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Characterisation of Executive Deficits in Attention-Deficit/Hyperactivity Disorder and Avenues for their Remediation

by

Redmond G O'Connell

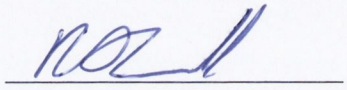
A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland

2006

Declaration

I declare that this thesis has not been submitted previously as an exercise for a degree at this or any other University and it is entirely my own work. I agree that Trinity College Library may lend or copy this thesis upon request.

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Redmond O'Connell

Acknowledgements

I would like to thank my supervisor, Ian Robertson. Over the last three years I have always been able to depend on his support, guidance and optimism. I am also hugely indebted to Mark Bellgrove and Paul Dockree. Believe it or not you guys inspired me to get into research so this is all your fault really.

Special thanks also to John Foxe and all the gang at NKI and St Vincents Hospital Fairview for allowing me into their wonderful world of ERPs. I am also very grateful to the Foxe family for their kind hospitality in City Island. Many thanks to Michael Fitzgerald, Aiveen Kirley and Adam Lau who conducted the clinical assessments and also to Alessandra Turin and Larissa Hull who collected the data for Experiment 1. I would also like to thank my appraisers Fiona Newell and Mac MacLachlan for their guidance. Thank you to Rob Hester and Hugh Garavan for letting me use the EAT and for many fruitful discussions. Thanks also to Simon Kelly for his vital help with the GSR and bumperball and for answering all those e-mails.

There's nothing quite like settling down with a pint on a Friday for a good moan about something or other to set you straight again so thanks a million to all my other friends and colleagues in Trinity especially Clare, Fiadhnait, Caren, Jason, Kylie, Katherine, Kevin, Mary, Richard, Doreen, Justin and all of the Botany Bay first XI soccer team. Its been a genuine pleasure working with all of you and carving out a niche in O'Neills.
Thank you to my family for their love and support and, of course, special thanks to everybody who participated in these studies.

So many people to thank but none more than Cora. I don't know what I did to deserve somebody so beautiful.

Summary

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that affects both children and adults and is associated with a range of behavioural and cognitive difficulties. This thesis aims to advance our understanding of this disorder by exploring two main themes. The first is that the neural abnormalities underlying executive dysfunction in ADHD can be elucidated by combining electrophysiological measures of brain function with cognitive paradigms for which valid brain-behaviour relationships have been established. The second part of this thesis is concerned with exploring the possibility that our knowledge of the neural instantiation of cognitive functions can provide a new avenue for the development of effective cognitive training strategies for ADHD. Chapter 1 begins by providing a broad overview of ADHD across the lifespan and outlines the theoretical basis for the experiments conducted in this thesis. Chapter 2 discusses the potential value of electrophysiological parameters in ADHD research.

Chapters 3 and 4 consist of experiments designed to assess the efficiency of two executive functions whose role in ADHD remains unclear: sustained attention and error detection. In both chapters, Event-Related Potentials (ERP) are employed to investigate the time-course of neurophysiological abnormalities. In addition, measures of Electrodermal Activity (EDA) provide an insight into the interplay between motivational and cognitive influences on executive function. Chapter 3 begins with a discussion of the reasons why sustained attention deficits have not been reliably demonstrated in ADHD and argues that when more sensitive methodologies are adopted, real deficits can be uncovered. This possibility is then explored in a series of three experiments. The first experiment conducts an electrophysiological validation of a sustained attention task for use in ADHD research by demonstrating that the ERP componentry that is associated with successful performance is qualitatively different to that associated with response inhibition. The second and third experiments reveal that children and adults with ADHD are more susceptible to momentary failures of sustained attention. In both of these experiments, attenuated EDA responses following errors point to reduced subjective appraisal of error significance, suggesting that sustained attention deficits are exacerbated by motivational abnormalities. In addition,

Experiment 3 identifies a number of ERP abnormalities indicating decreased engagement of top-down control over sustained attention amongst adults with ADHD.

A question that arises from the examination of sustained attention failures is, how do people with ADHD deal with their errors? Chapter 4 explores this issue and consists of two experiments. In the first, a baseline study is conducted with normal healthy participants in order to identify ERP components that are related to error detection. The Error Positivity (Pe) is identified as the key marker of conscious error processing. In addition, the results of source analysis implicate the anterior cingulate cortex (ACC) in both conscious and unconscious aspects of error processing. In the second experiment, the efficiency of error processing networks are systematically examined in a group of adults diagnosed with ADHD. This experiment reveals that adults with ADHD are significantly less likely to consciously detect their errors and identifies a number of ERP abnormalities relating to aspects of performance monitoring and conscious error processing. In addition, convergent EDA and source analysis evidence point to reduced subjective responsiveness to consciously detected errors. The findings of Chapters 3 and 4 emphasise the interaction of cognitive and motivational abnormalities and demonstrate that executive deficits in ADHD can only be properly understood by adopting methods that are capable of parsing complex cognition into its sub-components.

Chapters 5 and 6 form the second major section of this thesis. Chapter 5 presents a detailed review of work conducted with other clinical groups, such as traumatic brain injury and stroke, which indicates that significant experience-dependent changes in brain structure and function can be brought about by carefully structured practice. Several studies have also tested the efficacy of such methods with children with ADHD and these are also reviewed in Chapter 5. Finally, in Chapter 6, a new method of cognitive neuro-remediation, targeted towards alleviating sustained attention deficits, is piloted first with a group of normal healthy adults and then with a group of adults diagnosed with ADHD. This training produced substantial short-term improvements in sustained attention in the clinical and non-clinical groups and was accompanied by improvements in several electrophysiological markers.

Finally, Chapter 7 consists of a discussion of the issues raised in this thesis and offers suggestions for future research.

List of Publications

The following is a list of peer-reviewed journal articles that have arisen from this thesis:

Experiment 2

O'Connell, R. G., Bellgrove, M. A., Dockree, P., & Robertson, I. H. (2004). Reduced electrodermal response to errors predicts poor sustained attention performance in ADHD. *NeuroReport, 15*(16), 2535-2538.

Experiment 4

O'Connell, R. G., Dockree, P., Bellgrove, M. A., Kelly, S. P., Hester, R., Garavan, H., Robertson, I. H. & Foxe, J. J. (2007). The role of Cingulate Cortex in the detection of errors with and without awareness: a high-density electrical mapping study. *European Journal of Neuroscience*, 25(8), 2571-2579.

Chapter 5

O'Connell, R. G., Bellgrove, M. A., & Robertson, I. H. (in press). Avenues for the Neuro-Remediation of ADHD: lessons from clinical neurosciences. In M. Fitzgerald, M. Gill & M. A. Bellgrove (Eds.), *Handbook of Attention Deficit Hyperactivity Disorder*. London: Wyley.

Experiment 6

O'Connell, R. G., Bellgrove, M. A., Dockree, P., & Robertson, I. H. (in press). Cognitive remediation in ADHD - effects of periodic non-contingent alerts on sustained attention to response. *Neuropsychological Rehabilitation.*

Published Abstracts:

O'Connell, R.G., Dockree, P., Bellgrove, M.A., Kelly, S., Hester, R., Garavan, H., Robertson, I.H. & Foxe, J.J. (2006). The electrophysiological correlates of error detection. *Cognitive Neuroscience Society Annual Meeting (San Francisco, April 2006).*

O'Connell, R.G., Bellgrove, M.A., Dockree,P.M. & Robertson I.H. Effects of Self Alert Training (SA) on Sustained Attention Performance in Adult ADHD. *Neuropsychological Rehabilitation Annual Meeting (Galway, July, 2005)*

O'Connell, R.G., Bellgrove,M.A., Dockree,P.M. & Robertson, I.H. Do periodic non-contingent cues improve sustained attention to response and goal-related electrodermal activity in ADHD? *Symposium presentation, 16th World Congress Of The International Association For Child and Adolescent Psychiatry and Allied Professions (IACAPAP), (Berlin, August, 2004)*

List of Abbreviations

ACC	Anterior Cingulate Cortex
ADHD	Attention-deficit/hyperactivity disorder
ADHD-C	ADHD Combined Subtype
ADHD-H	ADHD Predominantly Hyperactive Subtype
ADHD-I	ADHD Predominantly Inattentive Subtype
ANOVA	Analysis of variance
BESA	Brain Electrical Source Analysis
CAARS	Conners Adult ADHD Rating Scale
CFQ	Cognitive Failures Questionnaire
CPT	Continuous Performance Task
CRN	Correct Response Negativity
DA	Dopamine
DAT	Dopamine Transporter
DART	Dual Attention to Response Test
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAT	Error Awareness Task
EDA	Electrodermal Activity
EEG	Electroencephalogram
EF	Executive Function
EMG	Electromyograph
EOG	Electro-oculogram
ERN	Error-Related Negativity
ERP	Event Related Potential
fMRI	Functional Magnetic Resonance Imaging
GoRT	Mean Reaction Time on Go trials
ISI	Inter-Stimulus-Interval
IQ	Intelligence Quotient
LC	Locus Coeruleus
LP	Late Positivity
µS	micro Siemens
µV	micro Volts
MPH	Methylphenidate
MTA	Multimodal Treatment Study of ADHD
NA	Noradrenaline
Pe	Error Positivity
PET	Positron Emission Topography
PFC	Prefrontal Cortex
RV	Residual Variance
SAT	Self-Alert Training
SART	Sustained Attention to Response Task
SCL	Skin Conductance Level
SCR	Skin Conductance Response
SSRT	Stop-signal Response Time
TBI	Traumatic Brain Injury
WRAT	Wide Range Achievement Test
WURS	Wender Utah Rating Scale

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Chapter 1 ADHD: An Overview

1.1 ADHD - impact

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent developmental disorders and is characterised by core behavioural symptoms of inattention, impulsivity and hyperactivity (A.P.A., 2000). ADHD sufferers can also present with a range of other behavioural, emotional and cognitive indicators making it a complex and heterogeneous disorder (Barkley, 1998). Prevalence estimates have varied considerably since its first classification in the Diagnostic and Statistical Manual for Mental Disorders (DSM-II) in 1968, reflecting changing trends in its definition and diagnosis but there is a broad consensus today that ADHD affects between 3% and 8% of school-age children worldwide (Faraone, Sergeant, Gillberg, & Biederman, 2003; Kutcher et al., 2004; NIH, 2000). Extensive media coverage in the U.S., where ADHD accounts for between one third and one half of all child referrals to mental health services (Swanson et al., 2004), has led to the impression in some quarters that it is a Western disorder reflecting social and cultural factors. However, this view does not stand up to recent cross-cultural epidemiological surveys which have indicated that countries such as China, Israel and India have prevalence rates that are roughly equivalent to those in the U.S. when the same diagnostic criteria are used (Faraone, Sergeant, Gillberg, & Biederman, 2003).

Although the precise etiology of ADHD has yet to be firmly established, estimates of heritability from twin studies range from 0.5 to 0.9 (DiMaio, Grizenko, & Joober, 2003; Faraone & Dobler, 2001) and a burgeoning neuroimaging literature appears to confirm that the disorder has a distinct biological basis (see Bush, Valera, & Seidman, 2005; Durston, 2003; Schneider, Retz, Coogan, Thome, & Rosler, 2006 for reviews). This work has identified decreased activation of predominantly fronto-striatal brain regions and abnormalities in the transmission of neurotransmitters such as dopamine as the likely neurobiological basis of this disorder. The field of cognitive neuroscience has also provided a strong body of evidence that the behavioural symptoms of ADHD are attributable, at least in part, to an underlying neuropsychological profile that includes

deficits in working memory, response inhibition, reinforcement processing and aspects of attention (see Pennington & Ozonoff, 1996; see Seidman, 2006; Tannock, 1998; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005 for reviews).

While ADHD was traditionally viewed as a disorder of childhood, 50-80% of adolescents and 30-60% of adults report persistent symptoms (Faraone, Sergeant, Gillberg, & Biederman, 2003; Ingram, Hechtman, & Morgenstern, 1999; Wilens, Faraone, & Biederman, 2004). The long-term outlook for individuals diagnosed with ADHD is poor due to functional impairments in academic, social and occupational aspects of the individual's life and a higher risk of secondary problems such as psychiatric comorbidity, criminality, drug abuse, increased rate of accidents, poor regulation of affect and low self-esteem (Biederman et al., 2006; DuPaul, 2006; Ernst et al., 2006; Rosler et al., 2004; Swanson et al., 1998; Swensen et al., 2004). In addition to the severe impact that ADHD can have on an individual's life, this disorder also places a significant burden on health care, criminal justice and educational systems amongst others. The National Institutes of Health in the U.S. estimated that the extra cost to the public school system attributable to ADHD exceeded $3 billion in 1995 (NIH, 2000). It is for these reasons that ADHD is one of the most widely researched and discussed psychiatric disorders yielding over 11,000 articles on the Medline search engine and 31 million hits on Google. In this introductory chapter, a broad overview of ADHD research will be provided and the theoretical background to the work reported in this thesis will be outlined.

1.2 Diagnosis in Childhood

Despite huge advances in elucidating the neuropsychological bases of ADHD (reviewed below) diagnosis is still almost entirely reliant on observational, and therefore subjective, reports of behaviour. ADHD can be reliably diagnosed using well-tested diagnostic interview methods and child behavioural rating scales (Pelham, Fabiano, & Massetti, 2005; Root & Resnick, 2003; Swanson et al., 1998). The generally accepted definition of ADHD is provided by the DSM-IV which specifies two symptom axes or dimensions, hyperactivity/impulsivity and inattention, each consisting of nine behavioural symptoms (A.P.A., 2000). Inattention is defined as a failure to pay attention

to details or distractibility and an inability to sustain attention over extended periods of time. Hyperactivity manifests as excessive movement, fidgeting and restlessness while impulsivity refers to a lack of patience, a need for immediate gratification and an inability to inhibit responses. Assessments usually involve parents, teachers and the child and the clinician may use other sources of information such as report cards or informal behavioural observations to develop an accurate clinical formulation. The goal of assessment is to establish whether or not the child has significant, developmentally inappropriate levels of at least six out of nine symptoms on one or both of these axes. The DSM manual provides decision rules for determining abnormality. For example, the clinician must establish that symptoms were present before the age of 7, that they have persisted for at least six months and that they are not better accounted for by other psychiatric conditions or transient events such as head injury or trauma. Crucially, the symptoms must cause functional impairments and be evident across at least two everyday-life settings.

The DSM manual specifies three ADHD-subtypes depending on the number of symptoms exhibited. ADHD Combined (ADHD-C) subtype applies to children who exceed the threshold for symptoms on both symptom dimensions. ADHD Predominantly Hyperactive/Impulsive (ADHD-H) subtype applies to children who are above threshold on the hyperactivity axis but below threshold on the inattention dimension and the inverse is the case for children diagnosed with ADHD Predominantly Inattentive (ADHD-I) subtype. As a result, children who receive a diagnosis of ADHD can have markedly different symptom profiles. ADHD-C accounts for 70-80% of all referred cases (Buitelaar, 2002; Milich, Balentine, & Lynam, 2001; Swanson et al., 2004). ADHD-I is the least likely to be referred but epidemiological surveys indicate that it is actually more prevalent than either ADHD-C or ADHD-H in community samples (Carlson & Mann, 2000; Milich, Balentine, & Lynam, 2001). It is likely that ADHD-I is less frequently diagnosed because its behavioural symptoms are less overt.

An issue which complicates diagnosis is that other disorders are often comorbid with ADHD. In the case of ADHD, comorbidity appears to be the rule rather than the exception with approximately 75% of cases being diagnosed with at least one other disorder and 33% having two or more other disorders of which oppositional defiant

disorder and conduct disorder are the most common (Asherson, 2005; Biederman & Faraone, 1996; Carlson & Mann, 2000; Millstein, Wilens, Biederman, & Spence, 1997; Root & Resnick, 2003; Tannock, 1998). Other common comorbidities include learning disabilities, anxiety disorders and depression (Paule et al., 2000; Root & Resnick, 2003). Differential diagnostic considerations are therefore of vital importance to the assessment procedure.

High comorbidity rates also present a problem for researchers who seek to identify neuropsychological and/or biological abnormalities that are specific to ADHD. Recruiting the minority of patients who have ADHD without a comorbid disorder is difficult and it can be argued that such cases are not actually representative of the general ADHD population (Tannock, 1998). That is, a 'nuisance' variable such as comorbidity could in fact be crucial to our understanding of ADHD. Instead the majority of researchers prefer to recruit participants with a range of comorbidities and it is assumed that, by replicating findings across studies, ADHD-specific effects should become readily apparent. In addition a smaller number of studies recruit enough participants to perform statistical analyses that are sensitive to different comorbid conditions (e.g. Wells et al., 2000).

1.3 Diagnosis in Adulthood

Historically it was believed that ADHD was outgrown by late adolescence but in recent years there has been recognition that ADHD can persist across the lifespan (Asherson, 2005; Barkley, 1998; McGough & Barkley, 2004; Riccio et al., 2005; Wilens, Faraone, & Biederman, 2004). At present, there are no specific criteria for the diagnosis of ADHD in adulthood and so clinicians are obliged to use the same criteria that are used for children as described above. This is a controversial matter since these criteria were designed for, and selected based on field trials with, child populations. According to Asherson (2005) many adults who met the criteria for ADHD in childhood no longer have a sufficient number of current symptoms to receive a diagnosis even though persistence of some symptoms still causes significant functional impairment. Symptom criteria such as "leaves his/her seat when he/she should not" or "often runs about or climbs excessively" were clearly not conceived for adult populations and as a result

persistence rates may still be under-estimated. Psychiatrists working with persistent cases of ADHD have observed that the core behavioural symptoms of hyperactivity tend to decrease over time which may account for the traditional impression that the disorder could be outgrown (Ingram, Hechtman, & Morgenstern, 1999; NIH, 2000). However, although overt behavioural symptoms dissipate with maturity, many adults still report internal forms of hyperactivity manifesting as a "distractible mind" or ceaseless mental activity (Asherson, 2005; Barkley, 1998). Since the DSM-IV criteria were designed for observational reports of behaviour, this kind of manifestation is not incorporated in the current formal diagnostic criteria.

Barkley (1998) reports that the most common complaints of adults seeking assessment for ADHD involve problems at school or work with organisation, memory and concentration. He argues that while childhood ADHD is characterised by behavioural hyperactivity and impulsivity, the hallmarks of adult ADHD appear to be the more subtle cognitive deficits within the inattention dimension. These findings were corroborated by Millstein et al (1997) who observed that 90% of adults with a childhood diagnosis of ADHD had prominent attentional symptoms while less than half had clinically important levels of hyperactivity and impulsivity. A six-year longitudinal study by Achenbach and colleagues has also reported that symptoms of hyperactivity and impulsivity decay over time but that symptoms of inattention persist (Achenbach, Howell, McConaughy, & Stanger, 1998). In light of these reports there is an urgent need to develop adult specific diagnostic criteria.

Prevalence studies indicate that ADHD is more likely to be diagnosed in boys by a ratio of approximately 3:1 (Levy, Hay, Bennett, & McStephen, 2005; Tannock, 1998). The reasons for these gender differences are not well known and further work is required to separate the effects of environmental and genetic risk-factors. Some authors have suggested that the difference may be a product of a referral bias associated with the fact that girls are less likely to manifest comorbid disruptive behavior disorders (e.g. Conduct Disorder, Oppositional Defiant Disorder) and learning disabilities which may affect identification of ADHD (Biederman et al., 2005). Several studies have shown that the male-to-female ratio for the disorder is significantly lower in community based samples (i.e. children who have not yet been referred for diagnosis) (Biederman

& Faraone, 2005). Similar sex ratios have also been found for the ADHD-I subtype in child populations but the ratio is heavily skewed towards males for the ADHD-C and ADHD-H subtypes (Milich, Balentine, & Lynam, 2001). Interestingly, epidemiological studies of adult ADHD also find that the disorder is approximately equally prevalent amongst males and females (Rowland, Lesesne, & Abramowitz, 2002). These sex ratios and the greater persistence of inattention symptoms across the lifespan seem to support the view that the most fundamental symptoms of ADHD are found on the inattention dimension and that a referral bias may lead to the over-diagnosis of hyperactivity symptoms in boys (Barkley, 1998; Castellanos, Glaser, & Gerhardt, 2006). These issues raise further questions regarding the reliability of subjective diagnostic measures and underline the need for more objective indicators.

As yet, very little is known about predictors of persistence of childhood cases into adulthood. In a retrospective assessment of childhood indicators amongst a group of over 3,000 adults, Kessler and colleagues (2005) investigated whether a variety of potential risk-factors including socio-demographics, childhood adversity and traumatic life experiences could predict symptom persistence. Unfortunately, the only significant predictor that emerged was childhood symptom severity. An earlier study by Biederman and colleagues (1996) did find evidence that familial adversity and psychiatric comorbidity might provide clinically useful predictors of persistence at least into adolescence. Since recognition of ADHD in its adult form has only recently evolved there is a major shortage of either retrospective or prospective studies to investigate whether persistence and remission can be linked to certain modifiable risk factors or predictors.

The assessment procedure for adult ADHD centres around two key requirements: evidence of current impairment and evidence of lifetime history of ADHD symptoms (Asherson, 2005; Riccio et al., 2005). To receive a diagnosis, an adult patient must meet the criteria for at least six of the nine symptoms on one or both of the DSM-IV symptom dimensions. As in childhood diagnosis, these symptoms should be pervasive, associated with significant impairment and should not be better explained by another disorder. Symptom levels are normally assessed by a semi-structured clinical interview with the patient and one or more observers. The assessment process has been aided by

the development of standardised symptom questionnaires that incorporate the DSM-IV criteria such as the Conners Adult ADHD Rating Scale (CAARS, Conners, Erhardt, & Sparrow, 2003). Establishing the early age of onset for these symptoms is key to the evaluation process since ADHD is a developmental disorder and therefore cannot strictly have an adult onset although certain types of brain injury can produce a very similar pattern of symptoms. To ascertain onset the clinician must conduct a retrospective evaluation of at least two situations such as school or home life to investigate the presence of ADHD symptoms in childhood. Since many adults will have difficulty giving an accurate account of their symptom levels prior to the age of seven many psychiatrists use a more lenient age of onset cut-off of 10-12 years (Asherson, 2005; Barkley, personal communication). Standardised retrospective questionnaires, such as the Wender Utah Rating Scale (WURS, Ward, Wender, & Reimherr, 1993), have also been developed for this purpose and can be administered to the patient and a parent. Retrospective reports of childhood ADHD symptoms by both adults and their parents have been found to be highly correlated ($R>0.75$) (Murphy & Schachar, 2000). Again, differential diagnostic considerations are important as epidemiological studies report that comorbidity rates for adult ADHD are comparable to those seen in childhood (Faraone et al., 1998). The most common comorbid disorders amongst adults include antisocial, substance abuse, anxiety and mood disorders.

Thus, it appears that the present diagnostic criteria for adult ADHD do not take into account developmental changes in symptom manifestation and as a result may be overly restrictive. While a proportion of cases may develop compensatory strategies or coping skills that allow them to overcome their symptoms in later life it appears that for the majority, ADHD represents a challenge across the lifespan.

Since many of the behavioural symptoms of ADHD are similar to those associated with other disorders, and are exhibited by all people to some extent, many commentators have expressed concern that the current diagnostic criteria, for both children and adults, are too vague and too subjective (Barkley, 2003; Bradshaw, 1999; NIH, 2000). The diagnostic criteria for ADHD have evolved over many years of field trials but uncertainty regarding the true nature of ADHD is reflected in the fact that successive versions of the DSM have offered quite different definitions (Swanson et al., 1998).

Nevertheless the usefulness of ADHD as a label can only be judged by its ability to inform clinicians and researchers about pathophysiology, treatment options, risk factors and preventative measures (Bradshaw, 1999). While a more refined definition will certainly be welcome, the evidence presented in the following sections will show that the current definition has proven value when judged in these terms.

1.4 Neurobiological Bases of ADHD

1.4.1 The Fronto-Striatal Hypothesis

The high incidence of ADHD and controversy regarding the subjective nature of its diagnosis has directed research towards clarifying its biological bases and identifying cognitive or physiological markers that would contribute to a more objective diagnostic procedure. Examining the pathophysiology of ADHD is complicated by the presence of other comorbid disorders, the impact of environmental factors and the heterogeneity of the disorder itself. Despite these difficulties, our understanding of the biological origins of ADHD has vastly improved with the advent of new brain imaging techniques, advances in the field of molecular genetics and the use of more refined neuropsychological tests that are based on relatively specific brain-behaviour relationships. The primary neurobiological hypothesis for ADHD is that of a dysfunction in fronto-striatal circuitry.

Accumulated evidence from functional neuroimaging and lesion studies with humans, animals and primates has provided evidence that the fronto-striatal system constitutes five semi-independent parallel circuits (Bradshaw, 1999; Chow & Cummings, 1999). These circuits share a common structure and organisation in the form of a closed loop originating in focal regions of the frontal cortex and projecting sequentially to the striatum, other regions of the basal ganglia, the thalamus and then back to the cortical region of origin (see Figure 1.1). These circuits can be at least partially dissociated according to the executive functions that they mediate (Alexander, DeLong, & Strick, 1986; Bradshaw, 1999; Chow & Cummings, 1999). Executive functions (EF) are a collection of high-order cognitive processes that provide us with the ability to behave in

a flexible and goal-directed manner by inhibiting inappropriate behaviours and thoughts, planning future behaviour, focusing our attention and monitoring our actions (Pennington & Ozonoff, 1996).

The dorsolateral prefrontal cortical (DLPFC) subcircuit appears to play a role in several executive functions but has been most closely linked with working memory, self-monitoring, goal-direction, and cognitive flexibility (Fuster, 1999; Hester & Garavan, 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Damage to the lateral orbitofrontal (OFC) subcircuit results in disinhibitory deficits in both social and cognitive domains (Pennington & Ozonoff, 1996). The anterior cingulate cortical (ACC) subcircuit has a well established role in monitoring conflicting responses, emotions and thoughts and is also involved in motivational processes and the regulation of arousal (see Bush, Luu, & Posner, 2000 for review, see also chapter 4). The occulomotor subcircuit originates in the frontal eye fields and has been implicated primarily in the voluntary control of eye movements and in visual selective attention (e.g. Ross, Harris, Olincy, & Radant, 2000) while the motor subcircuit, which projects from the supplementary motor area, plays a key role in planning and controlling movement (Bradshaw, 1999).

These circuits do not operate in isolation but have reciprocal connections with other structures in the brain including the medial temporal lobes and the cerebellum (Middleton & Strick, 2001; Sowell et al., 2003). The frontal lobe is the last brain region to mature and as a result it may be particularly vulnerable to maturational or neurodevelopmental disorders (Paus, 2005). Changes within these pathways have been implicated in the neurobiology of several neurodevelopmental disorders including Tourette's syndrome, autism, obsessive compulsive disorder and schizophrenia as well as ADHD which may account for many of the commonalities seen in cognitive, motor and emotional aspects of these disorders (Bradshaw, 1999).

The hypothesised link between ADHD and fronto-striatal dysfunction has its origins in two observations. First, lesions to the frontal lobes produce symptoms of hyperactivity, impulsivity and distractibility in both animals and humans (Fuster, 1989). Lesioning of the striatum in animals also produces many of the hallmarks of ADHD including hyperactivity, poor response inhibition and poor working memory (Max et al., 2002).

Second, the symptoms of ADHD can be successfully treated by administering psychostimulants that are known to enhance the activity of catecholamines such as dopamine and noradrenaline (Madras, Miller, & Fischman, 2005). The integrity of

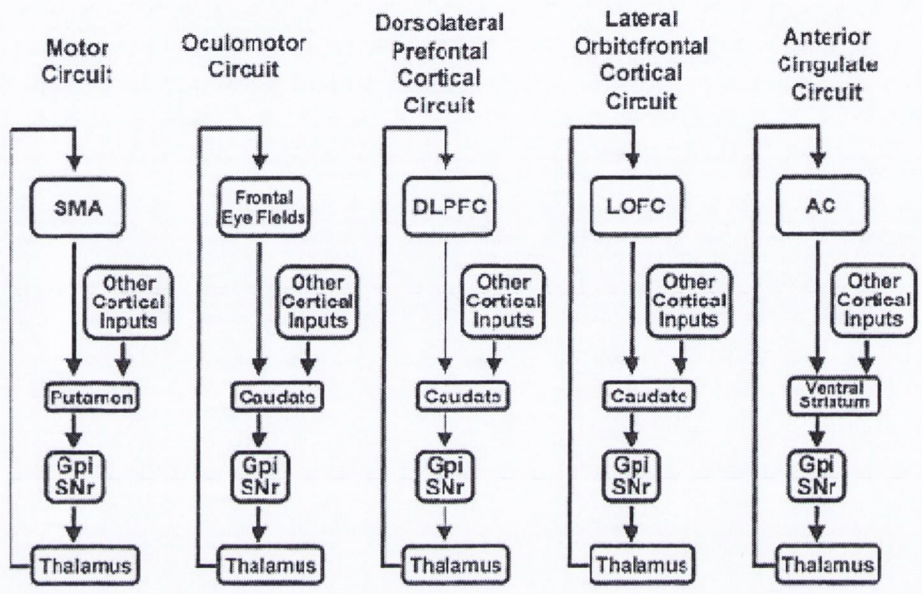


Figure 1.1 **The five fronto-striatal circuits**. Each circuit begins and ends in the same cortical location, passing through the striatum (caudate or putamen), globus pallidus pars interna (GPi) and substantia nigra pars reticulate (SNr) and thalamus. From Bradshaw (1999).

fronto-striatal regions is dependent on ascending modulatory projections from the dopaminergic and noradrenergic neurotransmitter systems and research with humans and animals indicates that subtle decreases in activity within these systems can have a profound effect on one's ability to control behaviour and produces symptoms that mimic those associated with ADHD (Arnsten, 1998; Arnsten & Li, 2005; Diamond, Briand, Fossella, & Gehlbach, 2004). In recent years, the neurobiological bases of ADHD have been explored in a far more direct manner using neuropsychological tests, structural and functional neuroimaging techniques and through the investigation of molecular genetic influences.

1.4.2 Neuropsychological Deficits

In the last 25 years, a vast body of research has been directed to the task of identifying a unique neuropsychological profile for ADHD. This work has demonstrated incontrovertibly that children and adults with ADHD do not have generalised cognitive deficits but do manifest deficits in a specific set of EF domains. According to recent reviews the largest effect sizes have been found when participants with ADHD perform tasks that are designed to assess response inhibition, visuo-spatial working memory, temporal processing and planning (Castellanos & Tannock, 2002; Pennington & Ozonoff, 1996; Seidman, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A recent meta-analysis by Willcutt and colleagues (2005) reviewed 83 neuropsychological studies of ADHD and calculated effect sizes for the most commonly used measures of executive function. The mean effect sizes for all the measures analysed fell in the range considered a medium effect replicating an earlier meta-analysis conducted by Pennington and Ozonoff (1996). A common and well founded criticism of neuropsychological research in ADHD has been that interpretation of findings is difficult due to methodological weaknesses such as differences in the sample sizes and diagnostic criteria used and whether or not potential confounding factors such as intelligence, reading ability and comorbidity were controlled. Further examination by Wilcutt et al revealed that apparent EF deficits could not be explained by group differences on these variables. Motivational differences could represent another potential confound in ADHD research however the available evidence suggests that while reinforcement has a positive impact on task performance, children with ADHD continue to perform significantly worse than controls (Carlson & Tamm, 2000; McInerney & Kerns, 2003; Slusarek, Velling, Bunk, & Eggers, 2001). These studies have in fact indicated that an insensitivity to reinforcements such as reward and response costs represents a major aspect of the ADHD neuropsychological profile in its own right (Luman, Oosterlaan, & Sergeant, 2005).

Although there has been far less investigation of neuropsychological deficits in adult populations, research in this area has intensified in the last ten years. A number of recent meta-analyses have shown that adults with ADHD have persistent problems with response inhibition, organisation, working memory and planning (Epstein, Johnson,

Varia, & Conners, 2001; Hervey, Epstein, & Curry, 2004; Schoechlin & Engel, 2005; Woods, Lovejoy, & Ball, 2002). This work confirms that EF deficits are stable aspects of ADHD that cannot be attributed to transient developmental processes.

1.4.3 Neuroimaging Evidence

More direct evidence for fronto-striatal dysfunction in ADHD has been garnered from studies of structural and functional neuroimaging that have identified abnormalities in specific fronto-striatal pathways. Valera and colleagues (in press) recently conducted a meta-analysis of all morphometric studies conducted on childhood ADHD to date and reported that the most consistently replicated brain structural alterations included significantly smaller volumes in frontal regions such as the DLPFC and anterior cingulate gyrus, areas of the striatum including the caudate and pallidum and other regions that project to frontal cortices including the cerebellum. In the first study of its kind, Sowell and colleagues (2003) carried out detailed spatial mapping of cortical morphology and grey-matter density in children with ADHD and also found clear support for structural abnormalities in fronto-striatal regions. However, differences were also seen in lateral temporal regions and inferior parietal regions suggesting that ADHD affects the brain in a more widespread and complex manner than was previously thought.

Several studies have indicated that frontal abnormalities are predominantly right lateralised (Casey et al., 1997; Semrud-Clikeman et al., 2000; Zametkin et al., 1990). For example, Casey et al (1997) found that performance on three response inhibition tasks correlated with anatomic measures of prefrontal cortex and caudate nuclei, particularly in the right-hemisphere. In keeping with this evidence, patients with ADHD tend to make more errors in left-space than right and are more severely disrupted by invalid cues for left-sided targets suggesting a reversal of the normal right hemisphere dominance in spatial attention (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; George, Dobler, Nicholls, & Manly, 2005).

Functional brain imaging studies with children have also consistently documented reduced activity in DLPFC, inferior frontal gyrus, anterior cingulate cortex and the

striatum during the performance of a variety of EF tasks confirming the involvement of this circuitry in ADHD (Bush, Valera, & Seidman, 2005; Seidman et al., in press). A general trend in this literature is that individuals with ADHD tend to show reduced recruitment of frontal regions during the performance of EF tasks but activate a more diffuse network of alternative brain regions than controls, possibly as a means of compensating for frontal hypoactivity (Durston, 2003; Fassbender & Schweitzer, 2006).

The physiological basis for these abnormal brain activations has been elucidated by studies showing that psychostimulants, that increase levels of extra-celullar dopamine, improve processing efficiency within fronto-striatal areas (Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Vaidya et al., 1998). One PET study has detected increased dopamine transporter binding potential, an index of DAT density, in the striatum of children with ADHD (Cheon et al., 2003). Excessive DAT levels increase the speed at which dopamine is removed from critical synaptic regions and hence hinders dopamine transmission. It is likely that other neurotransmitter systems also play a role in the pathophysiology of ADHD. For example, the noradrenergic system has been intimately associated with the modulation of higher cortical functions including attention/arousal systems and EF and is also preferentially distributed in frontal cortex (Arnsten, 1998; Biederman & Spencer, 1999). Atomoxetine, which targets the noradrenaline transporter, is effective for treating the symptoms of ADHD (Biederman & Spencer, 1999).

Although at a less advanced stage, neuroimaging work with adults has produced findings that are largely consistent with the paediatric data (Schneider, Retz, Coogan, Thome, & Rosler, 2006). The first volumetric study of adult ADHD was recently conducted by Seidman and colleagues (in press). Regions of interest were selected a-priori based on the hypothesis that consistent findings of prefrontal dysfunction in the paediatric literature would extend to adults. As predicted, a group of 24 adult patients were found to have significantly smaller overall volumes of DLPFC, anterior cingulate cortex (ACC) and grey matter when compared with matched controls. Importantly, controls and patients were carefully matched for psychiatric, intelligence, demographic and cognitive variables yet brain differences were still apparent. A greater number of functional imaging studies have been conducted on adults and these have also indicated

reduced activation of frontal regions, including DLPFC and ACC during the performance of EF tasks (Bush et al., 1999; Rubia et al., 1999; Schweitzer et al., 2000; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). PET studies have also detected increased striatal DAT densities in adults with ADHD (Dougherty et al., 1999; Dresel et al., 2000). Crucially, this work provides strong evidence to support the idea that adults with ADHD have a valid disorder with persistent biological features that are not explained by other comorbid conditions.

The stability of structural brain differences across development and into adulthood was confirmed by a major structural imaging study funded by the National Institutes of Health in the U.S. in which 152 children and adolescents with ADHD and 139 matched controls were scanned over a ten year period (Castellanos et al., 2002). The volume of cerebral white and grey matter of children and adolescents with ADHD was on average 3 to 4 percent smaller than that of children without the condition and differences remained at ten year follow-up. Interestingly, the brains of children with ADHD, though smaller, followed the same developmental trajectories as found in normal children (see Figure 1.2). This suggests that normal developmental changes are probably not affected by ADHD and that neurobiological abnormalities at some earlier point lead to the observed neuropsychiatric symptoms. Prefrontal white matter matures slowly throughout late childhood and adolescence and is accompanied by steady improvements in the ability to attend and maintain cognitive control (Klingberg, Forssberg, & Westerberg, 2002a; Liston et al., 2005; Paus, 2005; Sowell et al., 2003). Importantly, with respect to ADHD, dopaminergic projections to prefrontal cortex play a crucial role in its neurogenesis (Rubia et al 2000). It appears therefore that a neurochemical imbalance may limit, rather than delay, the development of frontal cortex, and other brain regions, in ADHD leading to deficits in frontally mediated neuropsychological processes which may account for the persistence of this disorder in adulthood.

1.4.4 Genetic Markers

Family, twin and adoption studies have indicated that there is an inherited susceptibility to ADHD. The heritability of the disorder is estimated at about 70% and is among the

highest for psychiatric disorders (Faraone & Dobler, 2001). Several genetic markers that convey vulnerability have been identified and these point to the involvement of multiple neurotransmitter systems. In light of the beneficial effects of stimulant medications, molecular genetics studies of ADHD have largely focused on candidate-genes associated with the dopamine system and a number of specific markers have been identified. These include genes coding for the dopamine transporter, D2 and D4

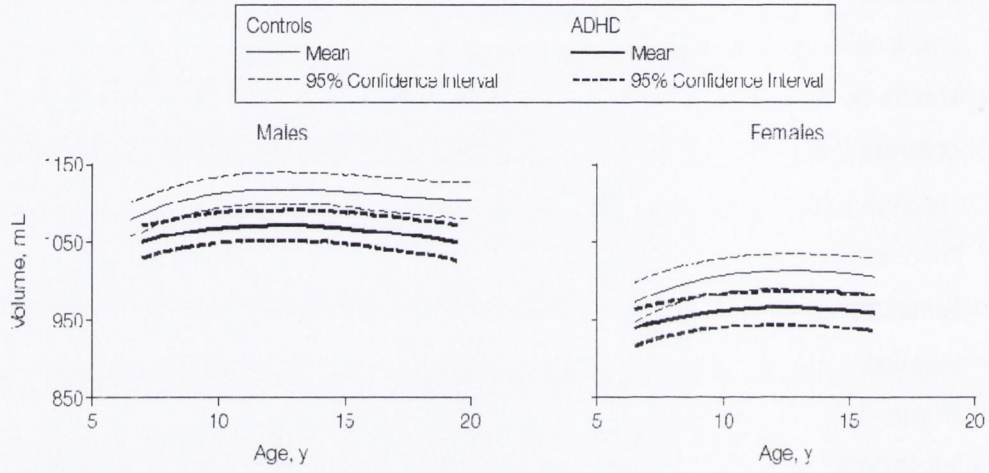


Figure 1.2 Predicted unadjusted longitudinal growth curves for total cerebral volumes for patients with ADHD and Controls. ADHD does not appear to alter brain developmental trajectories. From Castellanos, Lee et al (2002)

dopamine receptors and β-hydroxylase which catalyzes the conversion of dopamine to noradrenaline (findings reviewed by Madras, Miller, & Fischman, 2005). Genetic markers in the noradrenergic and serotonergic systems have also been identified (Biederman & Spencer, 1999; Kent et al., 2002). Attempts to localise single causative genes have not been successful and it is likely that ADHD results from a complex interaction of several "risk" or susceptibility genes (Faraone & Doyle, 2000; Madras, Miller, & Fischman, 2005). A number of less influential environmental risk factors have also been identified and these include complications of pregnancy or delivery, maternal health, socioeconomic status and brain injury (Faraone & Biederman, 1998). There is also increasing awareness of the potential role of gene-environment interactions

whereby certain genes may influence the onset of ADHD by affecting individual sensitivity to environmental adversity. For example Brookes and colleagues have reported that the association between DAT1 and ADHD was stronger in cases of maternal alcohol use during pregnancy (Brookes, Mill, Guindalini, & al, 2006).

Thus, although ADHD remains controversial due to the subjective nature of its diagnosis, the heritability of the disorder is well established and there is substantial evidence of structural, functional and neurochemical brain abnormalities that may account for a selective profile of neuropsychological deficits. Although probably too simplistic and requiring further elaboration in light of evidence of additional posterior brain differences, fronto-striatal accounts of ADHD pathophysiology have received consistent support from structural and functional neuroimaging studies.

1.5 Neuropsychological Models of ADHD

1.5.1 Single-process theories

Since its first clinical description, many researchers have tried to develop explanatory theories of ADHD that are based on a single primary neurocognitive deficit that would be common to all sufferers and that would account for all of the symptoms of ADHD. One of the most influential of these single-process models has been the behavioural inhibition model proposed by Barkley (1997). This model draws together existing models of frontal lobe function and asserts that behavioural inhibition represents a super-ordinate executive function that is necessary for other downstream processes, such as internalised speech, working memory, sustained attention and self-regulation to function effectively. As a consequence, a deficit in inhibitory control could produce secondary deficits in these subsidiary processes which could potentially account for most of the cognitive and behavioural symptoms that have been associated with ADHD. The prominence of this model can be attributed to the fact that poor performance on tasks that require response inhibition has been one of the most consistent findings in neuropsychological studies of ADHD (Nigg, 2001; Nigg, Willcutt, Doyle, & Sonuga-

Barke, 2005). In addition, functional imaging studies have reliably pointed to abnormalities in the inferior frontal gyrus, caudate and basal ganglia, regions that are thought to provide the neural substrate for response inhibition (Garavan, Ross, & Stein, 1999).

Other models that have driven ADHD research in recent years include the cognitive energetic model proposed by Sergeant (2000) and the delay-aversion model proposed by Sonuga-Barke and colleagues (Sonuga-Barke, Saxton, & Hall, 1998). The cognitive energetic model posits that problems in the allocation of effort and the moderation of arousal are central to ADHD and responsible for secondary deficits to executive functions. This theory is useful in accounting for the common finding that participants with ADHD have difficulty adjusting their performance to changes in task demands (e.g. Sergeant & van der Meere, 1988). In the delay-aversion model, ADHD is characterised as a motivational deficit relating to the processing of reinforcement. Experimental evidence indicates that children with ADHD experience a shorter delay of reward gradient such that a reward will lose its value more rapidly as the delay to its onset increases (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). Evidence from rodent models has indicated that these differences may arise from more fundamental abnormalities in the reward signals generated by the mesolimbic dopamine system (Sagvolden, Borga Johansen, Aase, & Russell, 2005). According to the delay aversion model, impulsive behaviour is not the consequence of an inability to inhibit responses but arises from a choice to avoid delay. Hence difficulties waiting for desired outcomes or engaging in tasks that take a long time to complete are argued to result from delay aversion. A dislike of delay could also potentially contribute to poorer performance on neuropsychological tasks (Slusarek, Velling, Bunk, & Eggers, 2001) and the model has received support from a number of empirical studies (e.g. Luman, Oosterlaan, & Sergeant, 2005; Solanto et al., 2001; Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004).

These theories have greatly advanced our understanding of ADHD by producing testable questions that have directed research and allowed for the coordination of seemingly disparate findings. Yet the latest research suggests that it is simply not possible to reduce a disorder as heterogeneous and complex as ADHD down to a single

core neuropsychological process. Overwhelming evidence from neuroimaging indicates that children and adults with ADHD exhibit a variety of neurological abnormalities including disruption of several fronto-striatal circuits that govern relatively distinct aspects of executive control. In addition, contrary to the predictions of these unitary models, deficits in separate neuropsychological functions are usually uncorrelated in ADHD (Schachar et al., 2004; Solanto et al., 2001). Finally, although a multitude of studies have demonstrated neuropsychological differences amongst children and adults with ADHD the original goal of isolating objective behavioural markers that could contribute to more reliable diagnostic criteria has proven far more elusive than originally hoped.

The major reason for this failure is that the performance distributions of neuropsychological tests overlap substantially in ADHD and control participants. In a recent paper by Nigg, Willcutt, Doyle, & Sonuga-Barke (2005) the authors tested a sample of 887 children with ADHD-C on a range of EF tasks and found that no more than half of the children could be classified as impaired, using the 90th percentile as a cut off, on any given measure. Thus, in any given sample a certain proportion of children with ADHD will perform within or even above the normal range suggesting that no single EF deficit measured by these tasks contributes causally to ADHD in *all* cases. As a result, any theory that makes recourse to a single fundamental deficit will inevitably fall short in accounting for ADHD symptomatology. This complexity is probably not unique to ADHD; rather most neurodevelopmental disorders are likely to have a neuropsychology that is complex and multifactorial (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Recognition of this fact has led to a paradigm-shift in ADHD research and a move towards embracing heterogeneity and defining the ADHD phenotype in terms of multiple, potentially independent, but not mutually exclusive, pathophysiological pathways.

1.5.2 Dual-pathway models

Although single-process models have failed to capture the complexity of ADHD, theoretical models that could link genetic, biological, cognitive and behavioural processes remain highly desirable given their potential to inform the development of

objective diagnostic approaches and improved treatment options. Recent dual-pathway models have sought to reconcile the consistent evidence of EF dysfunction in ADHD with knowledge that such deficits are neither necessary nor sufficient to cause all cases of ADHD (Nigg, Blaskey, Stawicki, & Sachek, 2004).

As discussed above, the dominant single-process models of ADHD have characterised the neuropsychological deficits as either executive or motivational. However, Sonuga-Barke and colleagues (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003) have argued that these are not necessarily competing views since they actually implicate distinct neurobiological systems that reflect the differentiation of functions within the fronto-striatal pathways. While the EF deficits are thought to be largely underpinned by disturbances in the DLPFC sub-circuit and changes in meso-cortical dopamine pathways, motivational accounts centre on the OFC and ACC sub-circuits that are modulated by meso-limbic branches of the dopamine system (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003 see also Figure 1.3). Therefore, Sonuga-Barke et al suggest that the EF and motivational theories of ADHD may describe complimentary developmental pathways to the same disorder. An interesting aspect of this kind of model is that the separate pathways can originate with distinct etiological mechanisms meaning that there would be no single common cause of ADHD. Separate pathways may have interactive effects however, since parallel brain circuits must work together to perform a variety of cognitive and behavioural functions (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). In what may prove to be a landmark study, Solanto and colleagues (2001) tested 45 children with ADHD and 29 controls on a measure of response inhibition and a choice delay task in which children chose between small immediate rewards and larger delayed rewards. The observed deficits on both tasks were uncorrelated but, when used together, correctly classified almost 90% of children with ADHD. Hence, a more complex model that allows for multiple pathophysiological mechanisms to the same disorder is able to account for a far greater portion of the observed variance in neuropsychological testing. This kind of model is also capable of accounting for the heterogeneity of symptom profiles since some children may manifest primarily motivational difficulties while others will have mainly cognitive deficits (Sonuga-Barke, 2003).

The weight of evidence suggests that multi-process models will be useful in guiding ADHD research. An important corollary of this development is that the original aim of identifying a unique neuropsychological profile for ADHD need not be abandoned but should rather be intensified. In fact, even when allowing for the inclusion of

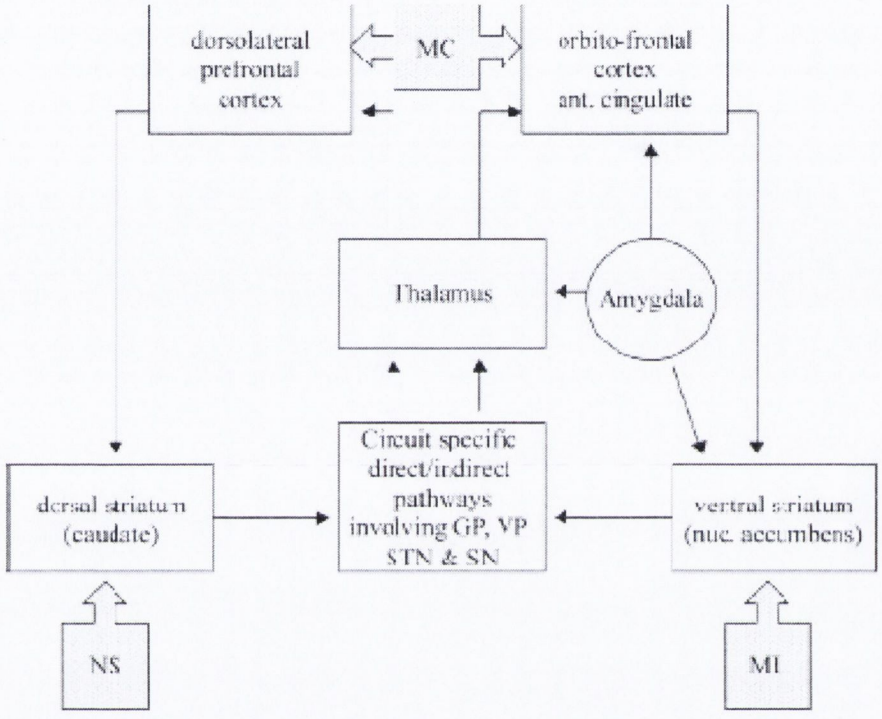


Figure 1.3 **A dual-pathway model of ADHD.** This is a simplified representation of the dorsal and ventral striatal circuits associated with EF and reward and their association with dopaminergic branches. GP, Globus Pallidus; VP, Ventral Pallidum; STN, Subthalamic Nucleus; SN, Substantia Nigra. Boxed arrows indicate main dopaminergic system – MC, meso-cortical; ML, Meso-limbic; NS, Nigro-striatal. From Sonuga-Barke (2003).

motivational influences, the unitary nature of the EF deficits that arise from ADHD remains highly questionable. For example, the idea that an inhibitory deficit could be the primary upstream process leading to executive dysfunction does not tally with evidence from neuroimaging or electrophysiology (see chapter 2), or the roughly equivalent effect sizes that are found for other EFs such as working memory (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A major methodological weakness in much of this work has been the reliance on tasks that potentially require the operation of multiple cognitive processes that are subserved by a range of brain networks. For

example, the Stop Signal Reaction Time Task (SSRT, see Epstein, Johnson, Varia, & Conners, 2001; Logan, 1994) which is a commonly used test of response inhibition, requires participants to respond to a stream of Go stimuli and to withhold responding on the occurrence of a rare and unpredictable No-go stimulus that is identified by a stop-signal, usually in the form of an auditory tone. It can be argued, therefore, that successful response inhibition on the SSRT is also heavily reliant on the participants' prior ability to orient to and process the stop signal as well as other functions such as sustained attention and motor control (Bekker et al., 2005).

As a result, behavioural measures alone provide only limited information regarding underlying pathophysiological processes and there is a still a need for studies that aim to refine the ADHD phenotype by identifying specific EF deficits that can be related to known brain-behaviour relationships from the field of cognitive neuroscience. In addition, increasing evidence supporting dual-process models of the disorder suggests that EF deficits cannot be fully understood without taking into account the possible influence of motivational processes. Castellanos and colleagues (2006) predict that disruption of reinforcement contingencies would influence EF in situations that are characterised by high affective involvement or that demand the flexible appraisal of the affective significance of stimuli. Following on from this theoretical work, the first major aim of this thesis will be to explore two areas that have been neglected in physiological investigations of EF dysfunction in ADHD; sustained attention and error processing. The studies conducted in Chapters 3 and 4 will use paradigms that emerged from careful analysis of specific brain-behaviour relationships and employ a number of electrophysiological measures to relate performance differences to specific neurophysiological processes. Importantly, the possible influence of abnormal motivational processes on EF will be explored in each case. Chapter 2 provides an overview of the potential value of electrophysiological parameters for studying both cognitive and motivational processes in ADHD research.

As will be discussed in the remaining sections of this chapter, the second major aim of this thesis is to investigate avenues for the remediation of neuropsychological deficits in ADHD.

1.6 Treatment of ADHD

Based on empirical research conducted to date, there are only two treatments that can be considered 'evidence-based' and they are psychostimulant medication and behaviour modification therapies (AACAI OFFICIAL ACTION, 2001; NIH, 2000; Pelham, Wheeler, & Chronis, 1998; Root & Resnick, 2003).

1.6.1 Pharmacological Therapies

Indirect dopamine agonists such as methylphenidate (MPH, also known by trade names such as 'Ritalin', 'Concerta' and 'Equasym') and amphetamine derivatives, have been used to treat ADHD since the 1960s and have proven efficacy in treating the three core behavioural symptoms in 70-80% of child patients (Biederman & Faraone, 2005). Although the usefulness of medication for treating the symptoms of adult ADHD has yet to be sufficiently verified, these psychostimulants are also widely prescribed for adult patients (Asherson, 2005) and recent clinical trials have indicated efficacy rates equivalent to those of child populations (Spencer et al., 2005; Wilens, Faraone, & Biederman, 2004). The precise neurobiological mechanism by which they have their effect on symptoms is not known but drugs such as MPH block the reuptake of dopamine from the synaptic cleft by inhibiting dopamine transporters (Madras, Miller, & Fischman, 2005). MPH, which has been the subject of the most empirical investigation, has been shown to normalise EEG measures of cortical arousal (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Loo et al., 2003) and selectively increase metabolism within regions of the striatum (Vaidya et al., 1998; Wolraich & Doffing, 2004). MPH also appears to alleviate neuropsychological deficits that are seen when participants with ADHD perform laboratory tasks that assess visuo-spatial attention (Nigg, Swanson, & Hinshaw, 1996), working memory (Schweitzer et al., 2004; Tannock, Ickowicz, & Schachar, 1995), vigilant attention (Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004) and inhibition (Overtoom et al., 2003). Although the extent to which these cognitive improvements transfer to everyday-life activities such as academic performance remains unclear, Volkow et al (2004) have reported an association between methylphenidate-induced dopamine increases and more positive

ratings of motivation and interest amongst normal healthy participants who performed a mathematical task.

After almost 200 randomised controlled clinical trials demonstrating their safety and efficiency in reducing disruptive behaviour and improving concentration levels, psychostimulants are now considered to be the 'gold standard' treatment for ADHD (NIH, 2000). However, it is also important to be aware that there are several disadvantages and limitations to the pharmacological treatment of ADHD. For example, 20-30% of patients will not respond to medication, loss of appetite is a common side-effect and occasionally there are reports of other side-effects such as insomnia and motor tics (Fone & Nutt, 2005). Another obvious difficulty is that stimulants represent a short-term treatment that is only effective while in the system. There has been very little investigation of the long-term effects of pharmacotherapies either positive or negative but so far, there is little evidence to suggest that they affect the long-term outlook of individuals with ADHD in key areas such as social functioning, occupational success or criminality (DuPaul, 2006; Wells et al., 2000).

Importantly also, available evidence suggests that long-term stimulant treatment does not affect the underlying neurobiology of ADHD in a lasting manner. The longitudinal fMRI study by Castellanos et al (2002), mentioned previously, found that brain volume abnormalities were still evident at ten-year follow-up even amongst children who had been receiving pharmacological treatment in the interim. In another study, Schweitzer and colleagues (2000) found that adults with ADHD failed to activate frontal regions while performing a working memory task. Administration of methylphenidate led to significant improvements in performance but did not alter frontal activation. There is also evidence that cognitive impairments are only partially and temporarily improved by medication. For example, while stimulants have been shown to increase academic productivity only moderate improvements in academic achievement or social skills have been observed (Chacko et al., 2005; NIH, 2000; Swanson et al., 1998). According to Barkley (1998), even when medicated, patients frequently report difficulty performing tasks that are long, drawn-out and tedious. These findings suggest that psychostimulants do not directly alter cortical abnormalities but rather temporarily bypass them which

may explain why so many adults who have been medicated since childhood, are still symptomatic.

Several authors have also noted the ethical problems associated with medicating children for behavioural problems (Bradshaw, 1999; Fone & Nutt, 2005; Greene, 2001). As mentioned in a previous section, the diagnosis of ADHD is particularly difficult since its characteristic behaviours are displayed by all children to some extent and can be difficult to discriminate from other disruptive disorders. Since no objective behavioural or biological marker exists for ADHD there is a danger that, in a minority of cases, problematic, 'boisterous' behaviours that are not rooted in neurobiological dysfunction are being medicated (Bradshaw, 1999). This is increasingly a matter of concern since over the past ten years there has been an eight-fold increase in the prescription of MPH (Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004) and such drugs can produce abuse and dependence (Fone & Nutt, 2005). These problems have spurred on research seeking to identify effective non-medical alternatives.

1.6.2 Behavioural Therapies

Behavioural psychosocial therapy is the only empirically validated non-medical treatment for ADHD in childhood (MTA Cooperative Group, 2004; NIH, 2000; Pelham, Wheeler, & Chronis, 1998). This intervention is based on operant conditioning principles and involves reinforcing adaptive behaviours in the child's natural everyday environment. Effective variants include contingency management which usually takes place at school or other such settings where contingencies can be directly controlled by time outs, over correction and token economies. A well-known example is the Summer School program which has been successfully implemented in the U.S. (Pelham, Wheeler, & Chronis, 1998; Wells et al., 2000). This intervention has been found to be as effective as low dosages of medication and, when combined with low dosages, is proven to be as effective as a high dose (Root & Resnick, 2003). A second effective variant is clinical behaviour therapy during which the clinician instructs the parent or teacher on how to implement contingency management techniques themselves. Studies show that clinical behaviour therapy normalises aggressive behaviour even without

medication and is associated with a range of reported behavioural improvements (Root and Resnick 2003).

While behaviour modification therapies of this kind are not designed for adult populations there is good accumulating evidence that cognitive-behaviour therapies (CBT) provide an effective alternative for adults with ADHD (McDermott & Wilens, 2000; Safren et al., 2005; Wasserstein, 2001). In a study by Safren et al (2005) it was found that 31 patients who received CBT in conjunction with ongoing pharmacological treatment reported significantly greater improvements, as rated by themselves and an independent evaluator, than those who received medication alone.

Psychosocial therapies provides important feedback on appropriate behaviour and self-regulation for children with ADHD and therefore addresses many issues that cannot be treated with medication alone. Behaviour management techniques can be implemented in the classroom or home setting without disrupting the daily routine and therefore provide a valuable alternative to medical treatment. Disadvantages of this approach include that it is estimated to be effective in only 60% of cases and that it is a highly time-intensive and expensive treatment (Pelham, Wheeler, & Chronis, 1998; Root & Resnick, 2003). Similar to medication, behaviour therapy is a short-term intervention and symptoms are generally found to return after contingencies are removed (Pelham, Wheeler, & Chronis, 1998). Another important consideration is that behaviour therapy does not address underlying neuropsychological deficits and has not been found to improve academic performance (Miranda, Presentacion, & Soriano, 2002).

1.6.3 Multimodal Approaches

Recognition of the limitations of a purely pharmacological or purely behavioural approaches to the treatment of ADHD has prompted a move toward multi-modal treatment strategies. During the 1990s the National Institutes of Health in the U.S. commissioned the Multimodal Treatment Study of ADHD (MTA), one of the largest ever treatment trials for a psychiatric disorder (Wells et al., 2000). The study recruited 579 children with ADHD-C aged between 7 and 9.9 years and allocated them to four separate treatment modalities; behaviour therapy, medical management, community

care and a combined medical and behaviour therapy. The results showed that medical management alone or combined with behaviour therapy was more effective than either community care or behaviour therapy alone (MTA Cooperative Group, 2004). Based on a composite score combining parent and teacher symptom ratings, Conners and colleagues (2001) found that the combined treatment had significantly superior effects to those of medical treatment alone. Furthermore, improvements with the combined treatment were achieved with 20% lower dosages of medication. Behaviour therapy alone was less effective than medication but was still associated with significant improvements which, in 75% of cases, were maintained over a 14-month period without any medication. The MTA study has provided some of the strongest evidence that non-medical treatments can have effects beyond those of medication and, at the very least, reduce reliance on medication (Swanson et al., 2002).

To summarise, there are two 'evidence-based' treatments for child and adult ADHD. Children benefit considerably from psychostimulants and behaviour management and while there has been far less investigation of treatment effects in adults, there is growing evidence that psychostimulants and CBT are effective for older populations. A major limitation of these approaches is that while each has proven efficacy in reducing disruptive behaviour problems and improving general concentration levels they do not target the underlying pathophysiology of ADHD in a lasting manner. Of particular concern is the lack of effect that these treatments have on underlying neuropsychological deficits. While problematic behaviour may present the most pressing concern for ADHD sufferers and their families, processes such as working memory, attention, and response inhibition can be thought of as 'supportive' or 'core' cognitive functions that are a prerequisite for the acquisition of skills and knowledge needed for continued learning and are therefore vital for academic success (Penkman, 2004). Poor academic achievement plays a central role in the 'cycle of disadvantage' with which many ADHD sufferers must contend and neither medication nor behaviour management can fully eradicate this problem (DuPaul, 2006). It is surprising, given the well documented neuropsychological problems that ADHD sufferers experience, that very little research has been directed towards developing new treatments that would target these deficits.

For these reasons, the second major aim of this thesis is to examine a new avenue for the remediation of neuropsychological deficits that capitalises on our increasing understanding of brain function arising from the field of cognitive neuroscience. Chapter 5 begins by providing an extensive review of the evidence that experience-dependent changes in neural plasticity can be encouraged by carefully structured practice on cognitive tasks. In Chapter 6, the first steps are taken towards the development of a new cognitive training strategy designed specifically to target sustained attention deficits in ADHD.

Chapter 2. The use of electrophysiological parameters in ADHD research

The methods described in this chapter will be used throughout this thesis and have potential to provide valuable insights into the precise time-course of neuropsychological deficits in ADHD.

2.1 Event-Related Potentials

Event-Related Potentials (ERPs) are patterned voltage changes arising from changes in the polarisation of the cell membranes in the central nervous system that are extracted from the ongoing electroencephalogram (EEG) (Hillyard & Picton, 1999). ERP waves consist of positive and negative deflections known as components that are identified by their polarity (positive or negative) and latency, hence P100 or P1 and N200 or N2. Specific components of an ERP waveform are associated with specific sensory, motor and cognitive events but such fluctuations are generally too small to appear on a normal EEG reading and therefore a process of averaging and filtering is required to isolate only the activity that is consistently associated with stimulus or event processing in a time-locked manner. To increase signal-to-noise ratios evoked activity is collected over many trials, typically varying from 20-100 (Picton et al., 2000). The result is a wave of activity whose changes in amplitude and latency can be accurately time-locked, within milliseconds, to the occurrences of external stimuli providing unparalleled temporal information about mental operations. This accuracy can be contrasted with neuroimaging methods such as PET and fMRI which have a temporal resolution in the order of several seconds.

Different ERP components are subject to varying degrees of exogenous and endogenous influence (Picton et al., 2000). Exogenous components are obligatory responses that are determined by the physical characteristics of a particular stimulus or event while endogenous components are manifestations of information processing in the brain that are not necessarily determined by the stimulus itself. The sequence of components following a stimulus indexes the sequence of neural processes triggered by the stimulus beginning with early sensory processes and proceeding through decision and response

processes. Valid interpretation of ERP activity is only made possible through careful manipulation of experimental paradigm parameters and over many years of empirical testing the functional significance of specific ERP components for particular cognitive processes has been elucidated (Hillyard & Picton, 1999; Luck, Woodman, & Vogel, 2000). Knowledge of the characteristics of ERPs is also invaluable to researchers investigating the neurophysiological substrates of clinical disorders since they make it possible to identify the precise processing stage at which abnormalities occur.

As mentioned in Chapter 1, the major limitation of testing by behavioural means alone is that cognitive processes must be inferred since mental operations are not directly observable. This can be highly problematic since a seemingly simple behavioural measure, such as reaction time, can be the product of the compound contributions of several different cognitive functions. ERPs provide a solution to this problem since they allow one to fill the gap between stimulus and response by providing a direct insight into the timing of covert cognitive processing activities in the brain. The importance of this kind of information is most obvious in the case of neurological conditions such as ADHD where neuropsychologists have struggled to disentangle overlapping cognitive deficits and to identify an accurate neuropsychological profile that distinguishes it from other disorders. A good example is the case of response inhibition.

Recent reviews agree that the strongest effect sizes are obtained when individuals with ADHD are asked to perform tasks that require response inhibition (Nigg, 2001; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Seidman, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). This finding has been so consistent that it was the basis for one of the most influential single-process models of ADHD (Barkley, 1997). Response inhibition is most frequently measured using Go/No-go tasks in which participants make speeded responses to a series of Go stimuli but must withhold responding on the appearance of a No-Go stimulus. As would have been predicted, studies that have recorded ERPs while participants performed such tasks have found differences in componentry relating to response inhibition (No-Go N2, No-Go P3). But these studies have also reported that the clearest group differences were seen on components relating to the ongoing allocation of attentional resources, response preparation processes and the orientation of attention to the No-go stimulus

(Banaschewski et al., 2004; Bekker et al., 2005; Brandeis et al., 1998; Fallgatter, Ehlis et al., 2004; Overtoom et al., 2002). The behavioural deficit in response inhibition therefore appears to be preceded by a deficiency in state regulation and attentional control throwing doubt on the idea that a basic inability to inhibit a prepotent response is the core upstream deficit. In this case, a reliance on behavioural assays of cognitive performance may have led to a misrepresentation of ADHD deficits.

The use of electrophysiological measures may provide a more parsimonious representation of neuropsychological deficits than is currently available if ostensibly distinct cognitive deficits can be attributed to the same underlying neurophysiological process. Equally, recent work suggests that a truly representative neuropsychological model of ADHD cannot rely on single core processes but instead must account for the possibility that there are multiple etiological pathways to this disorder that are not mutually exclusive (Castellanos et al., 2002; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003). As in the example of response inhibition, this could mean that poor performance on a single cognitive task may arise from several potentially distinct neuropsychological deficits. In this regard also, electrophysiological measures provide an invaluable methodology by which multiple overlapping deficits can be disentangled.

Electrophysiological processes, as measured by EEG and ERP signals, are heritable traits or characteristics and researchers have already begun to isolate genetic markers for specific ERP components (e.g. Birkas et al., 2006; Fallgatter, Hermann et al., 2004). Pharmacological alteration of dopamine transmission changes the expression of ERPs during attentional and inhibitory performance suggesting that the integrity of the catecholamine system, can be gauged by electrophysiological techniques (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004; Klorman, Brumaghim, Fitzpatrick, & Borgstedt, 1991; Lopez et al., 2004; Zirnheld et al., 2004). Accordingly, electrophysiological phenotypes provide a powerful approach to the identification of key biomarkers, in the form of electro-cortical signals, for psychiatric conditions that lie on the pathway between gene action and observed symptoms. It is hoped therefore, that the ERP studies conducted in this thesis can contribute to the development of causal models that will link genetic variations to functional differences in molecular biology,

physiology, cognition and behaviour. Such work may have important implications for the development of new, objective diagnostic tools.

Most studies of children with ADHD have focused on P3-type components. P3 components can be divided into three broad categories; the No-Go P3, P3a and P3b (see Polich & Criado, 2006 for review). The No-Go P3 is commonly seen on trials that require a prepotent response to be withheld and is thought to index response inhibition (e.g. Bekker et al., 2005). The P3a or 'oddball P3' is elicited by unexpected or rare stimuli and reflects orienting aspects of attention. P3b components can be distinguished from the P3a by their more posterior scalp distribution and can be elicited by any motivationally significant stimulus or event (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; Polich & Criado, 2006). Different theories of the P3a and b suggest that they represents an updating of working memory (Donchin & Coles, 1988) or a facilitation of task-related brain regions mediated by ascending sub-cortical arousal systems (Nieuwenhuis, Aston-Jones, & Cohen, 2005). P3 components are largely endogenous and can be present even in response to an expected missing stimulus and have larger amplitudes under attention demanding conditions (Knight, 1991; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). As a result, although their precise function is still controversial, P3 components are frequently used as an index of the endogenous mobilisation of attentional resources in response to a critical event. Reduced P3a and P3b components have been observed on a range of different tasks in both children (e.g. Jonkman, 1997; Satterfield, 1990) and adolescents (Lazarro et al 1997; 2001) with ADHD. Klorman and colleagues (1991) found that methylphenidate increased the amplitude of the P3b on a vigilant attention task and shortened its latency. This change was accompanied by an improvement in performance on the task

Other ERP studies of ADHD have examined earlier visual attention processes reflected in components such as the P1, N1 and P2 where group differences have also been observed in the processing of critical task stimuli (e.g. Brandeis al 1998; Perchet et al 2001). In addition, differences have been noted for ERPs that reflect anticipatory mechanisms of expectancy and motor strategic planning. For example, when participants performed an orienting paradigm, Perchet and colleagues (2001) found that the Contingent Negative Variation (CNV), which normally indexes the increase in

expectancy of the incoming stimulus which occurs over time in the absence of visual cues, was absent in children with ADHD.

Only one ERP study has been conducted on adults with ADHD. In a study of the stop signal task Bekker et al (2005) noted smaller No-go P3s in the ADHD group that were preceded by smaller early responses in the auditory cortex (N1) following a stop signal suggesting that poorer behavioural performance in the ADHD group reflected problems processing and orienting to the stop-signal as well as a difficulty inhibiting responses. Further ERP studies with adult populations are of vital importance to identify developmentally stable neurophysiological abnormalities in ADHD and two such studies are reported in Chapters 3 and 4.

2.2 Source Analysis

Traditionally, the major limitation of ERPs as a method of understanding the brain has been that they provide only limited spatial resolution when trying to identify the intracranial source of activity. While the distribution of voltage over the scalp can be used to estimate the neural generator of a particular component this can only be done with very limited accuracy since the same pattern of activity can be potentially generated by a variety of intracranial source configurations. This difficulty, known as the inverse problem, is aggravated by the fact that the scalp, skull and other tissues diffuse even highly localised electrical brain activity over most of the scalp. Increasing the density of electrode arrays can help to alleviate this problem but the major advance in electrophysiological research has been the development of source analysis methods that allow the neuroanatomical loci of specific ERPs components to be identified.

The fundamental premise of source analysis is that a particular deflection in the ERP recording is related to a change in the local activity of a limited number of brain regions (Sehatpour, Molholm, Javitt, & Foxe, 2006). Source localisation procedures mitigate the inverse problem by using a least squares fitting algorithm which identifies the location that explains the maximum amount of variance in the observed scalp activity within a realistic volume conductor head model that approximates the additional influences of the scalp, skull and other tissues. The selected region or regions are then modelled and

overlaid on a standard brain, constructed from MRI images, using an equivalent dipole. Source waveforms are also generated and these provide information regarding the time-course of activity within the identified brain regions. The position of each dipole and the amount of variance it contributes can then be used to determine whether or not the model provides a realistic approximation of the intracranial generator/s. The upper bound of the number of modelled dipoles is identified by adding a test dipole. If the current model is adequate then the addition of a further dipole should not further reduce the residual variance above that attributable to noise (Foxe, McCourt, & Javitt, 2003). Several different source analysis algorithms exist but Brain Electrical Source Analysis (BESA) will be used in this thesis (see Sehatpour, Molholm, Javitt, & Foxe, 2006; Van Veen & Carter, 2002 for other examples of this technique).

The resultant solution inevitably represents an oversimplification of the activity in the areas indicated and should only be considered as the centre of gravity of the observed activity rather than a precise localisation of exact generators (Sehatpour, Molholm, Javitt, & Foxe, 2006). As a result, source analysis does not provide spatial resolution of the magnitude offered by fMRI or PET but is at its strongest when interpreted in conjunction with good a-priori evidence from the functional imaging literature regarding probable intracranial sources (Dias, Foxe, & Javitt, 2003). Source analysis is employed in Chapter 4 of this thesis.

2.3 Quantitative EEG (QEEG)

In quantitative EEG, multi-electrode recordings are quantified in the frequency range of interest, which usually extends from about 1 Hz to 25 Hz. This frequency range has traditionally been separated into five frequency bands, delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), beta (13-30 Hz) and gamma (30-70 Hz). In ADHD research EEG has been most commonly utilised as a method of investigating differences in arousal. During the wake/sleep cycle activity within the EEG bands follows a reliable pattern. As arousal and wakefulness decreases, activity in the theta and alpha bands increases while there is a gradual drop in activity in the beta band (Aeschbach et al., 1999). Experimental manipulation of activity within subcortical structures that mediate arousal also affects EEG band activity in the same way (Nieuwenhuis, Aston-Jones, &

Cohen, 2005). The ratio of slow (theta, alpha) to fast (beta) oscillatory activity, acquired while the participant is not engaged in a particular task, is therefore frequently used as a general measure of basal arousal levels. Children with ADHD have consistently displayed a resting-state arousal deficit in EEG studies of this kind (Clarke, Barry, McCarthy, & Selikowitz, 2001; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002; Loo, Teale, & Reite, 1999). These abnormalities are so consistent that QEEG identifies ADHD sufferers in 90% of cases and non-ADHD sufferers in 94% of cases (Chabot, 1996). Research with adolescents and adults suggests that EEG abnormalities decline significantly with age but are nonetheless still apparent at maturity (Bresnahan & Barry, 2002). EEG differences are alleviated, in children and adults, by the administration of psychostimulants (Bresnahan, Barry, Clarke, & Johnstone, 2006; Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002)

In addition to the spontaneous oscillatory activity that is measured when a person is at rest, there are also several distinct patterns of 'functional' EEG activity that are strongly interwoven with sensory and cognitive functions (Basar, Basar-Eroglu, Karakas, & Schurmann, 2001). For example, Dockree and colleagues (Dockree et al., 2004) have shown that a high tonic level of activity in the alpha band during sustained attention is associated with better performance but that alpha frequency power is phasically reduced during critical periods of attention deployment such as prior to an anticipated target stimulus. There is also increasing recognition that background EEG activity provides the critical setting condition for the emergence of transient ERPs (Aston-Jones & Cohen, 2005; Basar, Basar-Eroglu, Karakas, & Schurmann, 2001 see also Chapter 4). To date no study of ADHD has investigated EEG measures during performance of neuropsychological tasks and therefore this issue will be explored in Chapters 3 and 4 of this thesis.

2.4 Electrodermal Activity

Electrodermal Activity (EDA) is recorded as changes in electrical conductance due to sweat gland activity and is controlled by sympathetic enervation of the autonomic nervous system. EDA can be characterised as tonic (Skin Conductance Level, SCL) or phasic (Skin Conductance Response, SCR). SCL refers to the ongoing baseline level of

skin conductance in the absence of any particular discrete environmental event. SCRs are event-related phasic increases in conductance superimposed on the tonic level which can be elicited by a variety of events or stimuli. SCRs are thought to be independent of SCL since a given increment in the number of active sweat glands will produce the same increment in the total conductance of the pathway regardless of the level of basal activity (Dawson, Schell, & Filion, 2000). EDA is subject to complex excitatory and inhibitory influences from a variety of cortical and subcortical regions of the brain reflecting its different functional roles. For example, EDA elicited by activation of the reticular formation is likely to be associated with gross movement and muscle tone while EDA associated with amygdala and prefrontal activation is likely to be associated with affective and motivational processes (Boucsein, 1992; Critchley et al., 2003).

In cognitive research, EDA has been used primarily as an index of psychophysiological responsiveness to motivationally significant events (Dawson, Schell, & Filion, 2000). Investigations of the cortical influences on EDA have indicated that prefrontal regions, and the ACC in particular, play a central role in integrating motivationally important information with adaptive changes in bodily states of arousal, mediated by the autonomic nervous system (Damassio, Tranel, & Damassio, 1991; Dawson, Schell, & Filion, 2000; Tranel & Damassio, 1994; Zahn, Grafman, & Tranel, 1999). For example, Damassio and colleagues demonstrated that reckless performance of a gambling task by patients with PFC and ACC lesions was associated with an absence of the normal EDA response prior to making a risky decision (Damassio, Tranel, & Damassio, 1991). Zahn, Grafman and Tranel (1999) noted that patients with prefrontal lesions had normal EDA responses to external stimuli, such as auditory tones, but had attenuated EDA responses to psychologically significant events including significance attained by instructions to attend and respond suggesting that damage to this region produces selective deficits in the subjective processing of significance.

Convergent functional imaging evidence with healthy and clinical groups points to a rostral-ventral sub-division of the ACC as the key cortical region mediating top-down influences on EDA in a task-independent manner (Bush, Luu, & Posner, 2000; Critchley, Elliot, Mathias, & Dolan, 2000; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001, , 2002; Patterson, Ungerleider, & Bandettini, 2002). Importantly with

respect to ADHD, EDA is predominantly cholinergically mediated and the rostral subdivision of the ACC, which has strong connections to the amygdala and OFC, forms part of the ventro-fronto-striatal pathway implicated in motivational accounts of the disorder (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003 see Figure 1.3 in Chapter 1). Hence, in this thesis, EDA provides an ideal measure for investigating the interplay between motivational and cognitive deficits in ADHD as suggested by Castellanos and colleagues (2006).

A number of previous studies have examined EDA in ADHD and while no consistent differences in SCL have been found (Zahn & Kruesi, 1993), children with ADHD do exhibit reduced SCRs to task-related stimuli (Mangina & Beuzeron-Mangina, 2000; Shibagaki, 1993; Zahn & Kruesi, 1993) suggesting that ADHD, like frontal pathology, may also involve a selective EDA deficit. No studies, however, have investigated how attenuated autonomic system activity might actually relate to the cognitive deficits implicated in ADHD. In addition, no studies have investigated EDA in adult ADHD.

Chapter 3. Exploring sustained attention deficits in ADHD

3.1 Why is it so hard to find the attention deficit in ADHD?

According to the DSM-IV criteria (A.P.A., 2000), poor sustained attention is a key behavioural characteristic of ADHD (e.g. "often has difficulty sustaining attention in tasks or play activities", "avoids tasks requiring sustained effort" and "often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities"). Sustained attention has been defined by Robertson and colleagues as:

"*the ability to self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing qualities, would otherwise lead to habituation and distraction by other stimuli*" (Robertson et al, 1997, pp 747).

This definition helps us to understand why a child who suffers from ADHD might excel at complex and challenging video games, which he or she might play for hours on end, but when it comes to sitting down and completing a series of relatively simple maths problems he or she finds it extremely difficult to concentrate and tends to make 'silly' mistakes (Barkley, 1998). The difference here is that the exogenous stimulation provided by the vibrant colours, exciting sound effects and fast movement of video games actually captures one's attention. As a result the demands placed on sustained attention are very limited when compared to the endogenous or top-down control of attention required to perform a rather boring maths assignment. ADHD sufferers tend to report that attentional problems manifest themselves when a task is long, drawn-out and monotonous (Barkley, 1998). Therefore, it will surprise many people to learn that despite being clearly emphasised in the DSM-IV criteria, the existence of sustained attention deficits in ADHD is considered controversial within the field of cognitive neuroscience. In the present chapter the reasons for this discrepancy will be discussed and it will be proposed that adopting a more sensitive methodology can unmask sustained attention deficits experienced in the ADHD population.

Based on a review of extensive evidence gathered from neuropsychology, neuroimaging, lesion studies and animal studies Posner and Raichle (1994) proposed an influential model in which attention consists of three distinct neural processes that act in close unison to influence how the brain processes information:

- Orienting - the capacity to prioritise certain sensory inputs in response to expected processing requirements. This process is associated with activity in posterior regions of the parietal lobes as well as the superior colliculus and thalamus.

- executive attention - responsible for directing behaviour toward a goal by overseeing and coordinating multiple low-level neural processes. This process has been primarily linked to activity in the anterior cingulate cortex (ACC) and basal ganglia

- alerting – suppression of neural noise by inhibiting competing irrelevant activities and increasing responsiveness to a particular task set or goal. Alerting is linked to a predominantly right hemispheric fronto-parietal network and the locus coeruleus arousal system.

The 'alerting' component of this model bears a close relationship to the cognitive concept of sustained attention. Since that review researchers have made use of technological advances in human brain mapping to provide an even clearer understanding of the attention system. Gathering together the available evidence from more recent fMRI, PET and pharmacological studies, Sturm and Wilmes (Sturm et al., 1999; Sturm, Longoni, Fimm et al., 2004; Sturm & Willmes, 2001) observed that an amodal sustained attention system has been consistently localised to a right lateralised cortical network that includes the ACC, the right dorsolateral prefrontal cortex and the inferior parietal lobule.

Investigation of the cytoarchitecture of the human brain stem indicates that subcortical nuclei have multiple ascending pathways each linked to different neurotransmitters and each projecting to different regions of the cortex (Olszewski & Baxter, 1982). Arousal,

or non-specific neuronal excitability, within cortical regions is dependent on these innervatory pathways. Sustained attention has been most closely associated with the action of the neurotransmitter noradrenaline (NA) which is produced by the locus coeruleus (LC) and has its strongest projections in right fronto-parietal regions (Foote & Morrison, 1997). Aston-Jones, Chiang and Alexinsky (1991) acquired extracellular recordings from noradrenergic neurons in the LC of monkeys performing a visual discrimination task. It was found that LC responses varied with behavioural performance and were attenuated during periods of poor performance. LC responses became reduced in magnitude over time in parallel with a behavioural performance decrement supporting the view that LC activity is linked to sustained attention and arousal. The influence of NA mediated arousal on sustained attention in humans was demonstrated by Smith and Nutt (1996) who found that reducing NA release by administering the drug clonidine resulted in an increase in the kinds of attentional lapse characteristic of poor sustained attention.

The LC receives prominent, direct inputs from the prefrontal cortices and work by Paus (Paus et al., 1997) and by Critchley and colleagues (Critchley, Elliot, Mathias, & Dolan, 2000; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002) has shown that increased activity in prefrontal regions, particularly the ACC, *precede* increases in activity within subcortical arousal structures. In keeping with Posner and Raichle's earlier model, Sturm and Wilmes (2001) therefore propose that goal-directed or top-down increases in sustained attention are achieved by the frontal cortex which monitors and modulates activity in the LC/NA arousal system to match current task demands hence increasing activation of the right fronto-parietal cortical network. Interestingly, when Smith and Nutt exposed their participants to loud white noise during the same study mentioned above they actually found an improvement in performance. What this tells us is that the cortical sustained attention system is also subject to bottom-up or exogenous modulation from peripheral sensory systems. In addition, Coull et al (Coull, Middleton, Robbins, & Sahakian, 1995) showed that the effect of clonidine on sustained attention performance was greatest when participants were familiar with the task, while Arnsten and Contant (1992) showed that the negative effects of clonidine were reduced by making a simple delayed response task *more* difficult. Thus, features such as task novelty and task difficulty are also sources of exogenous input. More recently, a study

by O'Connor et al (2004) found that presenting participants with periodic auditory alerts during a sustained attention task led to a deactivation of right frontal regions clearly demonstrating that bottom-up support to the sustained attention network reduces its reliance on top-down modulation. As we will see, the distinction between endogenous and exogenous inputs to the sustained attention system is of critical importance to the development of valid experimental analogues and in assays of clinical populations.

The functional and anatomical separation between sub-components of attention, highlighted by Posner and Raichle (1994), means that dysfunction in different regions of the brain can lead to relatively specific attention deficits. As a result neuropsychologists have sought to develop increasingly specific assessment tools with the aim of measuring each of these sub-component in relative isolation. In ADHD research, sustained attention has typically been examined using variants of the continuous performance task (CPT) during which participants monitor a stream of stimuli over an extended period of time for the occurrence of a rare target stimulus to which they must make a response. These tasks were designed to mimic 'real world' situations in which low signal probability places us at increasing risk of a critical lapse of attention (e.g. the train driver who passes a red light or the airport security officer who fails to notice a weapon on the luggage x-ray). Performing such tasks is tedious and undemanding leading to a gradual decrement in performance over time resulting from under-arousal. This phenomenon is known as the 'vigilance decrement' (Parasuraman, Nestor, & Greenwood, 1989). A recent meta-analysis by Willcutt and colleagues (2005) reports that children with ADHD do exhibit poorer target detection in 77% of the CPT studies reviewed yielding effect sizes that are comparable to those found for tests of response inhibition and working memory. However, most studies have failed to show that these performance differences are accompanied by a disproportionate vigilance decrement (e.g. Van der Meere & Sergeant, 1988) leading many researchers to argue that poorer target detection rates in ADHD are not necessarily related to a gradual decline in sustained attention (e.g. Barkley, 1997; Corkum & Siegel, 1993; Huang-Pollock & Nigg, 2003; Sergeant, 2000). As a result sustained attention has tended to be relegated to the status of a secondary deficit arising from dysfunction in more fundamental upstream processes (Barkley, 1997; Sergeant, 2000)

Nevertheless, the notion of an ADHD sustained attention deficit has not gone away and evidence from several sources has ensured that research in this domain continues. This evidence includes functional and structural imaging studies that consistently point to abnormalities in cortical regions strongly linked to sustained attention, including the right prefrontal cortex and regions of parietal cortex (see Krain & Castellanos, 2006 for review), and the effectiveness of drugs such as atomoxetine, a NA reuptake inhibitor, and guanfacine, an alpha 2 NA agonist (Biederman & Spencer, 1999; Scahill et al., 2001). In light of strong evidence indicating that the sustained attention system is subserved by a right fronto-parietal cortical network that is directly involved in the modulation of NA arousal systems there is a clear rationale for expecting the sustained attention network to be disrupted in ADHD. So why is it so difficult to isolate these deficits in the lab?

It is increasingly recognised that time-on-task decrements during CPT performance may not provide a sensitive index of the sustained attention network. According to Coull (1998) there is an important distinction between vigilant attention, in which critical stimuli have a very low probability resulting in extremely monotonous situations, and sustained attention, which refers to any situation that requires prolonged maintenance of an alert state but with more regular occurrence of critical stimuli. Neuroimaging work indicates that vigilant and sustained attention are manifestations of the same alertness network (Sturm & Willmes, 2001). The distinction between vigilant and sustained attention arises from the susceptibility of the alertness network to short-term momentary decreases in top-down control as well as the more commonly studied long-term drifts of arousal. Robertson et al (1997) argue that while time-on-task CPT decrements measure gradual decreases in arousal over long periods of time, in everyday life we are also susceptible to fluctuations in attention over much shorter periods. These slips are most likely to manifest themselves in the context of routine or mundane tasks when we are prone to persist with mindless automated behaviours at times when task demands have changed and increased attention to action is required. These brief reductions in sustained attention can disrupt our goal-directed behaviour with consequences that range from the comical (e.g. putting salt in our tea and sugar on our chips) to the tragic (e.g. road traffic accidents and work related injuries). Imaging studies have supported this observation by demonstrating that the sustained attention network can be active

over periods as short as a few seconds (Paus et al., 1997) and that brief lapses of attention are preceded by momentary reductions of activity in frontal control regions (Weissman, Roberts, Visscher, & Woldorff, in press). Yet traditional vigilance paradigms are designed to measure longer-term processes in the region of minutes to hours. Since there are large gaps between responses made by the participant during CPT performance it is not actually possible to gauge the efficiency of sustained attention in this kind of moment-to-moment manner. Hence, by requiring participants to respond only to rare targets the CPT fails to capture a key element of real life slips of attention: most everyday attentional failures occur in the context of routine action.

Keeping in mind the previous discussion of exogenous and endogenous influences, another important methodological concern relating to CPTs is that the novelty of the rare target stimulus might be sufficient to orienting attention to its presence (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). This exogenous input would allow the task to be performed in a largely automatic manner irrespective of the extent of endogenously guided attention. This may explain in part why the performance of normal healthy participants is close to ceiling in most studies and why even patients with frontal injuries can perform faultlessly for long periods of time (Manly, Robertson, Galloway, & Hawkins, 1999). Hence, it may be that the inconsistent findings of ADHD sustained attention studies reflect the limited sensitivity of the paradigms used rather than an absence of impairment.

Recently, a group led by Ian Robertson (e.g. Bellgrove, Dockree, Aimola, & Robertson, 2004; Dockree et al., 2006; Manly et al., 2003; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) has developed a simple paradigm specially designed to provide a more continuous measure of sustained attention; the Sustained Attention to Response Test (SART). In this task, a predictable series of single digits (1-9) is presented in sequence and participants are required to press a response key to each number except the number 3, which occurs every ninth digit. Thus, unlike traditional CPTs, the SART requires participants to *respond* to non-target stimuli while *withholding* their response on the appearance of the target stimulus. The simplicity of the SART tends to encourage a routine response set, placing heavy demands on the individual's ability to endogenously sustain attention to the overall goal of withholding to the No-Go target during the inter-

target intervals. The regular occurrence of target stimuli means that the task can be sensitive to relatively brief lapses of attention and provides minimal levels of exogenous input. In this manner the SART is thought to provide a better analogue of the kinds of real life situations in which failures of attention occur. Importantly, PET and fMRI studies have confirmed that performance of the SART activates the same aforementioned right-lateralised sustained attention network (Fassbender et al 2004; Manly et al 2003; O'Connor et al 2004) and it has been demonstrated that the SART is more sensitive to prefrontal brain injury than traditional CPTs (Manly et al., 2003; O'Keeffe, Dockree, & Robertson, 2004; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). In addition, performance on the SART is well correlated with rates of everyday attentional failures as indexed by the Cognitive Failures Questionnaire (CFQ) in both patients with traumatic brain injury and healthy undergraduates (Robertson et al 1997; Dockree et al 2006). Thus, there is good evidence to suggest that the SART is a more valid analogue of everyday sustained attention abilities than the CPT. Hence, in accordance with the research objectives outlined in Chapter 1, the SART appears to represent an ideal paradigm for investigating sustained attention deficits in ADHD. In experiments 2 and 3, the sensitivity of the SART to the kinds of attentional problems experienced by people with ADHD will be investigated.

Before conducting these investigations it is important to ask whether the SART is an appropriate measure for answering questions regarding the neuropsychology of ADHD given that this disorder has been associated with a variety of other EF deficits. As noted previously, a meta-analysis by Nigg et al (2006) found that the strongest effect sizes were obtained when comparing participants with ADHD to their healthy peers on tasks that measure response inhibition. In addition, several studies have highlighted ADHD-related abnormalities in ERP components that are directly related to the inhibitory process (e.g. Bekker et al., 2005; Brandeis et al., 1998; Overtoom et al., 2002). It is important therefore to rule out the possibility that disinhibition could contribute to performance deficits on the SART. Response inhibition is usually measured by requiring participants to respond to Go stimuli and to withhold their response on the appearance of an unpredictable No-Go stimulus. Performance of such tasks has been described in terms of a horse-race model whereby the inhibition process races with the conflicting response process (Logan, 1994). Whichever process is completed first

determines whether the response will be executed or not. The SART also asks participants to withhold their responses to the No-Go target and hence correct performance is partly reliant on response inhibition. It is assumed, however, that the predictable nature of the task favours the withhold response to such an extent that there is virtually no competition with the prepotent response by the time the target appears. Hence, it is argued that errors on the task should arise almost exclusively from brief lapses of sustained attention. Nevertheless, the argument that poor response inhibition might also account for SART errors cannot be ruled out without providing objective evidence. For this reason Experiment 1 begins by using the high temporal resolution of ERPs to directly investigate the extent to which fixed SART performance is reliant upon response inhibition.

3.2 EXPERIMENT 1. Electrophysiological Validation of the Sustained Attention to Response Task (SART)

3.2.1 Introduction

The present study aims to provide an electrophysiological validation of the SART by testing whether successful performance is primarily reliant upon sustained attention as opposed to response inhibition. To do this, ERPs will be recorded while participants perform the standard fixed-sequence version of the SART and a second version (random SART) which, due to its unpredictable stimulus sequence, is thought to load more heavily on response inhibition.

A previous study by Manly et al (2003) compared the performance of patients with traumatic brain injury and a group of normal healthy controls on the same fixed and random versions of the SART. It was found that while both groups made more errors on the random version, the fixed version actually discriminated better between the two

groups. Furthermore, PET data indicated that the fixed SART was associated with stronger activation of the right-hemispheric sustained attention network than the random SART. Thus, increasing the overall task demand by making the targets unpredictable provides a degree of exogenous stimulation which appears to reduce the demand on the sustained attention. Fassbender et al (2004) also investigated the functional anatomical correlates of fixed and random SART performance this time using fMRI. Again, fixed SART performance was associated with activity in a mostly right-hemispheric network but the random SART was associated with stronger activation in brain regions implicated in response inhibition including right ventral prefrontal, left dorsolateral prefrontal and right inferior parietal cortices (Garavan, Ross, & Stein, 1999).

More recently, Dockree and colleagues (Dockree, Kelly, Robertson, Reilly, & Foxe, 2005) used high-density electrical mapping to identify key electro-cortical markers for alert responding on the fixed SART. Sufficient data was collected from participants to allow a direct comparison between activity relating to both successful and unsuccessful task performance. The most prominent markers of successful performance included late positive potentials (LP1 and LP2) over occipito-parietal and central scalp sites that were evident on all trials and gradually enhanced on trials preceding a correct withhold. This modulation led the authors to conclude that the late positive potentials were likely to reflect the recruitment of the sustained attention network for the activation and maintenance of task goals. Another notable finding was that the No-Go P3, a component strongly linked to response inhibition, appeared to be absent on correct withholds. The No-Go P3 is a stimulus-locked component with a central scalp distribution and a latency of 300-600ms. Previous work has demonstrated that the No-Go P3 is enhanced on No-Go trials and, in keeping with Logan's (2004) race model, the speed and strength of this component predicts accuracy of performance on response inhibition tasks (Bekker, Kenemans, & Verbaten, 2004; Bekker et al., 2005; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004).

The present study is designed to build on the findings of Dockree et al (2005), Manly et al (2003) and Fassbender et al (2004) by directly comparing the ERP markers for performance on the fixed and random versions of the SART. Utilising the random

SART as a comparison for the fixed SART will facilitate the investigation of three principle hypotheses:

1. Correct performance on the fixed SART should place few demands on inhibitory processes since participants are able to anticipate targets and prepare their responses. A replication of Dockree et al's (2005) finding that the No-Go P3 was absent on fixed SART correct withholds is therefore predicted. In contrast the random SART should show a strong No-Go P3 reflecting the increased demands on urgent suppression of the motor response on the appearance of the unpredictable No-Go targets.

2. When two competing response tendencies are activated simultaneously, as in tasks that require response inhibition, response conflict is generated (Botvinick, Cohen, & Carter, 2004). Two ERP components that are thought to arise from the detection of response conflict are the No-Go N2 (a stimulus-locked component with a latency of 300-400ms) and the Error-Related Negativity (ERN, a response locked component with a latency of 0-120ms) (Falkenstein, 2006; Van Veen & Carter, 2002). The predictable nature of the fixed SART should result in increased activation of the No-Go response such that conflict with the Go response would be virtually absent on correct trials. In the present study the extent of response conflict on the fixed and random SART will be investigated by comparing the amplitudes of the No-Go N2 and the Error-Related Negativity (ERN).

3. Finally, the PET study by Manly et al (2003) suggested that the undemanding and monotonous nature of the fixed SART places heavier demands on endogenously controlled sustained attention than the random SART. In the present study, increased goal maintenance should be evident on the fixed SART in the form of increases in the late positive components, initially identified by Dockree et al (2005), relative to the random SART.

3.2.2. Methods

3.2.2.1 Participants

Thirteen normal healthy right-handed college undergraduates (8 female, mean age=22.3, SD=4.2) were recruited by poster advertisement. For all studies in this thesis, hand dominance was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). All participants gave written informed consent and all procedures were approved by the ethical review boards of St Vincents Hospital, Fairview and the Trinity College School of Psychology. All participants reported normal or corrected-to-normal vision.

3.2.2.2 SART paradigms and procedure

All participants completed two separate testing sessions: one for the fixed SART and one for the random SART. The order in which each session was completed was counterbalanced. Fixed SART digits were presented sequentially from '1' through '9'. For each block, 225 digits were presented (25 runs of the 1 to 9 sequence). In order to maximise the number of errors that would be included in the ERP analysis participants undertook an average of 14.1 blocks (range 10 – 18) within the testing session. Participants were seated in a dimly lit, sound-attenuated, electrically shielded room. For each trial, a digit was presented for 150 ms followed by an Inter-Stimulus-Interval (ISI) of 1000ms. Participants were instructed to respond with a left mouse button press with their right forefinger upon presentation of each digit (go-trials) with the exception of the 25 occasions per block when the digit 3 (target) appeared, where they were required to withhold their response. Participants were instructed to time their button presses to the offset of each stimulus. This kind of 'response-locking' has been shown to reduce inter-individual variability and eliminate speed accuracy trade-offs (Manly, Davison, Heutink, Galloway, & Robertson, 2000; Stuss, Murphy, Binns, & Alexander, 2003). In the present study, response-locking helped to ensure that similar response strategies were employed by participants for both tasks. Participants completed a short practice block before testing to ensure they had understood the task instructions. Timing of task stimuli and the basic response requirements are demonstrated in Figure 3.1.

Five randomly allocated digit sizes were presented to increase the demands for processing the numerical value and to minimize the possibility that participants would

set a search template for some perceptual feature of the target trial ('3'). Digit font sizes were 100, 120, 140, 160 and 180 in Arial text. The five allocated digit sizes subtended 1.39°, 1.66°, 1.92°, 2.18° and 2.45° respectively in the vertical plane, at a viewing distance of 152cm. Digits were presented 0.25° above a central white fixation cross on a grey background. The task specifications were programmed and stimuli were delivered using the Presentation® software package (Version 0.75, www.neurobs.com).

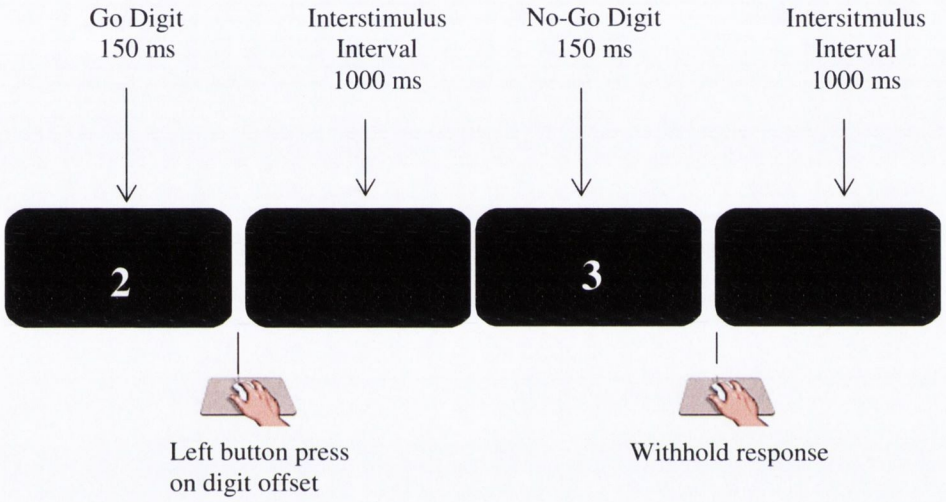


Figure 3.1 **Fixed SART task schematic**. Demonstrates the sequence of events contained within a Go trial (the digit 2) and a No-Go trial (the digit 3).

The random SART shared the exact same parameters as the fixed SART except that stimuli were presented in a completely random sequence. As in the fixed SART each digit was represented 25 times. Again participants completed a short practice block before testing to ensure that they had understood the task instructions. Since participants made more errors on the random SART it was only necessary for participants to complete an average of 9.8 blocks of random SART (range 8 -12) to obtain sufficient single trials for ERP analysis.

3.2.2.3 ERP acquisition and analysis

Continuous EEG was acquired through the ActiveTwo Biosemi™ electrode system from 72 scalp electrodes, digitized at 512 Hz. Vertical eye movements were recorded

with two electrodes placed below the left and right eye, while horizontal eye movements were measured with two electrodes at the outer canthus of each eye recorded horizontal movements.

Data were analysed using BESA Version 5.1 (Brain Electric Source Analysis) software (www.besa.de). For analysis and display purposes, data were average referenced and filtered with a low-pass 0-phase shift 96 dB 40 Hz filter. Stimulus-locked data was segmented into epochs of 100ms before to 800ms after stimulus onset and baseline corrected relative to the interval -100 to 0ms. In the study by Dockree et al (2005) a wider epoch was used (-100 to +1150) but due to the small number of errors made by participants in the present study a shorter epoch was needed to maximise the number of error trials that would still be available after artifact rejection. As a result it was not possible to analyse the LP2 components, which occurs between 800 and 1000ms, in the present study (see Experiment 3 for analysis of this component). Stimulus-locked data were acquired for Go stimuli that were followed by a button press, targets (3) that were followed by a correct withhold and targets that were followed by an error of commission. Response-locked data were segmented into epochs of 400msecs before to 500msecs after button press, and baseline-corrected relative to the interval -400 to -200 ms. Response-locked data were averaged separately for errors of commission and correct Go presses. Single ERP trials are highly sensitive to noise artifacts that arise from movement, muscle tension and electrical interference as well as blinks and eye movements. To remove these artifacts all electrode channels were subjected to the standard rejection criterion of 100μV such that any activity above this threshold would be rejected. The single trial EEG signals were also corrected for horizontal and vertical eye movement artifacts by means of a correction procedure developed by Berg and Scherg (1994) and implemented by BESA.

ERP componentry was investigated following the same strategy outlined in Dockree et al (2005). ERP component structure was confirmed by visual inspection of grand-average waveforms. The width of the latency window used to measure component amplitudes was based on the duration and spatial extent of each component. The early sensory components, P1, N1 and P2 were analysed in the correct-Go stimulus waveform. Subject-specific maximal amplitude scalp locations and peak latencies at

these locations were selected for each individual. This was done to account for significant spatial and temporal variations in sensory ERPs across individuals (Docrkee et al 2005). The next component evident in the Go stimulus waveform was a P3b-like positive deflection over centro-parietal scalp regions between 250 and 350 ms. The topography of this component was stable across participants and so the measurement criteria were the peak positive voltage between 250-350ms at CPz. A negative-going, late positive potential (LP1) similar to that observed by Dockree et al was observed on Go stimuli immediately preceding a correct withhold on the fixed SART. The criteria for measuring the LP1 were selected a priori based on the findings of Dockree et al (2005) and they were the mean amplitude between 550 and 800 ms post-stimulus at POz on the Go stimulus immediately preceding each correct withhold for both the fixed and random SART.

The No-Go N2 and No-Go P3 were analysed on the stimulus-locked correct withhold and error waveforms. These components showed little spatial variation between individuals and had longer drawn-out peaks. For this reason a set electrode location and latency window was used for all participants but latency windows were calculated separately for the fixed and random SART. The No-Go N2 was strongest at electrode Fz and was measured as the peak negativity between 255ms and 295ms on the random and between 235 to 275 on the fixed SART. On the random SART, the No-Go P3 was strongest over FCz and was measured as the peak positivity between 339 and 379ms. There was no equivalent component in the fixed SART ERP so the peak positivity at the same electrode and latency was measured.

Finally, the response-locked waveforms for commission errors on the random SART contained an early negative deflection over fronto-central sites known as the Error Related Negativity (ERN) and a more posterior late positivity known as the error positivity (Pe). No ERN was evident on the fixed SART error waveform but there was a clear Pe component. The ERN was strongest over Fz and had a similar peak latency for both tasks. ERN was therefore measured as the peak negativity between 20 and 100 ms post-response. The Pe was strongest over CPz for both tasks but had an earlier peak in the random SART compared to the fixed SART. Therefore, a window of 150-350ms was chosen for the random SART and a window of 200-400ms was chosen for the fixed

SART. Because the Pe is a very large component with no well defined peak it was measured in terms of the average positive voltage within the latency window (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000).

Because participants made more errors of commission on the random than the fixed SART it was important to equate the number of single trials that contributed to the averages for these comparisons. This was achieved by randomly excluding individual random SART trials until the number of trials entered into fixed and random averages were equivalent.

3.2.3 Results

3.2.3.1 Behavioural Differences

Individual performance data was calculated as an average score over the first 8 blocks owing to the different number of blocks completed by each participant. Individual fixed and random SART scores for errors of commission, errors of omission (failure to press following a Go stimulus), mean reaction time on Go stimuli (GoRT), mean standard deviation of GoRT (GoRT variability) and mean reaction time on errors of commission are summarised in **table 3.1**.

Participants made significantly more errors of commission on the random SART but made more errors of omission on the fixed SART. There were no significant differences in terms of GoRT or mean GoRT across the two tasks confirming that the response locking instruction imposed equivalent response strategies across the two tasks. Nevertheless, the average reaction time on a commission error was significantly faster on the random SART than the fixed SART [$t_{(12)}$=2.78, p=0.021]. Further paired samples t-tests indicated that while random SART commission error RTs were significantly

faster than the average GoRT on that task [$t_{(12)}$=6.5, p=0.00], commission error RTs on the fixed SART were not significantly different from average GoRT [$t_{(12)}$=-0.9, p=0.3].

Table 3.1. Comparison of behavioural performance measures on the fixed and random SART

	Fixed Mean (SD)	**Random** Mean (SD)	$t_{(12)}$	p
Errors of commission	3.49 (2.5)	7.5 (5.3)	-3.25	0.007**
Errors of omission	1.68 (1.48)	0.02 (0.05)	3.35	0.01**
Mean GoRT	408.6 (85.1)	415.5 (97.9)	-0.4	0.693
Mean GoRT Variability	146.6 (81.6)	129.4 (58.3)	1.24	0.248
Mean Error RT	429.44 (114)	353.3 (86.38)	2.78	0.021*

3.2.3.2 ERP findings

3.2.3.2.1 Early Sensory Processing

In order to compare the extent of early visual attention processes across task duration the amplitude of the sensory P1, N1 and P2 components were averaged across all Go trials and compared across tasks (see Figure 3.2). Paired samples t-tests revealed significantly increased processing on the random SART at the latency of the P1 [$t_{(12)}$=2.61, p=0.022] and N1 [$t_{(12)}$=-2.9, p=0.014] but not the P2 [$t_{(12)}$=1.16, p=0.264].

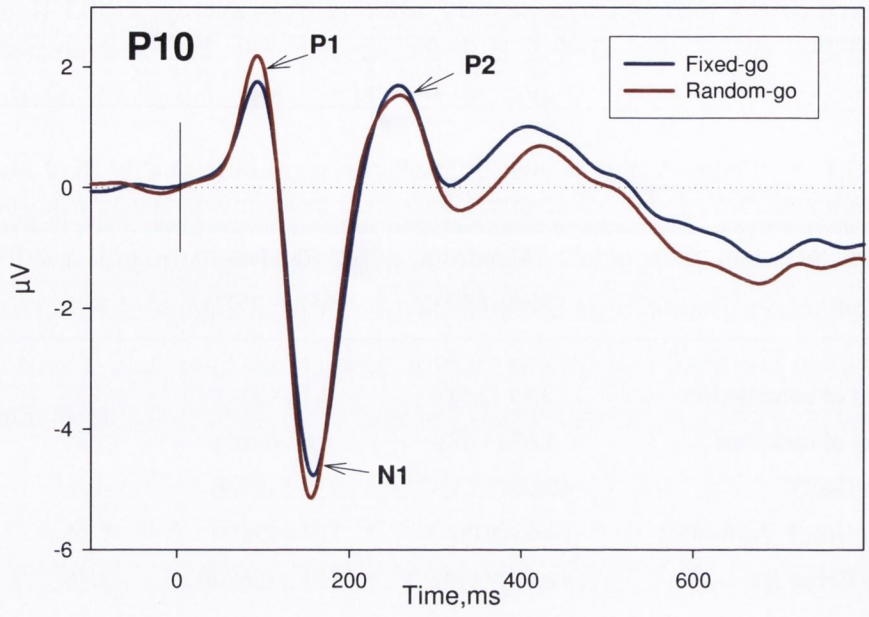


Figure 3.2 **Early stimulus processing on the fixed and random SART**. Displays grand-average waveforms at electrode P10 averaged separately for correct go trials and time-locked to stimulus onset (time-point 0). Here we see that the early sensory components P1 and N1 are enhanced on the random SART relative to the fixed SART reflecting the increased processing requirements associated with the unpredictable stimulus sequence of the random SART.

3.2.3.2.2 Goal Maintenance

In a previous study Dockree et al (2005) identified a late positive component (LP1) that was enhanced immediately prior to a target on the fixed SART and was associated with ongoing goal maintenance. Using the same measurement criteria as Dockree et al (2005) the amplitude of the LP1 was compared on fixed and random SART Go trials (see Figure 3.3). Visual inspection revealed a larger LP1 on the fixed relative to the random SART at all occipito-parietal scalp sites. A paired samples t-test indicated that the LP1 was significantly larger on the fixed SART [$t_{(12)}$=-3.4, p=0.005]. In addition, an earlier, P3b-like component, often used as an index of attention resource allocation, was unaffected by task [$t_{(12)}$=-1.9, p=0.08].

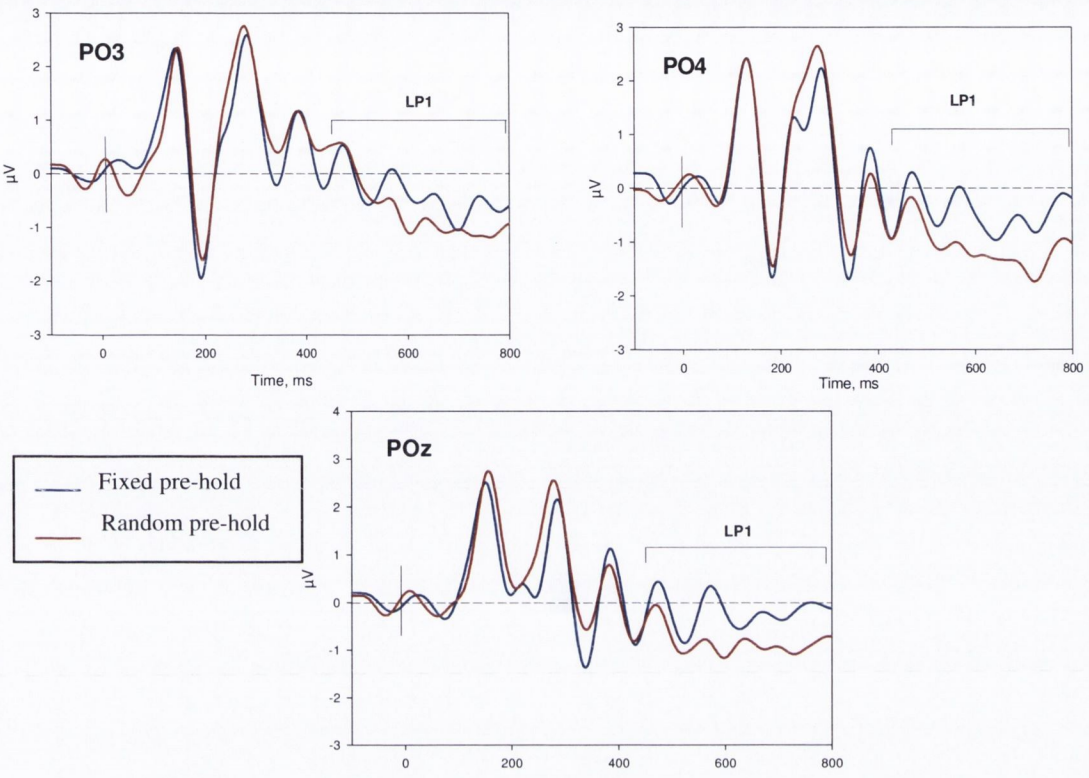


Figure 3.3 **Electrophysiological correlates of goal maintenance on fixed and random SART**. Displays grand-average waveforms at POz for fixed and random SART averaged separately for the Go trial immediately preceding a correct withhold and time-locked to stimulus onset (time-point 0). The late positive component (LP1) occurs between 550 and 800 ms after stimulus onset and is enhanced on the fixed SART.

3.2.3.2.3 Processing the No-Go target

Stimulus-locked No-Go target waveforms for fixed and random SART were averaged separately for correct withholds and errors of commission (see Figure 3.4). Inspection of the No-Go target waveforms preceding correct withholds on the random SART revealed a classic N2/P3 complex over fronto-central regions. These two components appeared to be attenuated on error of commission. On the fixed SART, in contrast, a reduced No-Go N2 component was observed but the No-Go P3 was absent. Furthermore these components did not appear to distinguish between correct and incorrect performance on No-Go trials. To test this observation separate within-subjects

ANOVAs were conducted for the N2 and P3 with two levels of task (fixed vs random SART) and two levels of response (correct withhold vs. commission error).

For the No-Go N2 there was no main effect of task [$F_{(1,12)}$=1.5, p=0.22] and no main effect of response [$F_{(1,12)}$=3.34, p=0.09] but there was a significant task by response interaction [$F_{(1,12)}$=12.03, p=0.005]. Post-hoc t-tests with Bonferonni corrections indicated that the interaction was driven by the No-Go N2 effect on the random SART which showed a significantly larger amplitude on withholds relative to lapses [p=0.002]. This effect was absent on the fixed SART [p=0.7]. For the No-Go P3, there was a main effect of task [$F_{(1,12)}$=14.97, p=0.002] and of response [$F_{(1,12)}$=7.55, p=0.018] and a significant task by response interaction [$F_{(1,12)}$=9.85, p=0.009]. Again post-hoc t-tests indicated that the interaction was driven by larger amplitudes on holds relative to lapses on the random SART. On the random SART there were significantly larger No-Go P3s on correct withholds relative to errors [p=0.006], this effect was absent on the fixed SART [p=0.6].

3.2.3.2.4 Error Processing

Commission errors on the random SART elicited an ERN with maximal amplitude over Fz but no ERN was observed for the fixed SART. A paired samples t-test confirmed that the random SART ERN was significantly larger following errors than following a correct Go press [$t_{(12)}$=-2.6, p=0.023]. There were no significant differences in the amplitude of the Pe which was maximal over CPz [$t_{(12)}$=-1.67, p=0.119]. Error-related ERP components for fixed and random SART are illustrated in Figure 3.5.

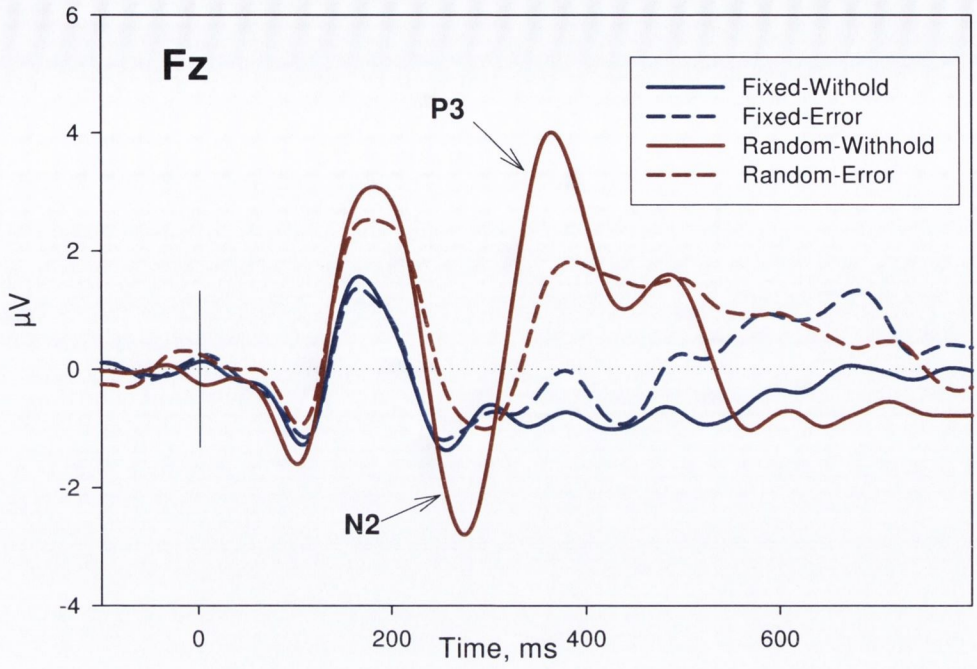


Figure 3.4 **Electrophysiological markers of response inhibition on the fixed and random SART.** Displays grand-average waveforms at Fz for fixed and random SART averaged separately for correct withholds and commission errors on 3 and time-locked to stimulus onset (time-point 0). On the random SART we see that the strong No-Go N2/P3 complex on correct withholds is attenuated when participants make an error. On the fixed SART the No-Go N2/P3 is virtually absent and does not differentiate between correct and incorrect responses.

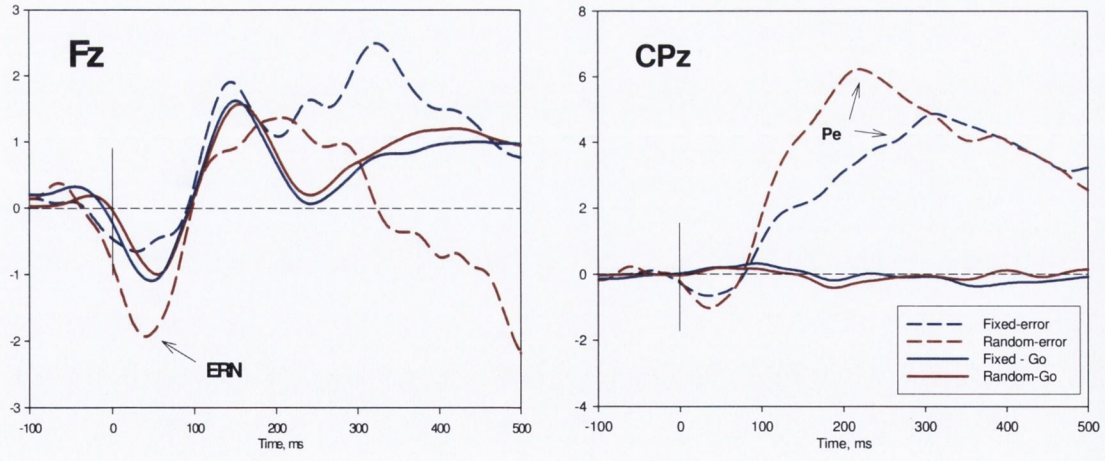


Figure 3.5. **Electrophysiological markers of error processing on fixed and random SART.** Displays grand-average waveforms at Fz and CPz for fixed and random SART averaged separately for commission errors and time-locked to button press response (time-point 0). At Fz we see a clear ERN for random SART errors but not for fixed SART errors. At CPz we see that errors on both tasks elicited Pe amplitudes of similar magnitudes.

3.2.4 Discussion

Consistent with previous reports (Fassbender et al 2004; Manly et al 2003) participants made significantly more errors of commission on the random SART reflecting the more challenging nature of the task due to its unpredictable stimulus sequence. Asking participants to time their responses to the offset of each stimulus ensured that there were no over all differences in the response strategies employed for the two tasks. The only reaction time difference observed was on commission errors themselves. On the random SART, error RTs were significantly faster than the average GoRT on that task. This has been a common finding with Go/No-Go tasks and suggests that the erroneous response has been executed before the inhibition process was completed (Logan, 1994). Conversely, commission error RTs on the fixed SART did not differ from the average GoRT consistent with the view that sustained attention errors occur when participants mindlessly persist with the default Go-press mode. Although participants made very few errors of omission in general, significantly more errors of this kind were made on the fixed SART. Errors of omission occur when a participant fails to make the requisite response following a Go stimulus and are therefore likely to reflect instances where the participant has drifted off task. The increased prevalence of these errors on the fixed SART suggests that the monotony of the task engendered a greater number of momentary drifts of attention than the random SART.

The ERP data provides clear evidence that the fixed and random versions of the SART emphasise different neural processes. The P1, N1 and P2 are early visual attention potentials evoked in the occipital cortex that reflect the initial extraction of information from sensory analysis of the stimulus (Luck, Woodman, & Vogel, 2000). The present data indicates that both the P1 and N1 are enhanced on Go trials for the random SART relative to the fixed SART. According to biased-competition models of attention, frontal control regions bias sensory regions to favour the processing of behaviourally relevant stimuli (e.g. Hopfinger, Buonocore, & Mangun, 2000). Thus, stimulus processing, even at the earliest stages, is subject to top-down modulation. Since Go stimuli on the fixed SART are entirely predictable and require the same default response their behavioural relevance is limited. In contrast, since the random SART is unpredictable, enhancement

of early sensory processing would facilitate the speedy detection of a potential No-Go stimulus.

While early visual attention processes appear to be enhanced on the random SART, it was found that later aspects of stimulus processing were more prominent on the fixed SART. Dockree et al (2005) noted that one of the distinctive markers of fixed SART performance was late positivity over occipito-parietal regions on Go trials. This activity was interpreted as a reflection of goal maintenance and predicted performance on subsequent No-Go trials. It is significant therefore that in the present study there was a marked attenuation of the LP1 on random SART Go trials relative to fixed SART Go trials. Given that Manly et al (2003) observed an increased activation in the sustained attention network on the fixed SART the present ERP data suggests that this increase is driven by increased goal-maintenance reflected in the LP1 as opposed to stimulus processing (P1,N1,P2).

The analysis of ERPs on No-Go trials provides clear evidence that correct responses on the fixed SART were not primarily reliant on response inhibition. Random SART No-Go trials were characterised by a strong N2/P3 complex which was attenuated when participants made an error. On the fixed SART, in contrast, only a reduced No-Go N2 component was evident and it did not distinguish between correct responses and errors. In keeping with the present data on the random SART, most studies report that the No-Go N2 is larger for successful than unsuccessful inhibitions (see Falkenstein, 2006 for review). Since a similar component is also observed on trials where there is no inhibitory requirement but where response conflict is high it has been argued that the No-Go N2 does not index response inhibition per se but rather reflects related performance monitoring processes (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Van Veen & Carter, 2002). Detection of response conflict, reflected in the No-Go N2, may provide a 'red flag' that precedes or initiates response inhibition (Kok et al 2004). The fact that the No-Go N2 did not distinguish correct responses from errors on the fixed SART suggests that the detection of response conflict was not a critical element of task performance.

In contrast to the No-Go N2, there is a clear link between the No-Go P3 and response inhibition in ERP research (e.g. , 2005). In the present study, the No-Go P3 was clearly modulated by No-Go trial performance on the random SART but was absent irrespective of performance on the fixed SART. Thus, the two ERP components most closely associated with response inhibition (No-Go N2 and No-Go P3) were found to be irrelevant to task performance on the fixed SART.

Errors of commission on the random SART elicited a distinctive Error Related Negativity (ERN) in the response-locked ERP waveform but no such component was evident on the fixed SART. Like the No-Go N2 the ERN is thought to reflect performance monitoring processes such as detection of response conflict or uncertainty (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Van Veen & Carter, 2002). It is therefore revealing that, on the fixed SART, even when participants incorrectly responded to No-Go stimuli, comparatively little response conflict was generated. Coupled with the finding that RTs did not differ for Go and No-Go trials, these data are again consistent with the original proposal that errors on the fixed SART occur due to a temporary deactivation of the primary task goal (withhold on 3) leading to persistence with the routine response mode (Manly et al., 2003). In contrast, commission errors on the random SART elicited stronger No-Go N2s and stronger ERNs and were associated with faster RTs suggesting that errors on this task are more closely related to a failure to cope with two active and competing response contingencies. The second error-related component that was seen was a late low frequency positive component frequently noted in error processing literature and known as the error positivity or Pe (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). The function of the Pe is poorly understood but it has been suggested that, given its late onset, this component may index conscious evaluation of the error event (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001, see also chapter 3 for an extensive investigation of this component). The absence of any amplitude differences points to equivalent levels of conscious error processing in both tasks.

The present study provides direct evidence that electrophysiological processes relating to response inhibition are absent during performance of the fixed SART. Instead, activity relating to continuous goal maintenance appeared to be the distinguishing

feature of this task. While only limited neuroanatomical inferences can be drawn based on the current data set, when coupled with previous behavioural and clinical work these findings do suggest that the fixed SART is a good measure of sustained attention and that interpretation of performance is unlikely to be confounded by the need for response inhibition. Therefore, in the next two experiments the fixed SART will be used to test the hypothesis that right frontal dysfunction associated with ADHD leads to a disruption of the sustained attention network.

3.3 EXPERIMENT 2. Uncovering Sustained Attention Deficits in Children with ADHD

3.3.1 Introduction

The present experiment will verify whether children diagnosed with ADHD exhibit sustained attention deficits as measured by the fixed SART. EDA measures are also acquired to investigate the potential influence of motivational processes.

Two previous studies have used the SART to examine sustained attention deficits in children with ADHD. Shallice et al (2002) tested a group of 31 children diagnosed with ADHD on the random version of the SART. It was found that the ADHD group made more errors of commission and omission and were significantly more variable in their response times to the go digits. Higher intra-individual variability may be a marker of the efficiency with which frontal control processes can deploy attention (Bellgrove, Hester, & Garavan, 2004; Stuss, Murphy, Binns, & Alexander, 2003) and children with ADHD have been shown to be more variable than controls across a range of tasks with an executive demand (Mullins, Bellgrove, Gill, & Robertson, 2005; Van der Meere & Sergeant, 1988). However, Shallice et al's findings regarding error rates are difficult to interpret in light of the results of Experiment 1 which demonstrated that correct performance of the random SART was also reliant on response inhibition.

More recently, Bellgrove and colleagues (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005) tested 22 children with ADHD on the fixed version of the SART and found that they made more errors of omission and had greater reaction time variability than matched controls but there were no group differences for errors of commission. Participants in Bellgrove et al's study (2005) completed only a single run of the fixed SART so it is likely that, given the simplicity of the task, the variance in error rates was insufficient to allow for the detection of relatively subtle group differences. In the present experiment participants were asked to complete a new variant of the fixed SART designed to increase the demand on sustained attention resources. The Dual Attention to Response Task, developed by Dockree et al (2006) requires participants to monitor for the appearance of an unpredictable grey coloured digit within the 1 to 9 sequence to which they press a separate response button. In addition participants must withhold on the appearance of the predictable No-Go target (3). By embedding a CPT within the fixed SART, both types of task demonstrably challenging the same right-fronto-parietal sustained attention/vigilance system (Manly et al., 2003; Sturm & Willmes, 2001), the DART increases the monitoring load for participants and should maximally challenge the sustained attention system. Dockree et al demonstrated the sensitivity of the DART to index everyday lapses of attention measured by the CFQ and reported strong correlations between DART and fixed SART errors. It is predicted that when the sustained attention system is taxed in this manner that deficits will become apparent in children with ADHD.

The second goal of this experiment was to investigate the possible interaction of cognitive and motivational abnormalities in ADHD, suggested by dual-process explanatory models, by acquiring EDA measures during task performance. As discussed in chapter 2, several studies of ADHD have identified selective abnormalities in autonomic arousal responses to significant task stimuli (Mangina & Beuzeron-Mangina, 2000; Shibagaki, 1993; Zahn & Kruesi, 1993) that are reminiscent of those reported following damage to the prefrontal cortex (Zahn, Grafman, & Tranel, 1999). None of these studies, however, have investigated how attenuated autonomic system activity might actually relate to the cognitive deficits associated with ADHD.

3.3.2 Methods

3.3.2.1 Participants

13 male and 2 female (1 left handed) ADHD participants were recruited from an existing participant panel set up by the Trinity College ADHD research group (Kirley, 2003) and 15 right-handed control children (1 female) were recruited from primary schools in the Dublin area. Parental consent was obtained for all children in accordance with the ethical guidelines of the School of Psychology, Trinity College Dublin and St James' Hospital, Dublin, Ireland. All children were recruited via information letters sent to their parents. Parents who were interested in having their children participate in the study sent a signed consent form to the researcher. Parents were then contacted by telephone to confirm their consent and explain the precise nature of the study. The study was also described to the children who were given the opportunity to opt out of testing if they did not want to take part. The patient group had a mean age of 11.4 (SD=1.7) and a mean IQ, as assessed by the WISC-III, of 97.7 (SD=11.6). The control group had a mean age of 11.2 (SD=1.5) and an average IQ of 112.1 (SD=14.8).

3.3.2.2 Diagnostic and Screening Procedures

ADHD group children received a diagnosis following a clinical assessment which included the Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 1995) and the Child ADHD Teacher telephone interview (Holmes et al., 2004) administered by a trained interviewer. Diagnoses were made according to DSM-IV, DSM-III-R and ICD-10 criteria. The presence of learning disability in both patient and control groups was assessed using the Reading and Spelling sub-tests of the Wide Range Achievement Test (WRAT-3) (Wilkinson, 1993). In this study 8 of the ADHD participants had a diagnosis of ADHD Combined type (ADHD/C), 3 had a diagnosis of ADHD Hyperactive type (ADHD/H) and 4 had a diagnosis of ADHD Inattentive type (ADHD/I). 11 members of the ADHD group also met criteria for other disorders including Oppositional Defiant Disorder and Conduct Disorder. ADHD symptom levels were assessed in the control group using the Conners' Parent Symptom Questionnaire

(Conners, 1985). Patients were withdrawn from stimulant medication 24 hours prior to testing.

Exclusion criteria for patient group participants included any known neurological condition, psychosis, IQ less than 70 or learning disability as indicated by the WRAT. Control group participants were excluded if they had a familial history of ADHD or ADD, had a personal history of neurological or psychiatric illness, had a learning disability as indicated by the WRAT or received a score of more than 20 on the abbreviated version of the Conners' Parent Symptom Questionnaire (Conners, 1985). The abbreviated Conners Rating Scale is a 10-item brief questionnaire that outlines the core symptom domains of ADHD-C and a score of 20 (1.5 standard deviations above the normative mean) is the cutoff for a child to be considered as having probable ADHD.

3.3.2.3 DART paradigm and procedure

Participants were presented with a series of digits in a fixed sequence from 1 to 9 and were required to press the left mouse button, in time with a response cue, after each digit (Go-trials), except when the digit 3 was presented (No-Go trial). The secondary task requirement was that participants were required to respond to the occasional appearance of a grey-coloured digit by pressing the right mouse button. The presentation of grey-coloured digits was restricted to numbers 5 through 9 in order to avoid any interference with performance in the period before and immediately after the presentation of a target. To avoid confusion participants were told that there would be no grey 3s. The timing of task stimuli and response requirements are illustrated in Figure 3.6.

The digits, masks and response cue were presented centrally in white on a computer monitor against a black background. The response cue, an emboldened cross, was designed to reduce within and between participant variability and minimises the potential for a speed/accuracy trade off. This instruction decreases the likelihood that performance deficits can be attributed to impulsive response strategies. A full DART block consisted of 225 stimuli in total of which 179 were Go-trials (requiring a left

button press), 25 were No-Go trials (requiring the withholding of responding on the 3) and 17 were grey trials (requiring a right button press) resulting in a total block duration of approximately 6 minutes. Each participant completed four DART blocks, two with 8 randomly presented auditory tones (659Hz, 30ms duration, 62dB intensity) as a cue to concentrate on the task, and two without. Cues were presented between the numbers 5 and 9 inclusive, again to avoid any competition with the withhold response to the

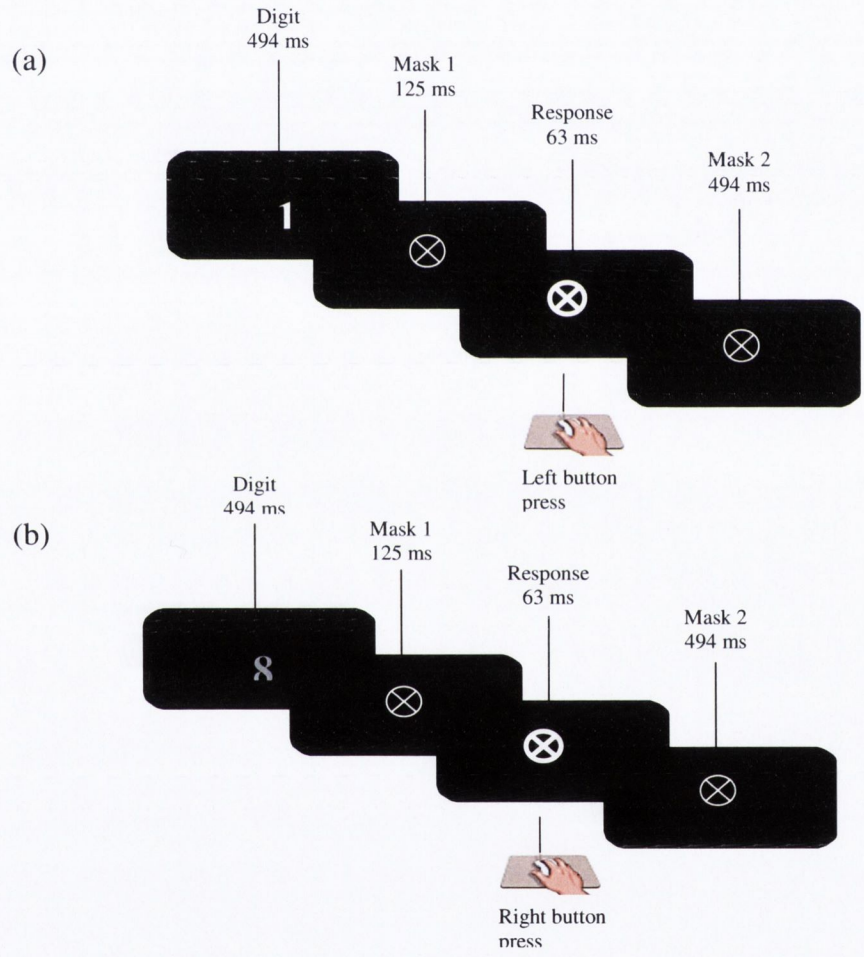


Figure 3.6 **DART task schematic**. Demonstrates the sequence of events contained within (a) a Go trial and (b) a trial containing a grey digit.

number 3. The manipulation of alerting cues was included as part of a concurrent study examining their effect on sustained attention in ADHD (see Chapter 6, which reports a full analysis of the effects of alerting cues in the same data set). Statistical analyses revealed no effect of cues on any of the dependent variables between or within groups

and therefore in the present study, results were analysed by collapsing across the alerting conditions. An analysis of arousal responses to alerts is included below as a baseline measure of EDA responsiveness.

DART testing was preceded by a short practice block to ensure that participants had understood the task instructions. To reduce the influence of non-attentional processes, such as working memory, participants had to achieve 100% accuracy, in terms of grey digit detection, on the practice block before they could proceed to test. A rest period of approximately 5 minutes was allowed between each block.

3.3.2.4 Electrodermal Activity

EDA measurements were taken from all participants during DART testing with a 5 channel BIOPAC MP30B unit, calibrated to skin conductance responses (SCRs) in microsiemens (μS). Two Ag/AgCl BIOPAC electrodes, with contact areas of approximately 6mm, were filled with SIGNA electrode gell and secured with a velcro strap to the volar surface of the distal phalanges of the index and middle fingers of the participant's non-dominant hand. After a five-minute rest period to ensure skin hydration by the gel, the BIOPAC software was calibrated to the participants' own electrodermal parameters before DART testing began.

EDA data was analysed using BIOPAC Student Lab Pro software according to previously established criteria (Dawson, Schell, & Filion, 2000). A rise in skin conductance level (SCL) was considered to be a response (SCR) if its onset was between one and five seconds after a particular event (presentation of No-Go stimulus or alert). SCRs were measured by subtracting the SCL at stimulus onset from the peak SCL within the latency period. The criterion for the smallest acceptable SCR was set at 0.02 μS. Any response below this threshold was recorded as 0. The amplitude of the largest SCR within this latency period was measured.

3.3.3 Results

The patient and control groups were successfully matched for sex, handedness, age [$F_{(28)}$=-0.02, p=0.9], and WRAT composite score intervals based on frequency of occurrence of participants with achievement scores within each of the categories defined within the WRAT3 manual [x^2=9.5, df=6, p=0.2]. The groups were not matched for IQ [$F_{(1,28)}$= 2.9, p=0.006] however IQ did not correlate with any of the dependent measures and primary analyses for the behavioural measures included IQ as a covariate.

Table 3.2 displays the means, standard deviations and significance levels for between group differences (based on one-way ANOVAs with Group as the between subjects factor) on each of the behavioural and EDA measures. Relative to control participants, children with ADHD made more errors of commission (pressing on 3) and of omission (failing to press on a Go stimulus) and exhibited greater GoRT variability during DART performance, indicating impaired sustained attention. Partial correlations, controlling for the effect of Group, indicated that there was a significant relationship between GoRT variability and both errors of omission [r=0.59, p=0.001] and errors of commission [r=0.7, p=0.00]. There was also a significant correlation between errors of omission and errors of commission [r=0.8, p=0.00].

Table 3.2. Comparison of DART and EDA data for childhood ADHD and Control groups.

	Child ADHD Mean (SD)	**Controls** Mean (SD)	$F_{(1,28)}$	p
Errors of commission	5.4 (3.6)	2.9 (1.7)	6.3	0.02*
Errors of omission	1.6 (1.4)	0.4 (0.5)	9.6	0.004**
Mean Go RT	682.4 (93)	697.7 (120)	0.2	0.7
Mean Go RT variability	159.7 (52.7)	108.4 (33.1)	10.1	0.004**
Post-withhold SCR	0.25 (0.3)	0.27 (0.22)	0.2	0.7
Post-commission error SCR	0.37 (0.38)	0.69 (0.49)	4.7	0.04*
Post-cue SCR	0.52 (0.39)	0.64 (0.43)	1.4	0.24

The two groups did not differ in their SCRs to successful withholds or to the alerting cues but a significant difference was found for SCRs to commission errors. A Repeated-measures ANOVA with Response (mean SCR amplitude to correct withholds vs. mean SCR amplitude to commission errors) as the within-subjects factor and Group as the between subjects factor was carried out and a significant main effect of Response [$F_{(1,28)}$=15.5, p=0.001] and a Response by Group interaction [$F_{(1,28)}$=4.72, p=0.038] was indicated. Post-hoc t-tests with Bonferonni corrections for multiple comparisons revealed a significant increase in SCR to commission errors relative to correct withholds in the control group [$F_{(1,28)}$=18.67, p=0.000] that was absent in the ADHD group [$F_{(1,28)}$=1.55, p=0.223]. These differences are illustrated in Figure 3.7 below. After controlling for the effects of group, age and IQ the post-error vs. post-withhold SCR difference accounted for a significant percentage of the variance in commission errors [$\underline{R}^2$change=0.10, $F_{(1,28)}$=3.66, p=0.035, 1-tailed based on the a-priori assumption that a reduced arousal response to errors would result in decreased engagement of sustained attention].

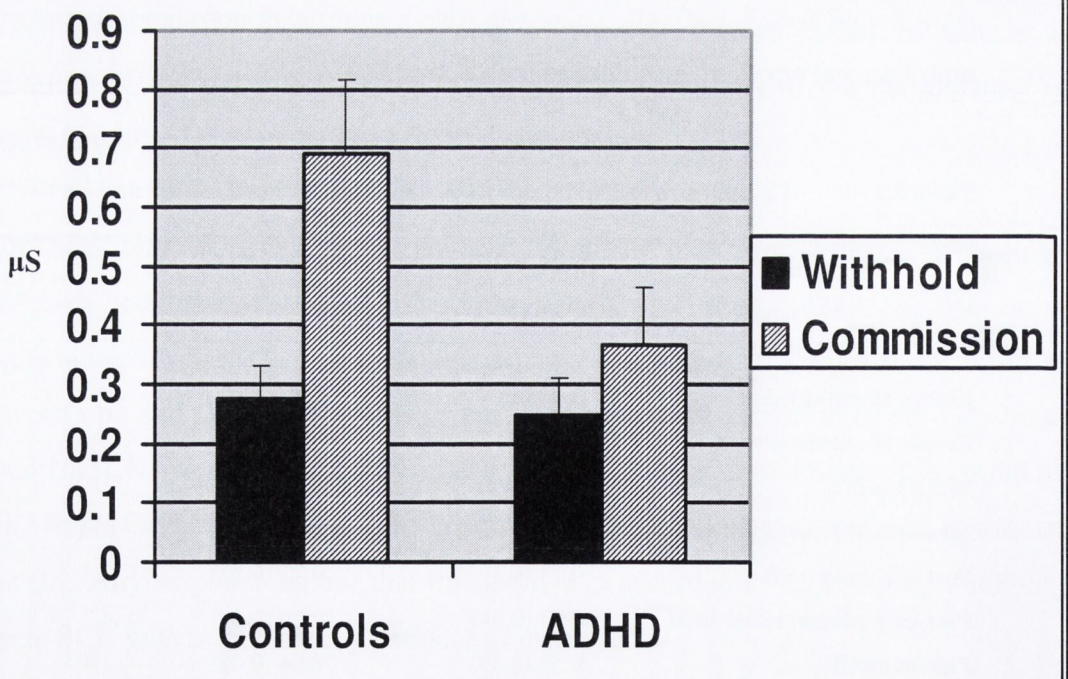


Figure 3.7 **Mean Skin Conductance Responses for each Group to No-Go targets as a function of No-Go Response** (Withhold vs. Commission Error). The extent to which participants discriminated between errors and withholds in their SCRs predicted accuracy on the DART.

3.3.4 Discussion

The findings of the present experiment confirm that, when more sensitive methodologies are adopted, children with ADHD do experience an increased rate of sustained attention failures. On a specially modified version of the SART ADHD children made more errors of commission and omission and showed significantly more variability in their response times than control children.

Increased intra-individual response variability has been an almost ubiquitous finding in neuropsychological studies of ADHD (see Castellanos and Tannock, 2002 for review). Until recently, variability has tended to be dismissed as the result of random experimental noise. However, an extensive investigation of patients with brain injuries conducted by Stuss et al (2003) revealed that rather than being the consequence of indiscriminate brain damage, increased variability was associated with focal lesions to specific regions of the prefrontal cortex (dorsolateral and superior medial). In addition, an fMRI study by Bellgrove et al (2004) demonstrated that RT variability was related to the extent of brain activation within frontal regions during the performance of a response inhibition task. These findings suggest that dorsolateral prefrontal activation seen during the SART may be responsible for controlling variability of alert responding. This interpretation is supported in the present experiment by the strong correlation found between response time variability and errors of commission on the DART. Errors of omission occur when participants fail to respond to a Go trial. Given the strong correlations found between this type of error and both reaction time variability and errors of commission it is likely that they too reflect failures in top-down attentional control. Thus, although confirmation with a larger sample is necessary, the present experiment provides good behavioural evidence to suggest that children with ADHD are more prone to momentary lapses of attention than their non-ADHD peers.

The EDA data provided a further insight into the nature of sustained attention deficits in ADHD. The ADHD and control groups exhibited similar SCRs following correct withholds on the DART but the arousal responses of the control group were far larger following an error of commission. Given that there were no group differences in arousal

following either successful withholds or auditory tones our findings are similar to those of Zahn and Kruesi (1993) and indicate a selective impairment in responsiveness to significant events as opposed to a generalised phasic arousal deficit. Importantly, the regression analysis indicates that attenuated autonomic arousal in response to errors is consequential for sustained attention performance. This finding may correspond with a recent fMRI study by Konrad and colleagues (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006) in which participants performed the Attention Network Task which is designed to measure the orienting, executive and alerting components of attention simultaneously. The authors found that poorer alerting performance in the ADHD group was associated with decreased activation of the right ACC and abnormal activation of the locus coeruleus suggesting impaired top-down modulation processes. Performance of a repetitive and predictable task like the DART is heavily dependent on the participant's ability to maintain an alert state. Equally however, if attention does wane, the participant's ability to respond to a lapse by mobilising attentional resources and returning to a more controlled response style is central to reducing the likelihood of future errors. Given that the ACC is also known to play a role in modulating autonomic activity, the connection between electrodermal responsiveness to errors and overall error rates suggests that attenuated EDA in the ADHD group reflects disruption of top-down modulation processes in the post-error period.

As noted previously, prefrontal regions, such as the ACC, modulate arousal according to prevailing task demands and motivational states (Bush, Luu, & Posner, 2000; Holroyd, Niuwenhuis, Mars, & Coles, 2004). Patients who have suffered damage to the ACC tend to show a reduced responsiveness to emotionally significant events, such as errors, and continue to persist in behaviours that are obviously detrimental to their goals (e.g. Tow & Whitty, 1953). In the present study therefore, attenuated post-error EDA may reflect a reduced subjective appraisal of error significance in the ADHD group which in turn decreases the likelihood that they will engage greater top-down control of attention after an error. As discussed in Chapter 1, recent theoretical models of ADHD postulate that neuropsychological deficits may arise from a combination of cognitive and motivational processes (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003). Interestingly, the present findings appear to support Castellanos and colleagues' (2006) prediction that abnormal reinforcement processes in ADHD

would impact on EF in situations that demand the flexible appraisal of the affective significance of events or stimuli. Hence, the present results lend further support to dual-process models of ADHD by suggesting that an insensitivity to errors may further hamper an already suboptimal sustained attention system.

Another possible explanation for the EDA findings which must be considered is that children with ADHD had smaller responses because they were less aware of their errors than controls. Levels of error awareness have never been explicitly investigated in ADHD although a study by Schachar et al (2004) did provide some indirect evidence of abnormality in the form of reduced corrective adjustments following errors. Reduced error awareness has been observed in other clinical conditions with prefrontal abnormalities (McAvinue et al 2006; O'Keeffe et al 2004) and may itself represent a kind of attentional lapse (McAvinue et al 2006). An extensive investigation of error processing in ADHD is therefore conducted in the chapter 4.

In summary, the present study has provided evidence to support the initial hypothesis that ADHD is associated with impaired sustained attention. In order to demonstrate that this particular neuropsychological deficit represents a stable aspect of ADHD, as opposed to a transient developmental process, the next step is to investigate sustained attention in an adult population. The acquisition of ERP data in this study, will make it possible to link any observed performance deficits to specific cognitive operations.

3.4 EXPERIMENT 3. Evidence of Persistent Sustained Attention Deficits in Adult ADHD

3.4.1 Introduction

The present experiment will verify whether problems with sustained attention are a persistent characteristic of ADHD by testing a group of adults diagnosed with ADHD

on the fixed SART. ERP and EDA measures will be acquired in order to obtain a more direct insight into the neural mechanisms underlying sustained attention deficits in ADHD.

Although research on ADHD in adulthood is still at a relatively early stage a number of recent meta-analyses suggest that children and adults with ADHD do exhibit a very similar pattern of neuropsychological deficits (Seidman, 2006). This finding is consistent with accumulating evidence showing the persistence of front-striatal abnormalities into adulthood (see Chapter 1 for discussion). Similar to child ADHD research, the CPT has been the most commonly used measure in sustained attention studies of adult ADHD. A meta-analysis by Woods, Lovejoy and Ball (2002) found that 92% of studies that included CPT reported significant differences on at least one variable. Stronger evidence of attention problems in adults with ADHD may tie in with longitudinal studies that show that while childhood ADHD is characterised by overt behavioural manifestations such as hyperactivity, these disruptive behaviours tend to decline with age while cognitive symptoms such as inattention and impulsivity appear to be more persistent (Wilens, Faraone, & Biederman, 2004). As a result, ADHD in its adult form may be more closely tied to problems of attention than childhood ADHD. However, as in the paediatric literature, these studies have not reported a disproportionate vigilance decrement and to date no study has investigated whether adults with ADHD are more prone to the kind of momentary lapse of attention measured by the SART.

A small number of ERP studies have investigated CPT performance amongst children with ADHD. Most of this work has focused on late components such as the P3b which has been shown to successfully discriminate children with ADHD from their non-ADHD peers (e.g. Strandburg et al., 1996). During CPT tasks P3b components are elicited by both target and non-target stimuli. The P3b has probably been the most researched component of the ERP waveform and a large number of studies have demonstrated that it is strongly modulated by attention (Coull, 1998). As a result, even though they are not elicited by attentional processes themselves, P3b components can provide a good continuous measure of the extent of attention resource allocation during

task performance. To date, there have been no electrophysiological studies of sustained attention performance amongst adults with ADHD

Here the strategy outlined in the introduction to this thesis will be adopted by selecting a behavioural task (fixed SART) whose development was grounded within a cognitive conceptual framework and whose distinctive neuro-cognitive markers have already been identified (by Dockree et al 2005 and in Experiment 1) and systematically investigating these same processes in ADHD.

3.4.2 Methods

3.4.2.1 Participants

Eighteen outpatient adults diagnosed with ADHD-C [Mean age=23.7, SD=5.1; range 18-39; two female; one left-handed] and 15 controls matched for age [Mean age=21.7, SD=3.1; range 18-31; $F_{1,31}$=0.75, p=0.19], sex (one female) and handedness (one left-handed). Participants were recruited as part of an experiment investigating a new alertness training technique (see Experiment 8 in which the present data is used as a baseline condition). Note also that 15 of these participants were also included in Experiment 5. The two groups had comparable IQ scores as measured by the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale III [ADHD group mean estimated full scale IQ=107.8, SD=10.5; Control group mean estimated full scale IQ=113.9, SD=10.8; $F_{1,31}$=2.6, p=0.18] and were also matched for years of second [$F_{1,31}$=2.95, p=0.1] and third level [$F_{1,31}$=2.27, p=0.14] education. All participants had normal or corrected-to-normal vision. Patients were withdrawn from stimulant medication 36 hours prior to testing. All participants gave written informed consent and all procedures were approved by the ethical review boards of St Vincents Hospital, Fairview and the Trinity College School of Psychology.

3.4.2.2 Diagnostic and Screening Procedures

All patients had existing diagnoses made by a trained consultant psychiatrist attached to the Health Service Executive (HSE), Eastern Area of Ireland. The psychiatrist

conducted a detailed investigation of current symptom levels as well as a retrospective assessment of childhood symptoms. To receive a diagnosis patients must have met 6 of 9 DSM-IV criteria for inattention and hyperactivity/impulsivity for a diagnosis in childhood and 6 of 9 criteria for a diagnosis in adulthood. In addition the patient must report persistent ADHD symptoms from childhood to adulthood and experience moderate to severe levels of impairment across a range of different settings attributable to the symptoms of ADHD.

Patients volunteered for the present study following a telephone call or mail advertisement. Nine patients were currently taking psychostimulant medication, four had taken medication in the past but had stopped and five had no previous experience of medication. Controls were recruited via poster advertisements and received a gratuity of €32 for their participation. Before inclusion in the study all participants were screened with a telephone interview addressing personal and family history of ADHD, learning disability, psychiatric, neurological or medical disorders, use of medication and substance abuse. Also, prior to testing all participants filled out the Conners Adult ADHD Rating Scale (CAARS) (Conners, Erhardt, & Sparrow, 2003) and the Wender Utah Rating Scale (WURS, a retrospective measure of ADHD symptoms in childhood) (Ward, Wender, & Reimherr, 1993). The observer versions of both scales were also administered to a close family member or partner. Finally the Standard Clinical Interview for DSM-IV (SCID) was conducted with all patient participants by a trained psychiatrist to assess comorbid Axis I disorders.

Participants were excluded if they reported any previous history of psychosis, organic brain disorder, epilepsy, serious head injury or learning disability. Controls were only included if they had no family history of ADHD and if they themselves were not suspected of having ADHD based on the screening tests. The cut-off for inclusion was an average self and other rated t-score of 65 (95^{th} percentile) on each of the three DSM-IV symptom subscales of the CAARS and an average self and other rated score of less than 36 on the WURS. ADHD group participants were required to have an average self and other rated t-score greater than 65 on two of the three DSM-IV CAARS subscales and average self and other rated score of more than 36 on the WURS. Comorbid Axis I disorders in the patient group included lifetime depression (N=1), current depression

(N=1), bipolar disorder (n=1), current anxiety disorder (N=1) and substance abuse (N=4, alcohol and cannabis use). Three control participants were also engaged in ongoing substance abuse.

3.4.2.3 Fixed SART paradigm and Procedure

The fixed SART paradigm used in the present experiment was identical to the one described in Experiment 1 except for a single feature. Ten grey coloured digits (Grey) were embedded within each SART block. When a Grey stimulus appeared participants were instructed to make the standard Go press response but they were also instructed to say the word 'grey'. This element of the task was included as a baseline control for the training protocol reported in Experiment 8. Post-training, participants performed four more blocks of SART and were asked to use grey stimuli as a cue to implement the training technique. The present data was collected pre-training and the grey stimuli carried no significance other than the requirement for participants to make a verbal response. As a result the dual task requirement was similar to that of DART paradigm initially developed by Dockree et al (2004) and described in Experiment 2. Participants were seated in a dimly lit, sound-attenuated, electrically shielded room. All participants completed four blocks of the fixed SART and responded by pressing the left mouse button with their right forefinger. Again participants were instructed to time their button presses to the offset of each stimulus in order to eliminate speed-accuracy trade-offs.

3.4.2.4 Electrodermal Activity

EDA was acquired using BIOPAC software following the same procedures as outlined in Experiment 2. The occurrence of each SART stimulus was registered in BIOPAC by a series of trigger pulses sent through the serial port of the task presentation computer to the EDA acquisition computer. Data was then analysed using an algorithm coded in Matlab 6.1. This algorithm automatically detects SCRs for a given trial by taking the maximum recorded SCL within the interval 0.5-4.5s post-stimulus and subtracting the nearest preceding local minimum within that interval. EDA responses were averaged following correct withholds, errors of commission and Grey stimuli. As in Experiment

2, the Grey cues provided a means of verifying whether EDA differences were restricted to endogenous processes.

3.4.2.5 EEG Data Acquisition and Statistical Analysis

Due to technical problems ERP data was not acquired for one of the ADHD group participants. For analysis and display purposes, data were average referenced and filtered with a low-pass 0-phase shift 96 dB 30 Hz filter. The lower cut-off of 30Hz was used in this experiment to remove electrical noise associated with sending stimulus triggers to the EDA software. Stimulus-locked data was segmented into epochs of 100ms before to 1000ms after stimulus onset and baseline corrected relative to the interval -100 to 0ms. Stimulus-locked data were averaged separately for Go stimuli that were followed by a button press (correct Go) and No-Go targets that were followed by a correct withhold. The number of trials averaged to generate each ERP was equated for the ADHD and control groups by a process of random exclusion. Neither participant group made sufficient errors over the four SART blocks to generate a valid ERP for error trials.

Group comparisons were based on selected ERP components that were identified in Experiment 1 and by Dockree et al (2004) as key markers of sustained attention on the fixed SART. Visual inspection confirmed the presence of early visual components P1, N1 and P2 in both ADHD and control groups and these were analysed for correct Go stimuli. As in Experiment 1, maximal amplitude scalp locations and peak latencies at these locations were selected for each individual. Both groups exhibited a P3b-like component on Go trials that was maximal over centro-parietal regions (300-400ms). This component was measured as the peak positivity at CPz 310-370 ms post-stimulus. The late potentials, LP1 and LP2 were measured for correct Go stimuli based on criteria outlined by Dockree et al (2005). The LP1 was measured as the mean amplitude between 550-800ms post-stimulus at POz and the LP2 was measured as the mean amplitude between 850-1000ms post-stimulus at Pz. Finally both groups exhibited a clear No-Go N2 on correct withholds over fronto-central scalp sites and maximal at Fz. The No-Go N2 was measured as the peak negativity at Fz in the interval 270 to 330

post-stimulus. In keeping with the findings of Experiment 1 the No-Go P3 was not observed in either group.

Finally, the average EEG power spectrum over the 4 blocks of SART testing was calculated for each participant using the discrete Fourier transform. Each participant's tonic theta, alpha and beta power (μV^2) was calculated as the power in the 4-7 Hz, 8-12Hz and 13-29 Hz ranges respectively. Theta/Beta and Alpha/Beta ratios were subsequently calculated.

3.4.3 Results

3.4.3.1 Behavioural Findings

Individual behavioural and EDA measures were calculated as an average score for the four SART blocks. Table 3.3 displays the means, standard deviations and significance levels for group comparisons (based on one-way ANOVAs with Group as the between subjects factor) on each of the behavioural and EDA measures. Similar to the child ADHD group tested in Experiment 2, the adult ADHD group made significantly more errors of commission and exhibited greater response time variability. There was also a trend towards increased errors of omission in the ADHD group. Partial correlations, controlling for the effect of Group, indicated that there was a significant relationship between GoRT variability and both errors of omission [r=0.76, p=0.001] and errors of commission [r=0.59, p=0.00]. There was also a significant correlation between errors of omission and errors of commission [r=0.54, p=0.001]. EDA data indicated that the two participant groups had comparable SCRs to correct withholds and to Grey stimuli but the ADHD group had significantly smaller SCRs in response to errors of commission. After controlling for the effects of group, age and IQ the post-error vs. post-withhold SCR difference accounted for a significant percentage of the variance in commission errors [R^2change=0.223, $F(1, 31)=10.19$, p=0.004].

Table 3.3 **Comparison of SART and EDA data for adult ADHD and Control groups.**

	Adult ADHD Mean (SD)	**Control** Mean (SD)	$F_{(1,31)}$	p
Errors of Commission	6.3 (2.5)	3.3 (2.6)	10.9	0.002**
Errors of Omission	5.2 (4.5)	2.6 (2.9)	5.3	0.06
Mean Go RT	342.2 (75)	305.6 (81)	1.8	0.2
Mean Go RT Variability	175.2 (54.6)	107.3 (48.1)	14.0	0.001**
Mean SCR post withhold	0.06 (0.06)	0.11 (0.12)	2.5	0.125
Mean SCR post error	0.13 (0.09)	0.33 (0.3)	5.5	0.027*
Mean SCR post Grey	0.213 (0.18)	0.305 (0.28)	1.9	0.17

3.4.3.2 ERP Findings

3.4.3.2.1 Early Sensory Processing

Early sensory processing was investigated on correct Go trials over occipital scalp sites (see Figure 3.8). There were no significant group differences in the amplitude of either the P1 [$F_{(1,31)}$=0.007,p=0.93], N1 [$F_{(1,31)}$=0.002, p=0.96] or the P2 [$F_{(1,31)}$=0.09, p=0.7]. The groups were also compared in terms of the peak latency of these components but again there were no differences for either the P1 [$F_{(1,31)}$=0.19,p=0.67], N1 [$F_{(1,31)}$=0.26, p=0.6] or P2 [$F_{(1,31)}$=0.18, p=0.36].

3.4.3.2.2 P3b

Both groups exhibited a clear P3b component over centro-parietal scalp sites on correct Go trials (see Figure 3.9). A similar component was reported in a previous study of the fixed SART by Dockree et al (2005). Analysis of peak amplitude at electrode CPz indicated that the P3b was significantly attenuated in the adult ADHD group [$F_{(1,31)}$=5.04,p=0.03].

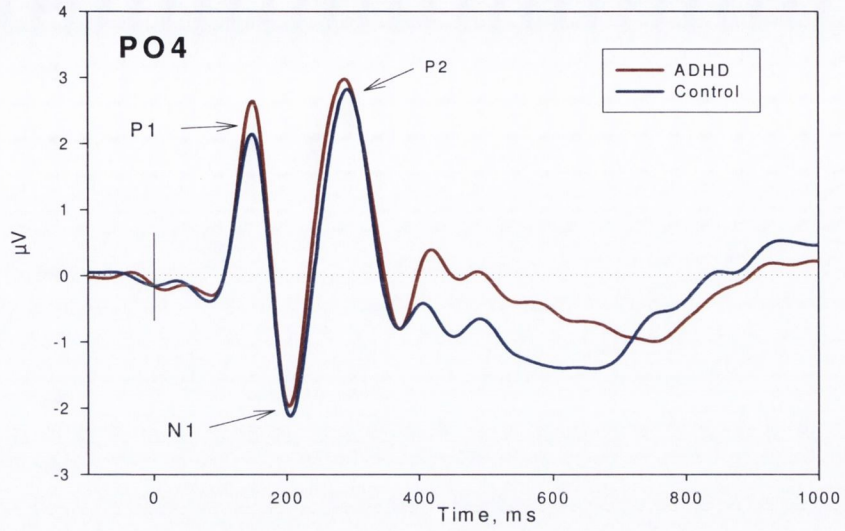


Figure 3.8 **ERP correlates of early stimulus processing on correct Go trials for adult ADHD and Control groups**. There were no group differences in terms of the amplitudes of the early sensory P1, N1 and P2 components.

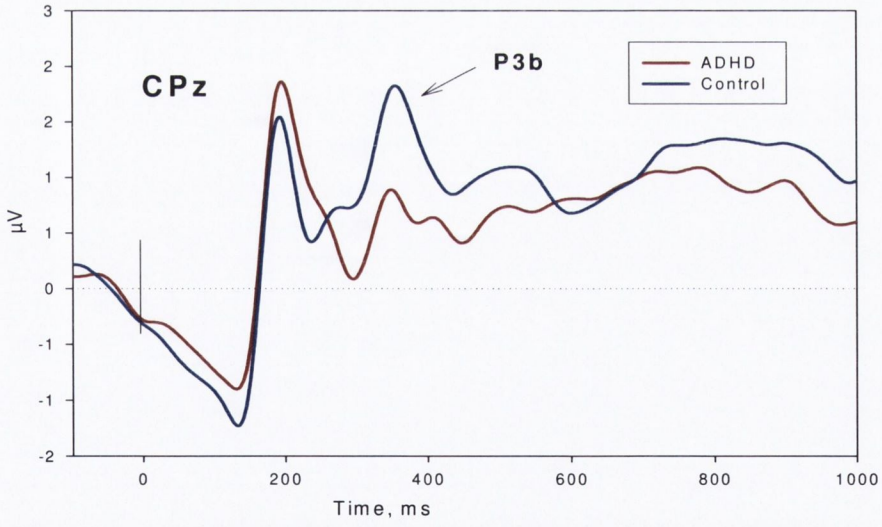


Figure 3.9. **Comparison of P3b component on Go trials for adult ADHD and Control groups**. The ADHD group had a significantly attenuated P3 component.

3.4.3.2.3 Goal Maintenance

There were no group differences in LP1 amplitude [[$F_{(1,31)}$=1.07,p=0.31] but the ADHD group did exhibit a significantly reduced LP2 component [[$F_{(1,31)}$=5.07,p=0.03]. These differences are illustrated in Figure 3.10.

3.4.3.2.4 No-Go N2

A No-Go N2 component was evident in both groups on correct withholds (see Figure 3.11). Statistical analysis indicated equivalent amplitudes of this component across groups [$F_{(1,31)}$=0.356, p=0.56].

3.4.3.2.5 Cortical Arousal

No significant group differences were found for EEG spectral power in the theta [$F_{(1,31)}$=0.7, p=0.79], beta [$F_{(1,31)}$=0.82, p=0.37] or alpha [$F_{(1,31)}$=0.03, p=0.86] bands and there were no differences in theta/beta [$F_{(1,31)}$=0.78, p=0.38] or alpha/beta ratios [$F_{(1,31)}$=0.6, p=0.45]. These data indicate that there were equivalent levels of cortical arousal during SART performance.

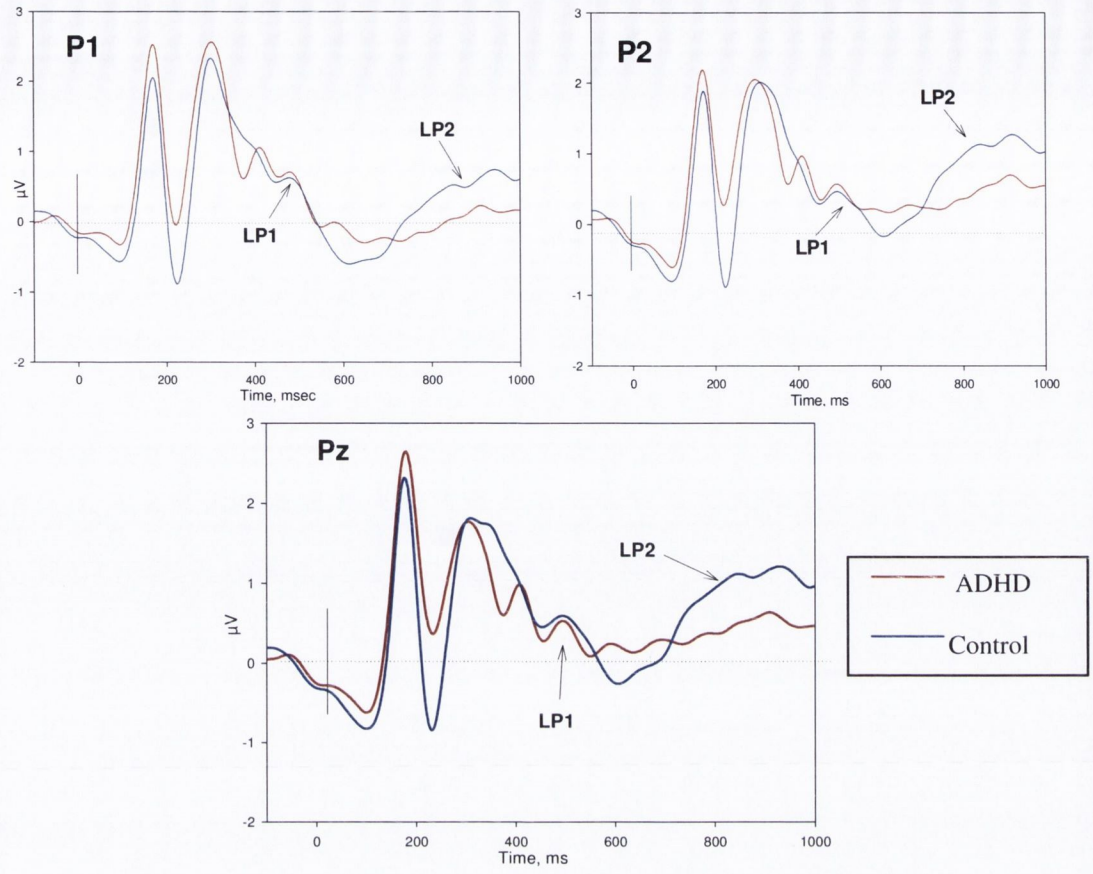


Figure 3.10 **Comparison of LP1 and LP2 components on correct Go trials for adult ADHD and Control groups.** Grand-average waveforms are displayed at P1, P2 and Pz. Only the LP2 distinguished between the two groups.

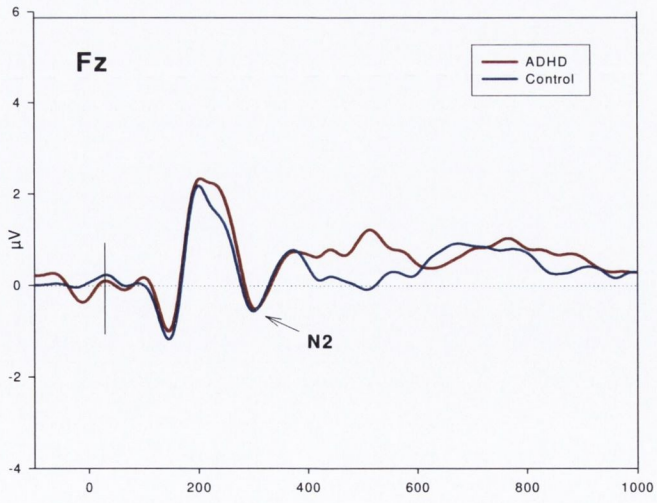


Figure 3.11 **Comparison of No-Go N2 component on correct withholds for adult ADHD and Control groups.** As in Experiment 1 the No-Go P3 was absent for both ADHD and control groups suggesting that successful task performance was not dependent on response inhibition. There were no group differences in No-Go N2 amplitude.

3.4.4 Discussion

In the present experiment, the adult ADHD group exhibited a very similar pattern of sustained attention deficits to those found in children in Experiment 2. Patient group participants made more errors of commission, had greater RT variability and showed a trend toward increased errors of omission. These data are consistent with previous CPT studies (reviewed in Woods et al 2002) that have highlighted vigilance deficits but extend these findings by demonstrating that adults with ADHD are also more susceptible to brief momentary lapses of attention measured over relatively short periods of time. As in Experiment 2, the adult ADHD group showed reduced SCRs to errors which predicted error rates on the task. Again, there were no group differences in arousal responses to correct withholds and Grey cues suggesting that group differences cannot be attributed to a generalised phasic arousal deficit. Thus, both children and adults exhibited abnormal error processing which impacted upon their ability to re-engage sustained attention following a lapse. Error processing deficits will be explored in detail in the next chapter.

Given the consistent evidence of abnormalities in spectral EEG activity reported in the paediatric literature it is interesting that no differences were observed in this adult group. The paediatric literature has focused on spontaneous, resting state EEG activity and has consistently reported excessive slow wave (theta, alpha) and reduced fast wave (beta) activity amongst children with ADHD relative to their peers (Barry, Johnstone, & Clarke, 2003a). However, a longitudinal study by Bresnahan, Anderson and Barry (1999) demonstrated that these differences decrease linearly with age suggesting that they may result from a delay in brain maturation that is eventually resolved. The present data suggests that abnormalities in basal levels of cortical arousal are not a persistent aspect of this disorder. Since the EEG measures were acquired during the performance of a cognitive task they are also likely to reflect task-related changes in arousal. As discussed at the beginning of this chapter, the SART was designed to be sensitive to short term fluctuations in top-down modulation via cortico-subcortical pathways as opposed to the long term arousal decrements measured by traditional CPTs. The absence of any group differences in EEG measures of arousal despite clear behavioural differences suggests that sustained attention failures are indeed attributable to more

localised or focal changes in activity at a cortical level that may not be reflected in these global EEG measures. Analysis of the ERP data gave valuable insight into the nature and timing of these cortical changes.

The first thing to note in the ERP data was that neither ADHD nor control participants appeared to rely on response inhibition to perform the SART. In the present experiment, as in Experiment 1, the No-Go P3 was completely absent from the No-go stimulus-locked ERP waveform of both groups. In addition the adult ADHD and control groups had comparable No-Go N2 amplitudes. Experiment 1 indicated that although a small No-Go N2 component was evident on the fixed SART it did not discriminate between correct withholds and errors of commission reflecting limited conflict between the Go and No-Go responses. This finding further highlights the absence of any inhibitory requirement on the fixed SART and confirms that poor performance on the task cannot be attributed to deficient response inhibition processes in ADHD.

The present data reveal that there were no group differences in the amplitude of the P1, N1 and P2 indicating that early stimulus processing was not affected in the adult ADHD group. Previously, Brandeis et al (1998) found that children with ADHD had increased N1 amplitudes in response to stop signals during performance of the stop task. Perchet et al (2001) noted a decreased effect of spatial cues on P1 amplitudes when children with ADHD performed an orienting paradigm. The key feature of these two studies is that the early sensory components were measured in response to stimuli that were critical to task performance. As mentioned previously, frontal control regions bias early sensory processing according to stimulus salience and behavioural relevance (Hopfinger, Buonocore, & Mangun, 2000). As Experiment 1 demonstrated, performance of the fixed SART does not require highly efficient processing of individual Go stimuli and is instead reliant on the participant's ability to sustained attention to the primary task goal while anticipating the target. The absence of any group differences in early sensory ERPs therefore suggests that while differences may become apparent when there is a greater need for top-down biasing of early stimulus processing, basic sensory processing does not appear to be affected in adults with ADHD.

The reduced centro-parietal P3b amplitudes on Go trials exhibited by the adult ADHD group extends one of the most common findings in ERP studies of children with ADHD to an adult sample (Barry, Johnstone, & Clarke, 2003b). As mentioned in Chapter 2 the precise function of P3 components is still considered controversial. However, since the P3b is reliably enhanced under attention demanding conditions this component is frequently used as an index of the endogenous mobilisation of attentional resources in response to significant task stimuli (Knight, 1991; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). Dockree et al (2005) noted a similar P3b component in their analysis of the fixed SART and found that its amplitude was markedly increased at the beginning of a new 1 to 9 sequence. This finding strongly suggested that the P3b reflected utilisation of the predictable stimulus sequence to guide performance.

In keeping with the findings of Dockree et al (2005) two prominent late positive components (LP1 and LP2), thought to reflect the extent of goal maintenance were observed over central and occipito-parietal scalp sites. In Experiment 1 it was demonstrated that this same late positivity is enhanced when a task is undemanding and monotonous and therefore places greater emphasis on the sustained attention system. In the present experiment adult ADHD participants had significantly smaller LP2 amplitudes than control participants. Previously, Perchet et al (2001) also observed that children with ADHD had smaller slow-wave ERP components preceding the appearance of target stimuli during performance of an attention paradigm. These slow components have also been linked to executive processes such as attentional control and anticipation (Brunia, 1993). The present data suggests that ADHD participants were less efficient at activating the task goals in a continuous manner which may have led to an increased susceptibility to lapsing into a mindless default mode.

Thus, there is convergent behavioural and ERP data to indicate that deficient SART performance in the adult ADHD group has its origins in a difficulty sustaining attention during the inter-target period. Importantly, abnormalities in previously established electrophysiological markers of sustained attention have been identified and these cannot be attributed to a primary deficit in response inhibition. As such, experiments 2 and 3 challenge the notion of a unitary EF deficit in response inhibition by demonstrating that behavioural deficits were linked to ERP markers that are specific to

sustained attention. In addition the finding of reduced SCRs to errors suggests that motivational differences in the appraisal of error significance further exacerbates these deficits.

3.5 Chapter Summary

In this chapter it has been demonstrated that the distinguishing electrophysiological features of the fixed SART relate to the maintenance of a goal-directed attentive state and not to response inhibition. As a result the fixed SART provides a means of verifying the existence of sustained attention deficits in ADHD without the potential confound of poor response inhibition. Both children and adults with ADHD made significantly more errors on the fixed SART than their non-ADHD peers and ERP data indicated that performance deficits could be attributed to reduced endogenous control of attention. Reduced SCRs to errors were found in both child and adult ADHD groups and this abnormality was a significant predictor of poor sustained attention performance. In order to better understand this apparent motivational deficit, post-error processing will be explored in the next chapter. In Chapter 6, a new cognitive training protocol that is designed to target sustained attention deficits in ADHD will be developed.

Chapter 4. Exploring Error Processing Networks in ADHD

4.1 Neural substrates of error processing – implications for ADHD

As discussed in Chapter 1 there is a wealth of evidence showing that individuals with ADHD make more errors than their non-ADHD peers on neuropsychological tests measuring a selection of executive functions. One thing we know less about is how ADHD sufferers actually deal with these errors. In everyday life our ability to detect errors and to adjust our behaviour accordingly is critical for smooth and flexible interaction with our environment and also for learning the consequences of different behaviours (Norman & Shallice, 1986). Error processing acts as a warning mechanism signalling that our current performance is not meeting task demands and that a greater level of attention or control resources need to be committed. Rabbitt (1966) was one of the first to investigate this phenomenon in the context of a neuropsychological task. Rabbitt found that during performance of a choice-response task participants' response times were markedly slower on the next correct response following an error than on other correct responses. Participants appeared to be engaging in compensatory performance correction linked to a recognition that they had made an error. Such slowing is thought to result from the adoption of a more cautious response style in order to decrease the likelihood of future lapses and is seen on a variety of tasks requiring high-level executive processes including reasoning, memory search, verbal analogy and speeded response tasks (Schachar et al., 2004). More recently, a number of theoretical models have been proposed in which error processing represents one component of a broader action monitoring system designed to oversee and modulate our behaviour (e.g. Duncan, 1995; Logan, 1985; Norman & Shallice, 1986). According to such models effective error processing would be reliant upon two necessary systems: one to monitor performance and signal when increased control is required and another to implement the necessary adjustments.

Recent functional imaging findings have supported the view that error processing represents a discrete component of executive control by identifying separate brain structures dedicated to error detection and correction. In a fMRI study of a Go/No-Go inhibition task Garavan and colleagues (Garavan, Ross, Murphy, Roche, & Stein, 2002) demonstrated unique error-related brain activations that could be distinguished from those recruited for response inhibition. Activation of a medial frontal region incorporating the anterior cingulate cortex (ACC) was associated specifically with the detection of a response/goal mismatch while performance adjustments were most closely related to activity in the left dorsolateral prefrontal cortex (DLPFC) which also predicted accuracy on the next No-Go target. Further investigation has suggested that the DLPFC implements post-error adjustments, in response to an ACC error signal, by re-establishing a strong tonic task set while suppressing task-irrelevant information (Fassbender et al., 2004; Hester, Fassbender, & Garavan, 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Convergent neuroimaging and electrophysiological findings have established the ACC as the key cortical region governing error processing (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

The ACC is a complex brain region which performs a variety of different functions during higher-order cognitive control. Convergent anatomic, connection, lesion, electrophysiology and imaging data have supported the conclusion that the ACC can be broadly divided into two overlapping subregions (Bush, Luu, & Posner, 2000; Garavan, Ross, Kaufman, & Stein, 2003; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Taylor et al., 2006). The dorsal ACC (dACC), which has strong reciprocal connections with dorsolateral prefrontal cortex, parietal cortex and premotor areas, is thought to represent a 'cognitive' division which plays a central role in cognitive and attentional tasks by allocating attentional resources when confronted with competing processing demands and/or by mediating response selection via monitoring and resolution of competition or conflict (Bush, Luu, & Posner, 2000). The rostral ACC (rACC), has been dubbed the 'affective' division due to its connection to limbic and paralimbic areas and is activated during emotional processing, motivational processing and autonomic control (Bush, Luu, & Posner, 2000) (see Figure 4.1 below). Several studies have shown that both of these sub-divisions are activated during different stages of error processing (Garavan, Ross, Kaufman, & Stein, 2003; Taylor et al., 2006). A recent

fMRI study by Taylor and colleauges (2006) indicates that the dACC processes early markers for unfavourable outcomes such as high response conflict or decision uncertainty, while activity in the rACC is more specifically associated with the actual detection of an error and resultant affective processing.

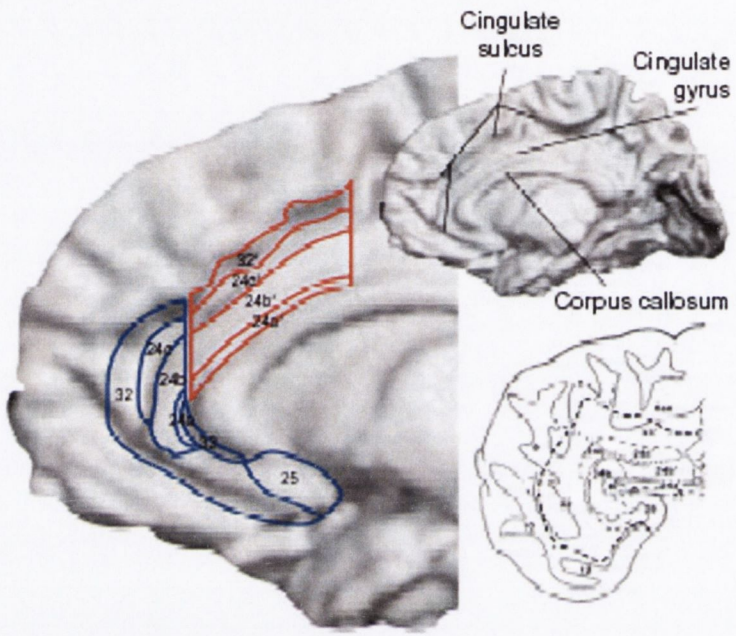


Figure 4.1 **Anterior Cingulate Cortex (ACC) Anatomy.** A schematic representation of the of cytoarchitectural areas of ACC is shown to the left and demonstrates the two major functional subdivisions that have been identified. The dorsally located 'Cognitive' division areas are outlined in red and the more rostral 'affective' division areas are outlined in blue. From Bush et al (2000). *Trends in Cognitive Sciences.*

Interestingly, these ACC subdivisions form part of the dorso-fronto-striatal (dorsal ACC) and meso-limbic (rostral ACC) pathways that have been highlighted in recent models that assert the dual role of cognitive and motivational problems in the etiology of ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003) (see Chapter 1 for further discussion). There is good evidence to suggest aberrant ACC functioning in ADHD. Morphometric neuroimaging studies have reported subtle volumetric reductions of the prefrontal cortex and ACC in children and adults with ADHD (Seidman et al., in press; Sowell et al., 2003). Seidman et al (in press) have recently reported clear volumetric differences amongst adults with ADHD in both

rostral and dorsal regions of the ACC (see Figure 4.2 below). In addition, a number of functional imaging studies of ADHD have found decreased activation of dACC in children and adults during the performance of tasks that require response inhibition (Durston et al., 2003; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004), sustained attention (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006), conflict resolution (Bush et al., 1999; Durston et al., 2003; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004) and working memory (Schweitzer et al., 2000). To date there have been no fMRI studies that have specifically investigated rACC function in ADHD.

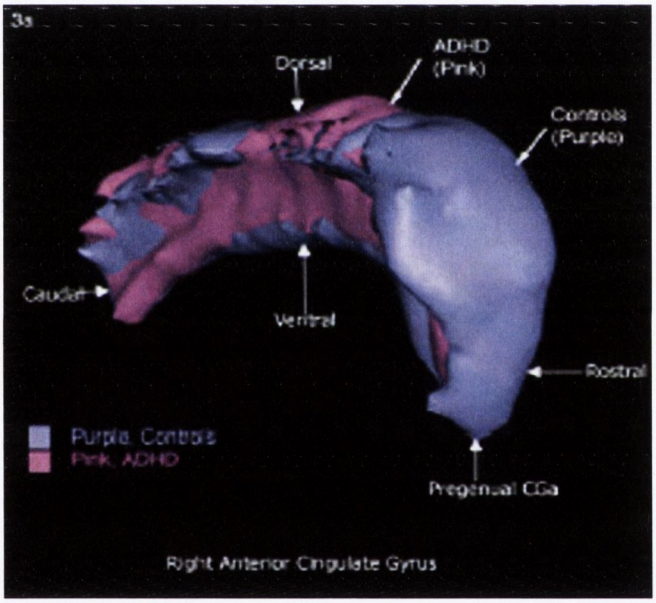


Figure 4.2 **Structural differences in ACC associated with ADHD**. This figure compares the average volumes of the control participants and persons with ADHD in the right anterior cingulate represented as 3-D isosurfaces. The purple colour represents areas where the control group has a larger isosurface than persons with ADHD. The greatest difference between the two groups is in the rostral part of the anterior cingulate gyrus. Changes are also observed in the dorsal part of the anterior cingulate gyrus. Adapted from Seidman, et al. (in press)

Although there is a clear neuroanatomical rationale for suspecting the presence of error processing difficulties in ADHD only a very small number of studies have investigated this possibility. Sergeant and Van der Meere (1988) administered a Sternberg visual

search task under varying memory load conditions to a group of 7 children with ADHD and 7 matched controls. The authors observed typical group differences in accuracy and response speed but in addition they found that the children with ADHD failed to adjust post-error response slowing as a function of processing load. In the context of a visual search task, post-error slowing allows for the prolongation of information processing on the current trial thus increasing the likelihood of a correct response. Therefore, as task difficulty increases there is an increased requirement to slow down in order to avoid another error. In this study the children with ADHD appeared to suffer from an inability to adjust post-error performance as a function of the degree of controlled processing required as opposed to a general failure to correct errors since post-error slowing was normal under low load conditions. A more recent study by Krusch and colleagues (Krusch et al., 1996) reported the same results in a larger group of ADHD children and showed that methylphenidate significantly enhanced post-error slowing.

Schachar and colleagues (2004) also investigated post-error slowing in ADHD but during the performance of the Stop-Signal response inhibition paradigm. A group of 151 ADHD children exhibited slower Go RTs, longer SSRTs and also slowed significantly less than controls after a failed inhibition. Importantly, post-error slowing was not correlated with mean RT, RT variability or response inhibition, providing further support for the conceptualisation of error processing as a distinct executive component. Furthermore, these results indicate that response inhibition and error monitoring deficits in ADHD are independent. Interestingly the authors found that there was no relationship between error correction and co-morbid disorders including reading disability, conduct disorder, oppositional defiant disorder and anxiety but there was a significant correlation with number of ADHD symptoms suggesting that the relationship with ADHD has a certain degree of specificity.

However, a major limitation in the research conducted on ADHD in this area has been a failure to explicitly investigate levels of error awareness. Damage to the frontal lobes has been associated with an increased tendency to miss errors during neuropsychological tasks (McAvinue, O'Keeffe, McMackin, & Robertson, 2005; O'Keeffe, Dockree, & Robertson, 2004). The initial study by Sergeant and Van der Meere (1988) did ask participants to correct errors and observed no group differences

though the sample size was very small (N=7). In fact, using a much larger sample, Schachar and colleagues (2004) reported that children with ADHD slowed after fewer errors than controls, possibly pointing to a reduced awareness of those errors. However, using post-error slowing as the sole measure of conscious awareness may be fraught because two recent studies found that participants actually engaged in significant levels of post-error slowing following undetected errors (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Rabbitt, 2002). The issue of error detection could be a serious confound in ADHD research and could contribute to the reduced post-error slowing that has been seen in the studies described above. Reduced awareness of one's deficits predicts behavioural disturbances in brain injured populations (Bach & David, 2006; Hart, Giovannetti, Montgomery, & Schwartz, 1998; O'Keeffe, Dockree, & Robertson, 2004) and could present a heretofore unrecognised problem for ADHD sufferers.

In Chapter 3, both child and adult ADHD participants exhibited abnormalities in their post-error processing, reflected in reduced SCRs that were found to be consequential for their general performance on a sustained attention task. This begs the question, to what extent are the neuropsychological deficits we are seeing in ADHD attributable to a failure to adequately process errors? We know that people with ADHD make more errors than controls but are they always aware of these errors? When an error is detected, are they able to re-establish cognitive control? An answer to these fundamental questions would greatly improve our understanding of the neuropsychological deficits experienced by ADHD sufferers and could be informative in the development of remedial interventions.

In fact, even in the broader error processing literature very few studies have made a clear distinction between error detection and error awareness. As a result, it is not clear how the error-related brain activations that have been demonstrated so far actually relate to the conscious experience of making an error. Therefore, in Experiment 4 the issue of error awareness is investigated. Key electrophysiological markers of error awareness will be examined in a group of normal healthy adults and then, in Experiment 5, this information will be used as a baseline from which to compare the efficiency of error processing networks in a group of participants diagnosed with adult ADHD.

4.2 EXPERIMENT 4. The Electrophysiological Correlates of Error Awareness

4.2.1 Introduction

The first of only two studies to explicitly measure electrophysiological correlates of error awareness was conducted by Nieuwenhuis and colleagues (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001) who focused on two response-locked ERP components previously discussed in Experiment 1; the Error Related Negativity (ERN) and the Error Positivity (Pe). The ERN is an early negative deflection with a frontocentral distribution peaking between 50 and 120msecs after an error. Its early onset, before the erroneous response has been completed, is suggestive of a rapid internal detection mechanism that is not dependent on conscious processing of the error (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). Rather than directly detecting errors, the ERN is thought to reflect related monitoring processes that are sensitive to response conflict (Van Veen & Carter, 2002) or changes in reward probability (Holroyd, Niuwenhuis, Mars, & Coles, 2004). Several studies have shown that the ERN amplitude predicts short-term post-error compensatory adjustments (Debener et al., 2006; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Pennington & Ozonoff, 1996; Rodriguez-Fornells, Kurzbuch, & Munte, 2002). In contrast, the functional significance of the Pe, maximal over parieto-central scalp sites, is poorly understood but this component peaks sufficiently late (300-500msec post error) for sensory or proprioceptive information to be available and is therefore more likely to index conscious aspects of error processing. Indeed, Nieuwenhuis and colleagues (2001), who asked participants to perform an antisaccade task, found that consciously perceived errors elicited far larger Pe amplitudes than unperceived errors while the ERN remained unaffected. This finding, which was recently replicated (Endrass, Franke, & Kathmann, 2005), provided the first evidence that the Pe, and not the ERN, specifically reflects

conscious aspects of error processing. However, the generalisability of this relationship beyond the occulomotor modality has yet to be verified.

Source localisation studies of the ERN and Pe have confirmed the critical role of the ACC in error detection by identifying generators in this region for both the ERN and the Pe. The ERN has been consistently localised to the dACC which, as discussed, has been heavily implicated in monitoring processes such as conflict and uncertainty and controlling interference (Dehaene, 1994; Herrmann, Rommler, Ehlis, Heidrich, & Fallgatter, 2004; Van Boxtel, Van der Molen, & Jennings, 2005; Van Veen & Carter, 2002). Attempts to identify the precise ACC generator for the Pe have been less consistent. While Van Veen and Carter (2002) and Van Boxtel et al (2005) located the source of the Pe in the rACC, associated with motivation and affective processing, the source identified by Hermann et al (2004) was located in a far more dorsal region.

There is some functional imaging evidence to suggest that the ACC is necessary for certain conscious processes. For example, Stephen et al (2002) asked participants to tap their fingers to a rhythmic beat and every now and then the beat was temporally distorted either above or below the threshold of conscious perception. The authors found that only adjustments to conscious perturbations elicited neural responses that included the ACC and DLPFC. Interestingly however, in the only fMRI study to explicitly distinguish between consciously perceived and unperceived action errors (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005), there was no additional ACC activity when participants were aware of their errors. This finding appears to be at odds with data suggesting an ACC source for the Pe. Thus, the neural processes necessary for conscious error awareness have not yet been clearly identified.

The present study was designed to shed further light on the neural substrates of error awareness by addressing three key questions:

First, given that error-related brain activity has primarily been investigated while participants performed manual response tasks, the present study aimed to verify the generalisability of Nieuwenhuis et al's (2001) findings beyond the oculomotor

modality. To do this the same Go/No-Go response inhibition task developed by Hester et al (2005) was used.

Second, previous attempts to localise the generators of the ERN and Pe have not taken awareness into account. In order to further explore the role of the ACC in error awareness the present study sought to localise the neural generators of the ERN and Pe while distinguishing between errors made with and without conscious awareness.

Third, a limitation of purely event-related approaches to error-processing is that we can learn little about potentially critical brain states that could provide the setting conditions for conscious awareness. Research has previously demonstrated an association between sustained attention deficits and failures in conscious error-detection in brain-injured populations (McAvinue, O'Keeffe, McMackin, & Robertson, 2005). In addition, several authors have suggested that the Pe may be part of the same evaluative process as the stimulus-locked P3 (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005) a component which is reliably modulated by arousal (see Nieuwenhuis, Aston-Jones, & Cohen, 2005 for complete discussion). A hypothesis that emerges from this work is that one's basal level of cortical arousal, as measured by the ratio of slow (theta, alpha) to fast (beta) wave oscillations across the task duration, will be associated with the extent of conscious error processing. Therefore the third aim of this study was to investigate the relationship between tonic EEG measures of cortical arousal and error awareness.

4.2.2 Methods

4.2.2.1 Participants

Nineteen (one female, one left handed) neurologically normal volunteers participated. Participants were aged between 18 and 30 years (mean age=22.07, SD 2.85). All participants gave written informed consent and all procedures were approved by the ethical review boards of St Vincents Hospital, Fairview and the Trinity College School of Psychology. All participants reported normal or corrected-to-normal vision.

4.2.2.2 Error Awareness Task (EAT) and procedure

The same error awareness paradigm developed by Hester et al (2005) was used in the present experiment. The EAT (see Figure 4.3) is a motor Go/No-Go response inhibition task in which participants are presented with a serial stream of single colour words with congruency between the word and its font colour manipulated. Participants were trained to respond to each of the words with a single 'Go trial' button press and to withhold this response when either of two different circumstances arose. The first circumstance was if the same word was presented on two consecutive trials (Repeat No-Go), and the second was if the word and its font colour did not match (Incongruent No-Go). In the event of a commission error (failure to withhold to either of these No-Go scenarios) participants were trained to press a second 'awareness button' on the next Go trial after the error and were not required to make the standard Go response. Participants were instructed to time their button presses to the offset of each stimulus. This kind of 'response-locking' has been shown to reduce inter-individual variability and eliminate speed accuracy trade-offs (Stuss, Murphy, Binns, & Alexander, 2003). In the present experiment response-locking was used to rule out the possibility that certain undetected errors could be attributed to an overemphasis on speed over accuracy. In addition, it was predicted that the increased task monotony associated with response-locking would increase the likelihood of unaware errors.

To maximise the number of errors for ERP averaging, participants completed an average of 11.2 blocks of the EAT (range: 8-14). Each EAT block consisted of 225 stimuli of which 200 were Go stimuli and 25 were No-Go stimuli (of which 13 were Repeat No-Gos and 12 were Incongruent No-Gos or vice versa). All stimuli were presented for 600msec followed by an inter-stimulus-interval (ISI) of 900msec and appeared 0.25^{o} above a white fixation cross on a grey background, at a distance of approximately 150 cm. Participants registered their responses with a right thumb press on a two-button gamepad. Participants were instructed to focus on the fixation cross during the task in order to minimise eye movements.

4.2.2.3 Electrodermal Activity (EDA) Acquisition and analysis

Previous work has demonstrated that EDA responses are absent when participants are not aware that they have made an error (O'Keeffe, Dockree, & Robertson, 2004). In the present study EDA was acquired to provide collateral evidence that errors after which there was no 'awareness' response were not associated with significant amounts of conscious processing. EDA measurements were acquired according to the procedures outlined in Experiment 1. EDA data was analysed using Matlab 6.1. Peak to peak SCRs were measured within the latency window of 0.5 to 4.5 seconds post No-Go stimulus and averaged separately for correct withholds, aware errors and unaware errors.

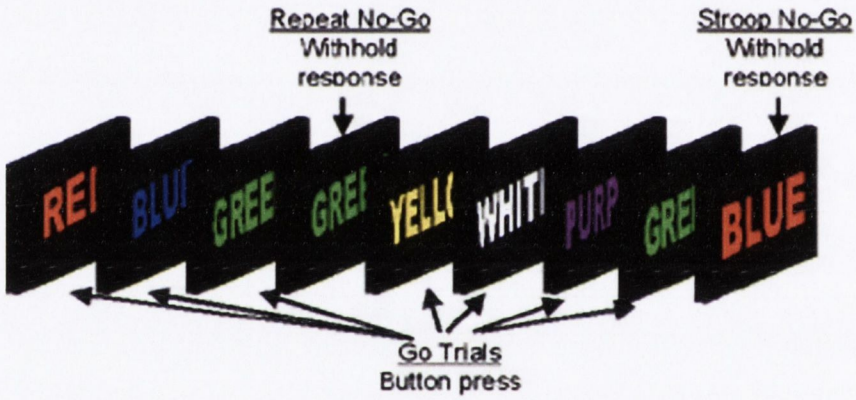


Figure 4.3 **Error Awareness Task (EAT) schematic**. The EAT required participants to respond with a button press to a stream of colour words and withhold their response when either a word was repeated on consecutive trials or the font and word were incongruent. Participants were trained to press a different 'awareness' button following any commission errors.

4.2.2.4 EEG Data Acquisition and Statistical Analysis

Following artifact rejection, accepted EEG trials were averaged separately to generate ERPs for correct Go presses, commission errors (Repeat and Incongruent No-Gos) after which the participants indicated awareness (Aware Error) and commission errors after which the participants did not indicate awareness (Unaware Error). Unaware Errors were rejected if the participant failed to make any response on the next Go trial or if they pressed the 'awareness' button within three trials of the No-Go error.

Inspection of the grand-average waveforms revealed a clearly defined ERN following both aware and unaware errors peaking at approximately 80msec after the button press. A smaller, ERN-like, negative component was also evident at the same latency after correct Go presses. For all three conditions the peak amplitude of the ERN was seen at FCz with little topographical variation across participants. The ERN was therefore defined as the most negative peak at FCz occurring in a window from 50-120 msecs post-response. In all three response conditions (correct go-response; aware error; unaware error) the ERN was immediately followed by a positive deflection with maximal amplitude also at FCz, and peaking at approximately 190 ms post-response. On aware errors this early positive peak (early positivity) was followed by the classic Pe component in the form of a large positive wave over posterior scalp regions and maximal amplitude at CPz. The early positivity was calculated for all three response conditions as the most positive peak at FCz between 140 and 240msecs post-response. Because the Pe is a more sustained low-frequency component the mean amplitude at CPz between 300-500msec post-response was used.

Finally, the average power spectrum over the first 8 blocks of EAT testing was calculated for each participant using the discrete Fourier transform[1]. Each participant's tonic theta, alpha and beta power (μV^2) was calculated as the power in the 4-7 Hz, 8-12Hz and 13-29 Hz ranges respectively. Theta/Beta and Alpha/Beta ratios were subsequently calculated.

The behavioural and EEG measures reported were calculated over the first 8 blocks for all participants. To ensure a clean signal, only those participants who made at least 20 aware and 20 unaware errors were included in the ERP analysis. This led to a reduced sample of 12 participants who made an average of 76 aware errors and 35 unaware errors. Because of the relatively low data yield for unaware errors, it was important to equate the number of single trials that contributed to the averages for these comparisons. Consequently half the aware errors were removed by selecting only even matches to ensure that they were not overrepresented either quantitatively or temporally in these comparisons.

[1] 8 blocks was the minimum number of EAT blocks that were completed by each participant

4.2.3 Results

4.2.3.1 Behavioural Performance

The means, standard deviations and significance levels for the primary performance measures are presented in Table 4.1. Participants successfully withheld their response on 69% of No-Go targets. A significantly greater portion of total commission errors occurred on Incongruent No-Gos (mean=60.6%, SD=16.5) than on Repeat No-Gos (38.4%, SD=18.5) [$t_{(18)}$=5.69, df=18, $p<0.001$]. Participants were aware of 76% (SD=13.8) of all commission errors (aware errors/total errors). Although more errors were made on Incongruent No-Go targets, participants were significantly less likely to be consciously aware of errors on Repeat No-Gos (mean=68%, SD=19.9) than on Incongruent No-Gos 81% (SD=13.9), $t_{(18)}$=3.301, df=18, $p<0.01$). This difference may be explained by the fact that when participants make an error on Incongruent trials, the current stimulus can be immediately identified as a No-Go target. In contrast, when an error is made on a Repeat trial, the participant must have a memory of the preceding trial in order to identify the current stimulus as a No-Go target. Given that participants appear to have found it easier to withhold on Repeat No-Go trials, the increased rate of unaware errors suggests that failed inhibitions on Repeat trials may have been accompanied by a more dramatic lapse of attention than errors made on Incongruent trials. The Mean Go RT (625msec, SD=96.87), indicates that participants were successfully timing their responses to stimulus-offset.

Table 4.1 **EAT performance data for 19 neurologically healthy adult participants.**

	Mean (SD)
Errors of commission	76% (13.8)
Errors of omission	0.6% (0.63)
Error awareness	62.9% (19.8)
Mean Go RT	625 (96.87)
Mean Go RT Variability	98.12 (31.78)
Mean aware error RT	593.4 (119.3)
Mean unaware error RT	676.3 (112.8)

4.2.3.2 Modulation of EDA by Awareness

As Figure 4.4 illustrates, strong SCRs were elicited by aware errors [mean=0.243, SD=0.19] and correct withholds [mean=0.203, SD=0.16] on No-Go Trials. In contrast, SCRs were almost completely absent on unaware errors [mean=0.080, SD=0.083]. An ANOVA on the magnitude of SCRs for the three No-Go conditions (aware error, unaware error, correct withhold) revealed a significant main effect of No-Go condition [$F_{(2,22)}$=7.96, $p<0.01$]. Post-hoc Bonferonni tests indicated that participants had comparable SCRs following aware errors and correct withholds [p=0.17], but SCRs following unaware errors were significantly smaller than those elicited by aware errors [$p<0.01$] or correct withholds [$p<0.05$]. These data indicate that the emotional-cognitive processes indexed by EDA were absent on unaware errors.

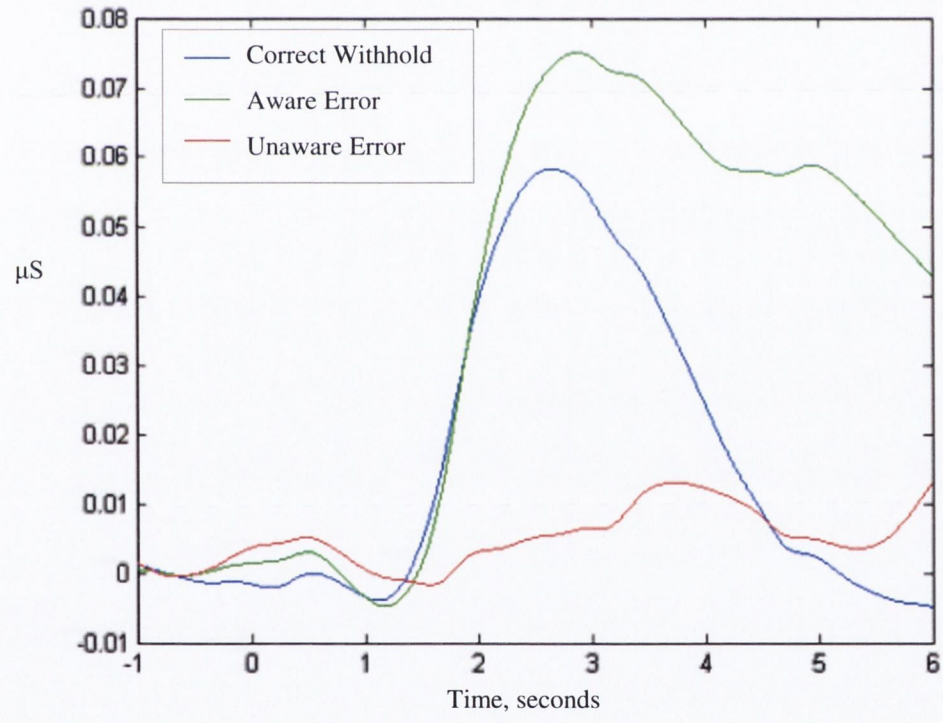


Figure 4.4 **Relationship between autonomic arousal and error awareness**. SCRs averaged separately for aware errors, unaware errors and correct withholds on No-Go trials and time-locked to stimulus offset (time-point 0). Here we see that, as expected, unaware errors did not elicit the autonomic response typically seen following significant events such as errors confirming that conscious processes were not active.

4.2.3.3 Modulation of Error-Related ERPs by Awareness

An ANOVA on the ERN amplitudes for the three Response conditions (aware error, unaware error, correct go press, see Figure 4.5a) indicated a significant main effect of Response [$F_{(2,22)}$=4.6, p<0.05]. Tests of within-subjects contrasts revealed that the ERN was significantly larger following both error types relative to correct go presses [Go vs Aware $F_{(1,11)}$=6.37, p<0.05; Go vs Unaware $F_{(1,11)}$=6.407, p<0.05], but importantly there was no difference between ERN amplitude for aware and unaware errors [$F_{(1,11)}$=0.015, p=0.872]. An ANOVA on the early positive peak immediately following the ERN revealed no reliable differences across conditions [$F_{(2,22)}$=2.88, p=0.083] (see Figure 4.5a).

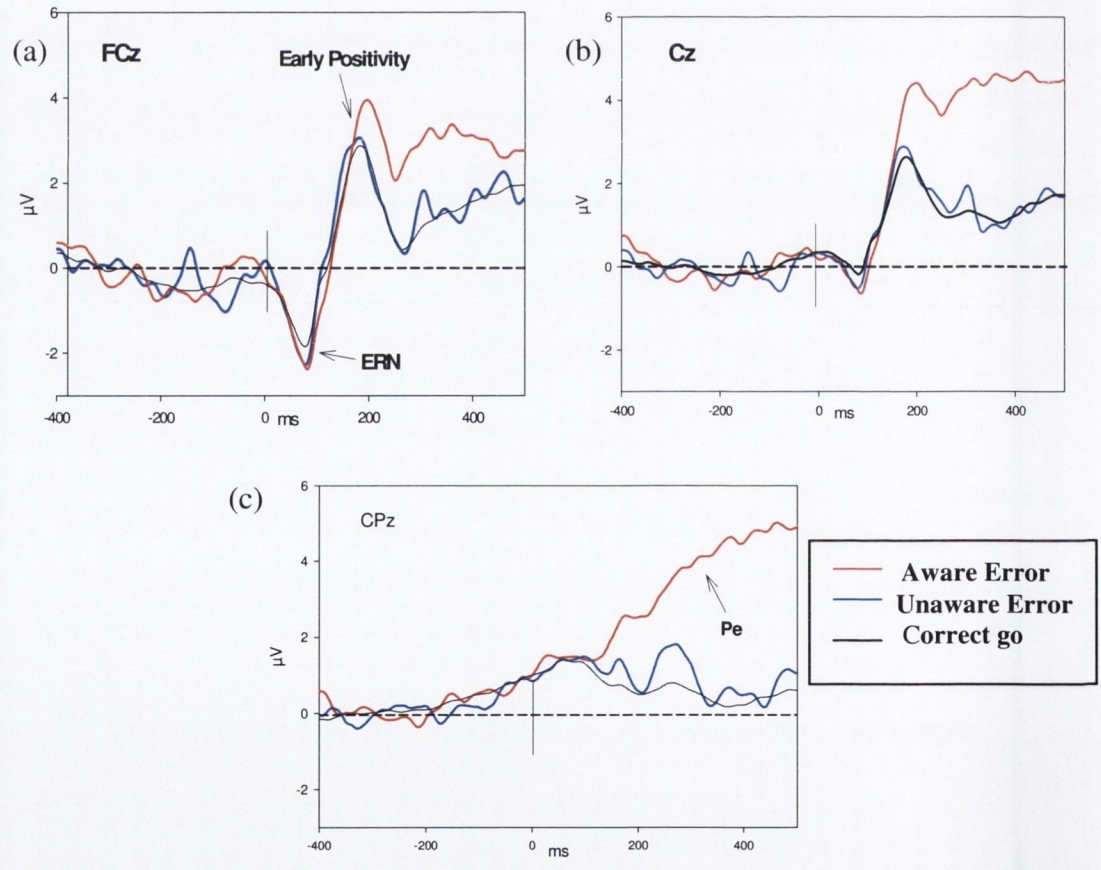


Figure 4.5 **Relationship between error-related ERPs and awareness**. Grand-Average ERP Waveforms at FCz (a), Cz (b) and CPz (c) time-locked to button press (time-point 0). Panel (a) shows that the ERN and early positivity are not modulated by participants' conscious awareness of errors. In panel (c) we note the large Pe wave following aware errors that is absent on unaware errors and correct-go presses.

Finally an ANOVA on the Pe amplitudes revealed a significant main effect of Response [$F_{(2,22)}$=68.73, p<0.001]. Tests of within-subjects contrasts confirmed that this late positive wave was significantly smaller on correct go presses and unaware errors relative to aware errors [correct go versus aware $F_{(1,11)}$=112.87, p<0.001; unaware vs. aware $F_{(1,11)}$=72.94, p<0.001]. Unaware error and correct go ERPs did not differ in terms of this late positivity [$F_{(1,11)}$=0.025, p=0.877] (see Figure 4.5c).

4.2.3.4 Source localisation of Error-Related ERPs

Strong ERN and early positive waves with identical scalp topographies (see Figure 4.6a) were evident in all three response conditions including correct go presses. Due to these similarities, source localisation of the ERN/early positivity was conducted on aware error ERPs instead of a difference waveform. Source localisation was implemented by BESA 5.1 using a four-shell spherical head model approximation. First the ERN was selected by highlighting a 20msec interval around its negative peak. A single dipole model located in the dorsal ACC accounted for most of the variance in the ERN [x=-14.7, y=0.1, z=45, R.V.=6.9%, Best=5.6%]. When selecting a 20 ms interval around the peak of this early positivity, the same ACC dipole accounted for most of the variance in this component [R.V=9.2%, Best=7.9%] (see Figure 4.6b). Keeping the location of the ERN source constant, free-fit source localisation was performed on the 20 ms interval around the peak of the error positivty. The resulting single dipole solution did not explain a significant amount of variance [change in R.V.<1%]. Finally, the ERN source was removed and a broader interval extending from 20ms prior to the peak of the ERN to 20ms after the peak of the early positivity was selected. Again, the free-fit algorithm indicated a generator in a very similar dorsal region of the ACC [x=-16.3, y=-13.6, z=50.6]. Although the ERN and early positivity share similar fronto-central scalp distributions, the early positivity does appear to be distributed more centrally (see Figure 4.6a). It is possible, therefore, that these two components are generated by areas of the dACC that are very close together and that the spatial resolution of source localisation was insufficient to distinguish their generators.

Keeping the location and orientation of the ERN/early positivity dipole constant, source localisation was then performed on the Pe between 300-500ms after response. A two-

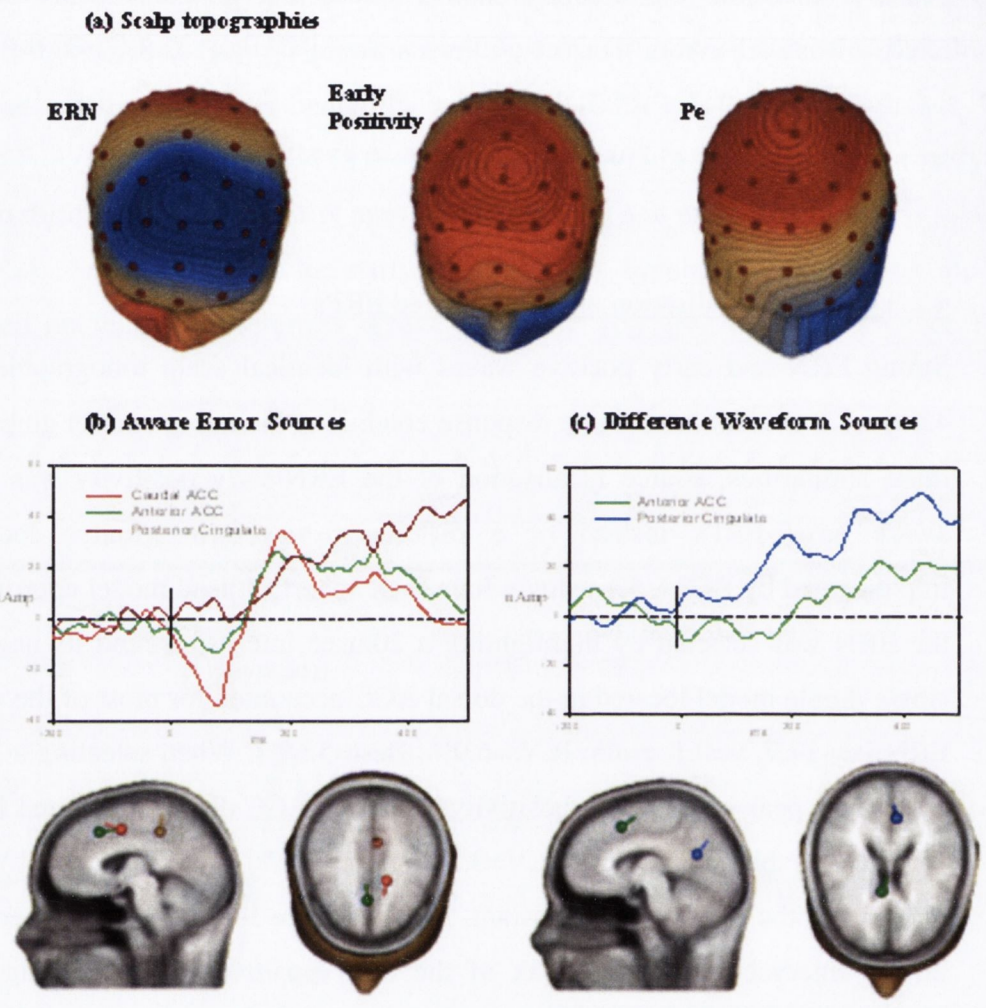


Figure 4.6 **Source localisation of error-related ERPs**. [a], Voltage scalp distribution maps for the three error-related ERP components. [b], Source time course and dipole locations for the aware error ERP waveform. The caudal ACC dipole (red) explains the ERN and the early positivity; the rostral ACC dipole (green) and the posterior cingulate/precuneus dipole (brown) accounts for the Pe. [c], source time course and dipole locations for the difference waveform in which the unaware error ERP was subtracted from the aware error ERP. The steps followed for [b] and [c] produced similar source models for the Pe.

source model was indicated for the Pe [R.V. 3.1%, Best 2.1%] with one dipole located in the ACC but more rostral to the ERN/early positivity dipole [x=2.9, y=20.5, z=42.5], and the other located in the vicinity of the posterior cingulate cortex and precuneus [x=-4.5, y=-37.6, z=39.9]. An additional source analysis of the Pe was conducted on a difference waveform, subtracting the unaware-error waveform from the aware-error waveform, thus isolating activity specifically associated with conscious error

perception. This analysis revealed a very similar two source Pe model with one dipole located in the same rostral ACC region [x=6.9, y=13.1, z=46.5] and another located around the posterior cingulate cortex and precuneus, though in a slightly more inferior location than that indicated by the first solution [x=-5, y=-59.1, z=20.7]. The dipole models and source waveforms for the aware error and difference ERPs are compared in Figure 4.6, b and c.

4.2.3.5 Tonic cortical arousal and error awareness

Finally, the relationship between tonic slow/fast frequency oscillations in the EEG power spectrum and errors of commission, error awareness and the amplitudes of the three error-related components (ERN; early positivity, Pe) on aware errors was investigated. Fifteen of the 19 participants made sufficient aware errors to be included in the correlation between the ERPs and slow/fast wave ratios but the remaining correlations included all 19 participants. A significant relationship was observed between tonic theta/beta ratios and the percentage of aware errors [$r=-0.478$, $p<0.05$] and the amplitude of the Pe [$r=-0.661$, $p<0.01$]. Alpha/beta ratios were also correlated with Pe amplitude [$r=-0.546$, $p<0.05$] and there was a close to significant relationship with percentage of aware errors [$r=-0.44$, $p=0.059$]. Thus, a low ratio of slow/fast wave activity in the EEG spectrum (indicating increased cortical arousal) was associated with better awareness of one's errors and a larger Pe amplitude. No significant correlations were observed between theta/beta or alpha/beta ratios and errors of commission or the amplitudes of the ERN or early positivity.

4.2.4 Discussion

In the present study, participants performed a Go/No-Go response task and were asked to indicate any commission errors by pressing a second 'awareness' button. Although this requirement imposes a dual-task element which could conceivably contaminate 'unaware' errors with dual-task failures, error awareness cannot be explicitly verified without requiring some form of secondary response. Moreover, the EDA data (Figure

4.4) indicates a marked absence of the cognitive-affective response that is frequently seen following conscious recognition of significant events such as action errors (O'Keeffe, Dockree, & Robertson, 2004) suggesting that the error awareness task (EAT) does provide an accurate measure of error awareness.

When participants made an error of commission, a response-locked waveform was generated which exhibited three clear components. The ERN was the earliest component and its amplitude was not modified by awareness of errors. Although the ERN was most pronounced for errors, an attenuated ERN-like component was also evident following correct Go responses. This phenomenon, noted previously and named the Correct Response Negativity (CRN), is thought to reflect levels of continuous performance monitoring during the task (Luu, Flaisch, & Tucker, 2000; Ridderinkhof, Nieuwenhuis, & Bashore, 2003; Vidal, Hasbrouc, Grapperonc, & Bonnet, 2000). Thus, while the processes reflected in the ERN are enhanced when one makes an error, they are also engaged in an ongoing manner throughout task performance. The latter probably facilitates the detection of subthreshold levels of conflict or uncertainty that do not necessarily result in errors but signal the need for fine-grained performance adjustments. The second component noted in the present study was a strong early positive deflection (early positivity) immediately following the ERN and maximal over fronto-central scalp sites. A similar component has been noted in two previous studies and because it was found to share the same cortical generator as the ERN (dACC) it has been interpreted as being part of the same performance monitoring process (Debener et al., 2006; Van Veen & Carter, 2002). Luu, Tucker and Makeig (2004) applied a theta band filter to individual ERN traces produced when participants performed a choice response task. Their results showed that the ERN was produced by transient phase-locking in the theta band and the early positivity reflected the reversal of this same oscillatory activity. Interestingly, in the present study the amplitude of the early positivity did not distinguish between any of the response types (correct go, aware error, unaware error). The strong ERN and early positive waveforms on correct trials may be explained by the introduction of two competing No-Go conditions in the EAT task (Repeat and Incongruent No-Gos) resulting in a higher degree of uncertainty on go trials and therefore increased engagement of monitoring processes.

In contrast, the classic Pe, which followed the early positivity and had a more posterior distribution, was only present when participants were aware of their errors. The marked absence of a Pe when participants were not aware of their errors provides clear confirmation of the findings of Nieuwenhuis et al (2001) and therefore these data demonstrate that modulation of the Pe by error awareness is not limited to the oculomotor modality but generalises to manual responses. It remains to be seen whether more divergent modalities, outside of the motor system (i.e. memory, language, visuospatial systems) also share the same awareness mechanism or whether different awareness processes are called upon for separate mental contents or objects. The presence of the ERN and early positivity, whether or not participants were aware that they had made an error, indicates that the brain possesses pre-conscious detection mechanisms while later processing stages indexed by the Pe only occur when an error has been consciously detected.

Although there is now a wealth of evidence implicating the ACC in error processing, there has been little investigation of the role that this region plays in error awareness. The present study conducted the first source analysis of electrophysiological activity that was specific to errors made with and without awareness. The results appear to confirm a role for the dACC in early aspects of error processing reflected in both the ERN and early positivity and in this respect confirm previous reports (Debener et al., 2006; Dehaene, 1994; Hermann, Rommler, Ehlis, Heidrich, & Fallgatter, 2004; Van Boxtel, Van der Molen, & Jennings, 2005; Van Veen & Carter, 2002). In common with two previous studies, it was found that the ERN and early positivity were generated by the same ACC region (Debener et al 2006; Van Veen and Carter 2002), thus supporting the contention that these components are part of the same monitoring process. However, the early positivity did have a more central scalp distribution than the ERN, suggesting that it may be generated by a slightly different region of the dACC. Further work will be necessary to confirm the functional significance of this component.

Source localisation of the Pe also indicated an ACC generator, but in a distinctly more rostral region. The location of this generator suggests that the Pe may reflect affective and motivational processes that occur when an error is consciously perceived (Taylor et al., 2006). The Pe model also indicated a second source around the posterior

cingulate/precuneus, a region which has been previously attributed a role in post-error processing (Badgaiyan & Posner, 1998; Menon, Adleman, White, Glover, & Reiss, 2001) and more broadly in self-awareness and consciousness (Cavanna & Trimble, 2006). The same regions were indicated when the unaware error waveform was subtracted from the aware error waveform, leaving only activity relating to conscious awareness.

There have been four previous attempts to localise the generator/s of the ERN and Pe simultaneously. Source analyses performed by Van Veen and Carter (2002) and by Van Boxtel et al (2005) also located an ACC generator for the Pe although in a more rostral region than in the present study. Hermann et al (2004) also found separate ACC sources for the ERN and Pe but the source of the Pe was found in a more caudal ACC region. A recent study by Taylor et al (2006) has noted significant inter-individual variations in the extent of affective and motivational responsiveness to making an error, and corresponding brain activations, which may explain in part why there has been a certain degree of inconsistency in localising the source of the Pe. It is also important to acknowledge that variation across studies may also arise from the limited spatial resolution of source localisation associated with the inverse problem. As a result, the model produced by source analysis is likely to be a simplification of the true cortical generators of these ERP components (Brazdil, Roman, Daniel, & Rektor, 2005). Nevertheless, the findings of the present study are consistent with those of Van Veen & Carter (2002) and of Van Boxtel et al (2005) such that the ERN and Pe do appear to be generated by distinct dorsal and rostral regions within the ACC.

The source model obtained in the present study does appear to be at odds, however, with the fMRI findings of Hester et al (2005) who found no additional ACC or posterior cingulate/precuneus activations when participants were aware of their errors. Such differences are not necessarily surprising given the ability of ERPs to separate minute portions of trial activity. The comparatively limited temporal resolution of fMRI may cause subtle effects, particular to finite portions of processing within a trial, to go undetected. For example, the subtle increases in regional ACC activity that are evident in source analysis might not be detected by fMRI if averaging across a longer epoch causes rostral and caudal activations to become convolved. Nevertheless, caution should

be exercised when interpreting the present source findings and further work will be required to explain the discrepancy between fMRI correlates of conscious error processing and repeated attempts to localise the generators of the Pe. These data highlight the potential pitfalls in making direct comparisons between different measures across studies.

It is important to note that the observed modulatory role of awareness does not necessarily imply causality in the generation of the Pe. These results are consistent with alternative accounts of the Pe as a reflection of compensatory adjustments (Hajcak, 2003) or subjective/emotional appraisal (Van Veen and Carter 2002) but suggest that these processes may be reliant on conscious awareness. The finding that the Pe was correlated with tonic EEG measures of arousal may be particularly illuminating in the context of recent models linking the Pe to the same underlying process as the P3; a component which can be elicited by any motivationally significant stimulus and which is thought to reflect the evaluation of that stimulus (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). The P3 and Pe share several obvious characteristics including centro-parietal scalp topography, positive polarity and relative peak latency (300-500ms relative to stimulus and response onset respectively). These similarities have led to speculation that the two components may be part of the same process whereby the Pe would reflect an additional P3-like evaluation of the incorrect response (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). This possibility raises a number of interesting and testable questions.

Recently, Nieuwenhuis, Aston-Jones and Cohen (2005) reviewed the accumulating evidence that the P3 indexes a phasic arousal response, originating in the locus coeruleus system, which is designed to increase the speed of information processing by enhancing neural responsivity in task-relevant cortical regions. Thus, when a motivationally significant stimulus has been detected, an arousal response is triggered which facilitates further processing of that stimulus. LC neuronal activity has been shown to precede changes in behavioural states and appears to play a modulatory role in maintaining the alert state, most likely via the action of the neurotransmitter noradrenaline. Experimental alterations of LC activity indicate a causal relationship

between LC activity and cortical arousal reflected in EEG power spectra (Swick, Pineda, & Foote, 1994). In addition, manipulations of tonic LC activity have been shown to affect the amplitude of the P3. Suppression of LC activity, associated with drowsiness and hypoarousal, precedes increases in slow wave (theta, alpha) EEG activity, decreases in fast wave (beta) activity and attenuation of the P3 (Swick et al 1994). When LC activity is enhanced, these effects are reversed. The present results show a significant relationship between tonic levels of cortical arousal (as measured by the ratio of slow to fast wave activity during task performance) and the amplitude of the Pe. Hence the present study offers new evidence that the Pe and P3 may share a key functional characteristic; modulation by cortical arousal. The absence of any such relationship with the ERN in the current study further distinguishes these two error-related ERP components.

Recent work has demonstrated that the ERN, and not the Pe, is sensitive to changes in dopaminergic neurotransmission relating to reinforcement learning (reviewed in Overbeek et al 2005). It is probably too simplistic to attribute the Pe to the action of a single neurotransmitter in light of neuroanatomical work demonstrating the manifold interactions of neurotransmitters such as dopamine, noradrenaline and serotonin. Cognitive abilities and motivational traits during error processing are most likely generated by complex interaction of environmental and experiential factors, along with a number of genetic influences (Benes, Taylor, & Cunningham, 2000). For example, given the potential role of limbic-serotonergic system innervation of rACC areas (Bush, Luu, & Posner, 2000), it might be predicted that serotonergic activity would also influence Pe-related processes. Nevertheless, evidence now exists that the ERN and Pe represent functionally distinct elements of error processing that are dependent on different brain regions and may have dissociable relationships with neurotransmitter systems. As a result, the ERN and Pe have the potential to provide informative biomarkers for error processing deficits associated with clinical conditions.

An obvious question which remains is how Pe-related processes actually influence task performance. With some exceptions, the majority of studies have failed to show any relationship between the Pe and post-error performance adjustments (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Fiehler, Ullsperger, & von Cramon, 2004;

Ullsperger & von Cramon, 2006). Most of these studies, however, have relied on a short-term measure of corrective behaviour, such as immediate reaction time slowing, that may not necessarily reflect a definite change in performance strategy. Research already cited (Fassbender et al., 2004; Garavan, Ross, Murphy, Roche, & Stein, 2002; MacDonald, Cohen, Stenger, & Carter, 2000) has demonstrated that error correction relies upon close coupling between the ACC and the DLPFC which increases the strength of the *tonic* task set. These findings tell us that there may be dissociable forms of post-error control. For example, Gehring and Knight (2000) showed that patients with prefrontal lesions exhibited normal post-error slowing but were less likely to correct their errors on the next target. In addition, there is evidence that post-error slowing can occur even when errors have not been consciously perceived (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Rabbitt, 2002). Therefore, it may be that success in this regard can only be truly evaluated by looking at longer-term performance measures such as change in RT variability or accuracy on the next target trial as well as RT slowing. One hypothesis is that while the ERN reflects short-term increases in cognitive control that are not reliant on awareness and result in remedial action on the current trial, the conscious error processes indexed by the Pe may engender broader adaptations of performance strategy that are likely to result in longer-term changes in behaviour. Experiments that use a wider variety of post-error correction measures (e.g. short term measures such as response force on error trials and post-error reaction time versus longer term measures such as performance on the next target or changes in RT variability) will be necessary to answer this question.

The present data also show a relationship between EEG measures of cortical arousal and individual rates of error awareness. Again this finding is consistent with evidence of LC functioning which indicates that low levels of tonic activity can lead to the absence of the normal phasic response to motivationally significant events (Nieuwenhuis, Aston-Jones, & Cohen, 2005). Reduced tonic activity in the LC, reflected in the tonic EEG measures, would lead to a dampening of the phasic response to error feedback, which as a result may be too weak for the error to reach conscious awareness. Thus, it is reasonable to speculate that when tonic levels of arousal fall below a certain threshold, the erroneous response will not trigger the phasic facilitation of cortical error processors, reflected in the Pe, that are necessary for awareness. Further investigation

using trial-by-trial couplings of error awareness, Pe amplitude and both tonic and phasic LC activity would be desirable to confirm this relationship.

The present study clearly demonstrates that a proper understanding of the error processing system requires differentiating error-related brain activations in terms of their relationship with conscious awareness. Verifying levels of error awareness may be particularly important in the context of studies that have used these ERP components to investigate self-monitoring deficits in clinical populations such as ADHD and schizophrenia (e.g. Mathalon et al., 2002; Wiersema, Van der Meere, & Roeyers, 2005). In the next experiment, the findings of the present study are used as a baseline from which the efficiency of error processing networks in ADHD can be assessed.

4.3 EXPERIMENT 5. Efficiency of error detection networks in adult ADHD

4.3.1 Introduction

Only two previous studies have investigated error-related ERPs in an ADHD sample (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Wiersema, Van der Meere, & Roeyers, 2005). In the study by Wiersema and colleagues (2005) 22 children with ADHD performed a Go/No-Go response inhibition task. Children with ADHD made more unsuccessful inhibitions and adjusted their response speed less after an error. No differences were seen in the amplitude of the ERN but the Pe was significantly attenuated in the ADHD group. The authors concluded that given the late onset of the Pe, a reduction in its amplitude probably indicates that ADHD error processing impairments occur at the level of conscious, subjective processing of the error event. This interpretation appears consistent with the findings of reduced post-error SCRs in Experiments 2 and 3 and data in Experiment 4 suggesting that the Pe has a generator in rACC. However, as demonstrated in Experiment 4, the Pe is only present when participants are aware of their errors. Therefore, attenuated Pe amplitudes in ADHD

populations could equally arise from a reduced rate of consciously detected errors. In addition, a recent study by Liotti and colleagues (2005) did find a significantly reduced ERN in a group of ten boys with ADHD, suggesting that further investigation is required to confirm the affected neural mechanisms.

In Experiment 4, the ACC was identified as the generator of the three error-related ERP components, ERN, early positivity and Pe. As discussed in section 4.1, numerous functional imaging studies have highlighted ACC abnormalities in participants with ADHD (Bush, Valera, & Seidman, 2005; Seidman et al., in press). In the present experiment, the high temporal resolution of ERPs will be employed to identify the precise components of error processing that are affected by ACC disruption in ADHD, using the findings of Experiment 4 as a normative baseline.

The use of a response inhibition paradigm to investigate error awareness also presents an opportunity to disentangle potentially independent neuropsychological deficits. Schachar et al's (2004) finding that post-error slowing and response inhibition deficits are uncorrelated challenges unitary models of ADHD that assign a core causal role to inhibitory deficits. In the present study, the possibility of independent neuropsychological deficits in ADHD will be investigated by the simultaneous measurement of response inhibition and error awareness during EAT performance.

4.3.2 Methods

4.3.2.1 Participants

Eighteen outpatient adults diagnosed with the combined subtype of ADHD (Mean age=23.71, SD=5.1; range 18-39; two female; one left-handed) and 21 controls matched for age (Mean age=21.98, SD=2.85; range 18-31; $F_{(1,37)}=1.73$, p=0.17), sex (one female) and handedness (one left-handed). Diagnostic procedures remained as in Experiment 3. The two groups had comparable IQ scores as measured by the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale III [ADHD group mean estimated full scale IQ=107.76, SD=10.46; Control group mean estimated full scale

IQ=113.3, SD=10.8; $F_{(1,37)}$=2.5, p=0.124] and were also matched for years of second and third level of education. All participants had normal or corrected-to-normal vision. Patients were withdrawn from any stimulant medication 36 hours prior to testing. All participants gave written informed consent and all procedures were approved by the ethical review boards of St Vincents Hospital, Fairview and the Trinity College School of Psychology.

4.3.2.3 EAT Procedure

The EAT task was run in the same manner as described in Experiment 4. Again participants were asked to time their responses to the offset of each stimulus in order to rule out the possibility that differences in awareness rates could be attributed to a speed/accuracy trade-off. All patient group participants completed 8 experimental blocks of the EAT but to maximise the number of errors for ERP averaging control participants completed between 8 and 14 blocks of the EAT (mean 9.8, SD=2.3).

4.3.2.4 EDA analysis

EDA measurements were acquired according to the same procedure described in Experiment 2 and analysed using Matlab 6.1 software. Peak-to-peak SCRs were measured within the latency window of 0.5 to 4.5 seconds post No-Go stimulus and averaged separately for correct withholds, aware errors and unaware errors. Due to technical difficulties EDA data was analysed for only 19 of the Control participants and 15 of the ADHD participants.

4.3.2.5 ERP and EEG analysis

For analysis and display purposes, data were average referenced and filtered with a 30 Hz low-pass filter. Response-locked data were segmented into epochs of 400msecs before to 500msecs after button press, and baseline-corrected relative to the interval -400 to -200 ms. All electrode channels were subjected to an artifact criterion of ±100μV. Accepted ERP trials were averaged separately for correct Go presses, Repeat and Stroop No-Go commission errors after which the participants indicated awareness (Aware Error) and commission errors after which the participants did not indicate

awareness (Unaware Error). The number of individual ERPs included for averaging were equated across error conditions (aware and unaware) and across participant groups by a process of random exclusion to ensure equivalent signal-to-noise ratios. Finally, the average EEG power spectrum was calculated over the first 8 blocks of EAT testing for each participant since this was the minimum number of blocks completed by all participants. Each participant's tonic theta, alpha and beta power (μV^2) was calculated as the power in the 4-7 Hz, 8-12 Hz and 13-29 Hz ranges respectively. Theta/Beta and Theta/Alpha ratios were subsequently calculated.

4.3.2.6 Source Analysis

The generators for the three error-related ERP components (ERN, early positivity and Pe) were localised following the same procedures outlined in Experiment 4.

4.3.2.7 Statistical Analyses

The behavioural, EDA and EEG measures reported were calculated over the first 8 blocks for all participants. Variability of reaction time (RT) was calculated as the average standard deviation of RT per block for each participant. To ensure a clean signal only those participants who made at least 20 aware and 20 unaware errors were included in the ERP analysis. This led to a reduced sample of 12 control (these are the same participants whose ERP data was analysed in Experiment 4) and 14 ADHD participants. The ERN was defined as the most negative peak at FCz occurring in a window from 50-120 msecs post-response. The early positive component, immediately following the ERN, was measured as the most positive peak at FCz between 140 and 240msecs post-response. Finally, the Pe was measured as the average positivity 300-500msec post-response at electrode CPz.

4.3.3 Results

4.3.3.1 Behavioural Performance

The means, standard deviations and significance levels for performance data are presented in Table 4.2. Both participant groups made more errors on Incongruent No-Gos [Control mean=37.5%, SD=16.7; ADHD mean=58.6%, sd=19.9] relative to Repeat No-Gos [Control mean=23.9%, sd=18.3; ADHD mean=46.7%, sd=21.5]. A repeated-measures ANOVA confirmed this difference with a significant main effect of No-Go type (repeat vs incongruent) [$F_{(1,37)}$=45.39, $p<0.001$] and no group by condition interaction [$F_{(1,37)}$=0.21, p=0.65]. A significant main effect of group [$F_{(1,37)}$=14.2, p=0.001] confirms the presence of a response inhibition deficit in adult ADHD with the patient group participants failing to withhold on a significantly greater percentage of all No-Go trials. ADHD participants also made significantly more errors of omission than controls and exhibited significantly greater GoRT variability. There were no group differences in mean GoRT on correct go trials, aware errors or unaware errors, confirming that both participant groups had successfully timed their responses to stimulus-offset.

Table 4.2 **EAT performance data for adult ADHD and control groups.**

	Adult ADHD Mean (SD)	**Control** Mean (SD)	$F_{(1,37)}$	p
Errors of commission	52.8% (19.6)	30.72% (16.6)	14.2	0.001***
Errors of omission	1.45% (1.23)	0.5 %(0.61)	9.1	0.005**
Error awareness	62.9% (19.8)	75.8% (14.7)	5.2	0.028*
Mean GoRT	607.8 (108.6)	625.4 (79.2)	0.34	0.5
Mean GoRT Variability	128.06 (47.69)	96.87 (31.6)	5.4	0.02*
Mean aware error RT	553.0 (104.5)	597.6 (110.8)	1.6	0.2
Mean unaware error RT	657.4 (107.5)	707.1 (175.9)	1.1	0.3

In addition to this apparent response inhibition deficit, adult ADHD participants were consciously aware of a significantly smaller percentage of their errors. In contrast to the distribution of commission errors, both participant groups had increased awareness rates

on Incongruent [control mean=82.1%, SD=13.6; ADHD mean=70.0%, SD=20.5] vs Repeat No-Gos [control mean=67.7%, SD=21.7; ADHD mean=54.6%, SD=23.7]. Again a repeated-measures ANOVA confirmed these differences with a significant main effect of No-Go type [$F_{(1,37)}$=20.1,p<0.001] and no Group by No-Go type interaction [$F_{(1,37)}$=0.025, p=0.86]. A significant main effect of group confirmed that the adult ADHD participants had impaired error awareness relative to controls [$F_{(1,37)}$=5.22, p=0.028].

All participants completed 8 blocks of EAT over a one and a half hour testing session. Although five minute breaks were allowed in between blocks to offset fatigue, the possibility that time-on-task effects could explain the group differences was investigated by plotting error awareness for each individual block. Figure 4.7 indicates no differential time-on-task effect on group but the ADHD group consistently exhibit reduced awareness on each block. To confirm this, a repeated-measures ANOVA was conducted with two levels of Group and eight levels of Block. This revealed a significant main effect of Block [$F_{(7,259)}$=2.25, p=0.03] but no Group by Block interaction [$F_{(7,259)}$=0.462, p=0.86]. Tests of within-subject effects indicated that the main effect of Block was driven by a significant linear trend [$F_{1,37}$=6.47, p=0.015]. Thus, error awareness declined with time-on-task but there were no group differences in this regard.

Separate bivariate correlations showed no relationship between awareness rates and commission errors in either group [controls, r=-0.178, p=0.44, ADHD, r=0.044, p=0.86] suggesting that conscious error awareness and response inhibition are likely independent processes. Further bivariate correlations within the ADHD group indicated that there was a significant relationship between awareness rates and errors of omission [r=-0.66, p=0.003] and GoRT variability [r=-0.615, p=0.007]. In the ADHD group, errors of commission were not correlated with either errors of omission [r=0.2, p=0.3] or GoRT variability [r=0.3, p=0.3]. Thus, an increased rate of conscious error detection was associated with a decreased number of omission errors and reduced GoRT variability. These relationships did not reach significance in the control group.

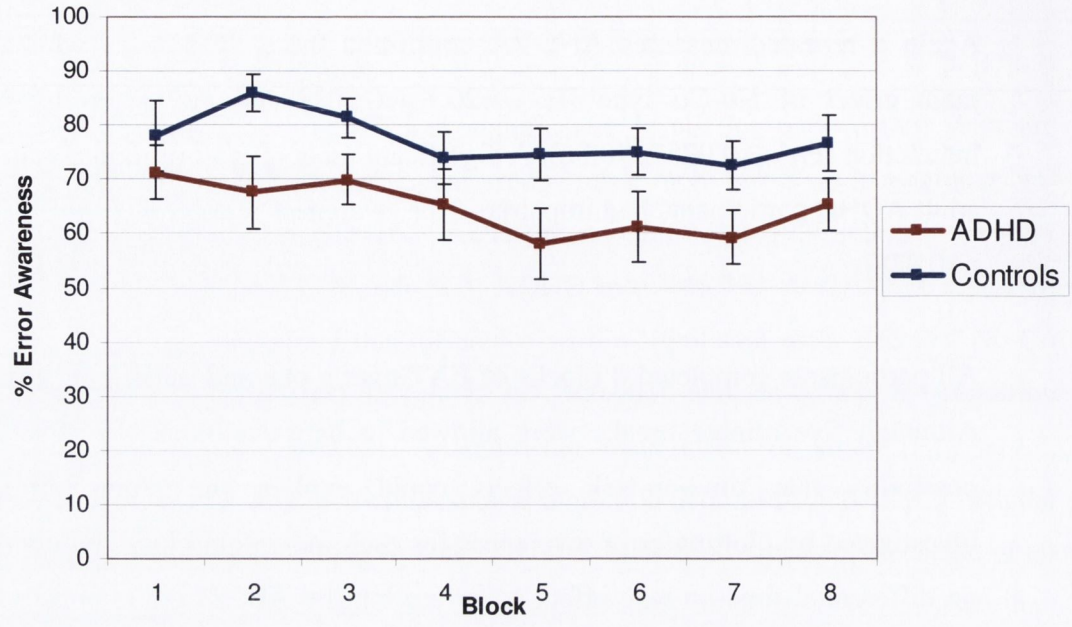


Figure 4.7 Time-on-task effects on error awareness. Although a slight decrease in awareness rates was observed over time there were no group differences in this trend. The ADHD group had reduced awareness across all 8 blocks.

4.3.3.2 Comparison of EDA

Mean SCR amplitudes for each No-Go response type are displayed in Figure 4.8. A repeated-measures ANOVA with three levels of SCR (post-withhold, post-aware error, post-unaware error) as the within-subjects factor revealed a main effect of SCR [$F_{(2,64)}$=6.59, p=0.005] and Group [$F_{(1,34)}$=5.9, p=0.022] but no SCR by Group interaction [$F_{(2,64)}$=0.915, p=0.414]. Bonferroni tests indicated that the Controls had significantly larger SCRs relative to participants with ADHD following correct withholds [p=0.013] and aware errors [p=0.036] but there were no significant differences for unaware errors [p=0.32].

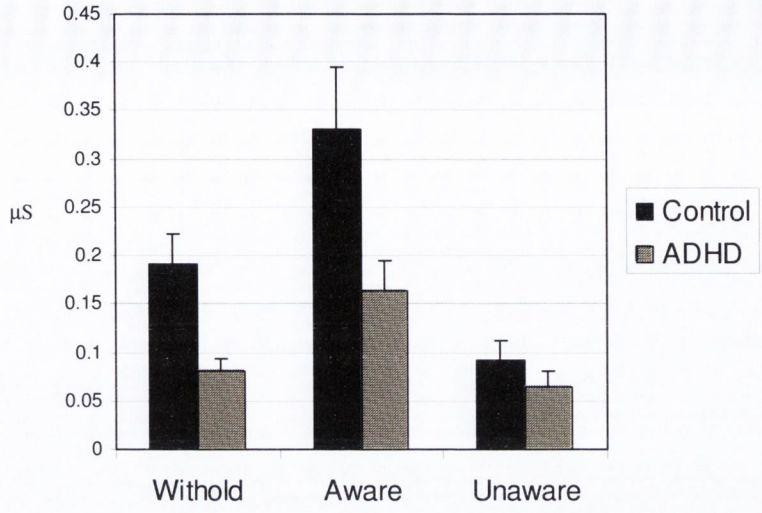


Figure 4.8 **Mean SCR as a function of EAT Response Type for ADHD and Control groups.** Both participant groups showed strong phasic arousal responses to making errors when they were aware that they had made an error but this response was virtually absent when an error was made without conscious awareness. The ADHD group exhibited significantly attenuated arousal responses to correct withholds and aware errors.

4.3.3.3 Comparison of Error-Related ERPs

Figure 4.9 displays ERPs elicited by aware and unaware errors at FCz and CPz for each group (for clarity, the correct Go press waveforms are not included). At FCz there was a significant main effect of Response Type on ERP ampliltude [$F_{(2,48)}$=4.48, p=0.017] but no main effect of Group [$F_{(1,25)}$=2.57, p=0.12] and no ERN amplitude by Group interaction [$F_{(2,48)}$=0.465, p=0.63]. The ERN amplitude was largest following an error but did not differ for aware and unaware errors [go vs aware p=0.01, go vs unaware p=0.017, aware vs unaware p=0.997].

A clear group difference was apparent in the latency of the early positivity (140-240msecs) after correct Go responses, aware errors and unaware errors. A repeated-measures ANOVA with three levels of Response Type (Go,aware,unaware) revealed no main effect of Condition [$F_{2,48}$=3.06, p=0.06] and no Group by Condition interaction [$F_{2,48}$=0.67, p=0.516]. A significant main effect of Group was found however [$F_{1,25}$=7.06, p=0.014]. To confirm that group differences were significant for all three response types post-hoc Bonferroni t-tests were conducted and these indicated that

control and ADHD participants differed in early positivity amplitude across all three conditions; Go [p=0.048], aware [p=0.014] and unaware [p=0.019]. These differences are illustrated in Figures 4.9 and 4.10.

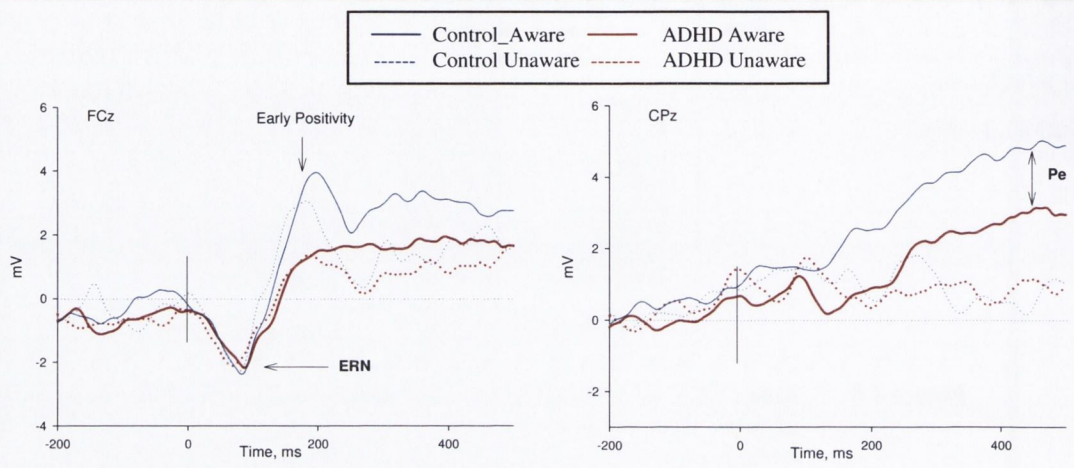


Figure 4.9 Comparison of error-related ERPs in Control and adult ADHD groups. Group grand-average ERP waveforms at FCz and CPz averaged separately for aware (solid lines) and unaware errors (dotted lines) and time-locked to button press (time-point 0). The ERN was maximal at FCz and did not discriminate between error types or Group. The early positive component, also evident at FCz, was not affected by Response Type but was attenuated in both conditions in the ADHD group. At CPz we see that the Pe (300-500ms) is modulated by awareness in both groups with the adult ADHD group exhibiting an attenuated Pe on aware errors.

In order to understand the functional significance of these Go-trial ERP components (see Figure 4.10), the relationship between the amplitudes of the CRN and of the early positivity on correct Go trials and mean commission errors, mean GoRT variability and awareness was investigated via partial correlations controlling for the effect of group (N=26). There was a close to significant correlation between CRN amplitude and mean commission errors [r=-0.41, p=0.07] but relationships with GoRT variability [r=0.07, p=0.4] and awareness [r=0.09, p=0.7] did not reach significance. The amplitude of the early positivity on correct Go trials was significantly correlated with mean commission errors [r=-0.57, p=0.008] but not with GoRT variability [r=0.03, p=0.9] or awareness [r=0.02, p=0.9].

Finally, for Pe amplitude, there was a significant main effect of Response Type [$F_{2,48}$=49.3, p=0.000] and a significant Group by Response Type interaction [$F_{2,48}$=6.15, p=0.007] but no main effect of Group [$F_{1,25}$=2.13, p=0.157]. Bonferroni t-tests indicated that, for both groups, the Pe amplitude was significantly larger for aware errors relative to both unaware errors [controls p=0.00, ADHD p=0.003] and correct go responses [controls p= 0.00, ADHD p=0.00]. Furthermore there was no difference in Pe amplitude between unaware errors and correct go responses in either group [controls p= 1, ADHD p=0.49]. Bonferroni t-tests indicated that Control group participants had significantly larger Pe amplitudes on aware errors than ADHD group participants [p=0.002] but there were no differences in amplitude at the same latency for correct go presses [p=0.89] or unaware errors [p=0.37]. Thus, the interaction appears to be driven by a group difference in Pe amplitude on aware errors.

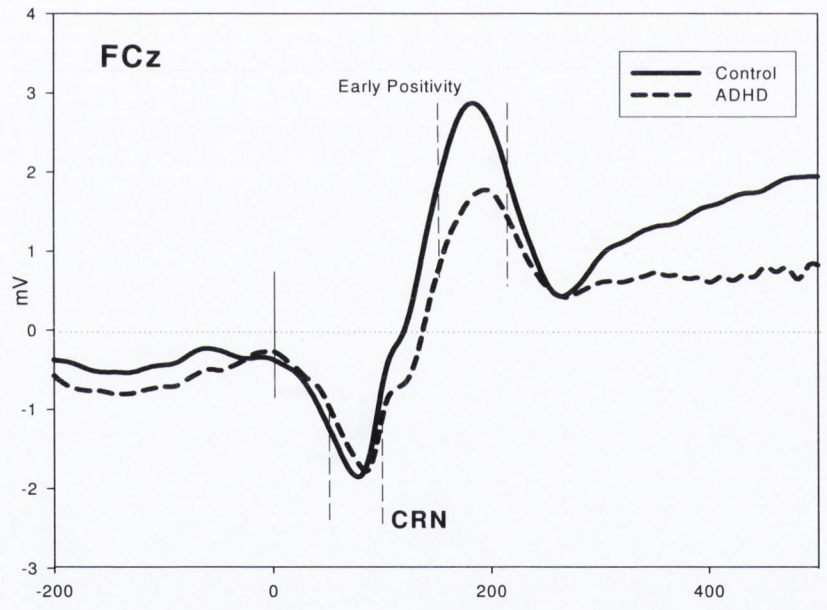


Figure 4.10 **Comparison of early positivity on correct Go trials for ADHD and Control groups.** Group grand-Average ERP waveforms at FCz averaged for correct go trial presses. The adult ADHD group had attenuated early positive component amplitudes across all conditions therefore this abnormality is not specific to errors.

4.3.3.4 Comparison of ERP generators

To investigate the functioning of key error processing regions in the ADHD group, free fit source localisation using BESA 5.1 was conducted, hence no restrictions were placed

on the possible source locations for the ADHD group. In Experiment 4, using the same control group data, source analysis indicated a dACC source for both the ERN and early positivity and separate rACC and posterior cingulate/precuneus sources for the Pe. In the present study, the same step-wise method of source analysis was followed to locate the generators of the three error-related ERPs for the adult ADHD group. The resulting model included a single generator that accounted for most of the variance in the ERN [residual variance (RV) 15.98%, best 13.4%] and early positivity [RV 11.78%, Best 10.9%] and was located in and around the dorsal ACC [x=-18.2, y=-1.7, z=41.5]. As can be seen in Figure 4.11, this source is very close to the one indicated for the ERN/early postivity of the Control group [x=-14.7, y=0.1, z=45]. The Pe of the ADHD group was also modelled using a single source, this time located around the posterior cingulate and precuneus [RV 6.5%, Best 4.2%, x=-3.5, y=-44.2, z=36.8]. Again a source in a very similar region was previously indicated for the control group Pe [x=-4.5, y=-37.6, z=39.9].

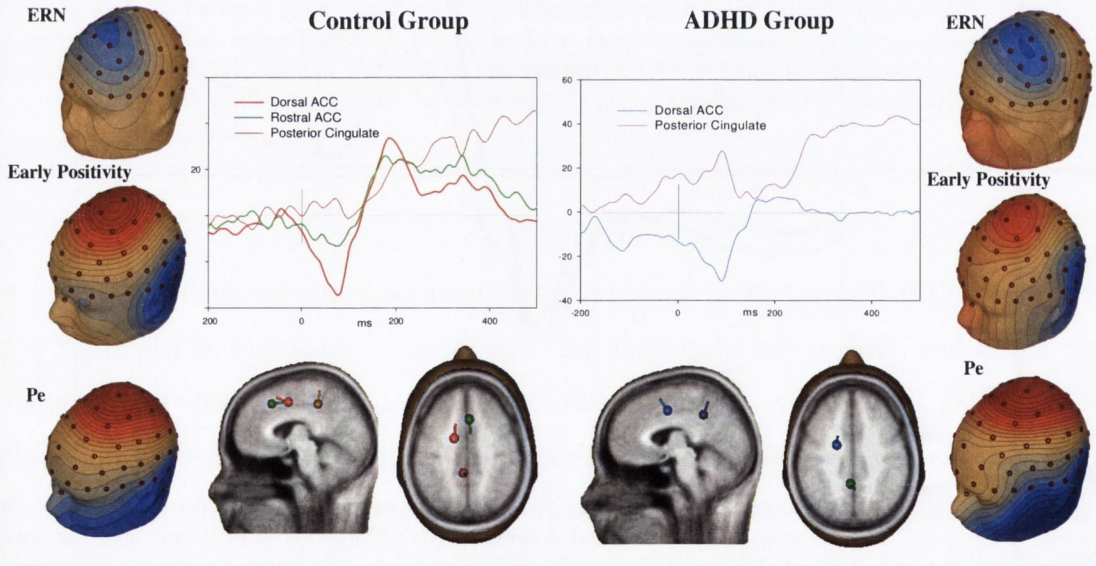


Figure 4.11 **Source localisation of ADHD group ERP components following aware errors.** The Control and ADHD groups showed very similar scalp topographies for all three components. Fitting of the activity around the peak of the ERN and error positivity resulted in a single dipole solution located near the dorsal ACC for both groups. Fitting of the activity around the peak of the Pe produced a two dipole solution for the Control group and a single dipole solution for the ADHD group. No rostral ACC generator was indicated for the ADHD group.

The most obvious difference between the two source models is that no rACC source was indicated for the Pe in the ADHD group. To confirm this finding, the coordinates of the control group's rACC source [x=2.9, y=20.5, z=42.5] were used to seed a dipole in the exact same location for the ADHD group. The two source models (which in the case of the ADHD group included the seeded dipole) were then applied to the ERPs of each participant and separate grand-average source waveforms were generated for the two groups. Figure 4.12 displays the source waveform for the seeded rostral ACC source of the ADHD group, the remaining waveforms are displayed in Figure 4.11). Statistical analysis of the posterior cingulate and rACC source waveforms of both groups (mean nAm 300-500ms post-response) indicated a significant group difference in rACC activity at the latency of the Pe [$F_{1,25}$=11.29, p=0.003], but no group differences at the same latency for the posterior cingulate source [$F_{1,25}$=0.05, p=0.8]. Thus, the attenuation of the Pe in the ADHD group appears to be accounted for by reduced activity in the rostral ACC.

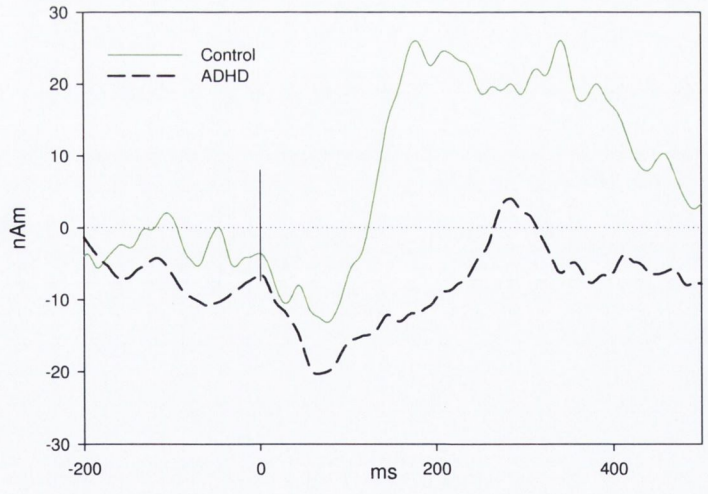


Figure 4.12 **Comparison of rostral ACC activity during conscious error processing for ADHD and Control groups**. The green line displays the activity associated with the aware error waveforms for the Control group that is accounted for by the rACC source. The dashed black line displays the same activity for the ADHD group aware error- ERP that is explained when a dipole is seeded in the same ACC region. The markedly reduced activity in the ADHD source waveform 300-500ms post- response is consistent with the initial source model indicating no rostral ACC contributions to the Pe.

4.3.3.5 Comparison of Tonic Cortical Arousal Levels

ADHD and Control groups were compared in terms of their average tonic theta, alpha and beta power as well as theta/beta and alpha/beta ratios measured over the entire testing session (means and standard deviations are presented in Table 4.3). These comparisons revealed significant group differences for beta activity, theta/beta ratio and alpha/beta ratio, indicating reduced cortical arousal during EAT performance amongst adults with ADHD. The correlation between tonic EEG measures and individual Pe amplitudes in the ADHD group did not reach significance.

Table 4.3. **Mean Tonic EEG band activity for Control and ADHD groups.** All values in μV^2 calculated over first 8 blocks of EAT testing.

	Adult ADHD Mean (SD)	**Control** Mean (SD)	$F_{(1,37)}$	p
Tonic Theta Power	2.37 (0.54)	2.16 (0.32)	2.06	0.16
Tonic Alpha Power	2.02 (0.58)	2.16 (0.55)	0.58	0.45
Tonic Beta Power	0.88 (0.22)	1.68 (0.49)	40.9	0.001***
Tonic Theta/Beta Ratio	2.76 (0.55)	1.36 (0.32)	90.9	0.001***
Tonic Alpha/Beta Ratio	2.35 (0.62)	1.32 (0.22)	46.1	0.001***

4.3.4 Discussion

The present experiment provides the first direct evidence that adults with ADHD are less aware of their action errors. The performance data show that the ADHD group participants made significantly more errors of commission on the EAT in keeping with previous work highlighting prominent response inhibition deficits in this disorder. Controlling for the total number of errors made by each participant, it was found that the ADHD group were aware of a significantly smaller portion of their errors than controls. Importantly these differences were not attributable to differential time-on-task

effects arising from fatigue or reduced compliance and group differences were stable across the whole testing session. This finding suggests that an important aspect of the neuropsychology of ADHD has hitherto been overlooked.

As in Experiment 4, the EDA data provides confirmation that the EAT is a valid measure of error awareness. As can be seen in Figure 4.7, aware errors elicited strong SCRs in both participant groups but this response was almost completely absent on unaware errors. The absence of group differences in EDA activity following unaware errors suggests that the ADHD participants were equally capable of pressing the 'awareness' button following an error of commission and that unaware errors were not attributable to dual-tasking failures. SCRs following aware errors and correct withholds were attenuated in the adult ADHD group indicating that the reduced post-error SCRs in Experiments 2 and 3 were not purely attributable to decreased error awareness but reflect differences in the processing of significant task events.

The absence of a correlation between error awareness and commission errors on the EAT suggests that response inhibition and error awareness deficits reflect independent neuropsychological processes in ADHD, consistent with an earlier finding by Schachar et al (2004). This finding argues against a fundamental causal role for disinhibitory processes in ADHD but instead points to separable neuropsychological deficits linked to distinct neural systems. Error awareness rates in the ADHD group were, however, correlated with GoRT variability and errors of omission. As discussed in Chapter 3 (Experiment 2), both errors of omission and response variability are thought to reflect the efficiency with which frontal systems can deploy attention (Bellgrove, Hester, & Garavan, 2004; Stuss, Murphy, Binns, & Alexander, 2003). This relationship suggests that both poor error awareness and poor response time variability may arise from dysfunction in the same higher-order executive control processes.

Poorer levels of GoRT variability and error awareness in the ADHD group were also accompanied by lowered cortical arousal as measured by tonic EEG measures. High activity within the beta band has been closely associated with wakefulness and the alert state (Aeschbach et al., 1999). Since no such differences were seen in Experiment 3 in the a group that contained many of the present participant group, it seems unlikely that

this finding reflects trait differences in basal arousal levels. Given the high levels of GoRT variability exhibited by the ADHD group, a more likely explanation for decreased beta activity may be that it reflects decreased top-down modulation of arousal during task performance. These differences may be quite subtle and, compared to Experiment 3, the longer task duration (EAT duration=5.6mins, SART duration=3.9mins) and greater number of blocks (8 blocks of EAT vs 4 blocks of SART) in the present study may have led to the emergence of these differences. Hester et al (2005) have speculated that an error will reach conscious perception if the participant is in an attentive state such that contextually appropriate stimulus-response or goal mappings are highly activated. The strength of goal representation may determine whether the ACC error-signal will trigger a cascade of events that result in awareness. In support of this view McAvinue et al (2005) and O'Keeffe et al (2004), demonstrated a link between sustained attention performance and error awareness rates when patients with traumatic brain injury performed the SART. Further to the correlation between GoRT variability in the present study, both participant groups exhibited slower RTs for unaware errors than for either aware errors or Go stimuli. As found in Experiment 1, errors of commission on tests of response inhibition are typically faster than the Mean RT, reflecting a more impulsive response style, whereas sustained attention errors are typically slower as the participant mindlessly persists with the default Go response. Hence, the different RTs for aware and unaware errors appear consistent with the view that unaware errors are precipitated by lapses of attention. It is possible therefore that ADHD-related deficits in error awareness and sustained attention arise from the same deficit in higher-order, frontally guided, executive control processes. Such an explanation must be considered speculative however since no direct measure of sustained attention was acquired in the present study.

The ERP results highlight abnormalities at specific stages of error processing. While the ADHD and control groups had comparable ERN amplitudes, significant differences were found at the latency of the early positivity. Interestingly, this abnormality was evident across all response conditions, including correct Go responses, suggesting that it is not specifically error-related. As noted previously, the Correct Response Negativity (CRN) is thought to reflect the ongoing action of a performance monitoring system which detects factors such as response uncertainty, conflict or changes in reward

probability (Ridderinkhof, Nieuwenhuis, & Bashore, 2003; Vidal, Hasbrouc, Grapperonc, & Bonnet, 2000). On error trials this signal is enhanced due to the greater presence of these factors, resulting in a larger ERN component, but it appears that both the CRN and ERN reflect activity in the same monitoring system. The present study, is the first to investigate the functional significance of the early positivity. Similar to the ERN/CRN the early positivity is evident on Go trials as well as error trials suggesting that it does not index error-specific processes. The source localisation results of Experiment 4 and the present study indicate that the ERN and early positivity are generated by the same dACC region which would suggest that the early positivity also arises from the same performance monitoring system. The dACC is well positioned to govern performance monitoring, given its strong reciprocal interconnections with DLPFC, parietal cortex and pre-motor and supplementary motor areas.

Interestingly, larger ERN and early positive components on Go trials were correlated with a decreased rate of inhibitory errors on the EAT. Previously, Ridderinkhof, Nieuwenhuis and Bashore (2003) reported that errors on a speeded reaction time task were foreshadowed by a diminished positive component on preceding Go trials suggesting disengagement of monitoring processes. The present results provides further evidence that the early positivity also reflects the engagement of dACC performance monitoring processes on a trial-by-trial basis and that task performance is related to the degree of this engagement. In the ADHD group, a normal CRN was followed by an attenuated early positivity indicating an abnormality in the time-course of the action monitoring system such that activity is more sustained in the control group. This deficit is not specific to error processing but may contribute to poorer response inhibition performance in the ADHD group. The finding of normal ERN/CRN amplitudes in the adult ADHD group indicates that the ACC abnormalities identified by fMRI and structural imaging studies affect neural processes involving the ACC in a specific manner rather than producing global deficits at all processing stages. Hence, this finding underlines the value of ERP methods in ADHD research.

In Experiment 4 it was demonstrated that the Pe is only present if participants are aware of their errors. Therefore, the finding that ADHD participants had attenuated Pe components on aware errors provides clear evidence that error-specific processing is

affected by this disorder. The source analysis results of the present study are striking in that they relate Pe dysfunction in the ADHD group to abnormalities in a specific brain region. While the Pe of the control group was modelled with a two source solution that included the rACC and a posterior generator in the region of the posterior cingulate and precuneus, only one, posterior generator was indicated for the ADHD group. By seeding a dipole in the rACC and applying the new model to the ERP waveform of each participant it was possible to demonstrate an absence of activity within this region following aware errors at the latency of the Pe. Furthermore, statistical analysis indicated that activity in the region of the posterior source was equivalent across groups indicating that Pe reductions in the ADHD group were directly attributable to the absence of activity in rACC. The fact that ADHD group participants were able to consciously perceive errors without rACC activity indicates that this region is not necessary for awareness in keeping with Hester et al's (2005) functional imaging data obtained with the same paradigm.

Since the ADHD group had attenuated Pe amplitudes, even when controlling for awareness, it follows that the Pe is probably not a direct, all-or-nothing reflection of awareness. The rACC has a well-established role in processes such as emotion and motivation (Bush, Luu, & Posner, 2000; Taylor et al., 2006) and a plausible characterisation of the Pe, in light of the present data, is that it partly reflects subjective processing of the error event that occurs only when a participant is aware that they have made an error. Attenuated SCRs following aware errors provide further evidence of a difference in the subjective processing of errors in the ADHD group. According to models of EDA, SCR amplitudes reflect heightened processing of stimuli with cognitive or affective significance to healthy individuals (Zahn, Grafman, & Tranel, 1999) and an fMRI study by Critchely and colleagues (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005) has demonstrated that the rACC modulates autonomic system activity following errors.

Hence, this experiment has produced convergent SCR and ERP evidence that ADHD and control participants differ in their subjective appraisal of erroneous behaviour. According to Damassio's (1991) 'somatic marker' hypothesis, the emotional response to an action's consequences guides decision-making. Patients with ACC lesions tend to

show a reduced responsiveness to emotional stimuli and continue to persist in behaviours that are obviously detrimental to their goals (e.g Tow & Whitty, 1953). It is possible therefore, that a difference in the processing of error significance accounts for the reductions in compensatory performance adjustment that have been seen in other studies of ADHD (Krusch et al., 1996; Schachar et al., 2004; Sergeant & van der Meere, 1988; Wiersema, Van der Meere, & Roeyers, 2005). It is not clear whether reduced processing of consciously perceived errors also influences whether or not a participant will be aware of future errors. In Experiments 2 and 3 it was found that SCR amplitudes predicted overall performance on the SART suggesting that responsiveness to errors predicted attentional failures on the task as a whole. As discussed above, an attentive state at the time of an error may be a prerequisite for awareness. It may be therefore, that reduced re-engagement of endogenous attention processes, due to an insensitivity to errors, may have contributed to an increased rate of unaware errors in the ADHD group.

To summarise, the present experiment has identified three potentially separate deficits in the adult ADHD group; poor response inhibition, reduced error awareness and abnormal subjective responsiveness to errors that reach awareness. Importantly, the independence of inhibition and error awareness deficits suggests that they do not arise from a single core behavioural inhibition deficit. Instead, the present data appears consistent with dual-pathway models of ADHD that assert the role of both cognitive and motivational processes (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). The ERP deficits exhibited by the adult ADHD group can be subdivided into those reflecting differences in ongoing performance monitoring and cognitive control (early positivity, dACC) and those reflecting subjective appraisal of errors (Pe, SCRs, rACC). Further work will be required to understand precisely how these deficits impact upon task performance and their relation to behavioural symptoms.

4.4 Chapter Summary

This chapter has identified key electrophysiological markers of error awareness in both normal healthy and ADHD populations. Of the three ERP components that are seen

following an erroneous response, only the Pe was found to be modulated by awareness. The Pe was also found to be modulated by cortical arousal suggesting that it may index a P3-like increase in processing of the error event. Adult ADHD participants exhibited a clear deficit in error awareness relative to a group of matched controls. Reduced awareness was accompanied by deficits in behavioural and EEG indices of top-down modulatory processes consistent with previous work suggesting that error awareness is dependent on efficient deployment of attention. Abnormalities were also observed in aspects of performance monitoring indexed by the early positivity and in conscious error processing as indexed by the Pe. In the ADHD group, Pe dysfunction was directly attributable to deactivation of the rACC, a region closely tied to processes such as motivation, affect and autonomic arousal. Reduced post-error SCRs were also consistent with the notion that error processing deficits in ADHD are attributable, in part, to differences in the subjective appraisal of errors. Thus, consistent with dual-pathway accounts of this disorder, ADHD group participants in the present study exhibited simultaneous cognitive and motivational deficits in executive function. Reduced responsiveness to errors may lead to decreased engagement of endogenous control processes leading to an increased likelihood of attentional drift and reduced error awareness.

Chapter 5. New Avenues for the Neuro-Remediation of ADHD: lessons from clinical neurosciences

5.1 Background

As reviewed in the introduction to this thesis, there is now a wealth of evidence to suggest that a significant proportion of those diagnosed with ADHD suffer from a prominent disturbance of executive functions linked to abnormalities in frontal-subcortical circuitry. ADHD is primarily a behavioural disorder but executive functions such as working memory, inhibition and attention are integral to cognitive development and may play a causal role in the emergence of behavioural symptoms in ADHD (Barkley, 1997; Castellanos & Tannock, 2002; Nigg, 2001; Sonuga-Barke, 2003). The second major aim of this thesis is to examine new methods by which these neuropsychological deficits might be remediated.

At present, there are just two well-established, 'evidence based', treatments for ADHD - psychostimulant medication and behaviour therapy. Psychostimulant treatments have proven efficacy in dealing with the behavioural features of ADHD and in fact also lead to significant improvements in cognitive performance (Overtoom et al., 2003; Schweitzer et al., 2004; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Tannock, Ickowicz, & Schachar, 1995) but these changes are achieved by increasing extracellular levels of dopamine without directly altering affected cortical networks in a lasting manner (Castellanos et al., 2002; Schweitzer et al., 2004). A number of highly effective behavioural interventions have also been developed for ADHD and have been reliably associated with reductions in primary and secondary behavioural symptoms (MTA Cooperative Group 2004; Pelham, Wheeler, & Chronis, 1998). Once again, however, improvements are achieved without addressing neuropsychological abnormalities. This may explain, in part, why despite long-term treatment both neuropsychological and neurological abnormalities associated with ADHD persist into adulthood in a significant proportion of cases (Castellanos et al., 2002; Seidman, 2006; Woods, Lovejoy, & Ball, 2002). As a result there is still a need for the development of new interventions that can directly target these deficits and bring about lasting improvements. Based on a growing understanding of the capacity of the human brain

for plasticity and self repair there is now strong evidence to suggest that neuropsychological functions can be improved by carefully structured cognitive training. This review examines the emerging evidence that experience dependent changes in brain structure and function can provide a new avenue for the remediation of the symptoms of ADHD.

5.2 Capitalising on Neural Plasticity

Research with both animal and human models has shown that normal associative learning and experience evoke important changes in cortical sensory and representational fields, synaptic connectivity, dendritic arborisation and axonal sprouting (Robertson & Murre, 1999). The brain modifies itself at the level of the synapse, constantly establishing and strengthening connections between neurons through the basic process of Hebbian learning (Hebb, 1949). Co-activation of neurons or networks of neurons strengthens the connections between them and improves their efficiency. With continued activation these simple changes at the synaptic level can eventually lead to experience-dependent dendritic/axonal sprouting and even neurogenesis (Cotman & Nieto-Sampedro, 1982; Gould, Beylin, Tanapat, Reeves, & Shors, 1999; Kempermann, Brandon, & al., 1998). Thus, different patterns of behaviour and experience will have tangible effects on neural circuitry.

Experience-dependent changes in synaptic connectivity can occur within a matter of minutes (Dinse, Recanzone, & Merzenich, 1993) but over much longer periods of time changes in large-scale neural networks and brain structures can be observed. For example, Munte, Altenmuller, & Jancke (2002) found increases in grey and white matter volume in several brain regions of highly experienced musicians while London taxi drivers show structural differences in the hippocampus associated with their increased use of spatial representations during navigation (Maguire et al., 2000). Hence the classical view that infancy and adolescence represent a critical period for brain development after which neural pathways become fixed and immutable has been replaced by an understanding that the human brain is always amenable to change.

Importantly it is thought that the same mechanism which underlies the processes of experience-dependent plasticity also promotes both spontaneous and guided recovery following brain injury (Robertson & Murre, 1999). That is, if a damaged brain area is regularly stimulated, be it directly or indirectly, there is the potential for lost functions to be restored by re-establishing damaged neural connections or by forming new compensatory connections (Seltzer, 1998). As with natural experience dependent-changes, functional recovery after brain injury can be seen in a matter of hours and further improvement can occur over weeks, months or even years (see Eslinger, 2002, for more discussion). The potential for massive cortical reorganisation is not always beneficial as in the case of phantom limb sensation in which deafferented cortical circuits are gradually activated by adjacent areas of the cortex leading to the sensation that the lost limb is actually present (Ramachandran, Stewart, & Rogers-Ramachandran, 1992). As a result, functional recovery will only occur in the context of particular patterns of behaviour. Our understanding of how areas of the brain collaborate to perform various functions is therefore crucial in allowing us to hypothesise novel methods for targeting damaged networks.

We are only beginning to identify mechanisms by which experience-dependent plasticity may be helped or hindered but increasingly, researchers and clinicians have been able to make use of the ideas emerging from the field of neuroscience to develop ingenious methods for improving or restoring brain function. In the field of cognitive rehabilitation researchers have combined what we know about neuroplasticity with knowledge of how sensory, motor and cognitive functions are achieved by the normal brain in order to develop highly structured training schedules designed to stimulate the affected brain area and thus re-establish or strengthen neural connections. For example Robertson, Hogg and McMillan (1998) showed that unilateral neglect was significantly reduced by simply encouraging patients to make voluntary contralesional hand movements. This approach was informed by previous work demonstrating the existence of multiple representations of space in the brain that interact to produce a coherent spatial reference system (Rizzolatti & Camarda, 1987). As a result of the interconnections between these representations when the somatosensory spatial map is activated by limb movement the damaged peripersonal spatial map will also be simultaneously activated. Through repeated indirect activation of the damaged circuit

neural connections are re-established and the lost function gradually returns. In this manner a detailed understanding of the neural processes underlying functional impairments resulting from brain injury has paved the way for the emergence of novel strategies for behaviourally inducing plastic reorganisation of lesioned brain systems in a variety of disorders including hemiparesis, phantom limb sensation and apraxia (Eslinger, 2002).

While it was initially thought that the principles of guided recovery applied only to low level sensory, perceptual and motor functions it has become apparent that high level cognitive functions such as attention, memory and language may also be amenable to experience dependent restitution. One common approach used to improve or rehabilitate high level cognitive impairments has been direct training of specific processes through intensive, highly structured practice. The rationale is simple: repeated use of particular cognitive processes during training stimulates plastic changes in the underlying neural circuitry leading to increased neural efficiency and a consequent increase in cognitive capacity. A key prediction arising from the process specific approach is that improvements in training should transfer to un-practiced tasks that require the same underlying cognitive function. The aim is to restore the lost function so that therapeutic gains can be applied to many facets of daily life. For example, limb activation training for unilateral neglect produces generalised improvements without the need for training to be repeated in every different context within which the patient operates (Robertson, McMillan, MacLeod, Edgeworth, & Brock, 2002). If process-specific training effects are not restricted to the training tasks themselves then improvements should be seen on un-trained tasks that recruit the targeted process. Processes such as attention and working memory are supportive processes that underpin a number of cognitive functions. These fundamental processes should therefore provide the foundation upon which broader improvements in cognitive functioning can be built and have been the most common targets of process-specific training.

Cognitive deficits in patients with brain abnormalities have also been successfully treated by implementing compensatory strategies. These strategies involve the use of environmental modifications, residual abilities and self-management strategies designed to bypass the defective cognitive processor (see Levine et al., 2000; see Manly,

Hawkins, Evans, Woldt, & Robertson, 2002; Wilson & Robertson, 1992). This represents another substantial and interesting area of research; however in this chapter the focus is exclusively on restorative strategies that are designed to capitalise on neural plasticity as a potential avenue for neuropsychological remediation in ADHD. First, a few illustrative examples of process-specific neuro-cognitive training in healthy and brain injured populations are reviewed.

5.3 Training of High-level Cognitive Functions

5.3.1 Cognitive Rehabilitation of Neuropsychological Deficits

At the outset it is important to note that proper evaluation of the efficacy of the process-specific approach in clinical groups has been hampered by great variation between studies in the intensity, duration and content of training schedules as well as important methodological weaknesses (see Park & Ingles, 2001 for more discussion). Nevertheless the possibility of restoring higher cognitive functions through neuro-cognitive training has gained support from a limited number of well-designed studies.

Attention problems are among the most common consequences of brain damage and perhaps as a result, the majority of direct training studies have targeted aspects of attention. Several studies targeting different components of attention have been conducted of which a number have shown positive effects of training with brain injured participants on both practiced and un-practiced psychometric measures (Ben-Yishay, Piasetsky, & Rattock, 1987; Neimann, Ruff, & Baser, 1990; Sohlberg & Mateer, 1987; Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000; Stablum, Umilta, Mogentale, Carlan, & Guerrinin, 2000).

Much of the published research on direct cognitive training of brain injured patients has focused on Attention Process Training (APT) developed by Sohlberg and Mateer (1987). APT consists of a set of tasks and drills of increasing difficulty in which participants respond to visual or auditory stimuli, designed to exercise the sustained, selective and orienting components of attention separately. The basic assumption here is

that discrete components of attention can be targeted through repeated individual stimulation. Tasks are organised around a hierarchical model of attention such that demands are placed on increasingly complex attentional processes. The training tasks range from simply pressing a buzzer when the number 3 is heard to complex semantic categorisation. Each task is performed until mastery has been accomplished. A major advantage of programs like APT is that therapy can be adapted to the individual according to their abilities from the outset.

Sohlberg and colleagues (2000) compared APT training with an educational and support method using a basic crossover design. Two randomly assigned groups were differentiated by the order in which they received APT (24 hours per week over 10 weeks) and a placebo intervention consisting of brain injury education and supportive listening (10 hours per week over 10 weeks). In this kind of design each participant serves as their own control while between-groups comparisons are made by analysing performance after each treatment block. Participants were two groups of 7 individuals with acquired brain injury between 18 and 60 years of age who were at least one year post-injury. Treatment effects were assessed on the basis of un-trained neuropsychological tests probing aspects of attention and working memory as well as questionnaires and structured interviews asking participants about their day-to-day functioning. The authors found that self-reported changes in attention and memory functioning, as well as improvement on neuropsychological tests of attention and executive functioning were greater after APT than after therapeutic support. Importantly, improvements on neuropsychological tasks that were not primarily attentional in nature (including Stroop, Trail Making Test, and memory for locations) indicated a generalisation of learning. It is thought that training a core, supportive process such as attention, has generalised effects by improving overall input to cognitive processing thus providing a more stable and effective substrate for other cognitive abilities (Sohlberg & Mateer, 2001).

A study by Sturm and colleagues (Sturm, Wilmes, Orgass, & Hartje, 1997) evaluated the effects of a more dynamic computerised attention training. In this study all participants completed two training periods of 14 one-hour sessions and were assessed on a standardised computerised battery of attention tests comprising separate tests for

sustained, selective, alternating and divided attention. The authors manipulated the order in which participants were exposed to high- and low-level attention training tasks. It was found that prior training on the most basic aspects of attention led to significant improvements on higher aspects whereas no such improvements were found in basic attention when the order was reversed. Additionally, the authors found improved performance on other computerised tests on which they had not been trained, but that were specific to the type of attention trained in each case. This finding is consistent with evidence indicating that there are separable neural circuits underlying different attentional processes (Posner & Peterson, 1990) and has implications for the structuring of rehabilitative training schedules. For example, in the study by Sohlberg and colleagues (2000) the authors noted that the vigilance level of individual patients influenced the extent of improvement with therapy on several tests of executive attention. Only patients who had poor vigilance levels showed improvement in basic attentional skills and only patients with higher vigilance levels showed improvement on more demanding attentional or working memory tasks. This finding suggests that patients with brain injury require training that is tailored to their specific needs. Other rehabilitation studies have tended to include patients with brain injuries of widely varying severity in the same treatment group which may explain, in part, why the results of direct-process training have been inconsistent thus far (Park & Ingles, 2001). Sohlberg and colleagues (2000) recommend that future studies should delineate specific patient profiles in order to determine who is likely to benefit from a particular training program.

Recent literature searches by Limond and Leeke (2005) and by Penkman (2004) yielded few studies that have examined the effectiveness of process-specific training techniques with paediatric groups (excluding ADHD) and these studies were hampered by serious methodological issues. One of the more methodologically sound studies was conducted by Butler and Copeland (2002) who examined the contribution of a broad cognitive rehabilitation program for 21 children and young adults (aged 6-22 years) with attention deficits arising from cancer treatment. A waiting list control group of 10 children and young adults was used but there was no control for non-specific treatment effects such as child-adult interaction. The multi-component programme included APT, a variety of meta-cognitive strategies from the educational field and cognitive-behavioural

interventions. Significant improvement for the experimental group was found on three attention/concentration measures (digit span, continuous performance task, sentence memory) but not on an arithmetic measure included to assess generalisation. Unfortunately it is not possible to determine how much of these benefits can be attributed to APT as opposed to the other components of the intervention as each participant was administered all three components. The absence of a non-specific effects control group also limits the drawing of any firm conclusions. Further empirical investigation using more rigorous experimental designs will be necessary before the efficacy of cognitive training for children with acquired brain injury can be properly evaluated.

The precise neural mechanisms underlying functional recovery with direct process training have yet to be firmly established but a small number of functional imaging studies have begun to shed some light on this issue. Sturm and colleagues (2004) conducted a PET and fMRI activation study of the effects of alertness training on patients with sustained attention deficits due to right-hemisphere vascular brain damage. The computerised training procedure required participants to drive a simulated vehicle as quickly as possible while looking out for occasional obstacles on the road. The difficulty level of the training was increased as each participant's performance improved. Before training none of the patients activated the right superior, middle or dorsolateral frontal cortex. After training however, patients who exhibited significant behavioural improvements in alertness showed reactivation of these right frontal regions. Importantly, patients who were included in a memory training control group did not show the same pattern of right hemisphere activations post-training. These results are indicative of a functional reorganisation of the sustained attention network.

In another study, Wexler, Anderson, Fullbright, & Gore (2000) used fMRI to study 8 patients with schizophrenia before and after 10-15 weeks of verbal working memory exercises. It had previously been shown that poor performance on these tasks by patients with schizophrenia was accompanied by lower than normal activation of the left inferior frontal cortex (Stevens, Goldman-Rakic, Gore, Fullbright, & Wexler, 1998). The degree of functional improvement on the memory tasks after training was significantly correlated with the percentage-change increase in left inferior frontal

activation (see Figure 5.1). These studies have provided some of the first evidence that improved cognitive performance in patients with neurological abnormalities is associated with a recovery of the affected neural networks.

Recent reviews by the Brain Injury Interdisciplinary Special Interest Group (BI-ISIG) of the American Congress of Rehabilitation Medicine (ACRM) concluded that there is sufficient empirical evidence to recommend direct-attention training for TBI or stroke during the post acute phase of recovery and rehabilitation (Cicerone et al., 2000; Cicerone et al., 2005). However, only a small number of training studies have included real- life measures of treatment efficacy and as a result a justified criticism of the direct-process approach to the remediation of higher cognitive function has been that there is little evidence of treatment effects beyond such proximal outcomes as training tasks or very similar untrained neuropsychological tasks (Park & Ingles, 2001; Wexler, in press). Transferring therapeutic gains to complex everyday life situations may be particularly difficult for patients with severe impairments. In fact as we will see, direct-process training may be best suited to individuals who maintain strong residual functions in the targeted area.

5.3.2 Neuro-Cognitive Training of Healthy Individuals

Studies with healthy participants have revealed that attention and working memory capacities may not necessarily be fixed, but may be amenable to significant change with experience. A recent review of the practice-effects literature by Kelly and Garavan (2005) highlights the major changes in neural activity that can occur with intensive practice on a cognitive task. With sufficient practice, the normal brain is capable of enhancing its efficiency by increasing or decreasing activations within a neural network, by improving connectivity between brain regions and even by reorganising the cortical areas that are employed during the execution of a cognitive skill. These processes may be particularly important with respect to ADHD as they suggest that the benefits of process-specific neuro-cognitive training may not necessarily be limited to the recovery of dramatic losses of function but could also be effective in the remediation of subtle cognitive impairments. A large number of fMRI and PET studies have explored the

neural correlates of practice on cognitive tasks. In addition, a small number of studies have examined the effects of extensive cognitive training on normal healthy individuals.

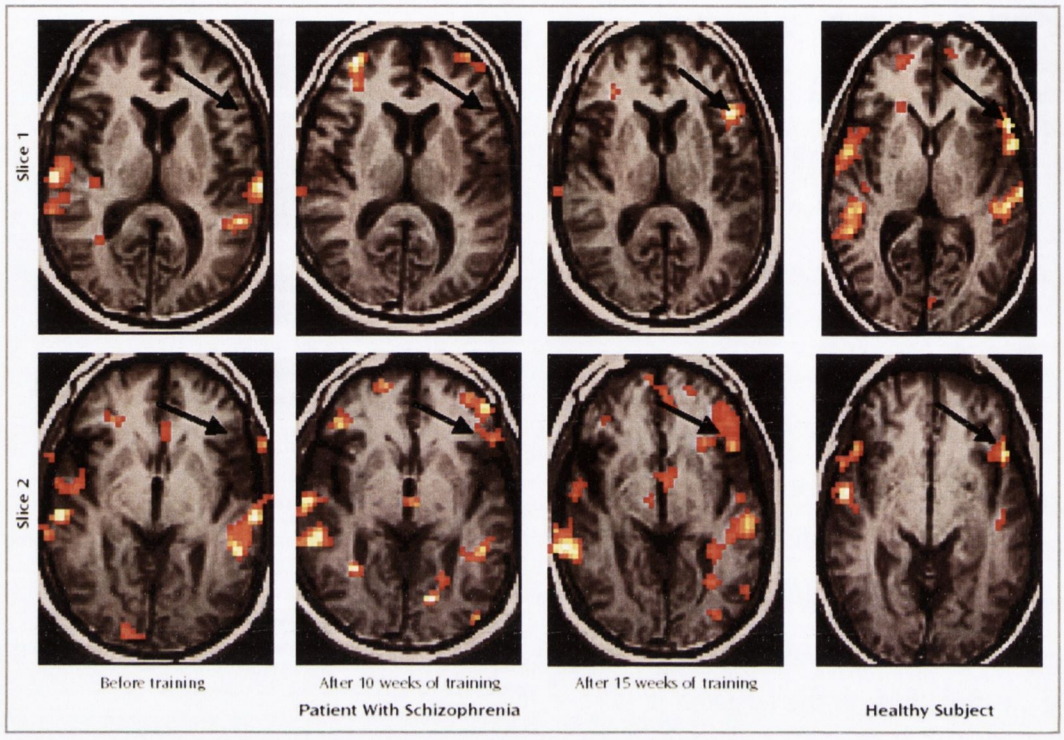


Figure 5.1 **fMRI images before and after memory training for a Patient With Schizophrenia and for a healthy participant.** The arrows in slice 1 point to the left inferior frontal gyrus, where activation is clearly evident in the patient after 15 weeks of training and in the healthy participant. The arrows in slice 2 point to the left lateral orbital gyrus, where activation is again clearly present in the healthy participant and in the patient after 15 weeks of training. From Wexler, Anderson, Fullbright, & Gore (2000), *American Journal of Psychiatry.*

Olesen, Westerberg and Klingberg (2004) conducted an fMRI study on the effects of extended working memory practice in healthy adults. Participants practiced 90 trials per day for 5 weeks on three visuo-spatial working memory tasks and were compared with an un-trained control group. Training improved performance on un-trained measures of working memory and was associated with significantly increased scores on measures of inhibition (Stroop) and general fluid intelligence (Raven's Advanced Progressive Matrices). Participants were scanned while performing a working memory task. After training there were clear increases in brain activity in the middle frontal gyrus and inferior parietal cortices. Previous work has shown that there is a positive correlation

between levels of activity in these regions and working memory capacity (Klingberg, Forssberg, & Westerberg, 2002a; Rypma & D'Esposito, 2000). Thus, significant and generalised improvements in cognitive capacity are possible even in the undamaged brain.

Research with healthy adults tells us that changes in brain activation with cognitive training follow a complex time-course. Another imaging study of working memory training has reported that training-related activation changes in fronto-parietal working memory regions are best described by an inverse U-shaped quadratic function with initial activation increases at the time of improved performance giving way to decreases after consolidation of performance gains (see Figure 5.2, Hempel et al., 2004). Kelly and Garavan (2005) note the common process of 'scaffolding' in which activity in attention and control areas (prefrontal cortex, anterior cingulate and posterior parietal cortex) gradually decreases after a task has been well rehearsed. Deactivation of frontal regions is associated with attainment of automatic or asymptotic performance and a decreased demand on control or attentional processes. Ensuring that task difficulty is increased as performance improves (not done in the study by Hempel et al) appears to be crucial to maintaining demands on high-level executive processes.

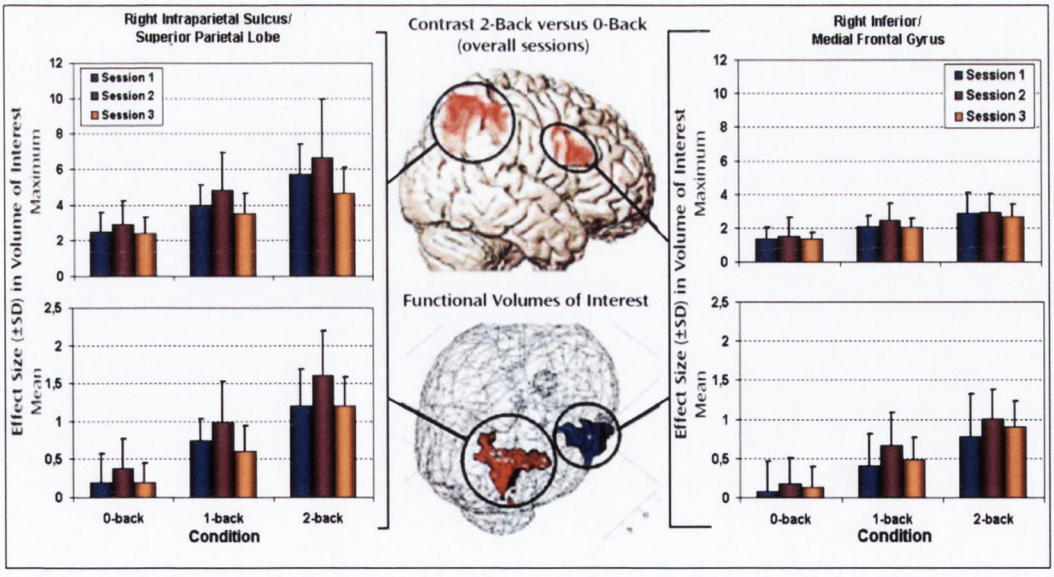


Figure 5.2 Training Related Cerebral Activation Changes in Nine Normal Participants During Performance of a Working Memory Task. Maximum and mean effect sizes of the volumes of interest (intraparietal sulcus/superios parietal lobe, inferior frontal gyrus/medial frontal gyrus) during the three different task conditions at baseline and after 2 and 4 weeks (sessions 1-3, respectively) of training. From Hempel et al (2004). *American Journal of Psychiatry.*

Few studies have examined cognitive training in healthy children. One recent and well designed study by Rueda and colleagues (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005) examined the influence of a computerised training program for executive attention that was specifically adapted for children. Each exercise was divided into a number of levels and gains to the next level were made upon achieving a criterion level of performance. Each training task exercised a particular executive process such as anticipation, conflict resolution, inhibitory control or stimulus discrimination and involved cartoon characters and concepts that were familiar to children. Training was administered over five sessions, within a two to three week period, to two groups of normally-developing children who differed in age (four and six years). In order to control for the number of sessions involving child-adult interaction, a third group of children watched popular videos during which at varying intervals the video was paused and the image of a fish appeared on screen: the control children had to press a button to restart the video. Training resulted in reduced difficulty in resolving conflict and exerting executive control. Two further effects of this brief training were particularly interesting. First, electrophysiological data suggested that in the four year old group, training produced an ERP pattern for conflict resolution similar to untrained 6 year olds. For 6-year olds the effect of training was to produce a more adult-like pattern of activity. Second, the authors also found evidence of generalisation of training benefits to measures of intelligence and reasoning ability. These data indicate that process-specific training at an early age may accelerate the development of attentional networks.

In sum, the strongest available evidence that experience dependent plasticity can be exploited to improve cognitive function in both brain injured and healthy populations has been outlined. Research with healthy participants indicates that gains in cognitive ability can be made with appropriately targeted training.

5.4 Is ADHD a Candidate for Neuro-Cognitive Remediation?

As reviewed in chapter 1, ADHD is associated with a range of neuropsychological impairments. In particular, converging evidence points to prominent deficits in executive functions such as response inhibition (Nigg, 2001; Oosterlaan, Logan, & Sergeant, 1998), working memory (Martinussen, Hayden, Hogg-Johnson, & Tannock,

2005), sustained attention (Manly et al., 2001; Shallice et al., 2002) and temporal processing (Barkley, Murphy, & Bush, 2001; Mullins, Bellgrove, Gill, & Robertson, 2005). These deficits have been reliably demonstrated in children but a number of recent reviews show similar problems in adults with ADHD (Woods, Lovejoy, & Ball, 2002).

Executive functions such as working memory, sustained attention, response inhibition and temporal processing are all dependent on communication between sub-cortical and frontal regions and imaging studies have consistently identified dysregulation of predominantly right hemispheric fronto-striatal circuitry in ADHD (reviewed by Bush, Valera, & Seidman, 2005). Thus, there are clear commonalities between the neural structures underpinning executive functions and the structural and functional brain changes in ADHD. Consequently, several of the most prominent theoretical models of ADHD have proposed that neuropsychological impairments play a causal role in the development of this behavioural syndrome (Barkley, 1997; Castellanos & Tannock, 2002; Nigg, 2001; Sonuga-Barke, 2000). Research has shown that non-affected relatives of patients with ADHD also show performance deficits on neuropsychological measures and that risk-genes for ADHD may also impair neuropsychological function in ADHD (e.g. Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005). These findings provide further evidence that neuropsychological deficits in ADHD are the result of genetically-linked neural impairment. It can be hypothesised therefore, that remediation of neuropsychological deficits in ADHD would have two potential benefits: improvement of cognitive function and an associated reduction in behavioural symptoms.

As mentioned in Chapter 1 a large scale imaging study conducted by Castellanos and colleagues (2002) found that brain developmental trajectories were not affected by ADHD. Thus, although normal maturational processes are taking place, an abnormality at some early stage of development appears to place children with ADHD at a persistent disadvantage. This presents the possibility that intensive neuro-cognitive training could limit the effects of this developmental deviation and lead to lasting improvements in cognitive and behavioural function in children with ADHD. Process-specific training of key neuropsychological impairments may provide one avenue for non-pharmacological remediation in ADHD.

5.5 Neuro-Cognitive Remediation Studies of ADHD

Only a small number of studies have attempted process-specific remediation of neuropsychological function in ADHD. One of the first steps in this direction was taken by Semrud-Clikeman and colleagues (1999) who examined the efficacy of the APT program in treating attention deficits in children with ADHD. A treatment group of 21 children with ADHD was compared to a waiting list ADHD group and a separate control group without attentional difficulties. At post-test, the intervention group showed normalised performance on un-trained visual cancellation and auditory attention tasks relative to the non-ADHD participants. In addition qualitative interviews with teachers indicated increases in attentive on-task behaviour in class. However, the potential influence of non-specific factors such as increased positive feedback or expectancy bias, could not be ruled out in this study as only a waiting list control group was included. Furthermore, APT was administered in combination with instruction in problem-solving and therefore it is not clear how much of the observed improvements can be attributed to increases in attentional capacity *per se*.

In order to overcome these limitations Kerns, Eso and Thomson (1999) conducted a further examination of APT in a group of fourteen children (average age 9 years) diagnosed with ADHD. In this study, the treatment group was trained on a new version of APT, named 'Pay Attention', that was specifically designed for use with children. Children were seen after school twice a week for eight weeks. A carefully matched control group engaged in a variety of computer-based games and puzzles in order to rule out the influence of one-on-one contact with the therapist and other non-specific factors. Pre-post measures included seven psychometric tests of attention and executive control, a measure of academic performance (age-appropriate arithmetic problems) and home and school versions of an ADHD symptom questionnaire. Significant treatment effects were found for the Mazes sub-test of the WISC-III, the Day-Night Stroop Task, the Attentional Capacity Test (ACTION) and sections of the Underlining Test (a measure of sustained visual attention). Some generalisation of training benefits was indicated by improved scores on the academic task and a marginally significant improvement in inattentive and impulsive behaviour noted by the teachers. Another interesting detail of this study was that five children in each group were receiving

medication at the time of training indicating that medication does not necessarily preclude neuro-cognitive training.

A rather different approach to neuro-cognitive remediation was taken by Shaffer and colleagues (Shaffer et al., 2000) who developed Interactive Metronome® Training. The severity of inattentive symptoms in boys with ADHD is a significant predictor of motor coordination difficulties (Piek, Pischer, & Hay, 1999) and fronto-striatal regions are associated with both high-order motor control and ADHD (Rubia et al., 1999). This evidence fuelled the hypothesis that training aspects of motor regulation such as planning, sequencing, timing and rhythmicity may play a concomitant role in improving the capacity to attend. During the training procedure children perform a series of prescribed movements in time with a steady metronome reference-beat sound heard in head-phones. Movements are registered by special sensors placed on the hands, the thighs and on the floor. The Interactive Metronome (IM) analyses the temporal accuracy of each movement and provides feedback to the participant in the form of spatially and tonally-changing guide sounds. Successful performance of this kind of training requires the participant to focus without interruption for extended periods of time. A matched random assignment process, based on medication dosage, age and baseline attentional ability was used to assign 56 boys, aged between 6 and 12 and diagnosed with ADHD to three groups: an IM group, a video-game practice placebo group and a waiting-list control group. Each participant underwent 15 one hour IM treatment sessions per day over a 3 to 5 week period. Fifty-eight pre-test factors assessing attention, clinical functioning and academic skills were used to examine treatment effects. Test-retest analyses revealed that the IM group had a significantly stronger improvement pattern than the video-game group, showing improvements over 53 test scores compared with 40 in the video-game group and 23 in the waiting-list group. The IM group made significantly larger gains in areas of attention, motor control, language processing, reading and aggressive behaviour than either the video-game or waiting-list groups. The comparatively strong improvements in the video-game group underlines the need for the inclusion of appropriate placebo conditions in any examination of ADHD interventions.

Working memory deficits in ADHD have also been targeted for process-specific training. As discussed earlier, Olesen and colleagues (2004) found that plastic changes in the neural networks underlying working memory could be encouraged by systematic training in normal, non-impaired adults. The commonalities between the cortical areas involved in working memory and those implicated in ADHD provided a neuroanatomical rationale for a series of studies conducted by Klingberg and colleagues. Based on a training regime previously used to induce cortical plasticity in sensory and motor cortices, Klingberg, Forssberg and Westerberg (2002b) developed a computerised working memory training program in which task difficulty was closely matched to the individual's performance on a trial-by-trial basis in order to maximise the training effect. Four subtests were presented during each training session: a visuo-spatial working memory task, backwards digit span, a letter-span task and a choice reaction time task. Task difficulty was adjusted by changing the number of stimuli to be remembered. Participants in the treatment group (7 children, mean age 11.0) were trained at a children's hospital for at least 20 minutes per day, 4-6 days a week, for at least 5 weeks. Participants in the control condition (7 children, mean age 11.4) were trained on a placebo program that included the same working memory tasks but without adjustment of difficulty level and for less than 10 minutes per day. The study operated a double-blind design.

Comparison of pre- and post-intervention measures indicated a significant treatment effect for the practiced visuo-spatial working memory task, an un-practiced and non-computerised visuo-spatial working memory task, a measure of impulsivity (Stroop accuracy), a measure of reasoning ability (Raven's Progressive Matrices, RPM) and for the number of head movements made during testing. Correlational analyses revealed that improvement on RPM was correlated with improvement on the trained working memory task. The latter relationship is consistent with the view that working memory facilitates higher-order processes such as reasoning ability by allowing information to be stored and manipulated on-line. The reduction in head movement was highly correlated with improvements on both the trained working memory task and RPM. As the authors note, the gradual improvement in working memory over a number of weeks is reminiscent of the slow re-acquisition of a perceptual or motor skill and the fact that each of the pre/post tests is dependent on prefrontal cortex may indicate that training did

induce change at the neural level. The clear evidence of generalisation to non-working memory tasks (Stroop, RPM) is particularly encouraging and provides good evidence that training a fundamental process such as working memory can lead to a general improvement in cognitive capacity.

Building upon these strong findings Klingberg and colleagues (2005) conducted one of the most thorough trials of a cognitive training program designed for children. Fifty-three un-medicated children with ADHD, aged 7 to 12 (mean 9.8) were recruited from four clinical sites and randomly assigned to a treatment or comparison group. The authors employed the same double-blind design as in their initial study however this time participants in the control condition (working memory training without adjustment of difficulty) were trained for the same duration as the intervention group. In addition, symptom ratings of ADHD were included in the outcome measures and there was a 3-month follow up to assess persistence of treatment effects. The training materials were saved on compact disc, allowing the children to complete the intervention independently either at home or at school. After training, participants in the treatment group significantly outperformed the comparison group on each of the executive outcome measures (Span Board, Stroop, Digit-Span, RPM) and these differences remained at follow up 3 months later. Importantly, the effect size for improvement on the untrained working memory task (0.93 on Span Board) represented a strong clinical effect and compares very favourably to those previously reported for stimulant medication. A comparison with previous studies of working memory and response inhibition indicated that, post-training, the spatial working memory and Stroop performance of the children was 0.3 standard deviations or less below normative levels. Most importantly, there was also a strong and specific clinical effect on parent ratings of ADHD symptoms using both DSM-IV criteria and the Conners' Parent Rating Scale. Effect sizes of 1.21 for parent-rated attention and 0.47 for parent-rated hyperactivity/impulsivity are particularly impressive given that all participants were un-medicated. Again, these differences were still evident at follow-up. These results represent some of the strongest evidence to-date that direct neuro-cognitive training in ADHD leads to generalised improvements in both the short and longer-term that extend to un-practiced cognitive tasks and aspects of every-day behaviour.

To summarise, there is good initial evidence that process-specific neuro-cognitive training can be an effective treatment for ADHD (see Table 5.1). Each of the studies reviewed above has implemented sound methodology and produced encouraging levels of improvement especially considering the comparatively limited success with paediatric and adult brain-injured patients. Evidence has been cited from research with brain injured and healthy groups that training related improvements in cognitive performance are accompanied by plastic changes in underlying neural networks although the neural consequences of cognitive training in ADHD have yet to be explored. Nevertheless it is possible to draw three tentative conclusions from the studies conducted so far. First, direct process-specific training of attention and working memory leads to significant improvements in the targeted cognitive function on trained and un-trained tasks even after controlling for non-specific effects. Second, these improvements appear to generalise to other cognitive tasks that bear little relation to the practiced tasks but depend in some way on the same fundamental process. Third, cognitive training of ADHD leads to reductions in behavioural symptoms supporting the notion of a causal role for neuropsychological deficits in ADHD.

As such these first studies have yielded encouraging results and will surely stimulate many more studies to explore this approach. The clinical division of the American Psychological Association has proposed operational criteria for a treatment to be considered "well-established": two or more studies must show that the treatment is superior to medication, placebo, or an alternative treatment or that it is equivalent to an already established treatment (Hoagwood, Burns, Kiser, Ringeisen, & Schoenwald, 2001). A series of case studies showing equivalence or superiority is also deemed acceptable. Therefore more studies of the kind carried out by Klingberg and colleagues (2005) will be required before cognitive training of ADHD can be established as an evidence-based treatment. Developing an effective non-pharmacological intervention for ADHD that can be carried out easily at home or at school with a minimum of participation from the clinician is an exciting prospect that may be particularly desirable to the patient for its convenience and cost-effectiveness. In Chapter 6, some new methods for the remediation of ADHD attention deficits are examined.

Table 5.1 Summary of neuro-cognitive training studies conducted with ADHD populations

Study	N[a]	Treatment	Control Procedure	Neuropsychological Generalisation	Everyday life improvement
Semrud-Clikeman et al (1999)	21(12)	Attention/Executive Control Practice	Waiting List	Not Measured	Not Measured
Kerns et al (1999)	7 (7)	Attention/Executive Control Practice	Video game practice	Measure of academic performance	Behavioural Reports (Teacher)
Shaffer et al (2000)	19 (18) (18)	Attention/motor coordination training	Video game practice + waiting list control	Language processing	Reading and aggressive behaviour
Klingberg et al (2002)	7 (7)	Working Memory Practice	Working memory practice without adjustment of difficulty	Stroop, Raven's Matrices, Reduced Head Movement	Not Measured
Klingberg et al (2005)	27(26)	Working Memory Practice	Working memory practice without adjustment of difficulty	Stroop, Raven's Matrices	Behavioural Reports (Parent & Teacher)

[a] Number of participants in treatment group (control group)

5.6 Future Considerations for neuro-remediation studies of ADHD

Finally it is important to highlight a number of issues that should be considered in future studies of neuro-cognitive remediation in ADHD (see also Box 5.1).

5.6.1 Elucidation of neural processes underlying cognitive training

As this review has demonstrated, there is evidence from research with brain-injured and healthy participants that improvements following process-specific training are accompanied by plastic changes in underlying neural networks. However, individuals with ADHD appear to use alternative strategies and more diffuse networks of brain regions while performing neuropsychological tasks (e.g. Durston, 2003; Schweitzer et al., 2000; Tamm, Menon, Ringel, & Reiss, 2004). As a result, it is not clear whether cognitive training consolidates compensatory activation patterns or causes a

reorganisation of the process-related network. Imaging the neural correlates of training in ADHD will be essential for a better specification of treatment effects.

5.6.2 Duration, intensity and maintenance

The literature on cognitive training is characterised by huge variation in the duration and intensity of the programs that are employed. For example, in just five studies of ADHD treatment intensity varied from 60 minutes twice a week (Semrud-Clikeman et al 1999) to 40 minutes per day 4-6 days a week (Klingberg et al 2005) and treatment duration varied from 3 weeks (Shaffer et al 2000) to 8 weeks (Kerns et al 1999). An important question that will need to be answered with respect to training of cognition in ADHD is how much and for how long? At what point does intensive cognitive training cease to be beneficial? Does training have to be repeated to maintain improvements in the longer term? Studies that employ identical training programs but vary their duration and intensity will be required before we can obtain a definitive answer. The relationship between maintenance of treatment effects and intensity requirements will be particularly important for cost-benefit analyses.

5.6.3 Neuropsychological Heterogeneity

A recent paper by Nigg, Willcutt, Doyle, & Sonuga-Bark (2005) has drawn attention to the fact that the performance distributions of neuropsychological tests overlap substantially in ADHD and control participants. The authors tested a sample of 887 children with ADHD-combined type on a range of executive functions and found that no more than half of the children could be classified as impaired (using the 90^{th} percentile as a cut off) on any given measure. Thus, in any given sample a certain proportion of children with ADHD will perform within or above the normal range on neuropsychological tasks suggesting that executive deficits measured by these tasks do not contribute causally to ADHD in *all* cases. However, by reviewing studies that have examined neuropsychologically-impaired children with ADHD in isolation, the authors did uncover convincing evidence of an etiologically distinct ADHD-subgroup in which neuropsychological deficits do appear to play a central role.

In clinical and neuropsychological terms, heterogeneity is the rule rather than the exception in ADHD. Matching a treatment to individual needs may be as important as

the actual components of the treatment itself. Careful titration of medication significantly enhances treatment effects (MTA Cooperative Group, 2004) and the same rigour should be applied to non-medical interventions. Using molecular genetics may provide a means of reducing heterogeneity by identifying sub-groups for who a particular genotype is associated with a distinct neuropsychological profile (e.g. Bellgrove et al., 2005). Carefully matching cognitive treatments to individual impairments in this manner may be one way of maximising treatment effects in future studies. In addition, studies of neuro-cognitive training in ADHD are once again well placed to potentially clarify the role of neuropsychological deficits by comparing treatment effects in neuropsychologically impaired and unimpaired children.

5.6.4 Multimodal Treatment

In recent years there has been an increasing consensus that treatments for ADHD should be targeted at more than one domain and this line of thinking has lead to the development of large-scale multimodal treatment programs (Hechtman, 2004; Wells et al., 2000). The studies reviewed above suggest that neuro-cognitive training may be effective both with (Kerns, Eso, & Thomson, 1999) and without medication (Klingberg et al., 2005). However, ADHD involves a range of primary and secondary behavioural and self-regulatory difficulties that are unlikely to be fully eradicated by a purely cognitive treatment. Behavioural therapies provide important feedback and instruction where ADHD may have hindered the development of adaptive patterns of behaviour. Pharmacological treatments may provide the focus required to facilitate participation in a neuro-cognitive remediation program but there is also evidence that medication acting upon neurotransmitter systems can influence recovery from brain injury (Barrett & Gonzalez-Rothi, 2002) and that dopaminergic projections to prefrontal cortex play a critical role in neurogenesis (Rubia et al., 2000). This leads us to the hypothesis that pharmacological and neuro-cognitive interventions may have synergistic effects on neural plasticity. While single component analyses of process specific training remain a priority in the short term, an interesting challenge for future work will be to investigate the potential adjunctive or synergistic effects that medical, behavioural and neuro-cognitive treatments have in combination.

5.6.5 Developmental Considerations

Knowledge of the timing of normal neuropsychological development may be helpful in maximising the effectiveness of neuro-cognitive treatments. While certain neuropsychological abilities are in place from early infancy others are not performed efficiently until adulthood when the protracted development of frontostriatal circuitry is finally complete. Prefrontal white matter matures slowly throughout childhood and adolescence and this maturation is accompanied by steady improvements in cognitive function (Liston et al., 2005; Paus, 2005). In particular, developmental studies indicate that there is a dramatic leap in the ability to maintain attention and exert executive control between the ages of 3 and 8 (Luciana & Nelson, 1998; Paus, 2005; Rueda et al., 2004). This is also the age group at which symptoms of ADHD begin to become apparent (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005) and may therefore represent a sensitive period during which neuro-cognitive training would be most beneficial. It would be of particular interest to explore the effects of a child's age on the extent of change effected by neuro-cognitive training. In addition, given the clear evidence of neural plasticity in the adult brain, remediation programs aimed at adults with ADHD would also be desirable.

Castellanos and colleagues (2002) have shown that although structural abnormalities are apparent in children with ADHD from an early age patterns of brain maturation do not seem to be affected. It has been suggested that acquired brain injury (ABI) in children may have a cumulative effect on ongoing development where specific cognitive deficits only become apparent years later at the stage when they would normally be expected to mature (Limond and Leeke, 2005). Parallels can therefore be drawn between ABI and ADHD. There is growing evidence that structured practice on cognitive tasks promotes plastic changes in the brain leading to enhanced efficiency of neural networks and cognitive function. The studies conducted so far with normal and impaired children indicate that process-specific training essentially accelerates development in the targeted areas. Therefore the early measurement and remediation of neuropsychological deficits at this stage may be critical in alleviating neural abnormalities in ADHD by encouraging maturation in key cognitive processors. Future work should investigate whether extensive training from an early age can lead to neural and behavioural improvements that last throughout and beyond development.

Box 5.1. Steps in the development of an effective neuro-cognitive remediation strategy.

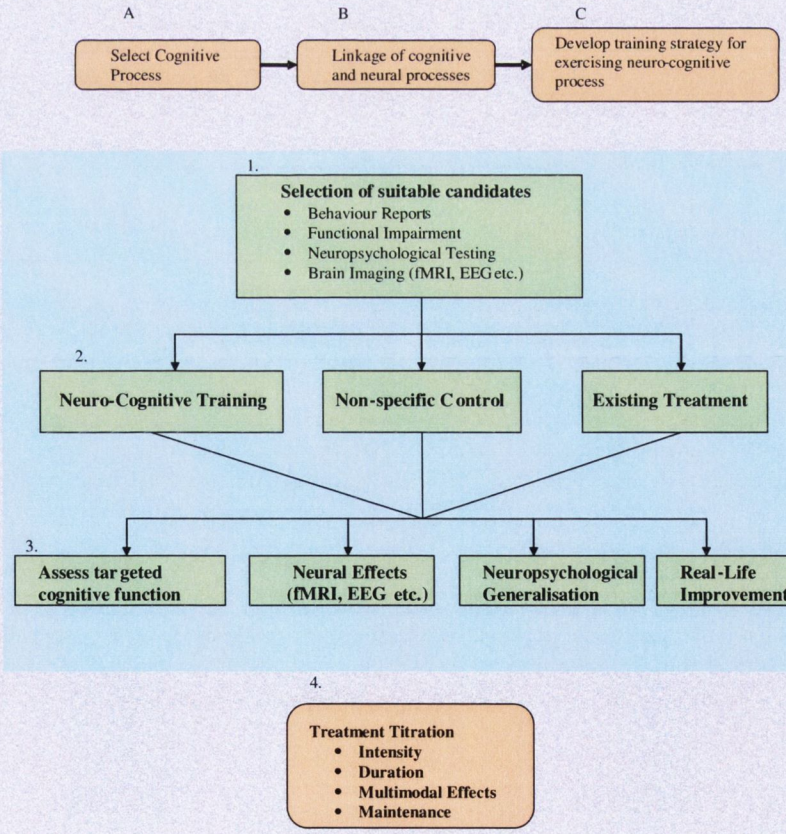
Steps (A, B and C). A detailed understanding of the neural processes underlying cognitive function is necessary for the development of effective training strategies. For example, frontal control regions tend to deactivate as performance reaches asymptotic levels therefore if these regions are being targeted then training difficulty must increase as performance improves. In addition, studies by Shaffer et al (2001) and by Klingberg et al (2005) have demonstrated how a knowledge of the overlap in brain areas employed for separate neuropsychological functions allowed them to hypothesise generalised improvements.

Step 1. Treatment effects will be maximised by establishing patient profiles and applying cognitive training only to those patients who have demonstrated a deficit in the targeted process.

Step 2. A crucial step in establishing neuro-cognitive training as an effective treatment will be the provision of appropriate comparison groups. A non-specific comparison group should control for possible confounds including interaction with the therapist, positive feedback, spontaneous improvement and practice effects. Neuro-Cognitive training strategies should also be pitted against existing treatments to establish their unique effects.

Step 3. A complete assessment of neuro-cognitive training effects should include neuropsychological and functional imaging measures assessing the targeted cognitive function but, most importantly, transfer of training benefits to everyday life function should be assessed.

Step 4. A final step in the development of cognitive training will be to investigate different treatment intensities and durations and their effect on maintenance of improvements. In addition cognitive training may be an effective component within a multimodal treatment framework.



Chapter 6. Exploring new methods for the neuro-cognitive remediation of Sustained Attention Deficits in ADHD

6.1. General Introduction

As we have seen in Chapter 5, the field of cognitive rehabilitation has used our increasing understanding of the neural instantiation of different cognitive processes to develop new innovative behavioural strategies that can restore function within damaged brain circuitry. The coexistence of EF deficits and both structural and functional changes in the prefrontal cortex of individuals with ADHD has led investigators to draw parallels between the effects of frontal dysfunction in ADHD and disorders of attention arising from frontal damage (Pennington & Ozonoff, 1996; Shallice et al., 2002; Swanson et al., 2004). This analogy presents the possibility that many of the rehabilitative strategies that have been successfully applied to patients with frontal pathology could also be useful in the treatment of ADHD. As reviewed in Chapter 5, studies that have sought to remediate cognitive deficits in ADHD have relied almost exclusively on a practice-based approach. In order to broaden the scope of remediation strategies for ADHD, the following set of experiments investigate whether alternative techniques developed by the field of cognitive rehabilitation are applicable to the deficits exhibited by individuals with ADHD.

6.2 EXPERIMENT 6. Modulation of sustained attention by periodic non-contingent alerting in childhood ADHD.

6.2.1 Introduction

One of the most elementary applications of cognitive rehabilitation principles was conducted by Manly and colleagues (2004) who demonstrated that the number of

commission errors made by TBI patients with frontal pathology on the SART dropped by as much as 35% with the introduction of brief auditory alerts that bore no relevance to the task other than to cue participants to be more aware of what they were doing (i.e. the cues were non-contingent). This very simple intervention was in fact informed by neural models of the sustained attention system. As discussed in Chapter 3, structural and functional imaging studies have highlighted the strong ascending and descending projections linking the cortical sustained attention network with subcortical arousal systems (Posner & Peterson, 1990; Sturm & Willmes, 2001). While most investigations of sustained attention in humans have focused on top-down influences on arousal, the sustained attention network is also subject to bottom-up influences mediated by ascending thalamic-mesencephalic projections (Kinomura, Larsson, Gulyas, & Roland, 1996). Sub-cortical arousal systems are particularly sensitive to exogenous stimulation such as noise, temperature or light received from peripheral sensory systems via the thalamic relay nuclei. For example, Smith and Nutt (1996) demonstrated that the negative effects of clonidine on sustained attention were attenuated when participants were exposed to loud white noise during task performance.

More recently, an fMRI study of the SART by O'Connor et al (2003) showed that uninformative auditory tones actually led to reductions in right frontal activity suggesting that the increased exogenous/bottom-up input to the sustained attention network decreases its reliance on endogenous, top-down processes. Therefore, in order to encourage increased top-down modulation of sustained attention following an alert, Manly and colleagues instructed their participants to use each alert as an 'alertness cue' that would remind them of their current task goal. Thus, it was hypothesised that a phasic alert would briefly activate the sustained attention network in a bottom-up manner and facilitate the re-engagement of endogenous processes associated with the added instruction. This hypothesis was supported in the data of Manly et al as participants' reaction times slowed significantly following an alert, suggesting that ongoing performance was momentarily interrupted, and error rates were significantly reduced on the target subsequent to an alert and on the task as a whole.

As a preliminary investigation of the applicability of techniques from the field of cognitive rehabilitation to the attention deficits of ADHD, the present study tested the

effectiveness of non-predictive alerting cues in improving the performance of children with ADHD on a discrete test of sustained attention (Dual Attention to Response Task, DART).

6.2.2 Methods

6.2.2.1 Participants

Since this experiment was conducted concurrently with Experiment 2, the same cohort was studied.

6.2.2.2 Alerting Procedure

The DART paradigm used in this experiment has been described in Experiment 2. The data for this experiment were acquired from the same participants and the same experimental testing blocks as analysed in Experiment 2. Participants were seated at a table with a Dell Latitude laptop monitor centred in front of them at a distance of approximately 50cm from their eyes. Each participant completed four DART blocks, two with periodic alerting cues and two without these cues. The order of these blocks was counterbalanced to neutralise possible ordering effects. In the 'alerts' condition, a tone of 659Hz, 30ms duration and approximately 62dB intensity, was programmed to sound eight times, from two external speakers, in a prefixed pseudo-random manner during the task. To avoid any competition with the withhold response to the number 3, alerts were only presented between the numbers 5 and 9 inclusive. Half of the alerts were programmed to occur in 1-9 digit sequences that included grey digits while the other half were presented during digit sequences with no grey digits. Participants were given the following instructions prior to DART blocks containing alerts: "*every now and then, you are going to hear some beeps coming from the speakers. Try to use them as a reminder to concentrate even more on what you are doing.*" A rest period of approximately 5 minutes was allowed between each block. Electrodermal activity (EDA) was measured during DART testing and SCRs to alerts were analysed. EDA was recorded and analysed according to the procedures outlined in experiment 2.

6.2.3 Results

To explore the immediate effect of alerts on reaction time the average difference in reaction time between the correct Go-response immediately preceding and immediately following the presentation of each alert was calculated for each participant. It was found that alerts had the effect of slowing control participants' responses by an average of 53.8ms (SD=11.9) and by an average of 23.1ms (SD=70) in the ADHD group. A repeated-measures ANOVA revealed a significant main effect of alerts on reaction times [$F_{(1,28)}$=7.2, p=0.005) with no Group by Alerts interaction [$F_{(1,28)}$=1.02, p=0.8] and no main effect of Group [$F_{(1,28)}$=1.5, p=0.2]. This data indicates that the alerts did serve to interrupt current activity as in Manly et al's (2004) earlier study. In addition, the two groups did not differ in their EDA responses to the alerts [$F_{(1,28)}$=0.8, p=0.4] indicating that the alerts carried similar arousing properties for both the control and patient groups. As discussed in experiment 2, children with ADHD made more errors of commission (pressing on 3) and of omission (failing to press on a go-target) and exhibited greater variability of reaction time (GoRT) during DART performance relative to a group of matched control children. The effect of alerts on each of these measures was verified via separate Group (ADHD vs Controls) by Alerting Condition (Alerts vs. No Alerts) repeated-measures ANOVAs. No significant main effects of Alerting Condition [errors of commission $F_{(1,28)}$=0.2, p=0.6; errors of omission $F_{(1,28)}$=0.02, p=0.8; GoRT variability $F_{(1,28)}$=0.6, p=0.5] or Group by Alerting Condition interactions [errors of commission $F_{(1,28)}$=1.04, p=0.3; errors of omission $F_{(1,28)}$=0.00, p=0.99; GoRT variability $F_{(1,28)}$=0.7, p=0.4] were found for any of these measures.

In addition to examining the effects of phasic alerting on commission errors per block, it was also important to investigate whether alerts conferred a short-term benefit to performance that was masked in the condition averages. To achieve this analysis the no-go targets (3s) were classified as occurring either pre- or post-alert. A 3 was deemed to be pre-alert if the preceding 1-9 sequence *did not* contain an alert. A 3 was deemed to be post-alert if the preceding 1-9 sequence *did* contain an alert. Thus, each DART block contained 8 post-alert no-go targets (as there were 8 alerts per block) and 17 pre-alert

no-go targets. The percentage of pre- and post-alert no-go trials on which commission errors were made was then calculated for each participant. Control participants had an error rate of 11% on pre-alert no-go targets increasing to 12% post-alert, yielding a short-term *increase* of 0.7%. In contrast the ADHD group had a pre-alert error rate of 24% dropping to 18% post-alert, yielding a 7% short-term *reduction*. These differences are illustrated in Figure 6.1. It should be noted that the comparatively low number of commission errors and the small number of alerts presented effectively precluded an accurate analysis of error probability relative to alert presentation in the control group.

A repeated-measures ANOVA revealed no main effect of alerting in the short term [$F_{(1,28)}$=0.4, p=0.6] but there was a significant interaction with group [$F_{(1,28)}$=5.1, p=0.05]. Post-hoc analysis with Bonferroni corrections revealed that this interaction was driven by the short-term beneficial effect of alerting cues on the performance of ADHD participants [p=0.02] that was absent in the control group [p=0.6]. Post-hoc analysis also revealed that while the ADHD group made a significantly greater percentage of errors than controls on *pre-alert* targets [p=0.01] there was no between groups difference on the percentage of errors made on *post-alert* targets [p=0.4]. Alerts appear to have temporarily brought the performance of children with ADHD into line with that of the control group.

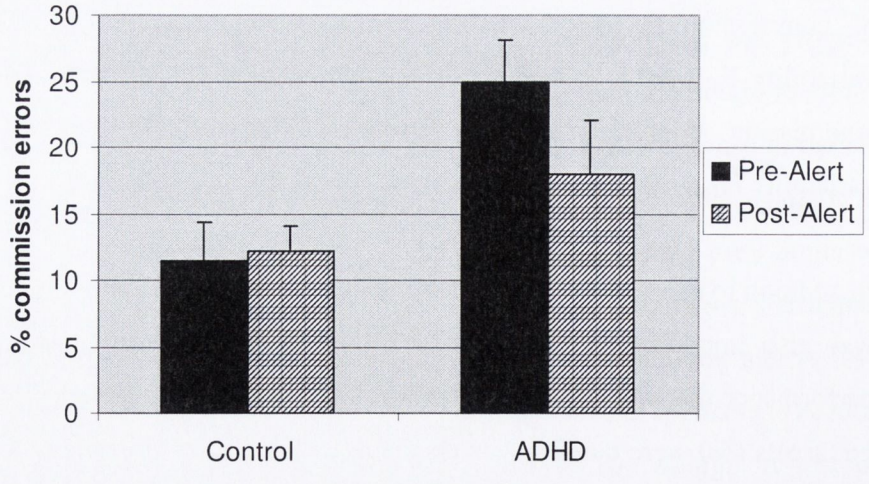


Figure 6.1 Short-term effect of periodic uninformative auditory alerts on commission errors

6.2.4 Discussion

The manipulation of periodic alerting cues was designed to achieve two principal aims. First, it was hypothesised that the alerting cues would intermittently activate the sustained attention network in a bottom-up manner and hence briefly interrupt current activity. The behavioural manifestation of this effect was slowed reaction times immediately following an alert in both groups. Additionally, the analysis of EDA revealed that alerts produced arousal responses of equal magnitude for the control and patient groups. These findings suggest that alerts were detected by participants, carried similar arousing properties for both groups and that current activity was indeed momentarily interrupted, providing a potential opportunity for participants to re-engage top-down control. The second aim of periodic alerting was to prompt participants to increase the allocation of top-down control over sustained attention for extended periods of time. In the ADHD group, significant reductions in error probability were found during the immediate post-alert periods indicating that alerts did trigger short-term improvements. While the children with ADHD benefited from the auditory alerts in the shorter-term, this did not translate to improved performance over the duration of the task.

A question which cannot be addressed in the present experiment is whether or not these short-term improvements reflect increased top-down control of sustained attention or whether they simply reflected the brief increase in exogenous input to the sustained attention system. At best it appears that participants in the ADHD group were only able to increase top-down processes for a short period, following each alert. The control group, in contrast, did not benefit from the non-contingent alerts in either the short or long term. This null result likely reflects the fact that the performance of the control children was near ceiling on this task.

The present data show that periodic alerts successfully enhanced sustained attention over short time periods but failed to engender lasting changes in the top-down control over performance that might have improved performance over the entire task. A potential explanation for these results may be that, while the participants in Manly et

al's (2004) study were adults, the participants in this study were children who may have lacked the meta-cognitive skills required to benefit from a non-contingent cue beyond the short term. Considering the short-lived nature of the effects in the present study, it appears that children with ADHD may require additional training in order to benefit fully from non-contingent cues. As mentioned in chapter 5, the vast majority of cognitive rehabilitation studies have focused on adult populations. Translating the techniques used in adult populations to child populations is a major challenge for future work. It is also important to note that the ADHD group in this study was not medicated during testing. It may be that the focus required to facilitate cognitive remediation can only be achieved when the putative right frontal dysfunction, that is thought to underpin sustained attention deficits in ADHD, is controlled pharmacologically (see Loo et al., 2003).

In summary, the present study has provided preliminary support for the hypothesis that techniques from the field of cognitive rehabilitation can be effectively applied to the attention problems associated with ADHD. The technique of periodic auditory alerting is based upon an established neural model of sustained attention (Posner and Peterson, 1990; Sturm and Wilmes, 2001) and can produce short-term improvements in sustained attention in childhood ADHD. From a rehabilitation perspective, the use of alerts that are independent of task or participant characteristics provides a highly flexible means of triggering controlled behaviour that is potentially applicable to a range of real-world settings (see Levine et al., 2000; Manly, Hawkins, Evans, Woldt, & Robertson, 2002). In the following set of experiments a new *endogenous* cueing technique, that also draws on previously established rehabilitative strategies, is developed and its efficacy for improving sustained attention amongst adults with ADHD is verified.

6.3 EXPERIMENT 7. Development of Self-Alert Training (SAT) for the remediation of sustained attention deficits

6.3.1 Introduction

As we have just seen in the case of children with ADHD, alerting cues can be used to improve performance on sustained attention tasks. Self Alert Training (SAT) seeks to capitalise on the known relationships between sustained attention and arousal by teaching participants to recognise and modulate their alertness levels in an endogenous and top-down manner and hence implement the cognitive control necessary to sustain attention.

SAT was designed to target some of the key neuropsychological processes that have been associated with ADHD in this thesis. In Experiments 2 and 3 it was demonstrated that both children and adults experience difficulties when a task is particularly reliant upon the endogenous maintenance of sustained attention. These difficulties manifested themselves in the form of increased attentional lapses (Experiments 2 and 3) and reduced conscious detection of errors (Experiment 5). The behavioural findings were accompanied by ERP evidence indicating reductions in goal maintenance (Experiment 3) and EDA and EEG evidence suggesting reduced modulation of arousal (Experiments 2, 3 and 5); these processes are strongly linked to frontal lobe function. Source localisation in Experiment 5 also provided evidence of reduced ACC activation, a region implicated in the modulation of arousal, during the critical post-error period when increased top-down control of attention is required. The goal of SAT was to fulfil the steps A, B and C outlined in Box 5.1 (see Chapter 5): a cognitive function was selected, links between that function and underlying neurophysiological processes were identified and finally, a training strategy was developed to address these same processes in order to improve the targeted cognitive function.

The procedures for SAT arose from work conducted by Robertson and colleagues (Robertson, Tegner, Tham, Lo, & Nimmo-Smith, 1995) in which the authors attempted

to directly rehabilitate sustained attention deficits in a group of eight patients with right-hemisphere lesions arising from stroke. The 5-hour intervention occurred while patients performed a variety of routine everyday tasks (e.g. reading or sorting). Intermittently, the experimenters re-directed the patients' attention to the task by combining a loud noise (clapping) with an instruction to attend. As in Experiment 6, the alerting effect of this exogenous cue was intended to activate the sustained attention system in a bottom-up manner and hence facilitate the engagement of top-down attention processes associated with the instruction to attend. Patients were then gradually taught to initiate this alerting procedure themselves by using a self-generated verbal cue. By the end of training, patients had learned to 'self-alert' without needing to generate verbal cues at all. Thus, patients acquired the ability to activate the sustained attention network in a covert, self-initiated and therefore endogenous manner without requiring any external cue. Importantly, this technique is not task-specific but has the potential to enhance performance on a variety of tasks that require sustained attention. After training, all participants showed clinically significant improvements on the training tasks and on a number of tasks on which they had never been trained. The duration of these training effects ranged from 24 hours to 14 days.

As is commonly seen in patients with right-hemisphere damage, the sustained attention deficits exhibited by the 8 patients in this study were accompanied by a tendency to neglect objects in left space. An explanation for the co-occurrence of deficits in sustained and lateralised aspects of attention has been provided by Posner and Peterson (1990). Ascending projections from the LC/NA arousal system are strongest in the right hemisphere and are first received by frontal cortex before spreading back into parietal regions (Morrison & Foote, 1986). It follows, therefore, that the sustained attention system, which modulates NA activity, should have a particularly significant impact on right-parietal regions that are involved in orienting attention to regions of left-space. Interestingly, Robertson et al (1995) were able to provide indirect support for this account by reporting that patients showed reductions in their neglect of left space following sustained attention training despite the fact that the training involved no lateralised components. These training effects cannot be attributed to a generalised improvement in all brain functions since performance on two control measures, backward digit span and line orientation, was not altered. Most importantly, in the

context of the present study, the results are consistent with the interpretation that participants had learned to increase activation of right fronto-parietal regions. Based on this encouraging evidence it was hypothesised that a similar self-alerting strategy would help to remediate sustained attention deficits in ADHD.

SAT extends Robertson et al's original training protocol by teaching participants to modulate their arousal during each 'self-alert' in a process known as biofeedback. Leahy and colleagues (1998) have demonstrated that patients who receive relaxation training are better able to control their arousal levels when they are made aware of their otherwise covert autonomic responses through visual or auditory feedback. During biofeedback participants receive feedback conveying the current level of a particular biomarker such as EEG power (Lubar, 2003) or autonomic arousal (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004) and learn to exert volitional control over that particular process. In the case of SAT, participants learn to produce transient *increases* in arousal, as indexed by SCRs, in order to offset the periodic decreases in the top-down modulation of arousal that have been associated with failures of sustained attention. Unlike Robertson et al's (1995) original training technique, participants do not perform any particular tasks during SAT other than observing and modulating their EDA. Thus, participants gradually learn to control their alertness levels in a manner that has the potential to be applied to a variety of situations.

Investigations into ACC function suggest that this region is critical in mediating top-down influences on the level of cortical and sympathetic bodily arousal (Aston-Jones & Cohen, 2005; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004). Within the sustained attention network, the ACC, which has strong projections to dorsolateral prefrontal cortex, parietal cortex and striatum, appears to modulate arousal in response to signals from lateral prefrontal cortices governing top-down control of attention (Posner and Peterson 1990; Sturm and Wilmes 2004). There is also good evidence to suggest that the ACC which also has anatomic connections to autonomic systems, is recruited during the volitional control of autonomic arousal (Critchley, Melmed, Featherstone, Mathias, &

Dolan, 2002; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004). For example, Nagai and colleagues (Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004) scanned participants while they performed a visual EDA-biofeedback task in which they were taught relaxation strategies in order to reduce transient skin conductance responses (SCR). The fMRI data revealed a neuroanatomical network that included the ACC, lateral prefrontal cortices, the thalamus and the hypothalamus. In addition, Patterson, Ungerleider and Bandettini (2002) have identified a region incorporating ventromedial prefrontal cortices and rostral ACC that is consistently activated during SCR generation irrespective of the cognitive task being performed. Thus, there is evidence to suggest that the volitional modulation of SCRs would activate frontal control regions that are also implicated in sustained attention.

In light of the evidence discussed above, it is hypothesised that SAT, which combines elements of Robertson et al's (1995) behavioural training strategy with a biofeedback arousal protocol, should teach participants to exert greater conscious, top-down control over their sustained attention system. The sustained attention deficits of children and adults with ADHD are subtle when compared to those experienced by patients with frontal brain damage. As a consequence it is possible that these deficient abilities can be improved through targeted practice. A key aim of the present study is to verify the extent to which adults with ADHD can be encouraged to increase the activation of top-down influences on sustained attention which could potentially form the focus of new restorative strategies. Although this approach represents a departure from the practice-based strategies that have been applied to children with ADHD (see Chapter 5), the anticipated outcome of strengthening task relevant neural regions and generalised improvement of performance, remains the same. In the present experiment the effectiveness of a brief pilot version of SAT for improving sustained attention is examined in a group of healthy adults. SART performance pre- and post-training is used as a measure of training effectiveness and EDA is measured during each of these baseline conditions as an independent measure of the extent of self-alerting. In Experiment 8, the same strategy is piloted with a group of adults with ADHD and combined measurements of EDA, ERP and EEG are acquired during SART performance to investigate the neurophysiological effects of SAT. The following SAT training effects are predicted:

1. Participants who implement SAT strategies during SART performance should show increased arousal, as measured by SCR magnitude, relative to un-trained participants.
2. Increased volitional control of arousal should lead to a reduction in momentary failures of attention.
3. Increased activation of the sustained attention system following SAT should also be reflected in on-going performance measures such as GoRT variability and errors of omission.
4. SAT-related improvements should also be reflected in key ERP markers of sustained attention such as the P3b, LP1 and LP2 (see Experiment 8).

6.3.2 Methods

6.3.2.1 Participants

A total of 31 healthy undergraduate participants, recruited by poster advertisement, completed baseline testing for the present study but participants who made less than 4 errors in total at baseline were excluded from further training. This was an arbitrary cut-off designed to eliminate participants who were already performing at ceiling. A reduced sample of 23 adults who made sufficient errors were then randomly assigned to the treatment or placebo conditions. The treatment group contained 11 participants (5 females, 1 left handed) with a mean age of 22.3 (SD=2.7), while the placebo group contained 12 participants (5 females) with a mean age of 24.3 (SD=4.2). Before testing all participants signed a consent form and completed the Cognitive Failures Questionnaire (CFQ, Broadbent, Cooper, Fitzgerald, & Parkes, 1982). Exclusion criteria were any known neurological condition, severe head trauma, psychosis, learning disability or reading disability. SAT and placebo groups were matched for sex, handedness, age [$F_{(1,21)}$=1.6, p=0.2] and CFQ score [SAT mean=46.9, Placebo Mean=36.1, $F_{(1,21)}$=3.6,p=0.07].

6.3.2.2. Pre-Testing

All participants completed 4 blocks of a modified version of the fixed SART. For each trial, a digit was presented for 150 ms followed by an Inter-Stimulus-Interval (ISI) of 1000ms. Participants were asked to press the left mouse button to each number except for 3. The task included 200 Go stimuli and 25 No-go stimuli. Ten of the Go stimuli were coloured grey, all other stimuli, including the No-gos were coloured white. Whenever a Grey Go stimulus appeared participants were instructed to press the left mouse button, as is typical in the SART, and to say the word 'grey' to indicate to the experimenter that they had noticed the colour change. To avoid confusion participants were told that there were no grey 3s and grey digits occurred only on the digits 5,6,7,8 or 9 to avoid interference with the task of withholding on the No-Go target.

In the present study, Grey stimuli were introduced as a cue for participants to implement the Self-Alert Training (SAT) during the post-testing phase. Asking participants to say "grey" when a grey digit appeared provided a way of verifying awareness of these grey digits (which were later to be used as a cue for self-alerting) and also as a means of controlling for the effect of vocalisation on EDA in the post-test condition (i.e. it made it possible to isolate changes in arousal that were specifically due to self-alerting). To reduce the extent to which grey numbers interrupted ongoing responding participants were told that the experimenters were not interested in how quickly they could say "grey" after seeing a grey digit but rather that they were just seeking an indication that participants had noticed the change in colour. Thus, the SART version used in the present study is different from the DART versions used in Experiments 2 and 6 because grey stimuli did not interrupt the prepotent Go response set and hence the additional dual-task load was limited.

During Baseline testing EDA data was acquired from all participants with a 5 channel BIOPAC MP30B unit. Participants were seated in front of a Dell Latitude laptop at a distance of approximately 60cm from the screen. The experimenter was seated at a separate table behind the participant and recorded the number of times participants correctly identified Grey stimuli.

6.3.2.3 SAT Protocol

During SAT participants gain volitional control of their EDA trace by following three main steps:

Training 1: Eliciting SCRs by external alerting

Participants are allowed to view the EDA reading on-line.

1. Participant is shown the EDA reading and the meaning of this measurement is briefly explained:

   '*This red line (the EDA trace) measures minute changes in levels of sweat on your skin which tells us how alert your brain is when you perform a task such as the SART*'

2. Illustration of EDA sensitivity to arousal: Participant is presented with a loud alerting tone (clap + calling "*wake up*!") and the participant is shown their SCR to this external alert in real time (see Figure 6.2). Since there tend to be large individual differences in the magnitude of SCRs, the scale of measurement in BIOPAC was adjusted for each individual to ensure that arousal responses were clearly visible, as is common practice in other biofeedback protocols (e.g. Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002). After the SCR has returned to baseline the experimenter says:

   '*Do you see how your skin showed that you woke up? That is an example of how you can experience a fast increase in how alert you are because of some external event. However, it is also possible to cause increases in how alert you are without any external events. Although we may not always be aware of it, we are able to change how alert we are by ourselves and this ability helps us in our everyday lives to stay focused on a task and to avoid making absent-minded errors. This is what we are going to try and work on during the next few minutes. I am going to clap a few more times and I want you to concentrate on*

how it feels each time. Try to make a link between what you feel inside and the increase you see in the red line.'

This step is repeated 5 times, and each time the participant is able to view increases in the EDA waveform online. A resting period of at least 20seconds is provided following each alert to allow the waveform to return to a resting baseline. Participants are also instructed to relax as much as possible in between each cue in order to reduce the number of non-specific SCRs and hence ensure that increases in arousal are more clearly observable in the EDA waveform.

Training 2: Cued internally generated SCRs

In this second stage, the aim is for the participant to begin producing internally driven increases in arousal without a loud alerting cue.

3. Experimenter says:

   '*Now I want you to try to wake yourself up without any loud noise to help you. When I say 'now', you try to recreate what it was that you felt earlier (when I clapped and shouted) that made the red line go up. You need to concentrate on the internal process of switching to a highly alert state on my cue and to try and get as large an increase in the red line as you can each time. Good (or, ok, let's try again, try to recreate that sudden increase in alertness you felt the first time that I clapped).*'

4. The participant is instructed to keep trying to make the red line go as high as possible for about 10-20 seconds after each cue. A gap of approximately 20 seconds is allowed between cues. This step is repeated until the participant can generate at least 5 clear increases in amplitude. In between each attempt, the participant is instructed to relax in order to reduce the number of non-specific SCRs and thus ensure that an increase in arousal will be readily observable. Experimenter says:

'Well done – you see how you can wake yourself up now without a loud external cue?'

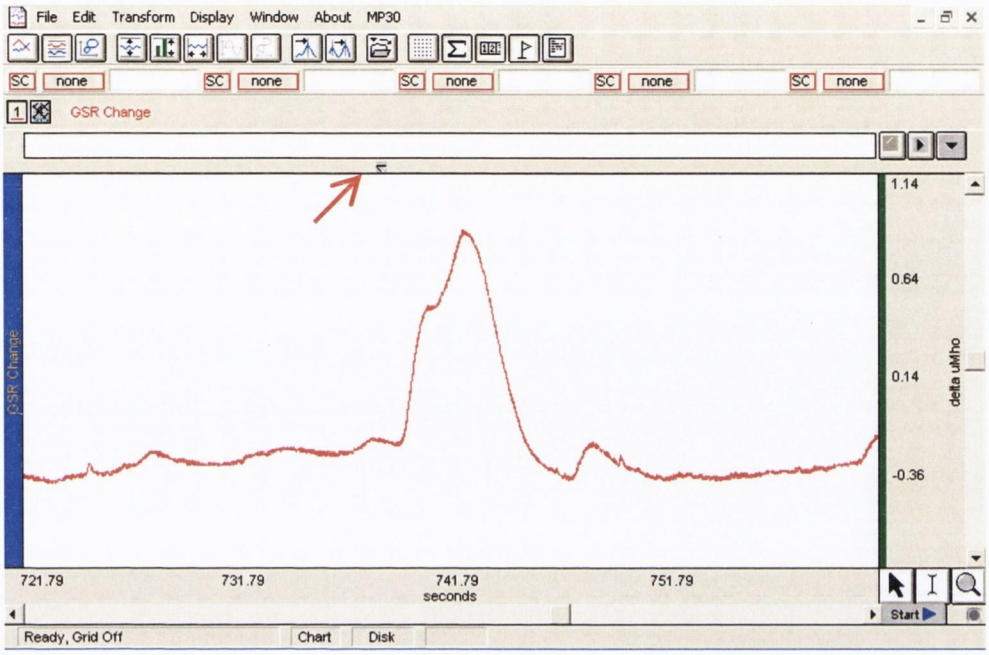


Figure 6.2 An example of a Skin Conductance Response (SCR) to an external alert. The alert was provided by the experimenter during SAT and its occurrence is marked online (an example of a trigger is identified here by the red arrow) and the participant is able to view the large arousal response that is elicited in real time.

Training 3: Un-cued internal generation of SCR amplitude change.

In the final step of SAT, the participant learns to take complete control of their EDA trace without any prompting from the experimenter.

5. The experimenter says:

'Now, I want <u>you</u> to decide when you are going to wake yourself up. Please say 'now' when you decide to do it, and see if you can make the line go up.'

Experimenter marks the GSR trace when the participant indicates that they are self-alerting. The experimenter and participant are able to observe the trace online.

'Well done – you see you decided there to make the line move up, and there it moved up. This time you have managed to do it without any external cue whatsoever'

This step is repeated, with visual feedback, until the participant can generate at least 5 increases in amplitude. The participant is instructed to leave at least 20 seconds after each attempt to allow the EDA trace to return to baseline and ensure that increases in arousal are readily observable. An example of successful self-alerting during training is provided in Figure 6.3.

6. Step 5 is repeated but this time visual feedback is removed and the participant is not able to view the EDA trace. The participant is asked to say 'now' when they are self-alerting and the experimenter marks the trace. This final step is repeated until the participant can generate at least 5 increases in amplitude.

Typical duration of training was 30-40 minutes.

6.3.2.4 Placebo Training

The aim of the placebo training procedure was to control for the key non-specific elements of SAT, including interaction with the experimenter, positive feedback and the placebo effect. Video game practice has been commonly used as a placebo condition in studies of cognitive rehabilitation. In the present study participants were trained on the video game 'Tetris' (see Figure 6.4).

As in SAT, the experimenter begins the placebo condition by allowing the participant to view the EDA reading on-line and explaining the basic premise of the measure.

'This red line measures minute changes in levels of sweat on your skin which tells us how alert your brain is when you perform a task such as the SART'

Participants are then presented with the computer game Tetris and told:

'Research suggests that playing certain computer games can actually increase one's ability to concentrate over time. If you perform a task that grabs your attention, a task that you can concentrate on easily and intensely for sustained periods of time, it can actually improve your ability to concentrate on less engaging tasks later on.'

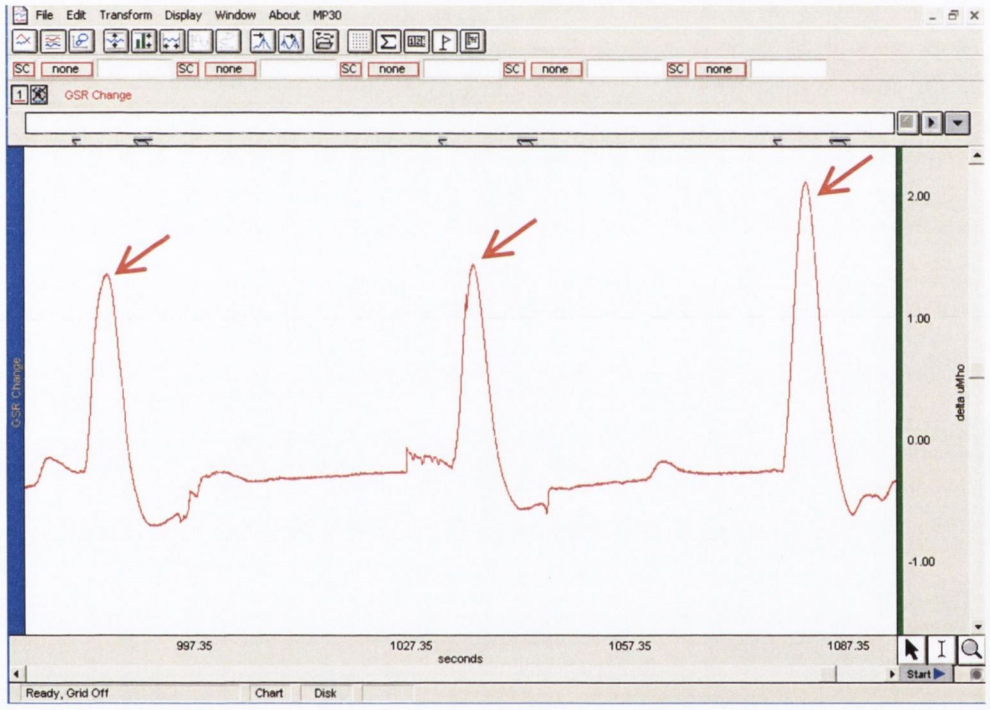


Figure 6.3 **Three 'self-alerts' generated by a participant during SAT**. This EDA trace covers a 90 second period. The participant has learned to produce large increases in arousal without any prompting from the experimenter.

The basic premise of the computer game training is that the participant must attempt to establish a top speed on Tetris, defined as the highest speed at which the participant is able to last for 3 minutes without a "game over". The speed of the Tetris game remains constant until it is reset by the experimenter. All participants started at level 7 and progressed up one level each time they managed to last for 3 minutes. Time was recorded on a stop watch and the experimenter called out each passing minute so that

participants could keep track of their progress. After each step participants were given positive feedback by the experimenter. If a participant failed repeatedly to last 3 minutes at a given level the experimenter set the short term goal of beating their previous time. Participants continued to practice Tetris until 30 minutes of Placebo Training had passed.

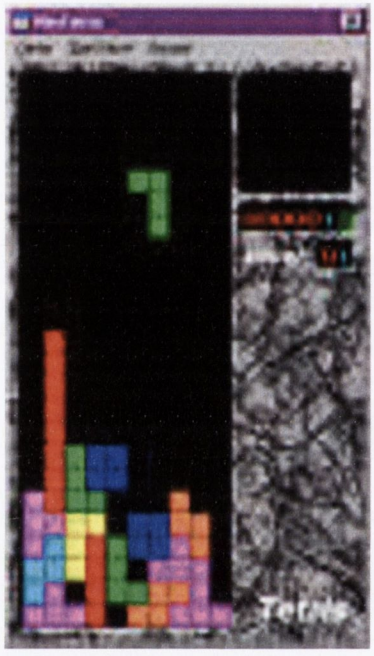


Figure 6.4 **Placebo condition video-game training task.**

6.2.2.5 Post-testing

As at pre-testing, participants performed four blocks of the modified fixed SART. The SAT and placebo groups were given slightly different instructions:

SAT Group

The experimenter says:

'Now we are going to try the task again but this time I want you to use the technique that we learned earlier to help you stay alert. We are going to use the grey digits as a cue to 'self-alert'. Now, when you see a grey digit I want you to self-alert in the way

that you learnt earlier. Please say "grey" each time so that I know that you are doing this. Make sure to use <u>each</u> grey digit as a cue to help you perform the task better'

This instruction is repeated before each SART block to ensure compliance.

<u>Placebo Group</u>

The experimenter says:

'Now we are going to try the task again but this time whenever you see grey digits I would like you to use them as a cue to remind yourself what you are doing and to concentrate harder on the task at hand. Please say "grey" each time so that I know that you are doing this. Make sure to use <u>each</u> grey digit as a cue to help you perform the task better'

This instruction is repeated before each SART block to ensure compliance.

EDA data was acquired during post-testing. SCRs to Grey stimuli during Baseline and Post-testing were analysed in BIOPAC 5.1.

6.3.3 Results

SAT and Placebo groups were successfully matched for baseline levels of mean commission errors, errors of omission, GoRT variability and SCRs to grey digits. Table 6.1 summarises the means, standard deviations and significance levels for group comparisons for each of these variables. A significant correlation was found between CFQ score and mean commission errors at baseline [$r=0.635$, $p=0.001$] suggesting that the modified version of the SART used in the present study represents a good experimental analogue of everyday attentional failures. Mean GoRT variability was significantly correlated with errors of commission [$r=0.57$, $p=0.005$] and errors of omission [$r=0.75$, $p<0.001$].

Table 6.1 **Comparison of pre-training baseline behavioural and EDA data for SAT and Placebo groups**

	SAT Mean (SD)	**Placebo** Mean (SD)	$F_{(1,21)}$	p
Mean commission errors	3.8 (3.3)	3.1 (0.2)	0.46	0.5
Mean errors of omission	0.4 (0.6)	0.9 (0.9)	2.3	0.14
Mean RT variability	82.9 (28.3)	90.4 (46.8)	0.21	0.65
Grey SCRs	0.503 (0.30)	0.606 (0.36)	0.4	0.52

Average Grey recognition was very high for both groups both pre- [treatment group mean= 98.5%, SD=1.6, placebo group mean= 98.4%, SD=1.3, $F_{(1,21)}$=0.05, p=0.8] and post-training [treatment group mean= 99.3%, SD=0.8, placebo group mean= 98.9%, SD=0.7, $F_{(1,21)}$=0.2, p=0.7]. By the end of training all SAT participants were able to generate 5 SCRs without any external prompting or visual feedback.

6.3.3.1 Effect of SAT on the SART performance of normal healthy participants

Errors of Commission

SAT group participants made an average of 3.84 (SD=3.33) errors of commission per SART block pre-training, dropping to an average of 2.5 (SD=2.28) errors per block post-training, thus there was a 34.8% decrease in errors. The Placebo group made an average of 3.06 (SD=2.07) errors of commission pre-raining dropping to an average of 2.94 (SD=2.55) errors post-training, thus a 4.1% decrease in errors. A repeated-measures ANOVA revealed a significant main effect of Phase (pre- vs post-training) [$F_{(1,21)}$=7.28, p=0.013] and a Phase by Group interaction [$F_{(1,21)}$=5.0, p=0.036]. There was no main effect of Group [$F_{(1,21)}$=0.03, p=0.87]. Post-hoc tests with Bonferroni corrections revealed a significant effect of Phase on the treatment group [p=0.003] that was absent in the control group [p=0.94]. The effect of SAT on commission errors is illustrated in Figure 6.5.

Errors of Omission

SAT group participants made an average of 0.41 errors of omission per block (SD=0.595) pre-training rising to 0.65 per block (SD=0.97) post-training. The Placebo group made an average of 0.89 errors of omission per block (SD=0.87) pre-training rising to 1.91 post-training (SD=2.38). A repeated-measures ANOVA revealed a main effect of Phase on errors of omission [$F_{(1,21)}$=5.86, p=0.02] but the Phase by Group interaction did not reach significance [$F_{(1,21)}$=2.35, p=0.14] and there was no main effect of Group [$F_{(1,21)}$=2.7, p=0.2]. Thus, there was a general increase in errors of omission over time which was not significantly altered by SAT.

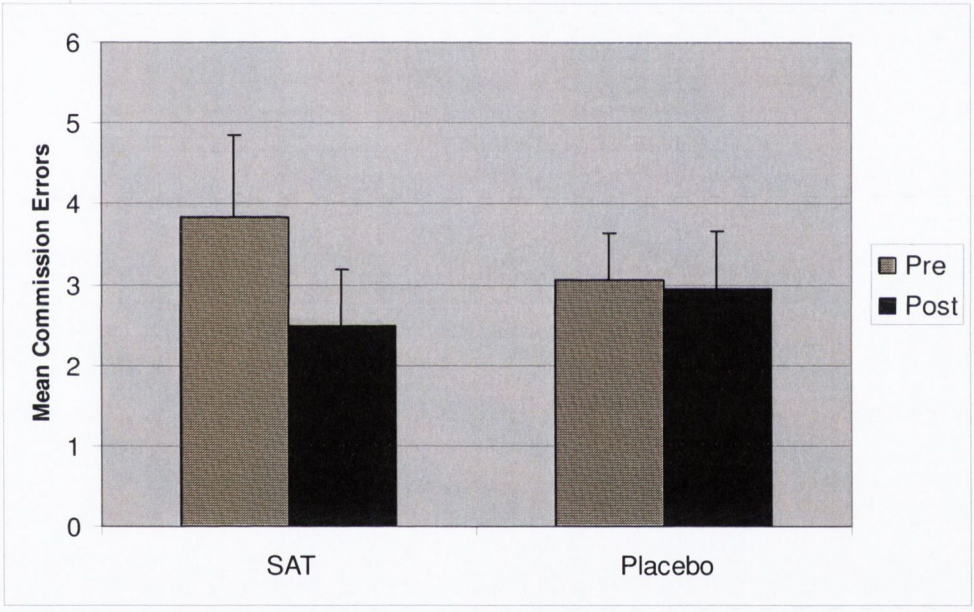


Figure 6.5 **Effect of SAT on SART errors of commission relative to the Placebo condition.**

GoRT variability

Mean GoRT variability was calculated separately for each group pre- and post-training. A repeated-measures ANOVA revealed no main effect of Phase [$F_{(1,21)}$=3.57, p=0.07] or Group [$F_{(1,21)}$=1.7, p=0.2]. A significant Phase by Group interaction was found [$F_{(1,21)}$=4.11, p=0.05] and post-hoc Bonferroni tests revealed that this effect was driven by significant increases in GoRT variability in the Placebo group over time [p=0.01] that were not found in the treatment group [p=0.923]. As can be seen in Figure 6.6 these

data suggest that while the participants in the Placebo group became more variable in their responding on the SART over time, SAT participants were able to maintain a more consistent level of performance before and after training.

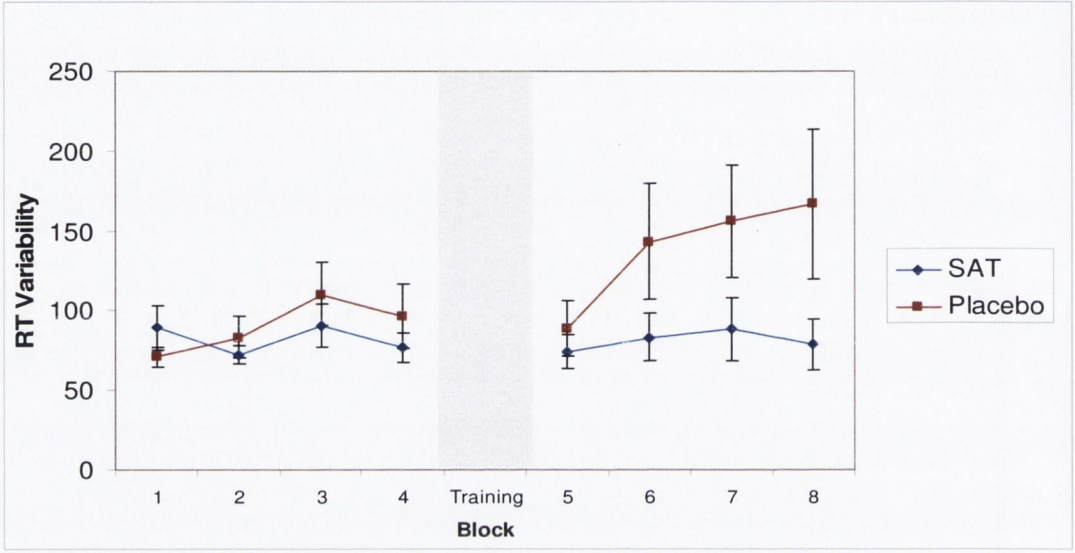


Figure 6.6 **Mean reaction time variability for each SART block pre- and post-SAT training**. The Placebo group exhibited a clear increase in variability over time while the SAT group maintained a more consistent performance after training.

6.3.3.2 Effect of SAT on the arousal levels of normal healthy participants

As a measure of self-alerting, SCR to each grey cue was measured and averaged before and after training (see Figure 6.7). A repeated-measures ANOVA revealed no main effect of Phase on SCR magnitude and no main effect of Group. A significant Phase by Group interaction was found [$F_{(1,21)}$=8.4, p=0.01] and post-hoc Bonferroni t-tests indicated that this effect was driven by a drop in SCR magnitude over time in the Placebo group [p=0.02] and a marginally significant increase in the SAT group [p=0.07]. These findings suggest that participants in the Placebo group experienced an overall drop in arousal responses to grey cues over time while participants who received SAT successfully increased their arousal responses to grey cues post-training. These data therefore confirm that SAT participants did engage in self-alerting during post-training SART blocks.

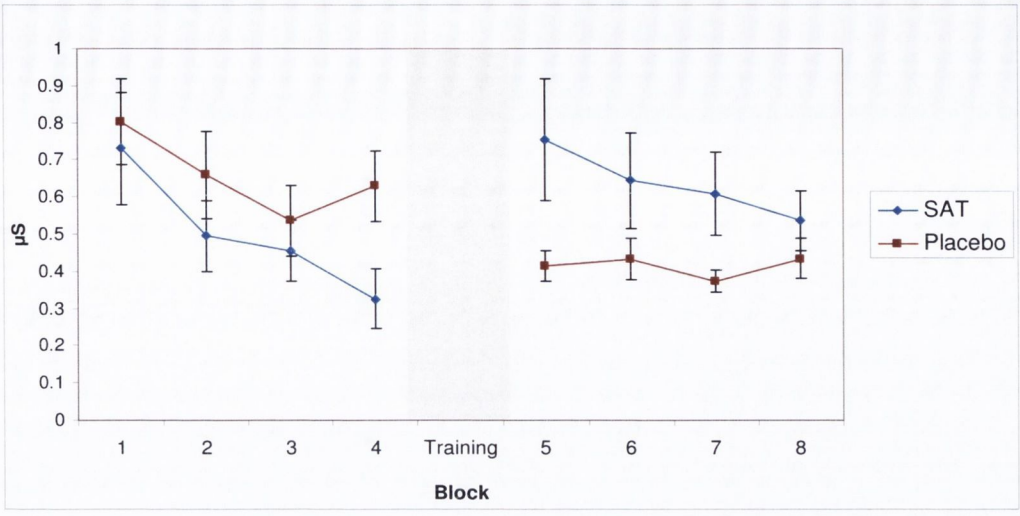


Figure 6.7 **Psychophysiological Evidence of Self-Alerting**. SCRs (measured in µS) to Grey Stimuli for each SART block pre- and post-SAT training. The SAT group show increased arousal responses after training while arousal in the placebo group gradually decreased over time.

6.3.4 Discussion

These data indicate that, as predicted, Self-Alert Training (SAT) produced improvements in behavioural and physiological indices of sustained attention. Participants who completed SAT exhibited fewer lapses of attention, more consistent GoRT variability and increased arousal during SART performance relative to a pre-training baseline. The absence of any such improvements in the Placebo condition suggests that the improvements in the SAT are unlikely to arise from influences that are not specific to training.

Participants in this experiment did not have any difficulty identifying the grey cues during SART performance with recognition rates in both groups averaging over 98% pre- and post-training. Thus, any group differences in behavioural performance or SCRs cannot be attributed to differences in grey recognition rates. SCRs to grey cues confirm that participants did implement the strategies they learned during SAT while they

performed the SART. Although the placebo group showed a gradual decline in arousal over time, the SAT group showed an increase in arousal relative to their baseline levels.

This increase in arousal was accompanied by a significant improvement in sustained attention performance. SAT participants made significantly fewer errors of commission post-training and maintained a consistent level of GoRT variability. A 35% decrease in commission errors in this healthy sample represents quite a substantial difference considering that these improvements were made from an already high baseline level of task performance. In contrast, the Placebo group showed no significant change in commission error rates but showed a significant increase in GoRT variability over time, mirroring their decline in EDA arousal. This gradual increase in variability may reflect a time-on-task decrement of the kind measured by traditional CPT tasks (discussed in Chapter 3). Previous work has demonstrated that, when a task is unstimulating, gradual decrements in performance with time appear due to underarousal (e.g. Parasuraman, Nestor, & Greenwood, 1989). A recent study of childhood ADHD by Johnson et al (in press) demonstrated that increased GoRT variability on the SART was attributable, in part, to a progressive slowing of reaction times consistent with the notion of a time-on-task decrease in arousal. Thus, whereas errors of commission are sensitive to brief reductions in the top-down control of sustained attention, the continuous response control that is indexed by trial-by-trial measures of GoRT variability may be particularly sensitive to any changes in arousal levels. In the present study, the fact that block-by-block increases in GoRT variability were accompanied by gradual decreases in arousal, as measured by SCRs to greys, strongly suggests that the Placebo group did experience a vigilance decrement. No such decline was seen in the SAT group suggesting that implementing the training strategies allowed participants to maintain a higher level of arousal over time. Importantly, previous work has linked increasing reaction time variability to decreased efficiency of frontal control mechanisms (Bellgrove, Hester, & Garavan, 2004; Stuss, Murphy, Binns, & Alexander, 2003) suggesting that, as predicted, SAT may preferentially target frontal control mechanisms.

The findings of this experiment indicate that the SAT protocol was successful in training healthy adult participants to gain control over their own arousal levels with a consequent improvement in performance on an untrained sustained attention task. In

the next experiment the SAT technique is applied to a group of adults with ADHD and chronic sustained attention deficits. ERP and EEG measures are also acquired to provide further insight to the neurophysiological effects of SAT.

6.4 EXPERIMENT 8. Effectiveness of SAT for the remediation of sustained attention deficits in adult ADHD

6.4.1 Methods

6.4.1.1 Participants

Eighteen adults diagnosed with ADHD were assigned to separate SAT-ADHD and Placebo-ADHD groups that were matched for age, sex, handedness, estimated IQ, Wender Utah Rating Scale (WURS) Self- and Other-rated childhood symptom scores and Connors Adult ADHD Rating Scale (CAARS) Self- and Other-rated symptom scores. Means, standard deviations and significance levels for each of these variables are summarised in Table 6.2. Procedures for participant recruitment and diagnosis remained the same as in Experiment 3.

6.4.1.1 Procedure

The same modified version of the SART used in Experiment 7 was used in the present experiment. During pre- and post-testing EEG and EDA measures were acquired. Participants were seated in a dimly lit sound attenuated room during SART testing and the experimenter recorded the number of times that participants correctly identified Grey stimuli. The validated procedures outlined in experiment 7 were followed for both the SAT and Placebo training. Training took place with the lights turned on. Due to technical problems EEG data was not acquired for one of the Placebo-ADHD group participants.

Table 6.2 **Summary of SAT-ADHD and Placebo-ADHD group demographics.**

	SAT-ADHD Mean (SD)	**Placebo-ADHD** Mean (SD)	$F_{(1,16)}$	p
N	9 (2 female)	9 (1 female)		
Age	23.6 (6.5)	23.8 (3.3)	0.01	0.9
IQ	106.4 (11.0)	112.9 (6.9)	1.9	0.2
WURS Self	62 (13.1)	66.5 (14.1)	0.5	0.5
WURS Other	63.4 (11.3)	60.0 (19.7)	0.2	0.7
CAARSDSM-IV Inattention Self	82.7 (8.8)	81.2 (8.9)	0.1	0.7
CAARS DSM-IV Hyperactivity Self	74.3 (11.7)	76.3 (10.2)	0.2	0.7
CAARS DSM-IV Total Self	82.3 (10.5)	84.9 (5.6)	0.4	0.5
CAARS DSM-IV Inattention Other	71.7 (7.7)	70.3 (11.2)	0.1	0.8
CAARSDSM-IV Hyperactivity Other	67.7 (14.4)	64.1 (20.8)	0.2	0.7
CAARSDSM-IV Total Other	72.1 (9.4)	72.3 (7.9)	0.01	0.9

ERP analysis focused on the three components that were identified in experiments 1 and 3 as key markers of sustained attention during SART performance. These components were the:

(i) P3b, measured as the peak positivity at CPz 310-370ms following each Go-stimulus.
(ii) LP1, measured as the mean amplitude at POz 550-800ms following the Go-stimulus immediately preceding a correct withhold.
(iii) LP2, measured as the mean amplitude between 850-1000ms following each Go-stimulus at Pz.

In order to investigate the effect of SAT on ERP components associated with sustained attention the P3b, LP1 and LP2 were averaged separately for SART blocks performed pre- and post-training. Tonic EEG power measures in the theta, alpha and beta bands as well as theta/beta and alpha/beta ratios were also calculated and analysed pre- and post-training.

6.4.2 Results

At pre-training baseline, the two groups were matched for errors of commission, errors of omission, GoRT variability and SCRs to Grey digits. Means, standard deviations and significance levels for each of these variables are displayed in Table 6.3.

Table 6.3 **Comparison of baseline behavioural and EDA data for SAT-ADHD and Placebo-ADHD groups**

	SAT-ADHD Mean (SD)	**Placebo-ADHD** Mean (SD)	$F_{(1,16)}$	p
Mean commission errors	6.2 (1.9)	6.3 (3.2)	0.01	0.9
Mean errors of omission	6.1 (5.4)	4.4 (3.5)	0.7	0.4
Mean GoRT variability	170.3 (45.5)	180.1 (64.9)	0.1	0.7
Grey SCRs	0.169 (0.10)	0.261 (0.24)	1.2	0.3

As in Experiment 7, average Grey recognition was very high both pre- [SAT-ADHD mean=98.9, SD=0.9, Placebo-ADHD mean=99.1, SD=0.8, $F_{(1,16)}$=0.3, p=0.6] and post-training [SAT-ADHD mean=99.3, SD=0.7, Placebo-ADHD mean=99.2, SD=0.7, $F_{(1,16)}$=0.1, p=0.7]. By the end of training all SAT-ADHD participants were able to generate 5 SCRs without any external prompting or visual feedback.

6.4.2.1 Effect of SAT on the SART performance of adults with ADHD

Errors of Commission

Participants in the SAT-ADHD group made an average of 6.2 (SD=1.91) errors of commission per block at pre-training dropping to an average of 4.19 (SD=2.23) errors per block post-training. Thus, participants in the SAT-ADHD group made 32.4% fewer errors post-training. The Placebo-ADHD group made an average of 6.31 (SD=3.16) errors of commission per block pre-training increasing to an average of 6.69 (SD=4.29) errors post-training. Thus, participants in the Placebo-ADHD group made 6% more errors post-training. A repeated-measures ANOVA indicated a significant Phase (pre- vs. post-training) by Group interaction [$F_{(1,16)}$=4.85, p=0.04] but there was no main effect of Phase [$F_{(1,16)}$=2.3, p=0.16] or of Group [$F_{(1,16)}$=0.95, p=0.3]. Post-hoc pairwise comparisons with Bonferroni corrections revealed a significant decrease in commission errors post-training in the SAT-ADHD group [p=0.02] that was absent in the Placebo-ADHD group [p=0.62]. The effect of SAT on commission errors for each participant is displayed in Table 6.4 while group differences are illustrated in Figure 6.8.

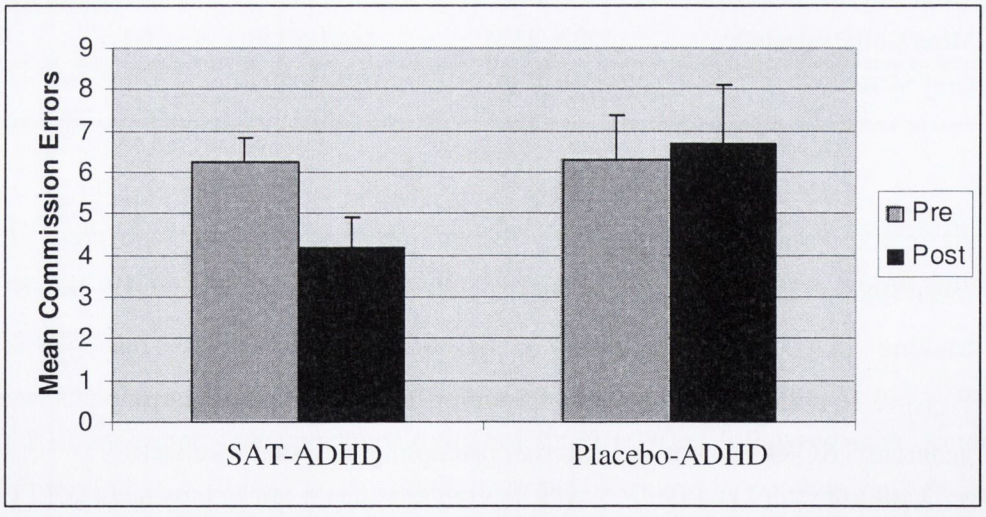


Figure 6.8 Mean SART errors of commission pre- and post- SAT-ADHD and Placebo-ADHD training.

Table 6.4 **SAT-ADHD and Placebo-ADHD training effects for each participant**. Displays the change in the total number of SART commission errors made by each participant pre- and post-SAT-ADHD or Placebo-ADHD training.

Code	Group	Errors Pre	Errors Post	Change	% Change
AdSAT1	SAT	6	8	+2	33.3
AdSAT2	SAT	18	13	-5	-27.8
AdSAT3	SAT	22	8	-14	-63.6
AdSAT4	SAT	19	7	-12	-63.2
AdSAT5	SAT	24	24	0	0
AdSAT6	SAT	33	19	-14	-42.4
AdSAT7	SAT	20	27	+7	35
AdSAT8	SAT	19	14	-5	-26.3
AdSAT9	SAT	16	6	-10	-62.5
AdPlac1	Placebo	24	12	-12	-50
AdPlac2	Placebo	26	26	0	0
AdPlac3	Placebo	32	43	+11	34.38
AdPlac4	Placebo	18	19	+1	5.6
AdPlac5	Placebo	38	49	+11	28.9
AdPlac6	Placebo	4	4	0	0
AdPlac7	Placebo	16	22	+6	37.5
AdPlac8	Placebo	13	17	+4	30.77
AdPlac9	Placebo	16	21	+5	31.25

Errors of Omission

SAT-ADHD group participants made an average of 6.1 (SD=5.4) errors of omission per block pre-training dropping to 4.5 (SD=3.5) per block post-training. The Placebo-ADHD group made an average of 4.4 (SD=3.5) errors of omission per block pre-training dropping to 3.8 (SD=2.8) post-training. A repeated-measures ANOVA indicated no significant main effects of Phase [$F_{(1,16)}$=2.7, p=0.12] or Group [$F_{(1,16)}$=0.5, p=0.5] and no Phase by Group interaction [$F_{(1,16)}$=0.5, p=0.5]. Thus SAT did not alter task performance as measured by errors of omission.

GoRT Variability

SAT had a strikingly similar effect on GoRT variability as that observed in Experiment 7. A repeated-measures ANOVA indicated that there was no main effect of Phase [$F_{(1,16)}$=0.7, p=0.4]or Group [$F_{(1,16)}$=0.8, p=0.4] but there was a significant Phase by Group interaction [$F_{(1,16)}$=5.5, p=0.03]. Post-hoc Bonferroni t-tests revealed that this interaction was driven by a significant increase in GoRT variability post-training in the Placebo-ADHD group [p=0.04] which was absent in the SAT-ADHD group [p=0.3]. These differences are illustrated in Figure 6.9. As in Experiment 7, the participants who received Placebo training became more variable over time while participants who received SAT training were able to maintain a more consistent level of performance.

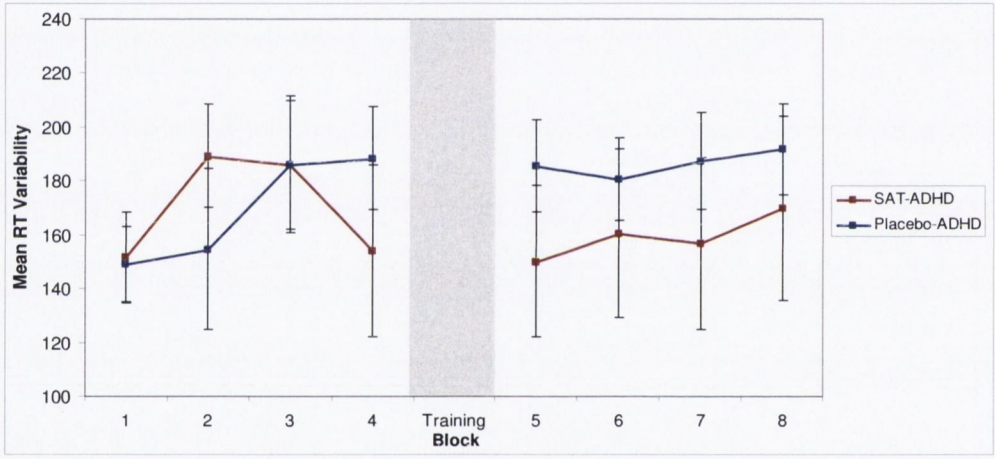


Figure 6.9 Mean GoRT variability pre- and post- SAT-ADHD and Placebo-ADHD training. As in Experiment 7 SAT appeared to stave off the time-on-task increases in variabililty that were seen in the Placebo-ADHD group,

6.4.2.2 Effect of SAT on the arousal levels of adults with ADHD

Mean SCRs to Grey stimuli for each SART block pre- and post-training are displayed in Figure 6.10. No main effect of Phase [$F_{(1,16)}$=0.9, p=0.35] or Group [$F_{(1,16)}$=0.001, p=0.9] was found but there was a significant Phase by Group interaction [$F_{(1,16)}$=8.9, p=0.01]. Post-hoc Bonferroni t-tests indicated that this effect was driven by a drop in SCR magnitude over time in the Placebo-ADHD group [p=0.016] that was not found in the SAT-ADHD group [p=0.16]. This result suggests that SAT had the effect of

preventing a decrement in arousal over time as opposed to actually increasing arousal beyond previous levels. However, closer inspection of the changes in SCRs over time illustrated in Figure 6.10 suggests that SAT-ADHD participants had increased arousal for the first two blocks post-training but that this effect dissipated by blocks 3 and 4. A further repeated-measures ANOVA was conducted comparing Grey stimulus SCRs for the four blocks of baseline testing to the first two blocks post-training. Again, there was no main effect of Phase [$F_{(1,16)}$=1.8, p=0.2] or Group [$F_{(1,16)}$=0.2, p=0.7] but there was a significant Phase by Group interaction [$F_{(1,16)}$=8.4, p=0.01]. This time however, post-hoc Bonferroni t-tests indicated that participants in the SAT-ADHD group experienced a significant increase in arousal during the first two blocks after training [p=0.008], while there was no such change amongst participants in the Placebo-ADHD group [p=0.3].

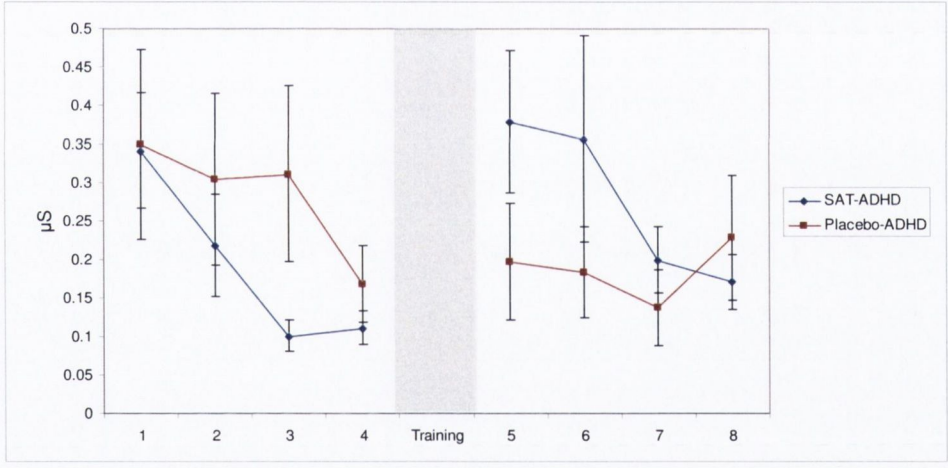


Figure 6.10 Psychophysiological Evidence of Self-Alerting in adult ADHD. Mean SCRs to Grey cues during SART performance pre- and post- SAT-ADHD or Placebo-ADHD training. The Placebo-ADHD group exhibited a significant decrease in SCRs post-training while the SAT-ADHD group had significantly increased arousal levels for the first two blocks post-training.

6.4.2.3 Effects of SAT on the EEG and ERP measures of adults with ADHD

To verify whether SAT had any effect on neurophysiological processes governing sustained attention, P3b amplitude on Go trials, LP1 amplitude on Go trials immediately

preceding a correct No-go response and LP2 amplitude on Go trials were selected for a pre-post analysis.

P3b

No main effects of Phase [$F_{(1,15)}$=0.06, p=0.8] or Group [$F_{(1,15)}$=0.5, p=0.8] were found but there was a significant Phase by Group interaction [$F_{(1,15)}$=4.4, p=0.05]. Post-hoc t-tests indicated that there was a significant reduction in P3b amplitude in the Placebo-ADHD group [p=0.01] but not in the SAT-ADHD group [p=0.3]. Training-related changes in P3b amplitude are displayed in Figure 6.11.

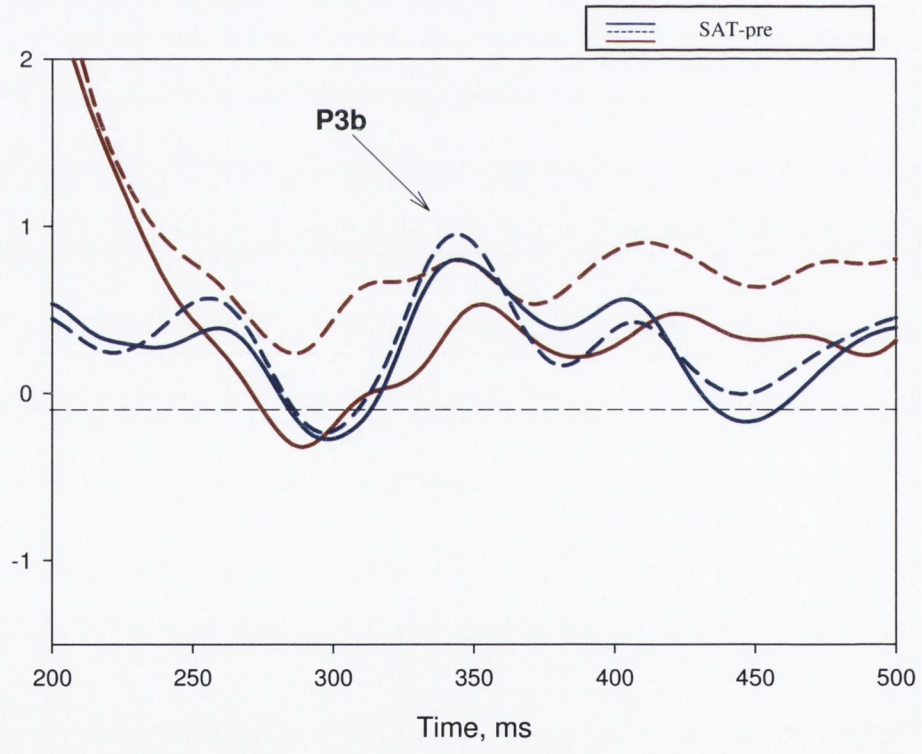


Figure 6.11 **Effects of SAT training on P3b amplitude**. Displays SAT-ADHD and Placebo-ADHD group Grand-Average waveforms at CPz averaged for correct Go responses pre- and post-training. In order to highlight changes in P3 amplitude these ERPs have been cropped to an epoch +200 to +500 ms after stimulus onset. The Placebo-ADHD group showed a significant decrease in P3 amplitude post-training but no differences were found for the SAT-ADHD group.

LP1

A significant main effect of Phase [$F_{(1,15)}$=16.5, p=0.001] was found but there was no main effect of Group [$F_{(1,15)}$=1.8, p=0.2] and no Phase by Group interaction [$F_{(1,15)}$=1.9, p=0.2]. Thus both groups exhibited a decrease in LP1 amplitude over time and this was not affected by SAT.

LP2

The same pattern of results was found as for the LP1 with a significant main effect of Phase [$F_{(1,15)}$=14.4, p=0.002] but no main effect of Group [$F_{(1,15)}$=0.1, p=0.7] and no Phase by Group interaction [$F_{(1,15)}$=0.2, p=0.6]. Therefore, LP2 amplitude was not affected by SAT.

Tonic Measures

No significant effects were found for any of the tonic measures analysed (all F values <1).

6.4.3 Discussion

In this experiment SAT produced a very similar pattern of improvements in a group of adults diagnosed with ADHD to those seen amongst non-ADHD adults in Experiment 7. During training, participants with ADHD showed no difficulty in gaining volitional control of their EDA responses and were able to fulfil the criteria of producing five un-cued SCRs within the 30-minute training period. The block-by-block analysis of SCRs post-training indicates that the SAT group did implement the training strategy during SART performance, although the improvement in arousal appeared to dissipate by the third and fourth blocks. Given that the healthy adults in Experiment 7 showed a more persistent training effect, this drop-off may reflect decreased capacity for volitional modulation of arousal in ADHD. The fact that the adult ADHD group successfully completed training, and were able to increase their arousal during the first two blocks of

post-testing, suggests that increasing the length and intensity of the training session might be sufficient to achieve longer lasting effects.

As in Experiment 7, an increase in SCRs during post-testing was accompanied by a significant improvement in the rate of SART commission errors, with SAT participants making 32% fewer errors after training. Thus, as hypothesised, volitional modulation of arousal did lead to improved sustained attention during performance of an untrained neuropsychological task. Similar to Experiment 7, the placebo group exhibited a clear increase in GoRT variability over time accompanied by a gradual decrease in arousal responses. In contrast, the SAT group were able to maintain a more consistent level of GoRT variability over time suggesting that increased modulation of arousal prevented the onset of time-on-task decrements in frontal-control.

Similarly, only the placebo group showed a post-training decline in P3b amplitude, a component that reliably indexes the allocation of attentional resources (Coull, 1998; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005 see also Experiment 3). As discussed in Chapter 4, extracellular recordings in the primate brain and pharmacological studies in humans have provided strong evidence for a close relationship between the LC/NA arousal system and the P3b (Nieuwenhuis et al, 2004). Given that the LC/NA system is heavily involved in innervating the cortical sustained attention network, it is interesting that increased arousal following SAT specifically affected this ERP component. Recent attempts to localise the generator of the P3b have implicated a distributed cortical network of bilateral prefrontal and parietal regions (Soltani & Knight, 2000). It is possible, therefore, that there is a degree of overlap between the cortical regions involved in sustained attention and those involved in P3b processes. Importantly, the P3b was measured over all Go trials of the SART and therefore this finding suggests that SAT-releated improvements in the allocation of attention sustained across the entire task duration.

The observed increases in phasic arousal, indexed by SCRs and P3b, did not translate to a generalised increase in cortical arousal as measured by spectral EEG power. Since the purpose of SAT was to teach participants to modulate their arousal levels in a periodic and phasic manner, it is not necessarily surprising that training effects do not come

through in tonic EEG measures that are averaged over the full SART block. SAT effects were seen in SCR amplitudes, the actual focus of the training, and in GoRT variability measures that may provide a more sensitive measure of frontal influences on task performance than the global tonic EEG measures. A speculative explanation for this dissociation is that increased volitional modulation of autonomic arousal encouraged SAT group participants to perform the task in a more consciously driven and controlled manner, perhaps via increased activation of frontal regions. While these improvements did not necessarily lead to a generalised increase in cortical arousal, they appear to have been sufficient to reduce the rate of attentional failures and limit GoRT variability. The addition of functional imaging methodologies in future studies of the SAT would provide futher insights into the precise brain regions that are affected.

The SAT protocol used in the present experiment was a brief pilot version designed to investigate, in a preliminary fashion, whether repeated volitional modulation of autonomic arousal would trigger increased activation of fronto-parietal networks involved in the top-down control of sustained attention. The training procedure lasted between 30 and 40 minutes in each case and therefore did not represent an extended attempt at cognitive remediation. Nevertheless, it was found that by the end of training all participants were able to phasically modulate their arousal levels in an endogenous manner without any visual feedback and without any external prompting from the experimenter.

Participants did not practice any neuropsychological task during SAT but were asked to implement the self-alert strategies they had learned while they performed four blocks of the fixed SART during post-testing. As a result, the clear behavioural improvements that were seen after SAT in normal healthy adults and adults with ADHD represent a neuropsychological generalisation of training effects. In the present study participants were cued to self-alert during SART performance. The inclusion of cues made it possible to measure the magnitude of arousal responses during self-alerting in an objective manner. However, a key feature of self-alerting is that it can, in theory, be performed in the absence of any external cue and could therefore be applied in a wide range of real world settings. Future work should investigate whether similar

improvements in performance can be achieved when participants are not cued to self-alert.

Although it cannot be directly demonstrated, the results of Experiment 7 and 8 are consistent with the initial hypothesis that increased volitional control of arousal would lead to improvements in sustained attention. Thus, while Experiment 6 targeted the sustained attention network via its bottom-up influences, SAT targeted sustained attention via its top-down influences. SAT may be particularly beneficial for adults suffering from ADHD since this disorder produces relatively subtle neuropsychological abnormalities that do not preclude direct training within the affected domains. These experiments have demonstrated that a relatively simple cognitive intervention can lead to substantial neuropsychological improvements amongst adults with ADHD. The possibility that extended SAT and implementation of training strategies in everyday life would lead to lasting improvement in frontal brain function and sustained attention is an exciting possibility worthy of further investigation.

6.4 Chapter Summary

In the present chapter, two new approaches to the cognitive remediation of sustained attention deficits in ADHD have been evaluated. In Experiment 6 it was demonstrated that children with ADHD benefit, at least in the short-term, from the periodic presentation of auditory tones that remind them to concentrate on the task at hand. In Experiments 7 and 8 it was demonstrated that adults both with and without ADHD could learn to consciously modulate a physiological measure of arousal during the performance of an un-trained sustained attention task. This training technique produced significant improvements on behavioural, EDA and ERP markers of sustained attention. The experiments described in this chapter have demonstrated that there may be valuable alternatives to the purely practice-based remedial strategies that have been applied to individuals with ADHD.

Chapter 7. General Discussion

7.1 Disentangling the Neuropsychology of ADHD

By combining cognitive conceptual research with direct investigation of brain function through studies of animal models, human lesioning, pharamacology and brain imaging, researchers in the field of cognitive neuroscience have been able to develop accurate neural models of the human executive control system. This work has demonstrated clearly that flexible, goal-directed behaviour is not achieved by a unitary process but arises from the complex and dynamic interaction of multiple overlapping executive sub-processes (Bradshaw, 1999; Fuster, 1999; Posner & Raichle, 1994). Our understanding of the causal role of executive function (EF) deficits in ADHD has followed a very similar course. Until recently single-cause etiological models were dominant. However, increasing evidence indicating that no single neuropsychological process could account for the majority of cases of ADHD has led to a realisation that the disorder probably arises from multiple pathophysiological pathways (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003). Importantly, a growing literature emphasising motivational abnormalities has suggested that cognitive deficits represent just one facet of this disorder. Hence, it has become clear that traditional behavioural descriptions of neuropsychological deficits have failed to reflect the complexity of pathophysiology underlying ADHD. A major theme of the first part of this thesis has been that cognitive neuroscience, with its focus on understanding the neural instantiation of neuropsychological functions, provides a means of disentangling cognitive deficits in ADHD and delineating their neural substrates.

In Chapters 3 and 4, this approach was employed by combining electrophysiological measures of brain function with cognitive paradigms for which valid brain-behaviour relationships had already been established. The high temporal-resolution afforded by Event-Related Potentials (ERP) allows one to assay the temporal characteristics of discrete components that underlie complex cognitive processes, such as executive control. In addition, measures of Electrodermal Activity (EDA) were acquired since the

autonomic nervous system is heavily influenced by the same ventro-limbic circuits that have been implicated in motivational accounts of ADHD (Bush, Luu, & Posner, 2000; Critchley, Elliot, Mathias, & Dolan, 2000; Sonuga-Barke, 2003). Hence, the co-acquisition of these two electrophysiological parameters provided a method for investigating the contribution of both cognitive and motivational processes to the performance of the same executive task. These methods were applied in Chapter 3 and 4 to investigate two potentially important aspects of the neuropsychology of ADHD that are still quite poorly understood: sustained attention and error processing.

Chapter 3 was concerned with the paradox that sustained attention deficits in ADHD remain controversial despite being emphasised in diagnostic criteria and despite substantial evidence of right-frontal abnormalities (Bush et al., 2005; Durston, 2003; Krain & Castellanos, 2006). It was argued that the traditional reliance on time-on-task performance decrements as an index of sustained attention is not in accord with data from functional imaging that activity in the right fronto-parietal cortical network governing sustained attention fluctuates over far shorter time-periods than was previously thought (Weissman, Roberts, Visscher, & Woldorff, in press). The SART (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) represented an ideal paradigm for investigating sustained attention deficits in ADHD for three reasons. First, the SART was specifically designed to measure sustained attention in a moment-to-moment manner. Second, unlike traditional CPT tasks, the SART places the emphasis on sustained attention in the context of routine action and has been shown to provide a better index of everyday attentional failures. Third, previous functional imaging work with the SART had established activation foci in right-fronto-parietal cortex (Fassbender et al., 2004; Manly et al., 2003) and ERP studies had identified a distinct pattern of electro-cortical activity (Dockree, Kelly, Robertson, Reilly, & Foxe, 2005). Hence, by acquiring ERP measures during SART performance it was possible to systematically verify the efficiency of the neural processes underlying sustained attention in ADHD.

Experiment 1 began with an electrophysiological validation of the fixed version of the SART which demonstrated clearly that response inhibition is not a prerequisite for successful performance of this task, hence removing a potential confound in ADHD

research. As predicted, Experiments 2 and 3 revealed that children and adults with ADHD had an increased propensity for momentary failures of sustained attention. In addition, the ERP data in Experiment 3 identified specific abnormalities in later stages of stimulus-processing associated with the allocation of attentional resources to utilising the predictable stimulus sequence (P3b) and maintaining goal activation (LP2). These findings provided confirmation that top-down influences on sustained attention are disrupted in ADHD and are in accord with reports of both fronto-striatal and fronto-parietal abnormalities in ADHD (Bush et al., 2005; Durston, 2003; Krain & Castellanos, 2006). Interestingly, the EDA data of children and adults also indicated that these sustained attention deficits were exacerbated by a physiological insensitivity to errors. However, since rates of error awareness had never been verified in an ADHD population, the possibility existed that lower rates of awareness contributed to decreased EDA responses and decreased post-error performance adjustment. This issue motivated the experiments conducted in Chapter 4.

The goal of Chapter 4 was again to disentangle separate neuropsychological processes, this time during error processing, and to test to what extent they were impaired in ADHD. Experiment 4 began by identifying electrophysiological markers for error awareness in a sample of healthy participants using a previously validated awareness paradigm (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005). This investigation revealed that the error positivity (Pe) is strongly modulated by awareness while two other components seen on error trials, the Error-Related Negativity (ERN) and early positivity, likely reflect aspects of performance monitoring that appear to occur outside of conscious awareness. In addition, source analysis indicated an anterior cingulate (ACC) contribution for all three of these components, however the Pe was distinguished from the ERN and early positivity by a more rostral generator. Rostral ACC (rACC) regions are thought to play a role in affective processes that are likely to be enhanced when we become aware that we have made an error (Bush, Luu, & Posner, 2000). Finally, a correlation between tonic EEG measures of cortical arousal and both error awareness and the amplitude of the Pe suggested that one's background state of alertness may determine whether or not an error reaches conscious perception.

Using this information as a normative baseline the same processes were then examined in a group of adults with ADHD in Experiment 5. The behavioural data indicated that ADHD participants were significantly less likely to be aware of their errors than matched controls. Importantly, there was no relationship between rates of error awareness and response inhibition performance, providing further evidence against unitary response inhibition accounts of ADHD (Barkley, 1997). The ERP data provided valuable insight into the nature of these deficits by identifying abnormalities in aspects of performance monitoring that impacted on response inhibition performance (early positivity) and an apparently independent deficit in the conscious processing of errors (Pe, EDA). Thus, although participants with ADHD had poorer error awareness they also exhibited abnormal error processing even when errors were consciously detected. Source analysis revealed that the attenuation of the Pe was attributable to reduced activation of the rACC which, in keeping with the EDA data, may reflect differences in the subjective appraisal of errors.

The experimental findings reported in Chapters 3 and 4 have therefore provided a clear illustration of the complex neuropsychology of ADHD. Both the SART and EAT were designed to assess discrete aspects of cognition in relative isolation of other cognitive processes, yet the electrophysiological data revealed that performance deficits were associated with multiple underlying neurophysiological abnormalities. In Chapter 3, momentary lapses of sustained attention were accompanied, and exacerbated by, additional deficits in error processing as indexed by EDA. In Chapter 4, poor performance on a response inhibition task was accompanied by disruption of performance monitoring processes (early positivity), reduced error awareness and differences in the subjective processing of detected errors (Pe, EDA). Hence, by adopting the methods of cognitive neuroscience it was possible to dissociate the neural processes underlying the performance of these neuropsychological tasks, allowing a more sophisticated analysis of cognitive deficits in ADHD. The work in Chapters 3 and 4 demonstrates that EF deficits in ADHD can only be properly understood by adopting methods that are capable of parsing complex cognition into its sub-components.

7.1.1 Interaction of cognitive and motivational processes in ADHD

An ever increasing literature has demonstrated the presence of impairments in incentive, motivational and reward-related processing in ADHD (Sagvolden, Borga Johansen, Aase, & Russell, 2005) and as a result there has been increasing interest in the interplay of cognitive and motivational abnormalities in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sagvolden, Borga Johansen, Aase, & Russell, 2005; Sonuga-Barke, 2000). A recently proposed dual-process model, that incorporates the latest beheavioural and neuroanatomical evidence, proposes that neuropsychological deficits in ADHD are attributable to dysfunction in separate dorso- and ventro-fronto-striatal pathways governing primarily cognitive and primarily motivational aspects of EF respectively (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003). According to this model, cognitive deficits in ADHD are largely underpinned by disturbances in the DLPFC sub-circuit and changes in meso-cortical dopamine pathways, while motivational problems arise from disruption of the orbitofrontal cortex (OFC) and ACC sub-circuits that are modulated by meso-limbic branches of the dopamine system (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, 2003 see also Figure 1.3). Taken together, it seems that the deficits observed in Chapters 3 and 4 could also be divided along similar lines. Behavioural deficits in response inhibition, sustained attention and response variability and their ERP correlates in aspects of performance monitoring and continuous attentional allocation appear to point to abnormalities in primarily cognitive aspects of EF. In contrast, EDA abnormalities and reduced Pe amplitudes during error processing may reflect deficits in primarily motivational aspects of EF.

Interestingly, the neuropsychological and electrophysiological processes examined in this thesis may also map on to separate dorsal and ventral EF pathways. A strong neuroimaging literature has already indicated that regions of the DLPFC modulate sustained attention and response time variability in a top-down manner (Bellgrove et al., 2004; Posner & Raichle, 1994; Sturm & Wilmes, 2001; Stuss et al., 2003). The findings of Experiments 4 and 5 suggest that error awareness is also dependent on top-down control of attention. In contrast, lesion and neuroimaging work has demonstrated that EDA is heavily influenced by ACC and OFC pathways and this measure has been

frequently used in psychological research for its sensitivity to affective processing of motivationally significant stimuli (Bush et al 2000; Critchley et al 2000; 2001; Dawson et al, 2000). A similar distinction may also be made between the two ACC regions implicated in error processing by source analysis in Experiment 4. In a recent article, Castellanos and colleagues (2006) suggest that the dorsal ACC, which oversees higher-order cognitive processes such as performance monitoring and conflict resolution, would form part of the dorsal EF pathway. In contrast, rostral regions of the ACC have strong connections to OFC and limbic regions and are more likely to form part of the ventral EF pathway. Hence attenuated early positivity and Pe components in ADHD might reflect separate pathophysiological processes in dorsal and ventral EF pathways respectively. Given the limitations of source analysis (see Chapter 2) this assertion could be profitably tested by combining the techniques of EEG and neuroimaging.

So how might motivational and cognitive deficits interact? According to Sonuga-Barke (2003), the ventral and dorsal EF pathways are not entirely independent but operate in parallel to guide our behaviour in accordance with our current goals and prevailing motivational states. In particular, Castellanos and colleagues (2006) predict that motivational impairments should impact upon EF in situations that have high affective content or when task performance is dependent on one's appraisal of the affective significance of an event or stimulus. Arguably the most motivationally significant event during relatively mundane tasks, like the SART and EAT, is the occurrence of an action error. The fact that EDA, which has been frequently employed as a measure of affective significance in psychological research (Dawson et al, 2000), was attenuated amongst children and adults following errors on both of these tasks provides some support for this model. Previous studies have found that patients who have suffered damage to ventral prefrontal regions tend to show reduced EDA responsiveness to emotionally significant events, including errors on cognitive tasks, and continue to persist in behaviours that are obviously detrimental to their goals (Damassio et al 1991, Zahn, Grafman and Tranel, 1999). Similarly, in the studies reported in this thesis, children and adults had normal EDA responses to correct withholds and external cues suggesting that error processing differences arose specifically from abnormal processing of significance. The findings of Chapter 4 did suggest that EDA differences were attributable, in part, to failures of error awareness but abnormalities were still evident

when the groups were compared on consciously detected errors. The fact that EDA responses to errors predicted SART accuracy suggested that a reduced subjective appraisal of error significance contributed to decreased allocation of top-down attentional resources following an error. Similarly, reduced Pe and SCR amplitudes on consciously detected errors in Experiment 5, may explain why several studies have found that individuals with ADHD are less likely to implement corrective response-time adjustments following errors on Go/No-Go tasks (e.g. Sergeant & Van der Meere, 1988; Schachar et al 2004; Wiersema et al 2004). These data suggest that poor EF on the SART and on the EAT may arise from a combination of cognitive and motivational abnormalities and demonstrate the importance of employing methodologies that reflect the multi-faceted nature of ADHD.

In contrast, the results of this thesis provide little support for a unitary executive deficit. For example, in Experiments 2 and 3 sustained attention performance was found to be correlated with both reaction time variability and errors of omission consistent with previous evidence that all three measures reflect the extent of frontally-guided top-down control. In Experiment 5, response inhibition was not correlated with reaction time variability, errors of omission or error awareness. Furthermore, the disruption of performance monitoring processes reflected in the early positivity appeared to affect response inhibition but not error awareness. This pattern of findings suggests that while error awareness and sustained attention may share common neural substrates, deficits in response inhibition appear to be independent of these processes.

7.1.2 Limitations

It is important to acknowledge that attributing the EF deficits seen in Chapters 3 and 4 to disruption of discrete fronto-striatal pathways is likely to be an oversimplification. The original focus on the role of prefrontal cortex in ADHD arose from evidence that patients with brain lesions in this area experienced difficulties regulating their behaviour. Indeed, Chapter 1 reviews the strong evidence that frontal regions are disrupted in ADHD. However, imaging work has also identified more widespread

structural and functional abnormalities in regions such as the parietal cortex and the cerebellum (see Bush, Valera, & Seidman, 2005; Schneider, Retz, Coogan, Thome, & Rosler, 2006; Seidman, Valera, & Makris for reviews). In fact, cerebellar abnormalities have been amongst the most consistent findings in imaging studies of ADHD and Castellanos and colleagues (2002) reported that volume reductions in this region were greater than those observed in the frontal lobe and also correlated with attentional problems and symptom ratings. The cerebellum has reciprocal projections to the frontal cortex, via the thalamus, forming a functional network which influences executive, inhibitory, affective and motor control processes (Schneider, Retz, Coogan, Thome, & Rosler, 2006). Like frontal lesion patients, patients with cerebellar lesions also display executive impairments and disinhibition of behaviour (Schmahmann & Sherman, 1998). Hence, disruption of fronto-cerebellar connections could equally account for many of the symptoms of ADHD.

Based on computational and animal models, Casey and Durston (2006) have recently proposed that top-down control deficits in ADHD could arise from abnormalities in bottom-up regions that are necessary for identifying situations when top-down control is needed. Regions such as the cerebellum, the basal ganglia and the parietal cortex all have projections to prefrontal cortex providing a means of signalling prefrontal regions to impose top-down control over behaviour. Interestingly, like the dual-pathway models mentioned earlier, this kind of model is capable of accounting for causal and neuropsychological heterogeneity in ADHD. Although some evidence was provided in this thesis that supports the notion of separate pathophysiological pathways in ADHD, the spatial resolution of ERPs and source analysis is limited. As a result, any inferences regarding the structure and location of these pathways must be considered tentative. Further work combining ERP and brain imaging methodologies would be desirable to advance our understanding of the biological bases of EF deficits in ADHD. Diffusion tensor imaging may be particularly useful in this regard since this technique makes it possible to examine the functional integrity of the white matter fibres innervating fronto-striatal pathways (Ashtari et al., 2005).

Aside from reducing statistical power, the relatively small sample sizes in each of the experiments in Chapters 3 and 4 limits the extent to which findings can be generalised

to all ADHD sufferers. As discussed in Chapter 1, DSM-IV specifies three ADHD-subtypes: combined (ADHD-C), predominantly inattentive (ADHD-I) and predominantly hyperactive (ADHD-H). A small sample size in Experiment 2 meant that it was not possible to conduct analyses that were sensitive to subtype differences while only ADHD-C participants were recruited for Experiments 3 and 5. As a result it is not possible to ascertain from the present data whether or not the observed deficits apply to all three subtypes. In fact, this issue is frequently neglected in the general literature despite some indication that the subtypes do differ. For example, recent studies have reported that patients with ADHD-C could be distinguished from patients with ADHD-I by significantly stronger deficits in time-estimation and response inhibition (Mullins, Bellgrove, Gill, & Robertson, 2005; Nigg, Blaskey, Huang-Pollock, & Rapply, 2002). Although it might be hypothesised that sustained attention and error awareness deficits would relate to behavioural deficits on the inattention axis of the DSM criteria it was not possible to verify this in the present set of experiments. Whether DSM-IV subtypes can be dissociated based upon the deficient cognitive processes and ERP componentry identified in this thesis, will be an important question for future research.

7.1.3 Future Directions

The experiments described in Chapters 3 and 4 have identified a number of ERP markers for sustained attention, error awareness and performance monitoring deficits in ADHD. A major challenge for future work will be to use this information to develop reliable biomarkers for this disorder. Individual ERP components are heritable characteristics with their own genetic and neurochemical influences (Fallgatter, Hermann et al., 2004). Moreover, several of the ERP components studied in this thesis have already been linked to specific neurotransmitter systems. For example, recent pharmacological work has demonstrated that the ERN, and not the Pe, is sensitive to changes in levels of dopamine (reviewed in Overbeek et al 2005). While no ERN abnormalities were found amongst adults with ADHD, the work in Chapter 5 suggests that the early positive component, which was attenuated in this sample, likely reflects the same monitoring process and is generated by the same cortical region. Hence the early positivity may provide a valid marker for dopaminergic insufficiencies in ADHD.

In addition, the P3b is closely tied to noradrenergic (NA) transmission (Nieuwenhuis et al., 2005) which has been proposed to be dysfunctional in ADHD (Biederman & Spencer, 1999). Recent studies, and Experiment 4, have provided evidence that both the P3b and the Pe index a phasic facilitation of task-specific brain regions mediated by activity in the NA/LC arousal system. A study by Sponheim, McGuire and Stanwyck (2006) has reported that P3b abnormalities distinguished first-degree relatives of schizophrenia patients from the relatives of non-psychiatric participants. A number of studies have also demonstrated that EDA characteristics are heritable (Crider et al., 2004; Iacono, Ficken, & Beiser, 1999).

Since many of the neuropsychological characteristics of ADHD are also seen in other neurodevelopmental disorders (Pennington & Ozonoff, 1996), the use of ERPs biomarkers that would allow us to link gene, physiology and cognition has the potential to provide a valuable and objective diagnostic tool and provide targeted intervention for rehabilitative efforts via pharmacotherapy or cognitive training. One possibility which arises from dual-process accounts is that the combination of multiple biomarkers might lead to a considerable increase in their sensitivity to ADHD. A possible prediction is that the combination of ERP and EDA biomarkers would increase their specificity to ADHD in a manner similar to that reported when behavioural measures of EF and reinforcement processing were combined by Solanto and colleagues (2001). While it is hoped that the findings of this thesis will help guide the development of biomarkers, further studies that include larger samples and a range of other clinical conditions will be required to establish their specificity for ADHD. In addition, further studies that would examine the association of ADHD candidate-genes in the dopaminergic, noradrenergic or serotonergic systems with electrophysiological markers such as ERN, Pe, P3b, LP2 and EDA are required.

As mentioned above, the investigations of sustained attention and error awareness identified neuropsychological abnormalities that could be classified as primarily cognitive or primarily motivational in character. One possible method to distinguish these two types of abnormality would be to increase the motivational saliency of the tasks and to examine whether this has a differential impact on performance deficits. For example, if rewards were provided for accurate performance of the SART one might

hypothesise that this would impact primarily on EDA responses to errors and less on the amplitude of the P3b and LP2. Similarly, if rewards were provided for the EAT one might expect the most prominent changes to be seen in conscious error processing, reflected in the Pe and EDA, as opposed to performance monitoring and response inhibition.

Another important challenge for future work will be to establish the extent of awareness difficulties in ADHD. Experiment 5 provided important first insights that individuals with ADHD are less aware of their errors. Prigatano and Schactar (1991) define two different types of awareness: "local awareness" of one's performance and "global awareness" which refers to awareness of one's disorder. Global awareness, often measured in terms of the discrepancy between self and other ratings of symptom severity (O'Keeffe, Dockree, & Robertson, 2004) is unlikely to be affected in ADHD since self and other symptom ratings for this disorder are highly correlated (Conners, Erhardt, & Sparrow, 2003). Reduced conscious detection of errors suggests that individuals with ADHD do have deficits in local awareness. Awareness of motor, language, cognitive and behavioural deficits are dissociable in clinical populations and some authors have proposed that the neural circuits responsible for self awareness in these different domains are at least partly separable (Turner & Levine, 2004). Therefore further work will be required to ascertain whether awareness deficits in ADHD extend beyond the detection of momentary action errors. Future studies should also investigate how reduced error awareness impacts on post-error correction and whether this problem exacerbates deficits in other cognitive domains in ADHD. In addition, studies that employ functional imaging will be necessary to confirm the source analysis findings of Experiments 4 and 5. Most importantly, studies that investigate whether individuals with ADHD experience awareness difficulties during everyday life activities are necessary.

7.2 Neuro-remediation via cognitive training

Chapter 5 explored what may prove to be a valuable new avenue for the non-medical treatment of ADHD: neuro-remediation via extended cognitive training. Chapter 5

reviewed the convincing evidence that the human brain retains a strong capacity for plasticity and self-repair across the lifespan. Using the knowledge gained from cognitive neuroscience, practitioners in the field of cognitive rehabilitation have demonstrated that carefully structured training protocols can produce clinically significant improvements in cognitive and motor abilities that have been disrupted by brain damage. While work in this area is still at a relatively early stage, a small number of functional imaging studies have shown that these improvements are accompanied by increased activation within the affected brain regions (Sturm, Longoni, Weis et al., 2004; Wexler, Anderson, Fullbright, & Gore, 2000).

Research has also revealed that even the cognitive capacities of healthy individuals are amenable to significant experience-dependent changes that are also accompanied by increased efficiency within underlying neural networks (e.g. Olesen, Westerberg, & Klingberg, 2004). This evidence has led to the proposition that neural plasticity could be exploited to address the comparatively subtle neuropsychological deficits associated with ADHD. Of the five studies that have attempted neuro-remediation of ADHD, all five reported significant improvements in the targeted cognitive function. In four out of five studies, extended training of a single cognitive process led to generalised improvements on untrained neuropsychological tasks and/or measures of everyday life functioning. In the largest of these studies, working memory training led to improvements in parent ratings of ADHD symptom severity that were comparable to those seen following pharmacological interventions (Klingberg et al., 2005). Thus, there is encouraging preliminary evidence to suggest that neuro-remediation by cognitive training can be developed as an effective alternative treatment for ADHD. The second major aim of this thesis was to add to this growing evidence base by developing a new training strategy that would target some of the neuropsychological deficits that were identified in Chapters 3 and 4.

Chapter 6 explored the possibility that sustained attention deficits in ADHD can be alleviated by techniques that are based on existing knowledge of brain-behaviour relationships in sustained attention. The periodic auditory alerting strategy employed in Experiment 6 was based on evidence that the sustained attention system receives influential bottom-up projections from subcortical arousal systems that can be

modulated by exogenous stimulation (Manly et al., 2004). The alerts were presented while children with ADHD performed the SART and were associated with the instruction to concentrate harder on the task at hand in order to encourage increased top-down control of sustained attention. Reduced error-rates on the next target following an alert indicated that this strategy was successful in the short-term. No long-term improvement was found suggesting that the children had difficulty increasing top-down control even when cued to do so.

Self-Alert Training (SAT), developed in Experiments 7 and 8, was designed with the specific aim of targeting these top-down difficulties. SAT represented a departure from the strategies described in Chapter 5 since participants did not practice a particular cognitive task during training but instead learned to consciously modulate a physiological measure of arousal (EDA). The rationale for this approach was that volitional modulation of arousal increases activation of prefrontal regions that are also involved in regulating sustained attention (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Sturm & Willmes, 2001). Using a protocol previously validated by Robertson and colleagues (1995), EDA responses were first elicited by the experimenter using a loud exogenous stimulus. Gradually the participant was taught to produce comparable increases in arousal without any external prompting. In Experiment 7, SAT was piloted with a group of healthy undergraduate participants and its effects on sustained attention were contrasted with those of a sham-training placebo condition. A modified version of the SART was used as the pre-post measure of sustained attention capacity. Grey coloured stimuli, embedded in the normal SART sequence were used as a cue for participants who had received SAT to 'self-alert' hence providing an opportunity to measure the physiological effects of this procedure. Significant SAT training effects on SART performance were found including a reduced error rate and reduced response variability. In addition, these improvements were accompanied by clear increases in EDA indicating that SAT participants had successfully modulated their arousal during task performance.

In Experiment 8, the same procedures were administered to a group of adults with ADHD. These participants had no difficulty acquiring conscious control of their EDA responses and, as in Experiment 7, SAT was associated with significant reductions in

errors on the SART as well as improvements in response variability and increased EDA. In addition SAT appeared to protect against time-on-task reductions in the amplitude of the P3b, one of the ERP markers for sustained attention deficits that was identified in Experiment 3. Hence, evidence was provided that increased endogenous maintenance of arousal can be encouraged in ADHD through SAT leading to improved sustained attention performance. Importantly, while previous attempts at neuro-remediation have focused purely on child populations, Experiments 7 and 8 demonstrated that significant improvements in cognitive function can also be achieved in adult populations. This work has demonstrated that an improved understanding of the neuropsychology of ADHD can inform the development of new and effective remedial strategies. The possibility that experience-dependent changes in brain function can be exploited to produce lasting improvements in neuropsychological functions affected by ADHD is an exciting possibility and it is hoped that the present set of experiments will stimulate further work in this area.

7.2.1 Limitations

The experiments conducted in Chapter 6 were designed to verify whether manipulating known brain-behaviour relationships could produce relatively short-term improvements in sustained attention. These experiments were not designed to achieve long-lasting cognitive remediation. It has been shown that activating bottom-up and top-down influences on sustained attention leads to significant performance improvements however the extent to which these improvements might extend to everyday life was not investigated. A further limitation of the approach taken in Experiments 7 and 8 is that although SAT teaches participants to modulate their arousal without any external prompting, cues to self-alert were provided during SART post-testing. These cues were inserted to allow for the objective measurement of the physiological changes following each self-alert providing insights into the neural correlates of this process and participant compliance. What is not clear from these studies is whether or not participants with ADHD would be able to implement SAT procedures during task performance if such cues were not provided.

Chapter 5 concluded with a series of limitations and issues that require consideration if neuro-remediation is to be established as an effective evidence-based treatment for ADHD. In particular, more studies with large sample sizes and neurophysiological measures of treatment effects are necessary. In addition, there is evidence that treatment effects may be strengthened by only selecting individuals who actually display impairment of the targeted cognitive function.

7.2.2 Future Directions

An interesting question for future studies of SAT is whether or not the observed increases in sustained attention are accompanied by changes in other cognitive processes. In the original study by Robertson and colleagues (1995) it was found that sustained attention training led to an indirect improvement in the ability of stroke patients with unilateral neglect to orient to objects in left space. This finding was in keeping with evidence that the sustained attention network activates the orienting network via its modulatory influence on the LC/NA arousal system (Posner & Peterson, 1990). Since SAT targets sustained attention, similar effects might be hypothesised in ADHD. Indeed there have been a number of reports of poorer awareness of left space in ADHD (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Sheppard, Bradshaw, Mattingley, & Lee, 1999; Voeller & Heilman, 1988), that may be exacerbated by time-on-task effects (George, Dobler, Nicholls, & Manly, 2005). In addition, the results of Experiment 5 suggested that error awareness deficits in ADHD may arise from disruption of the same frontal control processes implicated in sustained attention. Therefore, another issue for future work would be to investigate whether implementation of SAT techniques leads to indirect improvements in error awareness.

An important step in establishing SAT as an effective treatment for ADHD will be to demonstrate the generalisation of improvements to everyday activities. In theory, the techniques that are learned during SAT should be applicable to a range of tasks and situations that require sustained attention. It is likely that an extended version of the

SAT protocol would be required to produce improvements that would last beyond the short-term. In Experiments 7 and 8, participants received just 30 minutes of SAT as the goal was to verify whether sustained attention could be manipulated via the self-alerting technique. Through extended practice of SAT techniques it may be possible to stimulate lasting improvements in the targeted neural regions that are similar to those seen following extended practice of a particular cognitive task. In addition, future studies should investigate whether a version of SAT can be developed for child populations.

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Appendix 1. Ethical Approval and Consent Forms

Dr Kevin Tierney
Chair of Ethics Committee
Department of Psychology
Trinity College
Dublin 2

20 December 2004

Dear Dr Tierney

RE: "Cognitive and motor functions in Children and Young Adults with ADHD in relation to DAT1 allele dosage: An examination using fMRI and event-related potentials (ERPs)" – see attached copy.

We seek a number of amendments to the existing Ethics Committee approval of the above stated project. We believe these amendments are minor and do not raise any new ethical issues.

1. We propose adding seven new psychological assessment tools to the current set approved by the Committee. These assessment tools are needed for additional clinical understanding of the control and ADHD participants. We may not always use these tools in each experiment. We will ensure that any additional psychological assessment tools do not add more than an additional 30 minutes to any one testing session. The time taken to administer these tools is listed in brackets beside the name. These tools are:

- Wechsler Adult Intelligence Scale III for young adults and the Wechsler Intelligence Scale for Children for the children (shortened versions for research purposes) (30 mins)
- Wide Range Achievement Test (10 mins)
- Standard Clinical Interview for DSM-IV Axis I disorders (SCID-I) (30 mins)
- Autism Quotient (inventory of adult Autism-like symptoms by Baron-Cohen) (10 mins)
- Hospital Anxiety and Depression Scale (2 mins)
- Conners Adult ADHD Rating Scales (long versions of self-report and observer reports) (15 mins per version)
- Cognitive Failures Questionnaire (2 mins)

2. We propose adding two new experimental procedures to the current set approved by the Committee. These procedures represent separate new experiments, to be performed during new appointment times with the patient and control groups. These procedures are:

- Error Awareness Task (Stroop-like Go/No-Go sustained attention task)
- Self-Alert Training

The **Error Awareness Task** is a neuropsychological test in which participants are presented with a string of colour words. Participants are required to press a button in response to each word except when a word has been repeated or when the word and its

colour are incongruent. If the participant makes a mistake they are asked to indicate this by pressing a second "awareness" button. This task is designed to measure sustained attention and error monitoring. This experimental procedure will take approximately one hour to complete with suitable rests for participants. We plan to run this procedure with the ERP, EDA (electrodermal activity) and fMRI equipment.

Self-Alert Training Procedure – participants learn to produce self generated increases in alertness first in response to an auditory cue and later in response to an internally generated cue. During SAT, visual feedback conveying the magnitude of each self alert event is provided via on-line changes in electrodermal activity (EDA). As a measure of training efficacy all participants will complete 10 blocks of the fixed SART, 5 before and 5 after the training session. A placebo group will also be included in this study. These participants will be asked to practice a computer game (Tetris) for the same length of time as the SAT procedure and will be told that practicing this computer game is thought to improve sustained attention. Placebo group participants will also complete 10 blocks of the fixed SART, 5 before and 5 after the training session. All participants will be fully debriefed at the end of the testing session. The total length of the testing procedure for each participant will be approximately one and a half hours with appropriate rest breaks. We plan to run this procedure with the ERP, EDA (electrodermal activity) and fMRI equipment.

3. We propose to expand the potential participant pool to include adults of any age. The current Ethics coverage includes children and young adults.

4. We seek approval for some of the ERP testing to occur at Saint Vincent's Hospital Fairview. Saint Vincent's Hospital has provided testing space for our experiments (see attached letter).

5. We seek to include an additional four co-investigators on this Ethics submission
    - Dr Paul Dockree
    - Dr Gina Joue
    - Dr Katherine Johnson
    - Mr Redmond O'Connell

6. We seek approval to ascertain participants' DAT1 genotype (10/10, 9/10 or 9/9) using saliva samples as an alternative to the cheek swab. The cheek swab has approval of the Ethics Committee.

The requested amendments do not involve the deception or withholding of information. They do not involve physical risk to the participants. They do not involve any psychological or social risks to the participants. There are no greater risks posed to participants than would be encountered in every day life.

The additional psychological assessment tools will require participants to reveal information of a sensitive nature. For instance, the Standard Clinical Interview for DSM-IV Axis I disorders (SCID-I) asks participants if they have ever suffered forms of psychosis, mood disorders and substance abuse. This information is required as part of the screening process for the research. The psychological tools will be administered in a professional and respectful manner.

As stated in the original Ethics proposal, power calculations have been performed to ensure we obtain adequate numbers of participants in each study. Based on previous behavioural studies in ADHD with moderate effect sizes, 18 participants are needed per ADHD sub-group (10/10, 9/10 and 9/9 DAT1 genotypes) and 54 controls will also be required.

We look forward to your consideration of this matter.

Kind regards

Professor Ian Robertson

14/01/2005

Dear Committee members,

We enclose for your consideration the details of our research with adults with Attention Deficit Hyperactivity Disorder (ADHD) to be conducted in the Neurophysiology laboratory recently set-up by Dr John Foxe in St Vincent's Hospital, Fairview. The neuropsychological and neurophysiological procedures described herein have already been approved by the Ethics committee at the Department of Psychology, Trinity College Dublin and the collection and analysis of genetic information has received ethical approval from the ethics committee at St James' Hospital (we append both letters of approval for your records). However, since the testing for this project will take place at St. Vincent's Hospital Fairview, we are also submitting the current proposal for consideration by the St.Vincent's ethics committee.

To summarise, we propose to administer three neuropsychological tasks and a simple cognitive training intervention to a cohort of adult ADHD and healthy control participants with simultaneous measurement of EEG (Electroencephalography) and EDA (Electrodermal Activity). The present study will investigate to what extent attention, inhibition and error monitoring deficits, as well as EEG and EDA abnormalities, which have been previously demonstrated in child populations, are present in adult ADHD. It is now accepted that between 30 and 50% of ADHD cases persist into adulthood making proper understanding of this disorder in its adult form of paramount importance. As part of our ongoing research, in collaboration with the departments of genetics and psychiatry, into the cognitive genomics of ADHD a saliva sample will be taken from each participant using a standard "Saliva Self Collection Kit" in order to assess their DAT1 genotype.

We thank you for your attention and look forward to hearing from you in due course.

Yours,

_____

Prof. Ian H. Robertson

21 February 2005

Mr Redmond O'Connell
Department of Psychology
Trinity College
Dublin 2

Dear Mr O'Connell

An investigation of attention and awareness in adults with Attention Deficit Hyperactivity Disorder

Your application for the above study was considered by the Ethics Committee at its meeting today.

The Committee would make the following comments

1. The word "placebo" (p9 ff) should be replaced by the word "control".

2. The results of the genetic testing should he anonymised.

3. As no pharmaceutical company is involved in the study the answer to Q 20(a) should read "no".

4. In p2 of the letter of Consent for Research Participants the words "Beaumont Hospital" should, presumably, be replaced by "St Vincent's Hospital, Fairview".

5. We note, in Section 19 that, in accordance with ethical guidelines of Trinity College Dublin, all genetic material will be disposed of after 7 years. The Committee would wish to reiterate that all patient data should remain anonymous.

Subject to receipt of a revised application form incorporating these observations, the study is herby approved.

We wish you well in your study.

Yours sincerely

Edward J Byrne
Chairperson Ethics Committee
St Vincent's Hospital
Fairview, Dublin 3

From: "Yvonne Lyons" <yvonnelyons@svhf.ie>
To: "Redmond O'Connell" <oconnelr@tcd.ie>
Subject: RE: Response from Ethics Committee
Date: 24 February 2005 17:17

Sorry for not e-mailing earlier, received your amended form.

Thanks

Yvonne

-----Original Message-----
From: Redmond O'Connell [mailto:oconnelr@tcd.ie]
Sent: 21 February 2005 17:04
To: Yvonne Lyons
Subject: Re: Response from Ethics Committee

Yvonne, please find attached our updated ethics proposal with the requested ammendments. Should I also send a copy by mail?
thanks

Redmond O'Connell

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Information Sheet and Letter of Consent: For the attention of Research Participants

An investigation of attention and awareness in adults with Attention Deficit Hyperactivity Disorder

Research Team: Professors Michael Fitzgerald and Ian Robertson and Drs. John Foxe, Paul Dockree, Mark Bellgrove and Katherine Johnson and Mr. Redmond O'Connell, Trinity College Dublin

What is the project?

We would like to invite you to participate in a study which is looking at how the brain attends to information in the world. In particular we are interested in understanding the attention problems that are associated with Attention Deficit Hyperactivity Disorder (ADHD).

ADHD is characterized by deficits in attention, inhibition and hyperactivity. While ADHD is probably best known as a disorder in childhood, 30-50% of all cases of ADHD also persist into adulthood. Gaining a proper understanding of ADHD in adulthood is therefore vitally important. People who are diagnosed with ADHD often experience difficulties concentrating and attending to details in the world around them. We would like to learn more about why this happens and how we might be able to help to alleviate such problems. For this study we need the participation of adults who have been diagnosed with ADHD and adults who do not have this diagnosis.

Our study will involve two parts:

The first part involves performing two simple computerized tests of attention while we measure electrical changes in your brain using an EEG cap. The tasks are very simple and involve attending and responding to different pictures and words on the computer screen. The EEG measures your brain's electrical activity by simple recorders called electrodes embedded in a cap which is placed on your head. This is a harmless tool, commonly used in this kind of research, which is not unpleasant or invasive and is not associated with risk of any kind. At the same time we will be taking measures of skin conductance from you. Skin conductance measures how alert your body is and involves attaching two small finger electrodes to the index and middle fingers of one hand. Again this measure is harmless and there are no known risks involved. This first session will last for approximately 1 hour and thirty minutes.

In the second part we will go through a simple training technique designed to help people to concentrate for longer periods of time. As well as this we will ask you to

complete another computerized test of sustained attention. Again during the training and computer testing we will be measuring EEG and skin conductance.

There are no risks associated with any of the procedures in this study and participants will be provided with frequent breaks to avoid fatigue Any costs associated with your travel to St Vincent's Hospital for this research will be covered by the project..

What are my rights if I join the study?
Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

The information from this study will be kept strictly confidential and will not be made available to any other people.

We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

As participation is completely voluntary, you are free to withdraw from the study at any time without it affecting present or future care by St. Vincents Hospital.

Under the Freedom of Information Act you can have access to any information we store about you, if requested.

I, the undersigned, give my informed consent to participate in the "investigation of attention and awareness in adults with Attention Deficit Hyperactivity Disorder" conducted by the ADHD Research Group, TCD at St. Vincent's Hospital Fairview.

Full Name: _____

Signed _____

Date _____

Redmond O'Connell
Research Investigator
Department of Psychology & Institute of Neuroscience
Trinity College Dublin
(Tel 01 608 8405; Email: oconnelr@tcd.ie)