, to respond to a stimulus that was irrelevant to the task in question) produced an increase in the number of errors made on the inhibition task. In contrast, for the low CFQ group, a non-significant trend in the predicted direction (of disruption resulting from conflicting training) was found. This led to the claim that, in high CFQ participants, greater weight is placed on the motor output aspect of the task, while for low CFQs, the S-R association appears to be more important. This idea is consistent with the above proposal that higher levels of acetylcholine may be present in those who score high on the CFQ; a motor control system with a strongly learned association already present and already high in the concentration of acetylcholine would be more likely to produce a greater number of false presses than a system operating with normal levels of Ach. This claim will require further investigation before it can be stated with any certainty. However, the possibility exists that those who are highly impulsive, perhaps

by virtue of an overactive ascending acetylcholine system or some other reason, are more susceptible to disruption due to response conflict; that if any association is trained to a certain degree, these individuals will find it difficult to prevent themselves from making that motor action.

The exact mechanism by which low-level training affects this higher-order capacity is as yet unclear, but one may speculate as to its operation. It is likely that, due to training, a strengthened S-R association is stored in the basal ganglia (mediated by projections from hippocampus) which gives privileged access to a particular motor output pathway in premotor cortex. In terms of the race model, this effectively means a third "horse" has entered the race: in addition to processes for the making of the response to the target and processes aimed at inhibiting this act for a lure, this "potentiated" pathway, which shares the same motor output as the target response, also enters the fray. This has the effect of making the response even more likely, giving a further lead to the prepotent response processes over inhibitory processes. This is particularly true in the case of training with the task-relevant stimulus ("anti-training"), in which participants are trained to respond to the lure before the response inhibition task begins. Indeed, in some ways, this situation might prove a more valid indicator of inhibitory control than the Go/NoGo task on its own, as this scenario pushes the system to its limits, with inhibitory processes being forced to overcome what is close to an insurmountable lead for the respond processes. A high degree of inhibitory control would be required to successfully withhold a response to the lure in this situation, as was evident in both the high and low CFQ scorers in Chapter 7.

For the situation in which an irrelevant stimulus is paired with the target response ("irrelevant training"), other considerations emerge. The high CFQ group were found to produce more false presses following this type of training than after

anti-training or in the absence of any prior training at all. The most likely explanation, as was mentioned in Chapter 7, lies in the fact that the *strength* of the training was greater in the irrelevant condition compared to the anti-training; participants made more correct index-finger presses in response to the target in the irrelevant training condition.

8.3.2 Facilitation of Inhibitory Control through Training

The success of an attempt to disrupt performance through training of a conflicting cortical system creates the possibility that similar approaches might be successful in causing facilitation of response inhibition. Furthermore, the dissociation of CFQ scorers suggests that different emphases could be more effective for different groups based on individual differences. Specifically, the strength of learning was more important in disrupting high CFQ participants, regardless of the stimulus presented, whereas when the stimulus-response association was conflicting, the low CFQ group showed a trend toward disruption. As was suggested in Chapter 6, training involving the task-relevant stimulus and response may, if trained robustly, lead to task decrements in low CFQ respondents, while a strongly trained association between any stimulus and the task-relevant response should cause poorer performance in a high CFQ group.

The same principle may be useful in predicting potential task facilitation under such a training regime. High CFQ groups, with their apparent leaning towards the motor control aspects of the task, may be facilitated by training an association between the lure stimulus and a different response, perhaps a middle-finger press. Low CFQ participants may, on the other hand, benefit more from training with an

irrelevant stimulus paired with the normal task response. This should potentially produce a strongly-learned association between one aspect of the inhibition task's S-R association (i.e. lure---withhold index-finger press) and an irrelevant stimulus or response. Thus, High CFQs would have a propensity to respond with the middle-finger, which should facilitate the withholding of index-finger presses, while low CFQs would have learned to associate a different stimulus with the index-finger press, also facilitating withholding in response to a lure stimulus. This approach is consistent with Hebb's (1949) proposal of interacting phase sequences, in which cortical pathways that share key structures may be used to facilitate or disrupt each other.

8.4 Concluding Remarks

In this thesis I have investigated two key areas of interest in cognitive neuropsychology, arbitrary association learning and response inhibition. I have demonstrated that activity in the neural substrates of association learning can be detected by scalp-electrode recordings, and that this learning is influenced by attention and training. I have shown that the latency of key ERP components appears to be vital in determining whether successful response inhibition will occur, and that individual differences in absentmindedness/impulsivity produce different patterns of electrophysiological activity. It is suggested that resting levels of acetylcholine may play a role in both the amplitude of ERP components and the quality of performance in RI tasks. Finally, I have demonstrated that through training of the stimulus-response association involved in an RI task, the interaction of cortical systems can lead to performance decrements on a high-level cognitive activity.

Appendix I

Psychological Tests

- ***Cognitive Failures Questionnaire (CFQ)***
- ***National Adult Reading Test (NART)***
- ***Hospital Anxiety and Depression Scale (HADS)***
- ***Revised Strategy Application Task (R-SAT)***
- ***Test of Everyday Attention (TEA; Telephone Search Task)***
- ***Wechsler Memory Scale (WMS)***

CONFIDENTIAL

Name.....

Date of Birth.....

Sex (please circle) **m / f**

ID.....

CFQ

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

	Very often	Quite often	Occasio-nally	Very rarely	Never
Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
Do you fail to notice signposts on the road?	4	3	2	1	0
Do you find you confuse right and left when giving directions?	4	3	2	1	0
Do you bump into people?	4	3	2	1	0
Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
Do you say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
Do you lose your temper and regret it?	4	3	2	1	0

	Very often	Quite often	Occasio-nally	Very rarely	Never
Do you leave important letters unanswered for days?	4	3	2	1	0
Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
Do you have trouble making up your mind?	4	3	2	1	0
Do you find you forget appointments?	4	3	2	1	0
Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
Do you find you accidentally throw away the thing you want and keep what you meant to throw away as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
Do you daydream when you ought to be listening to something?	4	3	2	1	0
Do you find you forget people's names?	4	3	2	1	0
Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
Do you find you forget what you came to the shops to buy?	4	3	2	1	0
Do you drop things?	4	3	2	1	0
Do you find you can't think of anything to say?	4	3	2	1	0

National Adult Reading Test

Ache _____

Debt _____

Psalm _____

Depot _____

Chord _____

Bouquet _____

Deny _____

Capon _____

Heir _____

Aisle _____

Subtle _____

Nausea _____

Equivocal _____

Naïve _____

Thyme _____

Courteous _____

Gaoled _____

Procreate _____

Quadruped _____

Catacomb _____

Superfluous _____

Radix _____

Assignate _____

Gist _____

Hiatus _____

Simile _____

Aeon _____

Cellist _____

Zealot _____

Abstemious _____

Gouge _____

Placebo _____

Façade _____

Aver _____

Leviathan _____

Chagrin _____

Détente _____

Gauche _____

Drachm _____

Idyll _____

Beatify _____

Banal _____

Sidereal _____

Puerperal _____

Topiary _____

Demesne _____

Labile _____

Phlegm _____

Syncope _____

Prelate _____

HAD Scale **Subject no.____**

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or 'wound up'

- Most of the time ☐
- A lot of the time ☐
- Time to time, Occasionally ☐
- Not at all ☐

2. I still enjoy the things I used to enjoy

- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

3. I get a sort of frightened feeling as if something awful is about to happen

- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

4. I can laugh and see the funny side of things.

- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

5. Worrying thoughts go through my mind

- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not often ☐
- Only occasionally ☐

6. I feel cheerful

- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

7. I can sit at ease and feel relaxed

- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

8. I feel as if I am slowed down

- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

9. I get a sort of frightened feeling like 'butterflies' in the stomach.

- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

10. I have lost interest in my appearance

- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

11. I feel restless as if I have to be on the move.

- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

12. I look forward with enjoyment to things.

- As much as ever I did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

13. I get sudden feelings of panic

- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

14. I can enjoy a good book or radio or TV programme

- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Subtest 6: Telephone Search

For full text and procedure see Manual page 19.

- *'In this exercise, you should imagine that you are using a telephone directory to look up various services while you are on your trip.'*
- *'Here we have the yellow pages you would see in a telephone directory, in this case it lists plumbers/restaurants/hotels.'*
- Show subject the target symbol cues (in the test materials book), the relevant yellow pages sheet, and a pen.
- *'Imagine that during your vacation (holiday)...'*
- Prepare stopwatch.
- *'Begin'*
- Start watch as subject makes first mark.
  Stop watch when subject puts cross in box.

Time taken (seconds) ÷ ____ = **A** **Raw score** (time per target score)

Total number of correctly-circled symbols (ignore any false positives)

Subtest 7: Telephone Search While Counting

For full text and procedure see Manual page 20.

- *'Now you will search through a different set of yellow pages for the same double symbols as in the last subtest. But this time, I will ask you to do a second and equally important task at the same time – counting a number of series of tones on the tape recorder...'*
- Show subject the restaurants/hotels/plumbers yellow pages.
- Play practice item, and count with the subject.
- *'So you will be looking for the same double symbols...'*
- *'Get ready...'*
- Prepare stopwatch.
- Subject starts when tape-voice says *'Ready...'*
- Start watch as subject makes first mark.
  Stop watch when subject puts cross in box.
- Note the number of strings of tones which the subject attempts in the box marked **C** below.

	1	2	3	4	5	6	7	8	9
Response									
✓/✗									
Answers **A**	4	8	3	6	1	12	2	5	7
B	6	1	12	2	5	7	5	9	2
C	2	5	7	5	9	2	6	11	3

	10	11	12	13	14	15	16	17	18
Response									
✓/✗									
Answers **A**	5	9	2	6	11	3	6	3	5
B	6	11	3	6	3	5	5	4	8
C	6	3	5	5	4	8	3	6	12

Time taken (seconds) ÷ ____ = **B** Time per target score

Total number of correctly-circled symbols (ignore any false positives)

Number of strings of tones correctly counted ÷ **C** ____ = **D** Proportion correctly counted

Number of strings of tones attempted

Re-enter **B** here ÷ ____ = **E** Time per target weighted for accuracy of tone-counting

Re-enter **D** here

Re-enter **E** here − ____ = **Dual task decrement**

Subtract Re-enter **A** here

Subtest 8: Lottery

For full text and procedure see Manual page 21.

- *'While you are on your trip, you become interested in the state lottery...'*
- Show subject the target cues (version A, B or C in the test materials book) and give the subject a piece of paper and a pen.
- *'The radio programme goes on for quite a long time...'*
- Play the tape.
- Stop after first number ending in 55 / 88 / 33.
  Rewind and repeat until the subject responds correctly.

	1	2	3	4	5	6	7	8	9	10
A	HH	EA	LV	DR	CF	QO	TS	FN	FA	XT
B	WG	WA	LW	CT	YK	UF	CM	UA	RN	HY
C	FN	AT	XW	YG	EA	WN	RC	FO	HU	IT

Raw score Score 1 for each response with *at least* one letter correct *and* in the correct position (maximum = 10)

Revised Strategy Application Test (R-SAT)

Levine et al. (2000), Neuropsychology, 14, 491-500
Version: June 2001

Brian Levine, Ph.D.
Rotman Research Institute, Baycrest Centre for Geriatric Care and
Departments of Psychology and Medicine (Neurology),
University of Toronto
Voice: (416) 785-2500 x. 3593 Fax: (416) 785-2862
email: blevine@rotman-baycrest.on.ca
www: http://www.psych.utoronto.ca/~levine

These test materials are for research purposes.
Please do not distribute without permission.

Instructions

(BOLD *indicates instructions to be read to subject)*

The R-SAT involves three main phases: pre-test and instruction learning, performance of the task, and instruction recall/debriefing.

PRE-TEST AND INSTRUCTION LEARNING

Ask subject to remove his or her watch and place it out of view.

Lay out 3 stacks (order: counting, sentence copying, tracing). Orient the stacks so the page number is right side up to the examiner sitting across from the subject. Place the instruction sheet above the middle stack. Note that there are two instruction sheets indicating different time limits (10 or 15 minutes). Use the 15 minute sheet for slower subjects. Do not hand subject pencil.

In the next 10 (or 15) minutes I'd like you do to three different tasks for me. The tasks are to trace these drawings, copy these sentences, and count these objects.

To trace a drawing, take a pen and draw a line over the whole drawing. To copy a sentence, just write it on the line below. To count sets of objects, write a number inside each object within a set. For example, if you were to count this set of objects, you would put a one here, a two here, and keep putting numbers in until you've counted all the objects in the set. Each group of objects is a different set.

The items come in two sizes, small and large. These are small tracing items, and this is a large one. These are small sentence copying items, and this is a large one. These are small counting items, and this is a large one. You will receive 100 points for each small item and 0 points for each large item.

I'm giving you 10 (or 15) minutes to get as many points as you can. It is impossible to do all of these items in these stacks in 10 (or 15) minutes.

Which items you chose to complete is up to you. You can do as many or as few items within a stack as you want. You do not have to do all the items on a page. The most important thing is to get as many points as you can. The only thing I ask is that you to make sure you do some work in each of the three stacks. Do not spend all your time in just one or two stacks.

Some of these pages have this symbol on it *(point to symbol on instruction sheet).* The symbol is all over the page. If you see this symbol, do not do any items on that page. If you do any items on that page, small or large, you will lose all the points you have earned so far.

Finally, you are to put a check mark in these boxes each time a minute goes by. For example, put a check mark here at the end of the first minute, a check mark here at the end of the second minute, and so on. You have to estimate when each minute goes by.

Any questions? Before we start I need to make sure you understand the instructions. I want you to read this over and when you think you know them, I will take the sheet away and ask you to tell them back to me. You can say them in any order and in your own words.

Instructions recall is evaluated with a selective reminding procedure before beginning the task. Paraphrased instructions are acceptable, as long as the main idea is there. For each instruction, indicate recall on R-SAT Record Sheet. If all instructions are freely recalled, begin the task as specified below. If any instructions are incorrect or omitted, tell the subject the instruction(s), give back the rule sheet, and say,

I'd like you to read them over again and tell me when you think you've learned them, then I'll test you again.

Repeat selective reminding procedure. Record performance on the R-SAT Record Sheet. If all instructions are recalled, begin the task as specified below. If there are omissions or errors, correct them and ask the subject to study the list one last time. For the third recall trial use the cues as specified on the R-SAT Record Sheet. Correct any omitted/incorrect instructions and begin the task regardless of subject's performance.

The task instructions are readily understood and learned by most subjects. Memory-impaired subjects or those with mild dementia may have difficulties with the complexity of the task. It is not unusual for the selective-reminding procedure to interfere with the prior basic instructions on how to complete the items. If you suspect that this is the case, take a moment to briefly review the entire task protocol before beginning.

PERFORMANCE OF THE TASK

Place the instruction sheet in full view and accessible for placing check marks, hand the patient a pencil and say, ***"I'm going to start timing now. Go ahead"*** *Start the stopwatch.*

For each page completed, record the page number and the running time at which the subject switched to a new page. If the subject does very few (i.e., 1 or 2) items on a page and jumps around to different pages, you may not be able to record this information. In this case, record the running time each time the subject completes 10 items. It is more important to record the time than the page, so if the subject is moving very fast across pages, record the time first, then the page if you can. If you miss recording a page number, you can usually figure it out it after the test was completed, but this is harder to do for the time. If a subject comes back to a page, indicate how many items were completed each time the page was visited.

Also record the running time each time a check mark is placed. Again, this may be difficult. Many subjects will place a check mark after completing a page, in which case you can just indicate that a mark was placed when you record the time. Note any instances of double check marks placed (some subjects will do this to compensate for prior missed checkmarks).

If there are any questions at any point during the task, only give information already contained in instructions (e.g., "You do not have to do all the items on a page"). Patients may seek additional information. Your response should be: ***"I'm not allowed to tell you that."***

During the task, liberally note any unusual behavior, comments or questions. Intervene only in the case of gross violations (e.g., partial completion of items).

Do not stop any subject until they have completed at least 30 items on pages 3-20, 23-40, or 43-60. In other words, they must complete 30 items in any stack that are not in the first two pages of each stack. Healthy subjects can do this well within the 10-minute time limit for the task, but slower subjects may need extra time to complete this minimum number of items. For slow subjects, you will have to keep a tally of the number of items completed (not including pages 1-2, 21-22, or 41-42), and continue until you are sure that the 30-item criterion has been met before stopping.

Scores include the total number of items completed, the number of items completed on pages 3-20, 23-40, or 43-60, the number of those items that are brief, medium, or long, and the proportion of items on pages 3-20, 23-40, or 43-60 that are brief. This final score is speed-corrected and is the primary score reflecting strategy application. The classification of items into brief, medium, and long is determined from the R-SAT scoring templates (with items labeled "E", "M", "H" indicating brief, medium, and long, respectively). Action slips (large items and face-page items) and number of check marks are also recorded. Given that the R-SAT is an unstructured task, examiners may note other qualitative observations that reflect the subjects' strategic approach.

INSTRUCTION RECALL / DEBRIEFING

When the time is up, remove all the stacks and the instructions and administer instruction recall as specified on the R-SAT Record Sheet. While removing the sheets, it is helpful to set aside sheets where transgressions occurred (e.g. large items, lengthy items, or face-page items) to show them to the subject during debriefing.

The first step in debriefing is to obtain the subject's own unstructured description of how they performed the task ("How did you go about doing the tasks?") Record response verbatim. If response is minimal, non-specific cues can be used ("Tell me more"), but do not ask any question which would reveal a strategic approach. Note whether subject spontaneously mentioned the appropriate strategy (focusing on brief items) and record this on the R-SAT Record Sheet.

The next step is a brief interview designed to resolve discrepancies between a) the subjects' intentions and his or her behavior and b) the best strategy (i.e., the examiner's intentions) and the subjects' behavior. If a good strategy was adopted (i.e., only fast items, no large items, check marks placed, no pages with faces, sampling from all three stacks) there are no discrepancies to resolve and the task is terminated.

If any transgressions occurred, you have to find out if the subject was aware of the transgression, and why the transgression occurred. The transgression can occur because the subject intended to do well, but did not. This is typically the case with the faces, because there is no ambiguity in detecting the faces or knowing what they mean.

The transgression could also occur because the subject did not properly understand the task, so they never had a chance to set up the good intention. For example, if a subject believed that it skipping items was not allowed, they would never set up the intention to skip long items.

For each transgression, use the following questions to determine the subjects' level of awareness of the strategy and transgression. It may not be necessary to ask all the questions for each transgression. Allow subject to explain as much as possible. It is better for the subject to acknowledge the good strategy on his or her own rather than acknowledge it after it has been suggested by the examiner. Therefore, for each transgression, start with the first, non-specific question, then proceed to more constraining questions if the proper strategy isn't acknowledged. If it is clear that the subject does not spontaneously acknowledge the correct strategy, the examiner may then state the strategy and determine of the subject agrees. The questions may have to be modified according to the subject's behavior. A useful final question to establish the subjects' acknowledgement of the best strategy is: **"If you had it to do over again, would you do it the same way?"**

The subjects' level of awareness of the strategy and their transgression is recorded on the R-SAT record sheet. Their actual responses can be recorded below.
Spontaneous acknowledgement is defined as an unambiguous statement of the correct strategy during (or before) the task or during debriefing up to the point where the strategy is explicitly stated by the examiner.

Agree indicates that the subject did not spontaneously acknowledge the correct strategy, but agreed with it when directly queried by the examiner.
Incorrect is used for subjects who do not spontaneously acknowledge or agree with the appropriate strategy as defined by the examiner. This category is also used when subjects simply misunderstood the instructions. Misunderstanding instructions should be carefully noted so that these subjects can be distinguished from subjects who understood the instructions, but were not governed by the instructions when performing the task.

Debriefing Interview

How did you go about doing the task?

Large items

I noticed you did some of the large items.

Did you know you were doing them?

How much were the large items worth?

Would it have made sense to skip the large items?

(If answer was no) **Why not?**

Faces

I noticed you did a page with faces on it.

Did you see the faces?

Did you remember that doing the page with the faces meant losing all your points?

Check marks

I noticed you didn't place any (only placed X) check marks.

Did you remember that you were supposed to place check marks?

Long items

I noticed you did some of these really long items.

Could you have done some of these easy ones instead the harder, longer ones?

Did you think you had to complete a whole page?

Was it your understanding that you had to do those items?

Not sampling from all three stacks

I noticed that you didn't do any counting/sentence copying/tracing items.

Why didn't you do them?

Did you recall that you were supposed to do items from all three stacks?

WMS®-III UK

LER MEMORY SCALE – THIRD EDITION

Name_____

Examiner_____

Age _____ Date of Testing _____

Information and Orientation (Optional)

RECORDING:
All responses verbatim

SCORING RULE:
Items 1–14: 0–1 pt. for each item
Do not score Items 15–18.

m	Response	Score 0 or 1
What is your full name?		
How old are you?		
When were you born?		
Where were you born?		
What is your mother's first name? (If examinee does not know, ask, "Then what is your father's name?")		
Who is the Prime Minister of the United Kingdom?		
Who was Prime Minister before him?		
What year is this?		
What month is this?		
What day of the month is this?		
What is the name of the place you are in?		
In what city/town is it?		
What day of the week is it?		
Without looking at the clock, what time is it now? response ____:____ actual time ____:____ difference in mins.____		
Are you left-handed or right-handed?		
Do you have any difficulty in hearing?		
Do you need glasses for reading?		
Are you colour-blind?		

Total Score
Range = 0 to 14 ____

Logical Memory I

RECORDING:
Place a tick (✓) next to each story unit recalled verbatim. Write non-verbatim responses next to the story unit.

SCORING RULE:
0–1 pt. for each story or thematic unit
See Administration and Scoring Manual (Chapter 4 and Appendix A) for scoring criteria.

A

Thompson of South London, employed as a cook in a school canteen, reported at the police station he had been held up on the High Street the night before and robbed of fifty-six pounds. She had small children, the rent was due, and they had not eaten for two days. The police, touched by the n's story, made up a collection for her.

page to record Story A Responses.)

2. Logical Memory I *(continued)*

	Score 0 or 1		
Story A	Story Unit	Thematic Unit	Scoring Criteria
Anna			*Anna* or variant of the name
Thompson			*Thompson* is required
of South			*South* (in any context)
London,			*London* (in any context)
			indication of a main character who is female
employed			indication that she held a job
as a cook			*cook* or some form of the word is required
in a school			*school* is required
canteen,			*canteen* is required
			indication that main character is employed or is working
reported			indication that a formal statement was made to someone in authority (in any context)
at the police			*police* (in any context)
station			*station* (in any context) or a word or phrase denoting a police station
that she had been held up			indication that she had been held up (i.e., gunpoint or knife)
on the High Street			*the High Street* (in any context)
the night before			indication that the hold-up occurred the previous night
and robbed			indication that a robbery took place
of fifty-six pounds.			indication that an amount of money greater than £49 but less than £60 was taken from her
			indication that main character reported that she was robbed
She had four			*four* is required together with an indication that the children were hers
small children,			*children* or a synonym is required
			indication that main character had children
the rent was due,			a phrase indicating that the rent was due
and they had not eaten			indication that her children or the family were without food
for two days.			*two days* is required, or a phrase meaning about two days
			indication that characters were in need or required assistance
The police,			a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,			indication that her story evoked sympathy
			indication that the police felt sympathy for the woman
made up a collection			a phrase indicating that money was collected
for her.			indication that the money collected was for her or her children
			indication that the police directly responded to her need

Story A
Recall Unit Score
Range = 0 to 25

Story A
Thematic Unit Score
Range = 0 to 7

ory B–1st Recall — 2. Logical Memory I *(continued)*

6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. weather report interrupted the programme to warn that thunderstorms would move into the area thin the next two to three hours and remain until morning. The announcer said the storm could ng hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe cided to stay home. He took off his coat and sat down to watch old films.

	Score 0 or 1		
Story B — 1st Recall	Story Unit	Thematic Unit	Scoring Criteria
t 6:00			*6:00* is required
n Monday			*Monday* is required
vening,			*evening* (in any context)
oe			*Joe* or variant of the name
Grant			*Grant* is required
f Liverpool			*Liverpool* is required
			indication of a main character who is male
as watching television			indication that he was watching/listening to the television
s he dressed			indication that he was getting dressed
o go out.			indication that he was going out
			indication that the character was preparing to leave
weather report			indication that there was an announcement about weather
terrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
warn that thunderstorms			indication that there was a warning about a storm
ould move into the area			indication that the storm was coming
			indication of a storm moving into the area
thin the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
d remain until morning.			indication that the storm would stay until morning
			indication of storm duration
e announcer said			indication that someone was reporting about a storm
e storm could bring hail			indication that hail was possible
d up to 4 inches			*4 inches* is required
rain			*rain* is required
d cause the temperature to drop			indication that the temperature would drop or decrease
15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
e decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
e took off his coat			indication that he took off outer clothing
d sat down			indication that he was sitting down
watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

Story B — 1st Recall Unit Score Range = 0 to 25 [ ]

Story B — 1st Recall Thematic Unit Score Range = 0 to 8

1st Recall Total Score Calculation

[ ] + [ ] = [ ]

Story A Recall Unit Score Range = 0 to 25

Story B — 1st Recall Unit Score Range = 0 to 25

1st Recall Total Score Range = 0 to 50

Story B–2nd Recall

2. Logical Memory I *(continued)*

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

	Score 0 or 1		
Story B — 2nd Recall	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
At 6:00			*6:00* is required
on Monday			*Monday* is required
evening,			*evening* (in any context)
Joe			*Joe* or variant of the name
Grant			*Grant* is required
of Liverpool			*Liverpool* is required
			indication of a main character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			*4 inches* is required
of rain			*rain* is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

ry B—2nd Recall Unit Score
Range = 0 to 25

Story B— 2nd Recall Thematic Unit Score
Range = 0 to 8

Recall Total Score
Range = 0 to 75

Thematic Total Score
Range = 0 to 23

cail Unit Scores for Story A, Story B–1st, Story B–2nd)

(Sum Thematic Unit Scores for Story A, Story B–1st, Story B–2nd)

Learning Slope Calculation

[ ] − [ ] = [ ]

Learning Slope
Range =
-25 to + 25

Story B—2nd Recall Unit Score Range = 0 to 25

Story B—1st Recall Unit Score Range = 0 to 25

12. Logical Memory II

ADMINISTER 25–35 MINUTES AFTER LOGICAL MEMORY I.

Recall

RECORDING:
Place a tick (✓) next to each story unit recalled verbatim. Write non-verbatim responses next to the story unit.

SCORING RULE:
0–1 pt. for each story or thematic unit

Reminder Given? ❑ Yes ❑ No

	Score 0 or 1		
Story A	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
Anna			*Anna* or variant of the name
Thompson			*Thompson* is required
of South			*South* (in any context)
London,			*London* (in any context)
			indication of a main character who is female
employed			indication that she held a job
as a cook			*cook* or some form of the word is required
in a school			*school* is required
canteen,			*canteen* is required
			indication that main character is employed or is working
reported			indication that a formal statement was made to someone in authority (in any context)
at the police			*police* (in any context)
station			*station* (in any context) or a word or phrase denoting a police station
that she had been held up			indication that she had been held up (i.e., gunpoint or knife)
on the High Street			*the High Street* (in any context)
the night before			indication that the hold-up occurred the previous night
and robbed			indication that a robbery took place
of fifty-six pounds.			indication that an amount of money greater than £49 but less than £60 was taken from her
			indication that main character reported that she was robbed
She had four			*four* is required together with an indication that the children were hers
small children,			*children* or a synonym is required
			indication that main character had children
the rent was due,			a phrase indicating that the rent was due
and they had not eaten			indication that her children or the family were without food
for two days.			*two days* is required, or a phrase meaning about two days
			indication that characters were in need or required assistance
The police,			a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,			indication that her story evoked sympathy
			indication that the police felt sympathy for the woman
made up a collection			a phrase indicating that money was collected
for her.			indication that the money collected was for her or her children
			indication that the police directly responded to her need

Story A Recall Unit Score Range = 0 to 25			Story A Thematic Unit Score Range = 0 to 7

. Logical Memory II *(continued)*

eminder Given? ❑ Yes ❑ No

	Score 0 or 1		
Story B	Story Unit	Thematic Unit	Scoring Criteria
At 6:00			*6:00* is required
on Monday			*Monday* is required
evening,			*evening* (in any context)
Joe			*Joe* or variant of the name
Grant			*Grant* is required
of Liverpool			*Liverpool* is required
			indication of a main character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			*4 inches* is required
of rain			*rain* is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

y B Recall Unit Score
Range = 0 to 25

Story B Thematic Unit Score
Range = 0 to 8

Recall Total Score
Range = 0 to 50

Thematic Total Score
Range = 0 to 15

ll Unit Scores for Story A & Story B)

(Sum Thematic Unit Scores for Story A & Story B)

12. Logical Memory II *(continued)*

Recognition

RECORDING:
Circle Y or N.

SCORING RULE:
0–1 pt. for each item

Item	Circle Y or N	Score 0 or 1
Story A		
1. Was the woman's name Anna Thompson?	Y N	
2. Was the story setting in South London?	Y N	
3. Was the woman a cook?	Y N	
4. Did she work in a canteen?	Y N	
5. Did she have four children?	Y N	
6. Were the children teenagers?	Y N	
7. Did the robbery take place on the High Street?	Y N	
8. Did the woman report being robbed two nights before?	Y N	
9. Did she report the robbery at the Police Station?	Y N	
10. Was the woman robbed of 75 pounds?	Y N	
11. Did the family go without food for four days?	Y N	
12. Was the rent due?	Y N	
13. Did the police catch the thief?	Y N	
14. Did the police feel sorry for the woman?	Y N	
15. Did the police make up a collection?	Y N	
Story B		
1. Was the man's name Joe Green?	Y N	
2. Was it Sunday evening?	Y N	
3. Was it 6:00?	Y N	
4. Was the story setting in Liverpool?	Y N	
5. Was Joe dressing to go out?	Y N	
6. Was Joe watching television?	Y N	
7. Was the programme interrupted?	Y N	
8. Was the storm expected to move into the area on Tuesday?	Y N	
9. Was the storm expected to stay in the area through the night?	Y N	
10. Was the temperature predicted to drop 30 degrees?	Y N	
11. Did the announcer predict 10 inches of rain?	Y N	
12. Did the announcer warn of possible flooding?	Y N	
13. Did the announcer warn that it could hail?	Y N	
14. Did Joe decide to stay home?	Y N	
15. Did Joe sit down to watch a sports programme?	Y N	

Recognition Total Score
Range = 0 to 30 ____

cent Retention Calculation

____ ÷ ____ x 100 = ____ Percent Retention Range = 0 to 100%

gical Memory II call Total Score nge = 0 to 50

Logical Memory I Story A Recall Unit Score + Story B–2nd Recall Unit Score Range = 0 to 50

References

A

Acosta, V.W. & Nasman, V.T. (1992). Effect of task decision on P300. *International Journal of Psychophysiology*, **13**, 37-44.

American Encephalographic Society (1994b). Guidelines for standard electrode position nomenclature. *Journal of Clinical Neurophysiology*, **11,** 40-73.

Anderson, V., Fenwick, T., Manly, T. & Robertson, I. (1998). Attentional skills following traumatic brain injury in childhood: a componential analysis. *Brain Injury*, **12**, (11), 937-949.

B

Baddeley, A. (1986). *Working Memory*. Oxford: Clarendon Press.

Banaschewski, T., Besmens, F., Zieger, H. & Rothenberger, A. (2001). Evaluation of sensorimotor training in children with ADHD. *Perceptual and Motor Skills*, **92,** (1), 137-149.

Beck, A. (1890). Die Bestimmung der Localisation der Gehirn- und Rückenmarksfunctionen vermittelst der elektrischen Erscheinungen.

Benjamin, A.S., Bjork, R.A. & Schwartz, B.L. (1998). The Mismeasure of Memory: When Retrieval Fluency Is Misleading as a Metamnemonic Index. *Journal of Experimental Psychology: General*, **127**, (1), 55-68.

Benjamin, A.S. & Bjork, R.A. (2000). On the Relationship Between Recognition Speed and Accuracy for Words Rehearsed Via Rote Versus Elaborative Rehearsal, *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **26**, (3), 638-648.

Bennington, J.Y. & Polich, J. (1999). Comparison of P300 from passive and active tasks for auditory and visual stimuli. *International Journal of Psychophysiology*, **34**, (2), 171-177.

Berger, H. (1929). Über das electroenkephalogram des Menschen. *Archiv Psychiatiatrische Nervenkrank*, **87**, 527-570.

Berry, W., Buck, P. Mills, M. & Stipe, M. (1994). What's the frequency , Kenneth? On the role of frequency in auditory perception. *International Journal of Acoustics*, **21**, (3), 170-179.

Blackburn, R. (1969). Sensation seeking, impulsivity, and psychopathic personality. *Journal of Consulting and Clinical Psychology*, **33**, (5), 571-574.

Blanco, C., Orensanz-Muñoz, L., Blanco-Jerez, C. & Saiz-Ruiz, J. (1996). Pathological gambling and platelet MAO activity: a psychobiological study. *American Journal of Psychiatry*, **153**, (1), 119-121.

Bliss, T.V. & Collingridge, G.L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature*, **361**, (6407), 31-39.

Bokura, H., Yamaguchi, S. & Kobayashi, S. (2002). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clinical Neurophysiology,* **112**, 2224-2232.

Brandeis, D., van Leeuwen, T.H., Rubia, K., Vitacco, D., Steger, J., Pascual-Marqui, R.D. & Steinhausen, H-Ch. (1998). Neuroelectric mapping reveals precursor of stop failures in children with attentional deficits. *Behavioural Brain Research*, **94**, 111-125.

Broadbent, D.E., Cooper, P.F., FitzGerald, P. & Parkes, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology / the British Psychological Society*, **21**, 1-16.

Bruin, K.J., Wijers, A.A. & van Staveren, A.S.J. (2001). Response priming in a go/nogo task: do we have to explain the go/nogo N2 effect in terms of response activation instead of inhibition? *Clinical Neurophysiology*, **112**, 1660-1671.

Bussey, T.J., Wise, S.P. & Murray, E.A. (2001). The Role of Ventral and Orbital Prefrontal Cortex in Conditional Visuomotor Learning and Strategy Use in Rhesus Monkeys (Macaca mulatta), *Behavioral Neuroscience*, **115**, (5), 971-982.

Bussey, T.J., Wise, S.P. & Murray, E.A. (2001). Interaction of Ventral and Orbital Prefrontal Cortex With Inferotemporal Cortex in Conditional Visuomotor Learning, *Behavioral Neuroscience*, **116**, (4), 703-715.

C

Cahusac, P.M., Rolls, E.T., Miyashita, Y. & Niki, H. (1993). Modification of the responses of hippocampal neurons in the monkey during the learning of a conditional spatial response task. *Hippocampus*, **3**, (1), 29-42.

Carter, C.S., MacDonald, A.W. 3rd, Ross, L.L. & Stenger, V.A. (2001). Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. *American Journal of Psychiatry*, **158**, (9), 1423-1428.

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D. & Cohen, J.D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, **280**, (5364), 747-749.

Casey, B.J., Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Schubert, A.B., Vauss, Y.C., Vaituzis, A.C., Dickstein, D.P., et al. (1997). Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, **36**, (3), 374-383.

Castellani, B. & Rugle, L. (1995). A comparison of pathological gamblers to alcoholics and cocaine misusers on impulsivity, sensation seeking, and craving. *International Journal of the Addictions*, **30**, (3), 275-289.

Caton, R. (1875). The electrical currents of the brain. *British Medical Journal*, **278**. *Centralblatt für Physiologie*, **4**, 473-476.

Cherpitel, C.J. (1993). Alcohol, injury, and risk-taking behavior: Data from a national sample. *Alcoholism, Clinical and Experimental Research*, **17**, (4), 762-766.

Chen, W.J., Hsiao, C.K., Hsiao, L.L. & Hwu, H.G. (1998). Performance of the Continuous Performance Test among community samples. *Schizophrenia Bulletin*, **24**, (1), 163-174.

Coenen, A.M.L. (1995). Neuronal activities underlying the electroencephalogram and evoked potentials of sleeping and waking: Implications for information processing. *Neuroscience and Biobehavioral Reviews*, **19**, (3), 447-463.

Cole, K.J. & Rotella, D.L. (2002). Old age impairs the use of arbitrary visual cues for predictive control of fingertip forces during grasp. *Experimental Brain Research*, **143**, (1), 35-41.

Comerchero, M.D. & Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clinical Neurophysiology*, **110**, 24-30.

Coull, J.T. (1998). Neural correlates of attention and arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology*, **55**, 343-361.

Corr, P.J. (in press). Personality and dual-task processing: Disruption of procedural learning by declarative processing. *Personality and Individual Differences*, **33**, 1-25.

Curtis, C.E., Calkins, M.E. & Iacono, W.G. (2001). Saccadic disinhibition in schizophrenia patients and their first-degree biological relatives. A parametric study of the effects of increasing inhibitory load. *Experimental Brain Research/Experimentelle Hirnforschung. Experimentation Cerebrale*, **137**, (2), 228-236.

D

Davis, P.A. (1939). Evaluation of the EEG of schizophrenic patients. *American Journal of Psychiatry*, **96**, 107.

Dawson, G.D. (1954). A summation technique for the detection of small evoked potentials. *Electroencephalography and Clinical Neurophysiology*, **6**, 153-154.

Deiber, M.P., Wise, S.P., Honda, M., Catalan, M.J., Grafman, J. & Hallett, M. (1997). Frontal and parietal networks for conditional motor learning: a positron emission tomography study. *Journal of Neurophysiology*, **78**, (2), 977-991.

de Zubicaray, G.I., Andrew, C., Zelaya, F.O., Williams, S.C. & Dumanoir, C. (2000). Motor response suppression and the prepotent tendency to respond: a parametric fMRI study. *Neuropsychologia*, **38**, 1280-1291.

Donchin, E. & Coles, M. G. H. (1988). Is the P300 component a manifestation of component updating? *Behavioral and Brain Science*, **11**, 357-374.

Donner, T., Kettermann, A., Diesch, E., Ostendorf, F., Villringer, A. & Brandt, S.A. (2000). Involvement of the human frontal eye field and multiple parietal areas in covert visual selection during conjunction search. *European Journal of Neuroscience,* **12,** (9), 3407-3414.

Donner, T.H., Kettermann, A., Diesch, E., Ostendorf, F., Villringer, A. & Brandt, S.A. (2002). Visual feature and conjunction searches of equal difficulty engage only partially overlapping frontoparietal networks. *NeuroImage*, **15,** (1), 16-25.

Dowsett, S.M. & Livesey, D.J. (2000). The development of inhibitory control in preschool children: effects of "executive skills" training. *Developmental Psychobiology*, 36, (2), 161-174.

Doya, K. (2000). Complementary roles of basal ganglia and cerebellum in learning and motor control. *Current Opinion in Neurobiology*, **10**, (6), 732-739.

Duncan, J. & Owen, A.M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*, **23**, (10), 475-483.

E

Eglin, M., Robertson, L.C. & Knight, R.T. (1991). Cortical substrates supporting visual search in humans. *Cerebral Cortex*, **1,** (3), 262-272.

Ellison, A. & Walsh, V. (1998). Perceptual learning in visual search: Some evidence of specificities. *Vision Research*, **38**, 333-345.

Enright, S.J. & Beech, A.R. (1993). Reduced cognitive inhibition in obsessive-compulsive disorder. *The British Journal of Clinical Psychology / the British Psychological Society*, 32, (1), 67-74.

Eysenck, M.W. (1982). *Attention and arousal: Cognition and performance*. Berlin: Springer.

F

Falkenstein, M., Hoormann, J. & Hohnsbein, J. (1999). ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychologica*, **101**, 267-291.

Falkenstein, M., Koshlykova, N.A., Kiroj, V.N., Hoormann, J. & Hohnsbein, J. (1995). Late ERP components in visual and auditory Go/Nogo tasks. *Electroencephalography and Clinical Neurophysiology*, **96**, 36-43.

Fenwick, T. & Anderson, V. (1999). Impairments of attention following childhood traumatic brain injury. *Neuropsychology, Development, and Cognition. Section C, Child Neuropsychology: a Journal on Normal and Abnormal Development in Childhood and Adolescence*, **5**, (4), 213-223.

Filipović, S.R., Jahanshahi, M. & Rothwell, J.C. (2000). Cortical potentials related to the nogo decision. *Experimental Brain Research*, **132**, 411-415.

Fimm, B., Zahn, R., Mull, M., Kemeny, S., Buchwald, F., Block, F. & Schwarz, M. (2001). Asymmetries of visual attention after circumscribed subcortical vascular lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, **71**, (5), 652-657.

Fox, A.M., Michie, P.T., Wynne, C.D. & Maybery, M.T. (2000). ERP correlates of response inhibition to elemental and configural stimuli in a negative patterning task. *Clinical Neurophysiology*, **111**, 1045-1053.

Frensch, P.A., Wenke, D. & Runger, D. (1999). A Secondary Tone-Counting Task Suppresses Expression of Knowledge in the Serial Reaction Task. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **25**, (1), 260-274.

Fuster, J.M. (1997). *The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe (3rd Ed.).* Philadelphia – New York: Lippincott-Raven.

Fuster, J.M. (1984). Behavioral electrophysiology of the prefrontal cortex. *Trends in Neurosciences,* **7,** 408-414.

Friedman, J.I., Temporini, H. & Davis, K.L. (1999). Pharmacologic strategies for augmenting cognitive performance in schizophrenia. *Biological Psychiatry*, **45**, (1), 1-16.

G

Garavan, H., Ross, T.J. & Stein, E.A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 8301-8306.

Garavan, H., Ross, T.J., Murphy, K., Roche, R.A.P. & Stein, E.A. (2002). Dissociable executive functions in the behavioural control: Inhibition, error detection and correction. *NeuroImage,* **17**, 1820-1829.

Ghilardi, M.F., Ghez, C., Dhawan, V., Moeller, J., Mentis, M., Nakamura, T., Antonini, A. & Eidelberg, D. (2000). Patterns of regional brain activation associated with different forms of motor learning. *Brain Research*, **871**, 127-145.

Goodale, M.A. (1993). Visual pathways supporting perception and action in the primate cerebral cortex. *Current Opinion in Neurobiology*, **3**, 578-585.

Gratton, G., Coles, M.G. & Donchin, E. (1992). Optimizing the use of information: strategic control of activation of responses. *Journal of Experimental Psychology. General*, **121**, (4), 480-506.

H

Halgren, E., Marinkovic, K. & Chauvel, P. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalography and Clinical Neurophysiology*, **106**, 154-164.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J.P. & Biraben, A. (1995b). Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology*, **94**, (4), 229-250.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G.,Liégeois, C., Chauvel, P. & Musolino, A. (1995a). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography and Clinical Neurophysiology*, **94**, (3), 191-220.

Halsband, U. & Freund, H.J. (1990). Premotor cortex and conditional motor learning in man. *Brain*, **113**, (1), 207-222.

Hampson, P.J. (1989). Aspects of attention and cognitive science. *Irish Journal of Psychology*, **10**, 261-275.

Hart, T., Giovannetti, T., Montgomery, M.W. & Schwartz, M.F. (1998). Awareness of errors in naturalistic action after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, **13**, (5), 16-28.

Hebb, D.O. (1949). *The Organisation of Behavior: A Neuropsychological Theory.* New York – London: Wiley & Sons, Inc.

Hebb, D.O. (1982). *The Conceptual Nervous System (H.A. Buchtel, Ed.).* Oxford: Pergamon.

Hjorth, B. (1975). An on-line transformation of EEG scalp potentials into orthogonal source derivations. *Electroencephalography and Clinical Neurophysiology*, **39**, (5), 526-530.

Hoffman, J.E. (1990). Event-related potentials and automatic and controlled processes. In: Rohrbaugh JW, Parasuraman R, Johnson R, editors. Event-related Brain Potentials: Basic Issues and Applications. New York – Oxford: Oxford University Press, 145-157.

Hoffman, J.E., Houck, M.R., MacMillan, F.W., Simons, R.F. & Oatman, L.C. (1985). Event-related potentials elicited by automatic targets: A dual-task analysis. *Journal of Experimental Psychology: Human Perception and Performance*, **11**, (1), 50-61.

Hohnsbein, J., Falkenstein, M. & Hoorman, J. (1998). Performance differences in reaction tasks are reflected in event-related brain potentials (ERPs). *Ergonomics*, **41**, (5), 622-633.

Huettel, S.A.,Güzeldere, G. & McCarthy, G. (2001). Dissociating the neural mechanisms of visual attention in change detection using functional MRI. *Journal of Cognitive Neuroscience*, **13**, (7), 1006-1018.

Hur, Y.M. & Bouchard, T.J. Jr. (1997). The genetic correlation between impulsivity and sensation seeking traits. *Behavior Genetics*, **27**, (5), 455-463.

I

Inase, M., Li, B.M., Takashima, I. & Iijima, T. (2001). Pallidal activity is involved in visuomotor association learning in monkeys. *European Journal of Neuroscience*, **14**, (5), 897-901.

J

James, W. (1890). *Principles of Psychology*. New York: Holt.

Jimenez, L. & Mendez, C. (1999). Which Attention Is Needed for Implicit Sequence Learning? *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **25**, (1), 236-259.

K

Kaliski, S.Z. & Zabow, T. (1995). Violence, sensation seeking, and impulsivity in schizophrenics found unfit to stand trial. *Bulletin of the American Academy of Psychiatry and the Law*, **23**, (1), 147-155.

Kandel, E.R., Schwartz, J.H. & Jessell, T.M. (1995). *Essentials of Neural Science and Behavior*. Connecticut: Appleton & Lange.

Kertesz, A. (1994). *Localization and neuroimaging in neuropsychology.* San Diego, California – London: Academic Press.

Kiehl, K.A., Smith, A.M., Hare, R.D. & Liddle, P.F. (2000). An event-related potential investigation of response inhibition in schizophrenia and psychopathy, *Biological Psychiatry*, **48**, (3), 210-221.

Knight, R.T. (1990). Neural mechanisms of event-related potentials: Evidence from human lesion studies. In J.W. Rohrbaugh, R. Parasuraman & R. Johnson (Eds.), *Event-related Brain Potentials: Basic Issues and Applications.* New York – Oxford: Oxford University Press.

Kolb, B. & Whishaw, I.Q. (1996). *Fundamentals of Human Neuropsychology (4th Ed.)*. New York: Freeman & Co.

Konrad, K., Gauggel, S., Manz, A. & Schöll, M. (2000a). Lack of inhibition: a motivational deficit in children with attention deficit/hyperactivity disorder and children with traumatic brain injury. *Neuropsychology, Development, and Cognition. Section C, Child Neuropsychology: a Journal on Normal and Abnormal Development in Childhood and Adolescence*, **6**, (4), 286-296.

Konrad, K., Gauggel, S., Manz, A. & Schöll, M. (2000b). Inhibitory control in children with traumatic brain injury (TBI) and children with attention deficit/hyperactivity disorder (ADHD). *Brain Injury*, **14**, (10), 859-875.

Kramer, A.F., Larish, J.F. & Strayer, D.L. (1995). Training for Attentional Control in Dual Task Settings: A Comparison of Young and Old Adults. *Journal of Experimental Psychology: Applied*, **1**, (1), 50-76.

Kropotov, J.D., Alho, K., Naatanen, R., Ponomarev, V.A., Kropotova, O.V., Anichkov, A.D. & Nechaev, V.B. (2000). Human auditory-cortex mechanisms of preattentive sound discrimination. *Neuroscience Letters*, **280**, 87-90.

L

Laforce Jr, R. & Doyon, J. (2002). Differential role for the striatum and cerebellum in response to novel movements using a motor learning paradigm, *Neuropsychologia*, **40**, (5), 512-517.

Lange, J.J., Wijers, A.A., Mulder, L.J.M. & Mulder, G. (1999). ERP effects of spatial attention and display search with unilateral and bilateral stimulus displays. *Biological Psychology*, **50**, (3), 203-233.

Larson, G.E., Alderton, D.L., Neideffer, M. & Underhill, E. (1997). Further evidence on dimensionality and correlates of the Cognitive Failures Questionnaire. *British Journal of Psychology*, **88**, 29-38.

Lawrence, A.D., Watkins, L.H., Sahakian, B.J., Hodges, J.R. & Robbins, T.W. (2000). Visual object and visuospatial cognition in Huntington's disease: implications for information processing in corticostriatal circuits. *Brain*, **123**, (7), 1349-1364.

Lejoyeux, M., Feuché, N., Loi, S., Solomon, J. & Adès, J. (1998). Impulse-control disorders in alcoholics are related to sensation seeking and not to impulsivity. *Psychiatry Research*, **81**, (2), 149-155.

Leonards, U., Rettenbach, R. & Sireteanu, R. (1998). Parallel visual search is not always effortless. *Cognitive Brain Research*, **7**, (2), 207-213.

Levine, B., Dawson, D., Boutet, I., Schwartz, M.L. & Stuss, D.T. (2000). Assessment of strategic self-regulation in traumatic brain injury: its relationship to injury severity and psychosocial outcome. *Neuropsychology*, **14**, (4), 491-500.

Lezak, M.D. (1983). *Neuropsychological Assessment (2nd Ed.).* New York – Oxford: Oxford University Press.

Liu, Y. & Wang, Y. (2002). Cognitive functions of children with attention deficit/hyperactivity disorder. *Zhonghua Yi Xue Za Zhi*, **82**, (6), 389-392.

Logan, G.D., Cowan, W.B. & Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology. Human Perception and Performance*, **10**, (2), 276-291.

Luck, S.J. & Hillyard, S.A. (1995). The role of attention in feature detection and conjunction discrimination: An electrophysiological analysis. *International Journal of Neuroscience*, **80**, 281-297.

Luck, S.J., Fan, S. & Hillyard, S.A. (1993). Attention-related modulation of sensory-evoked brain activity in a visual search task. *Journal of Cognitive Neuroscience*, **5**, (2), 188-195.

M

Magliero, A., Bashore, T.R., Coles, M.G. & Donchin, E. (1984). On the dependence of P300 latency on stimulus evaluation processes. *Psychophysiology*, **21**, (2), 171-186.

Mangun, G.R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology*, **32**, 4-18.

Mataix-Cols, D., Junqué, C., Vallejo, J., Sànchez-Turet, M., Verger, K. & Barrios, M. (1997). Hemispheric functional imbalance in a sub-clinical obsessive-compulsive sample assessed by the Continuous Performance Test, Identical Pairs version. *Psychiatry Research*, **72**, (2), 115-126.

McCarthy, G. & Donchin, E. (1981). A metric for thought: a comparison of P300 latency and reaction time. *Science*, **211**, (4477), 77-80.

Mesulam, M.M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, **10**, (4), 309-325.

Mesulam, M.M., Mufson, E.J., Levey, A.I. & Wainer, B.H. (1983). Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *Journal of Comparative Neurology*, **214**, (2), 170-197.

Mitchell, S.H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacologia*, **146**, (4), 455-464.

Mitz, A.R. Godschalk, M. & Wise, S.P. (1991). Learning-dependent neuronal activity in the premotor cortex: activity during the acquisition of conditional motor associations. *Journal of Neuroscience*, **11**, (6), 1855-1872.

Miyashita, N., Hikosaka, O. & Kato, M. (1995). Visual hemineglect induced by unilateral striatal dopamine deficiency in monkeys. *Neuroreport*, **6**, (9), 1257-1260.

Moscovitch, M. (1994). Cognitive Resources and Dual-Task Interference Effects at Retrieval in Normal People: The Role of the Frontal Lobes and Medial Temporal Cortex. *Neuropsychology*, **8**, (4), 524-534.

Murray, E.A. & Wise, S.P. (1996). Role of the hippocampus plus subjacent cortex but not amygdala in visuomotor conditional learning in rhesus monkeys. *Behavioral Neuroscience*, **110**, (6), 1261-1270.

N

Nagoshi, C.T., Wilson, J.R. & Rodriguez, L.A. (1991). Impulsivity, sensation seeking, and behavioral and emotional responses to alcohol. *Alcoholism, Clinical and Experimental Research*, **15**, (4), 661-667.

Nakajima, Y., Hattori, T. & Mizuno, Y. (1995). Absence of P300 in patients with bilateral hippocampal lesions caused by herpes simplex encephalitis; No to Shinkei. *Brain and Nerve*, **47**, (3), 270-275.

Nakajima, Y., Miyamoto, K. & Kikuchi, M. (1994). Estimation of neural generators of cognitive potential P300 by dipole tracing method; No to Shinkei. *Brain and Nerve*, **46**, (11), 1059-1065.

Nieuwenhuis, S., Ridderinkhof, K.R., Blom, J., Band, G.P. & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology*, **38**, 752-760.

Nixon. P.D. & Passingham, R.E. (2000). The cerebellum and cognition: cerebellar lesions impair sequence learning but not conditional visuomotor learning in monkeys. Neuropsychologia, 38, 1054-1072.

Nordahl, T.E., Carter, C.S., Salo, R.E., Kraft, L., Baldo, J., Salamat, S., Robertson, L. & Kusubov, N. (2001). Anterior cingulate metabolism correlates with stroop errors in paranoid schizophrenia patients. *Neuropsychopharmacology*, **25**, (1), 139-148.

Nunez, P.L. (1990). Physical principles and neurophysiological mechanisms underlying event-related potentials. In J.W. Rohrbaugh, R. Parasuraman & R. Johnson (Eds.), *Event-related Brain Potentials: Basic Issues and Applications.* New York – Oxford: Oxford University Press.

O

O'Donnell, B.F., Swearer, J.M., Smith, L.T., Hokama, H. & McCarley, R.W. (1997). A topographic study of ERPs elicited by visual feature discrimination. *Brain Topography*, **10**, (2), 133-143.

O'Mara, S.M. (1995). Spatially selective firing properties of hippocampal formation neurons in rodents and primates. *Progress in Neurobiology*, **45**, (3), 253-274.

Orrison, W.W., Jr., Lewine, J.D., Sanders, J.A. *et al.*, (1995). **Functional Brain Imaging**. St. Louis, MO: Mosby.

P

Passingham, R.E., Toni, I., Schluter, N. & Rushworth, M.F. (1998). How do visual instructions influence the motor system? *Novartis Foundation Symposium*, **218**, 129-146.

Passingham, R.E. (1993). *The frontal lobes and voluntary action*. Oxford: Oxford University Press.

Patkar, A.A., Berrettini, W.H., Hoehe, M., Thornton, C.C., Gottheil, E., Hill, K. & Weinstein, S.P. (2002). Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. *Psychiatry Research*, **110**, (2), 103-115.

Paz-Caballero, M.D. & Garcia-Austt, E. (1992). ERP components related to stimulus selection processes. *Electroencephalography and Clinical Neurophysiology*, **82**, 369-376.

Perkel, D.J. & Farries, M.A. (2000). Complementary 'bottom-up' and 'top-down' approaches to basal ganglia function. *Current Opinion in Neurobiology*, **10**, (6), 725-731.

Petit, T.L., LeBoutillier, J.C., Markus, E.J. & Milgram, N.W. (1989). Synaptic structural plasticity following repetitive activation in the rat hippocampus. *Experimental Neurology*, **105**, (1), 72-79.

Petrides, M. (1997). Visuo-motor conditional associative learning after frontal and temporal lesions in the human brain. *Neuropsychologia*, **35**, 989-997.

Petry, N.M. (2001). Substance abuse, pathological gambling, and impulsiveness. *Drug and Alcohol Dependence*, **63**, (1), 29-38.

Phillips, A.G., & Carr, G.D. (1987). Cognition and the basal ganglia: a possible substrate for procedural knowledge. *Canadian Journal of Neurological Sciences*, **14,** (3), 381-385.

Picton, T.W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology*, **9**, (4), 456-479.

Pliszka, S.R., Liotti, M. & Woldorff, M.G. (2000). Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry*, **48**, (3), 238-246.

Pollmann, S. & von Cramon, D.Y. (2000). Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Experimental Brain Research*, **133,** (1), 12-22.

Porter, N. & Robertson, I.H. (2002). The highs and lows of sustained attention: An ERPs study. *International Journal of Psychophysiology*, **45**, (1-2), 129.

Posner, M.I. & Raichle, M.E. (1994). *Images of mind*. New York: Scientific American Library – Oxford: Freeman.

Posner, M.I. & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, **13**, 25-42.

Potter, D.D., Pickles, C.D., Roberts, R.C. & Rugg, M.D. (2000). Scopolamine impairs memory performance and reduces frontal but not parietal visual P3 amplitude. *Biological Psychology*, **52**, (1), 37-52.

Psatta, D.M. & Matei, M. (1995). Investigation of P300 in various forms of epilepsy. *Romanian Journal of Neurology and Psychiatry*, **33**, (3-4), 183-202.

R

Ravden, D. & Polich, J. (1998). Habituation of P300 from visual stimuli. *International Journal of Psychophysiology*, **30**, 359-365.

Rieger, M. & Gauggel, S. (2002). Inhibition of ongoing responses in patients with traumatic brain injury. *Neuropsychologia*, **40**, 76-85.

Robbins, T.W., Granon, S., Muir, J.L., Durantou, F. Harrison, A. & Everitt, B.J. (1998). Neural systems underlying arousal and attention. Implications for drug abuse. *Annals of the New York Academy of Sciences*, **846**, 222-237.

Robertson, I.H., Dixon, T.A., Brennan, P., Delanty, N., Fitzsimons, M., Hogan, M.J., Maguire, S., McMackin, D. & O'Mara, S. (personal communication). Rote learning impairs memory via a specific downregulation of left hippocampal function.

Robertson, I.H., Manly, T., Andrade, J., Baddeley, B.T. & Yiend, J. (1997). 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects, *Neuropsychologia*, **35**, (6), 747-758.

Robertson, I.H., Mattingley, J.B., Rorden, C. & Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature*, **395**, (6698), 169-172.

Robertson, I.H., Ward, T., Ridgeway, V. & Nimmo-Smith, I. (1996). The structure of normal human attention: The Test of Everyday Attention. *Journal of the International Neuropsychological Society,* **2**, (6), 525-534.

Roche, R.A.P. & O'Mara, S.M. (2003) Behavioural and electrophysiological correlates of visuomotor learning in a visual search task. *Cognitive Brain Research,* **15**, 127-136.

Roche, R.A.P., Garavan, H. & O'Mara, S.M. (*under review*). Individual differences discriminate event-related potentials but not performance during response inhibition. Submitted to *the Journal of Cognitive Neuroscience*.

Roche, R.A.P., Commins, S., Agnew, F., Corapi, K., Leibbrand, S., Lipson, Z., Rickard, J., Sorohan, J. & O'Mara, S.M. (*under review*). Concurrent task performance enhances low-level visuomotor learning. Submitted to *the Journal of Experimental Psychology: Learning, Memory and Cognition.*

Roland, P.E., Larsen, B., Lassen, N.A. & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organisation of voluntary movements in man. *Journal of Neurophysiology*, **43**, 118-136.

Rueckert, L. & Grafman, J. (1998). Sustained attention deficits in patients with lesions of posterior cortex, *Neuropsychologia*, **36**, (7), 653-660.

Rueckert, L. & Grafman, J. (1996). Sustained attention deficits in patients with right frontal lesions. *Neuropsychologia*, **34**, (10), 953-963.

S

Sarramon, C., Verdoux, H., Schmitt, L. & Bourgeois, M. (1999). Addiction and personality traits: sensation seeking, anhedonia, impulsivity. *L'Encephale*, **25**, (6), 569-575.

Sarter, M., Givens, B. & Bruno, J.P. (2001). The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Research Reviews*, **35,** (2), 146-160.

Schaul, N. (1998). The fundamental neural mechanisms of electroencephalography. *Electroencephalography and Clinical Neurophysiology*, **106**, 101-107.

Schubert, M., Johannes, S., Koch, M., Wieringa, B.M., Dengler, R. & Münte, T.F. (1998). Differential effects of two motor tasks on ERPs in an auditory classification task: evidence of shared cognitive resources. *Neuroscience Research*, **30**, (2), 125-134

Scoville, W.B. & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **20**, 11-21.

Simon, D.A. & Bjork, R.A. (2001). Metacognition in Motor Learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **27**, (4), 907-912.

Squire, L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review*, **99**, (2), 195-231.

Staines, W.R., Padilla, M. & Knight, R.T. (2002). Frontal-parietal event-related potential changes associated with practising a novel visuomotor task, *Cognitive Brain Research*, **13**, (2), 195-202.

Stanley, B., Molcho, A., Stanley, M., Winchel, R., Gameroff, M.J., Parsons, B. & Mann, J.J. (2000). Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. *American Journal of Psychiatry*, **157**, (4), 609-614.

Stevens, S.S. (1951). *Handbook of Experimental Psychology*. New York – London: Wiley; Chapman & Hall.

Strik, W.K., Fallgatter, A.J., Brandeis, D. & Pascual-Marqui, R.D. (1998). Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalography and Clinical Neurophysiology*, **108**, 406-413.

Stuss, D.T. & Gow, C.A. (1992). Frontal dysfunction after traumatic brain injury. *Neuropsychiatry, Neuropsychology and Behaviour Neurology*, **5**, 272-282.

Sugita, Y. (1995). Electrophysiological correlates of visual search asymmetry in humans. *Neuroreport*, **6**, 1693-1696.

T

Tancredi, V. & Dichter, M.A. (1990). Effects of repetitive activation and changes in external ionic environment on hippocampal CA1 pyramidal cell afterhyperpolarizations. *Epilepsia*, **31**, (2), 123-130.

Tarkka, I.M., Micheloyannis, S. & Stokicacute, D.S. (1996). Generators for human P300 elicited by somatosensory stimuli using multiple dipole source analysis. *Neuroscience*, **75**, (1), 275-287.

Terry, A.V., Jr., Risbrough, V.B., Buccafusco, J.J. & Menzaghi, F. (2002). Effects of (+/-)-4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol hydrochloride (SIB-1553A), a selective ligand for nicotinic acetylcholine receptors, in tests of visual attention and distractibility in rats and monkeys. *Journal of Pharmacology and Experimental Therapeutics*, **301**, (1), 284-292.

Thiel, C.M., Huston, J.P. & Schwarting, R.K. (1998). Hippocampal acetylcholine and habituation learning. *Neuroscience*, **85**, (4), 1253-1262.

Thornton, E.W. & Goudie, A.J. (1978). Evidence for the role of serotonin in the inhibition of specific motor responses. *Psychopharmacologia*, **60**, (1), 73-79.

Timmann, D., Shimansky, Y., Larson, P. S., Wunderlich, D. A., Stelmach G. E. & Bloedel, J. R. (1996). Visuomotor learning in cerebellar patients. *Behavioural Brain Research*, **81**, (1-2), 99-113.

Toni, I. & Passingham, R.E. (1999). Prefrontal-basal ganglia pathways are involved in the learning of arbitrary visuomotor associations: A PET study. *Experimental Brain Research,* **127**, (1), 19-32.

Toni, I., Ramnani, N., Josephs, O., Ashburner, J. & Passingham, R.E. (2001). Learning arbitrary visuomotor associations: temporal dynamic of brain activity. *NeuroImage*, **14**, (5), 1048-1057.

Treisman, A. & Gelade, G. (1980). A feature integration theory of attention. *Cognitive Psychology*, **12**, 97-136.

Treisman, A. (1986). Features and objects in visual processing. *Scientific American*, **255**, (5), 106-115.

Tremblay, L. Hollerman, J.R. & Schultz, W. (1998). Modifications of reward expectation-related neuronal activity during learning in primate striatum. *Journal of Neurophysiology*, **80**, (2), 964-977.

V

Varney, N.R., Bushnell, D.L., Nathan, M., Kahn, D., Roberts, R., Rezai, K., Walker, W. & Kirchner, P. (1995). NeuroSPECT correlates of disabling mild head injury: Preliminary findings. *Journal of Head Trauma Rehabilitation*, **10**, 18-28.

Vitacco, M.J. & Rogers, R. (2001). Predictors of adolescent psychopathy: the role of impulsivity, hyperactivity, and sensation seeking. *Journal of the American Academy of Psychiatry and the Law*, **29**, (4), 374-382.

W

Walsh, V., Ashbridge, E. & Cowey, A. (1998). Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. *Neuropsychologia*, **36**, (1), 45-49.

Walsh, V., Ellison, A., Ashbridge, E. & Cowey, A. (1999). The role of the parietal cortex in visual attention – hemispheric asymmetries and the effects of learning: A magnetic stimulation study. *Neuropsychologia*, **37**, (2), 245-251.

Walsh, V., Ellison, A., Batelli, L. & Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proceedings of the Royal Society of London*, **B265**, 537-543.

Wang, Y.P., Kawai, Y. & Nakashima, K. (1999). Rabbit P300-like potential depends on cortical muscarinic receptor activation, *Neuroscience*, **89**, (2), 423-427.

Weijers, H. –G., Wiesbeck, G.A. & Boening, J. (1997). Personality traits - especially impulsivity and sensation seeking - as related to dopaminergic and serotonergic drug challenge response in alcohol dependent men. *Biological Psychiatry*, **42**, (1), 35S.

Weisbrod, M., Kiefer, M., Marzinzik, F. & Spitzer, M. (2000). Executive control is disturbed in schizophrenia: Evidence from event-related potentials in a Go/NoGo task. *Biological Psychiatry*, **47**, (1), 51-60.

Whyte, J., Schuster, K., Polansky, M., Adams, J. & Coslett, H.B. (2000). Frequency and duration of inattentive behavior after traumatic brain injury: effects of distraction, task, and practice. *Journal of the International Neuropsychological Society*, **6**, (1), 1-11.

Wickens, C.D. (1984). Processing resources in attention. In: R. Parasuraman & D.R. Davies (Eds.), *Varieties of attention*. London: Academic Press.

Wilkins, A.J., Shallice, T. & McCarthy, R. (1987). Frontal lesions and sustained attention. *Neuropsychologia*, **25**, (2), 359-365.

Wilkinson, D.T., Halligan, P.W., Henson, R.N.A. & Dolan, R.J. (2002). The effects of interdistracter similarity on search processes in superior parietal cortex. *NeuroImage*, **15**, (3), 611-619.

Wise, S.P. & Murray, E.A. (1999). Role of the hippocampal system in conditional motor learning: Mapping antecedents to action. *Hippocampus,* **9,** (2), 101-117.

Wise, S.P. & Murray, E.A. (2000). Arbitrary associations between antecedents and actions. *Trends in Neurosciences*, **23**, 271-276.

Y

Yamazaki, T., Kamijo, K., Kiyuna, T., Takaki, Y. & Kuroiwa, Y. (2001). Multiple dipole analysis of visual event-related potentials during oddball paradigm with silent counting. *Brain Topography*, **13**, (3), 161-168.

Z

Zhang, X.L, Begleiter, H., Porjesz, B. & Litke, A. (1997) Visual object priming differs from visual word priming: An ERP study. *Electroencephalography and Clinical Neurophysiology*, 102, 200-215.

Zigmond, A.S. & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67, (6), 361-370.

Zuckerman, M. (1993). P-impulsive sensation seeking and its behavioral, psychophysiological and biochemical correlates. *Neuropsychobiology*, 28, (1-2), 30-36.