NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the Swinburne Library.
Brain Electrical Activity Topography in Attention-Deficit/Hyperactivity Disorder

Maree Farrow, BAppSc(Dist)

Thesis for Doctor of Philosophy
November 2003

Brain Sciences Institute
Swinburne University of Technology
Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder characterized by developmentally inappropriate levels of inattentiveness, impulsivity and hyperactivity. Current theories of ADHD cite evidence from neuropsychological and brain imaging studies suggesting that abnormalities in the structure and function of the frontal lobes and connected brain regions are associated with impaired behavioural inhibition, constituting the primary deficit in ADHD. While most reviewers conclude that neuropsychological studies have failed to find specific deficits in various aspects of attention in ADHD, poor performance on attentional tasks, including the continuous performance task (CPT), is a common finding and previous electrophysiological studies suggest evidence of impaired attentional processing. This study aimed to investigate the cortical activity associated with attentional processes in children with and without ADHD, using steady-state probe topography (SSPT). Seventeen boys diagnosed with ADHD and seventeen age matched control boys participated. Changes in the amplitude and latency of the steady-state visually evoked potential (SSVEP) associated with correct responses to targets in the ‘X’ and ‘AX’ versions of the CPT were examined. At critical time points in both tasks, the control group demonstrated SSVEP changes suggesting increased activation and increased speed of neural processing. These effects occurred predominantly in medial frontal, right prefrontal, right parietal and occipital regions, suggesting enhanced activity in regions previously shown to be involved in attentional processes. The ADHD group demonstrated much smaller increases in activation and processing speed in frontal regions and predominantly reduced activation and slower processing in parieto-occipital regions. Group differences suggesting reduced activity in the ADHD group were observed in response to the presentation of both cues and targets, as well as in the intervals leading up to target presentation, especially in the cued CPT-AX. These results suggest that processing of task relevant stimuli as well as preparatory and motor processes may be associated with dysfunctional activation of brain networks of attention in ADHD, involving deficits in both frontal and parietal cortical regions. These regions may also be involved in the maintenance of information required for correct task performance and the results also suggest possible deficits in these processes in ADHD. The findings are consistent with others of reduced activation and cognitive deficits in
ADHD involving these brain regions and networks, and with the idea that ADHD may be associated with a diminished ability to regulate levels of arousal and activation appropriate to task demands.
Acknowledgements

I sincerely thank my supervisors, Professor Richard Silberstein and Professor David Hay, for sharing their knowledge and experience with me and making this project possible.

I would also like to acknowledge the contribution of our colleague, Associate Professor Florence Levy, and thank her for the discussions which helped to formulate many of the ideas expressed in this thesis. Thanks also to Dr Rick Jarman for sharing his clinical expertise and referring ADHD children to the study.

I am also most grateful to several colleagues who provided technical, intellectual and practical assistance with this project, especially Dr Andrew Pipingas, Mr Geoff Nield, Dr Guy Burkitt, Dr Alex Sergejew and Dr Catherine Wood.

This project would not have been possible without the participants and their families and I sincerely thank all of them for their time and their enthusiasm for the research.

Finally, very special thanks go to my family and friends, especially Scott and Tristan, for their continuing love, support and patience through a sometimes difficult process.
Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any University and to the best of my knowledge contains no material previously published or written by another person or persons except where due reference is made.

Maree Farrow
November, 2003
Contents

List of figures ................................................................. x
List of tables .............................................................. xi
List of abbreviations, symbols and units .................................. xii

Chapter 1  Introduction ............................................................... 1

Chapter 2  Clinical Aspects of ADHD ................................................. 6
  2.1  Introduction .......................................................................... 6
  2.2  Prevalence ........................................................................... 9
  2.3  Symptoms ............................................................................ 10
    2.3.1  Inattention ................................................................. 10
    2.3.2  Impulsivity ............................................................... 11
    2.3.3  Hyperactivity ............................................................ 11
    2.3.4  Other characteristics .................................................. 12
  2.4  Comorbidity ........................................................................ 12
  2.5  Developmental course .......................................................... 14
  2.6  Diagnosis ............................................................................ 15
    2.6.1  DSM-III-R criteria ...................................................... 15
    2.6.2  Issues for diagnosis ...................................................... 16
  2.7  Treatment .......................................................................... 18
    2.7.1  Stimulant medication .................................................. 18
    2.7.2  Other pharmacological treatments .................................. 20
    2.7.3  Other non-pharmacological treatments ............................... 21
    2.7.4  The multimodal treatment study of ADHD .......................... 21
  2.8  Conclusions ........................................................................ 22

Chapter 3  Neurobiological Correlates of ADHD ...................................... 24
  3.1  Neurochemistry ................................................................. 24
    3.1.1  Dopamine ................................................................. 25
    3.1.2  Noradrenaline ........................................................... 29
    3.1.3  Other neurotransmitters ............................................... 30
3.1.4 Conclusions for neurochemical anomalies in ADHD 31

3.2 **Neuropsychological research** 32

3.2.1 Studies of attention 33

3.2.1.1 Orienting and encoding 33

3.2.1.2 Focused, selective and divided attention 34

3.2.1.3 Visuo-spatial attention 35

3.2.1.4 Sustained attention – the continuous performance task 36

3.2.1.5 Conclusions for attention 41

3.2.2 Studies of frontal lobe / executive functions 41

3.2.2.1 Executive function tasks 42

3.2.2.2 Inhibition tasks 45

3.2.2.3 Conclusions for executive functions 46

3.2.3 Studies of parietal lobe functions 46

3.2.4 Conclusions for neuropsychological deficits in ADHD 47

3.3 **Neuroimaging research** 49

3.3.1 Structural imaging 49

3.3.1.1 Computerized tomography 49

3.3.1.2 Magnetic resonance imaging 50

3.3.1.3 Conclusions for structural imaging 54

3.3.2 Functional imaging 55

3.3.2.1 Positron emission tomography 55

3.3.2.2 Single photon emission computed tomography 59

3.3.2.3 Functional magnetic resonance imaging 61

3.3.2.4 Conclusions for functional imaging 63

3.4 **Electrophysiological research** 64

3.4.1 EEG studies 64

3.4.2 Event related potential studies 68

3.4.2.1 N1 and N2 in ADHD 68

3.4.2.2 P3 in ADHD 72

3.4.2.3 ERP studies of the CPT in ADHD 77

3.4.2.4 Conclusions for ERP research 79

3.5 **Conclusions and unresolved issues** 80
Chapter 4  Steady-State Probe Topography .................................................. 84
  4.1  Steady-state evoked potentials .......................................................... 84
  4.2  Steady-state probe topography .......................................................... 86
  4.3  Research utilizing SSPT ..................................................................... 88
  4.4  Aims and hypotheses of the current study .......................................... 91

Chapter 5  Assessment and Selection of Participants ............................... 93
  5.1  Introduction .................................................................................... 93
  5.2  Recruitment .................................................................................... 93
  5.3  Assessment methods ........................................................................ 95
      5.3.1  Parent and teacher questionnaires ............................................. 95
      5.3.2  Wechsler intelligence scale for children – third edition .......... 97
      5.3.3  Boder test of reading-spelling patterns .................................... 99
      5.3.4  Learning history ...................................................................... 101
  5.4  Participant exclusions ....................................................................... 101
  5.5  Final subject groups ......................................................................... 102
      5.5.1  ADHD ratings .......................................................................... 103
      5.5.2  Comorbidity ratings ................................................................. 104
      5.5.3  WISC-III results ...................................................................... 104
      5.5.4  Boder test results .................................................................... 106
      5.5.5  Learning interventions .............................................................. 107
      5.5.6  Medication status ..................................................................... 108
      5.5.7  Summary of assessment findings .............................................. 109

Chapter 6  Methods .................................................................................. 110
  6.1  Introduction .................................................................................... 110
  6.2  Cognitive tasks ............................................................................... 111
  6.3  EEG recording ................................................................................. 114
  6.4  Steady-state probe stimulus .............................................................. 115
  6.5  Procedure ....................................................................................... 117
  6.6  Signal processing ............................................................................ 117
      6.6.1  SSVEP calculation ................................................................... 117
      6.6.2  Artifact detection and compensation ...................................... 118
      6.6.3  Event averaging ....................................................................... 119
<table>
<thead>
<tr>
<th>Chapter 7</th>
<th>Results</th>
<th>123</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>Behavioural results</td>
<td>123</td>
</tr>
<tr>
<td>7.2</td>
<td>Electrophysiological results</td>
<td>125</td>
</tr>
<tr>
<td>7.2.1</td>
<td>CPT-X results</td>
<td>126</td>
</tr>
<tr>
<td>7.2.1.1</td>
<td>SSVEP topography in the CPT-X</td>
<td>126</td>
</tr>
<tr>
<td>7.2.1.2</td>
<td>SSVEP amplitude dynamics in the CPT-X</td>
<td>132</td>
</tr>
<tr>
<td>7.2.1.3</td>
<td>SSVEP latency dynamics in the CPT-X</td>
<td>136</td>
</tr>
<tr>
<td>7.2.1.4</td>
<td>Summary of CPT-X findings</td>
<td>139</td>
</tr>
<tr>
<td>7.2.2</td>
<td>CPT-AX results</td>
<td>139</td>
</tr>
<tr>
<td>7.2.2.1</td>
<td>SSVEP topography in the CPT-AX</td>
<td>139</td>
</tr>
<tr>
<td>7.2.2.2</td>
<td>SSVEP amplitude dynamics in the CPT-AX</td>
<td>145</td>
</tr>
<tr>
<td>7.2.2.3</td>
<td>SSVEP latency dynamics in the CPT-AX</td>
<td>149</td>
</tr>
<tr>
<td>7.2.2.4</td>
<td>Summary of CPT-AX findings</td>
<td>153</td>
</tr>
<tr>
<td>7.3</td>
<td>Summary of results</td>
<td>153</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 8</th>
<th>Discussion</th>
<th>155</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>Behavioural findings</td>
<td>155</td>
</tr>
<tr>
<td>8.1.1</td>
<td>Reaction time</td>
<td>155</td>
</tr>
<tr>
<td>8.1.2</td>
<td>Omission errors</td>
<td>157</td>
</tr>
<tr>
<td>8.1.3</td>
<td>Commission errors</td>
<td>158</td>
</tr>
<tr>
<td>8.1.4</td>
<td>Conclusions</td>
<td>160</td>
</tr>
<tr>
<td>8.2</td>
<td>Electrophysiological findings</td>
<td>161</td>
</tr>
<tr>
<td>8.2.1</td>
<td>CPT-X findings</td>
<td>162</td>
</tr>
<tr>
<td>8.2.2</td>
<td>CPT-AX findings</td>
<td>164</td>
</tr>
<tr>
<td>8.2.3</td>
<td>Frontal region effects</td>
<td>166</td>
</tr>
<tr>
<td>8.2.4</td>
<td>Posterior region effects</td>
<td>172</td>
</tr>
<tr>
<td>8.2.5</td>
<td>Networks of attention</td>
<td>174</td>
</tr>
<tr>
<td>8.2.5.1</td>
<td>Executive control network</td>
<td>176</td>
</tr>
<tr>
<td>8.2.5.2</td>
<td>Alerting network</td>
<td>177</td>
</tr>
<tr>
<td>8.2.5.3</td>
<td>Orienting network</td>
<td>179</td>
</tr>
<tr>
<td>8.2.5.4</td>
<td>Conclusions for attention networks</td>
<td>181</td>
</tr>
</tbody>
</table>
8.2.6 Tonic/phasic effects and state regulation ........................................... 182

8.3 Conclusions, limitations and future directions ........................................ 186

References ....................................................................................................... 191
Appendix One: Parent and teacher questionnaires ......................................... 240
Appendix Two: Task instructions .................................................................. 254
Publications by the author ............................................................................. 257
List of Figures

Figure 6.1  Summary of task presentation .............................................................. 112
Figure 6.2  Location of the 64 recording sites ....................................................... 115
Figure 6.3  Experimental recording arrangement .................................................. 116
Figure 7.1  Topography of baseline – CPT-X differences for the control group .................................................. 129
Figure 7.2  Topography of baseline – CPT-X differences for the ADHD group ............................................................. 131
Figure 7.3  SSVEP amplitude time series in the CPT-X at electrode 16 ............ 133
Figure 7.4  SSVEP amplitude time series in the CPT-X at electrode 57 .......... 134
Figure 7.5  SSVEP amplitude time series in the CPT-X at electrode 61 .......... 135
Figure 7.6  SSVEP latency time series in the CPT-X at electrode 4 .............. 136
Figure 7.7  SSVEP latency time series in the CPT-X at electrode 16 ............ 137
Figure 7.8  SSVEP latency time series in the CPT-X at electrode 57 .......... 138
Figure 7.9  Topography of baseline – CPT-AX differences for the control group .................................................. 141
Figure 7.10 Topography of baseline – CPT-AX differences for the ADHD group ............................................................. 143
Figure 7.11 SSVEP amplitude time series in the CPT-AX at electrode 16 .... 146
Figure 7.12 SSVEP amplitude time series in the CPT-AX at electrode 57 .... 148
Figure 7.13 SSVEP amplitude time series in the CPT-AX at electrode 61 .... 149
Figure 7.14 SSVEP latency time series in the CPT-AX at electrode 4 ........... 150
Figure 7.15 SSVEP latency time series in the CPT-AX at electrode 16 ........... 151
Figure 7.16 SSVEP latency time series in the CPT-AX at electrode 57 ........... 152
List of Tables

Table 5.1  WISC-III subtests ................................................................. 97
Table 5.2  Boder reading-spelling patterns ........................................... 100
Table 5.3  Group ADHD symptoms ....................................................... 103
Table 5.4  Comorbidity rates in the ADHD group .................................... 104
Table 5.5  WISC-III subtest scores ......................................................... 105
Table 5.6  IQ and Freedom from Distractibility scores ............................. 106
Table 5.7  Boder test scores ................................................................. 107
Table 5.8  Learning intervention rates .................................................... 108
Table 7.1  Mean reaction times, number of correct responses and numbers of errors for ADHD and control groups ...................... 124
## List of Abbreviations, Symbols and Units

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD</td>
<td>attention deficit disorder</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>Ag/AgCl</td>
<td>silver/silver chloride</td>
</tr>
<tr>
<td>ATAP</td>
<td>Australian twin ADHD project</td>
</tr>
<tr>
<td>ATBRS</td>
<td>Australian twin behaviour rating scale</td>
</tr>
<tr>
<td>CD</td>
<td>conduct disorder</td>
</tr>
<tr>
<td>Cd/m²</td>
<td>candela per square metre</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COVAT</td>
<td>covert orienting of visuo-spatial attention task</td>
</tr>
<tr>
<td>CPT</td>
<td>continuous performance task</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebro-spinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computerized tomography</td>
</tr>
<tr>
<td>DAT1</td>
<td>dopamine transporter</td>
</tr>
<tr>
<td>dB</td>
<td>decibel</td>
</tr>
<tr>
<td>DLPFC</td>
<td>dorso-lateral prefrontal cortex</td>
</tr>
<tr>
<td>DRD4</td>
<td>dopamine-4 receptor</td>
</tr>
<tr>
<td>DSM-III-R</td>
<td>diagnostic and statistical manual of mental disorders, third edition, revised</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>diagnostic and statistical manual of mental disorders, fourth edition</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyogram</td>
</tr>
<tr>
<td>EOG</td>
<td>electo-occulogram</td>
</tr>
<tr>
<td>ERP</td>
<td>event related potential</td>
</tr>
<tr>
<td>FDG</td>
<td>[(^{18})F]fluoro-deoxyglucose</td>
</tr>
<tr>
<td>FDI</td>
<td>freedom from distractibility index</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GFP</td>
<td>global field power</td>
</tr>
<tr>
<td>HVA</td>
<td>homovanillic acid</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
</tbody>
</table>
ICD international classification of diseases
IQ intelligence quotient
LD learning disability
LED light emitting diode
LVF left visual field
m metre
MFFT matching familiar figures test
MHPG 3-methoxy-4-hydroxyphenylglycol
MMN mismatch negativity
MRI magnetic resonance imaging
MRT mean reaction time
ms millisecond
MTA multimodal treatment study of children with attention-deficit/hyperactivity disorder
NHMRC national health and medical research council
ODD oppositional defiant disorder
PET positron emission tomography
PN processing negativity
RQ reading quotient
RVF right visual field
s second
SAD separation anxiety disorder
SPECT single photon emission computed tomography
SPM significance probability mapping
SSPT steady-state probe topography
SSVEP steady-state visually evoked potential
TOL Tower of London task
WCST Wisconsin card sort task
WISC-III Wechsler intelligence scale for children - third edition
° degrees
π pi
NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the Swinburne Library.
Chapter 1 Introduction

This study is an investigation of deficits in cortical activity associated with attentional dysfunction in attention-deficit/hyperactivity disorder (ADHD). ADHD is characterized by developmentally inappropriate levels of inattention, impulsivity and hyperactivity that cause impairment in day-to-day life, and is thought to affect 3 to 5% of children (American Psychiatric Association, 1994). It can be associated with a range of behavioural, academic and social problems that may lead to adverse outcomes in adulthood. It is increasingly being seen as of major public health significance in Australia, with a national survey finding that 11% of Australian children and adolescents met diagnostic criteria for ADHD (Birleson et al., 2000). With increasing recognition of ADHD over the past two decades has come research and debate about what defines the disorder. Despite extensive research aimed at investigating neurochemical, genetic, neuropsychological and neurophysiological abnormalities that may account for the behavioural symptoms and cognitive deficits associated with ADHD, our knowledge of the brain dysfunction underlying the disorder remains incomplete.

Performance on a wide range of neuropsychological tasks has been examined in ADHD. Much recent research has focused on executive function deficits, which have been found in ADHD using a number of different tasks, and measures of motor inhibition in particular have consistently shown performance deficits in ADHD children (Pennington & Ozonoff, 1996; Sergeant et al., 2002). This poor performance on executive function tasks is suggested to reflect frontal lobe deficits in ADHD (Barkley, 1997), although subcortical and parietal brain regions may also be involved (Sergeant et al., 2002). Children with ADHD have also been found to perform more poorly than normal controls on a variety of tasks designed to measure attention, especially on measures of vigilance such as the continuous performance task (CPT). As these tasks require the efficient use of a range of cognitive processes in addition to attention, poor performance does not necessarily indicate deficits in attention. Children with ADHD are found to be slow and inaccurate responders, and this task inefficiency is thought to result from dysfunctional processes at the output or motor stage of information processing, rather than earlier attentional stages (Barkley, 1997; Van der Meere, 1996). In terms of
behavioural symptoms, children with ADHD are consistently reported by parents and teachers to demonstrate inattention and distractibility. This behavioural inattention might also arise from deficits in inhibition and self-regulation and the effects these deficits have on task persistence (Barkley, 1997; Van der Meere, 1996).

Functional neuroimaging and electrophysiological techniques permit investigation of the brain activity underlying cognitive task performance. Functional neuroimaging techniques detect task-related changes in blood flow and can localize activation to within a few millimetres in both cortical and subcortical regions. However, these techniques have relatively poor temporal resolution and are used mainly to investigate activity that is sustained throughout a task. Electrophysiological techniques on the other hand have a temporal resolution in the order of milliseconds and can therefore monitor more transient changes in activity initiated by the presentation and subsequent processing demands of specific stimuli. However, the spatial resolution of non-invasive electrophysiology is limited to broad regions of the cortex.

There have been relatively few functional neuroimaging studies of ADHD and most have been conducted in adult or adolescent populations. These studies have found reduced activation in ADHD subjects during attentional and inhibitory tasks, predominantly in the frontal lobes and the basal ganglia. Structural brain imaging studies have found that these same regions are smaller in ADHD children, and together these findings suggest that dysfunction of fronto-striatal networks may be involved in ADHD (Castellanos, 1997). However, the findings have been inconsistent in terms of the precise nature of this dysfunction, perhaps due in part to differences in the age groups studied and methods employed. Further research is needed to clarify the nature of functional abnormalities in ADHD, how they are affected by developmental changes, and their specificity to ADHD (Tannock, 1998). The application of functional neuroimaging techniques to this research is unfortunately limited, however, as the demands of the scanning procedures may be difficult for young children to comply with.

Electrophysiological studies have been conducted in children and also provide evidence of reduced task-related activation in ADHD. The most consistent finding from event related potential (ERP) studies is reduced amplitude of the P3 component to attended target stimuli recorded from the parietal region. This finding has been concluded to
suggest that children with ADHD are under-reactive to task-relevant stimuli and may have deficits in allocation of attention and later stages of stimulus processing (Klorman, 1991; Tannock, 1998). Reduced amplitude of the N2, an earlier, more frontal ERP component, has also been found in ADHD and this has been related to deficits in orienting and selective attention (Klorman, 1991; Satterfield et al., 1994). However, there are conflicting findings for the early negative ERP components. Overall, ERP findings appear to suggest that deviant processing in ADHD is most pronounced for relevant target stimuli and is associated with later, controlled stages of processing (Brandeis et al., 1998; Klorman, 1991). In addition, other ERP studies suggest differences in initial orienting to and allocating attentional resources to a cue or warning stimulus that precedes a target (Brandeis et al., 2002; Van Leeuwen et al., 1998).

Functional neuroimaging and electrophysiological studies have provided insight into the underlying brain dysfunction that may be associated with deficits in attentional task performance in ADHD, but the picture is by no means complete. Functional neuroimaging findings suggest reduced activation in frontal cortex in ADHD, but provide no information about whether this is a sustained task effect or is related to reduced activation in response to specific task events. Differences in activation in ADHD might occur in compromised cortical regions for only certain brief intervals associated with specific stimuli or with executing a response. These transient effects may be missed by imaging techniques that provide only an averaged representation of activation over much longer periods. ERP findings suggest reduced responses to task relevant stimuli in ADHD, but few studies have examined which brain regions are involved. Those that have suggest reduced activation of parietal cortex in attentional processing in ADHD (Brandeis et al., 2002; Van Leeuwen et al., 1998). Traditional ERP techniques examine changes in potential for perhaps one second after stimulus presentation, but do not provide information about dynamic patterns of activity over longer intervals that may be of interest. An investigation of concurrent frontal and parietal processes in ADHD during critical components of attentional tasks may help to uncover more about how processing in these highly interconnected brain regions is deviant in ADHD. The current study aimed to undertake such an investigation using the technique of steady-state probe topography (SSPT).
The SSPT technique, developed by Silberstein and colleagues (Silberstein et al., 1990, 1995), examines the effects of cognitive task performance on the steady-state visually evoked potential (SSVEP) generated by a rapidly repeating stimulus that is irrelevant to the task, at multiple scalp recording sites. In this study, the irrelevant probe stimulus was a 13 Hz visual flicker and the SSVEP generated by this flicker was recorded at 64 electrode sites. The resulting spatial resolution, although not as good as that achieved by functional neuroimaging methods, appears satisfactory for investigating activity within broad cortical regions. SSPT also provides the temporal resolution and temporal continuity required to investigate dynamic patterns of activity associated with important task components. Variations in the amplitude and latency of the SSVEP have been shown to reflect a range of cognitive processes, including attention (Silberstein et al., 1990, 1996).

The main aim of this study was to use SSPT to examine differences in brain activity associated with attentional task performance between children with ADHD and normal controls. Attention performance was investigated during target components of two versions of the CPT. The CPT-X is a simple vigilance task, where a series of stimuli must be attended to in order to detect and respond to randomly occurring targets. This task allowed examination of processes in preparation for and in response to the target stimulus. In the CPT-AX the target is cued, and so the cue – target interval in this task provided the opportunity to examine processes during a time of heightened attention triggered by an external cue.

Task-related SSVEP effects were found to differ between the ADHD and control groups, predominantly in right prefrontal, medial frontal, right parietal and occipital regions. The observed differences in SSVEP amplitude and latency responses suggest reduced activation and slower processing in frontal and posterior regions in ADHD. Reduced and slower activity in the ADHD group was associated with target presentation in both the CPT-X and CPT-AX, and also with the cue A in the CPT-AX, suggesting deficits in the priming of attentional processes by the cue. Right frontal and right parietal cortex have been shown to be involved in vigilance (Posner & Raichle, 1996), and in the on-line maintenance of task goals (Levy & Farrow, 2001), and the current findings suggest deficits in this attention network in ADHD. The medial frontal region is thought to be involved in the executive control of attention (Posner & Raichle, 1996).
and the reduced activation in this region in ADHD is consistent with other findings of frontal and executive function deficits in ADHD. The posterior parietal region is involved in a third network of attention responsible for orienting processes (Posner & Raichle, 1996), and so the observed parieto-occipital activation differences may suggest visual attention deficits in ADHD. The findings are consistent with others of reduced activation and cognitive deficits in ADHD that involve these brain regions and networks of attention (Swanson et al., 1998a), and with the idea that ADHD may be associated with a diminished ability to regulate levels of activation appropriate to task demands (Sergeant, 2000; Van der Meere, 1996).

This thesis is presented in eight chapters. This introductory chapter, chapter 1, presents an overview of the study. Chapter 2 discusses the clinical aspects of ADHD, reviewing literature related to how the disorder is defined, diagnosed and treated. A review of the neurobiological correlates of ADHD is then presented in chapter 3. The chapter begins with a brief discussion of the neurochemistry of ADHD, reviewing research that suggests the involvement of dopamine and noradrenaline dysfunction in the disorder. Neuropsychological research aimed at identifying the cognitive functions impaired in ADHD is then reviewed. Finally, structural and functional neuroimaging and electrophysiological research examining underlying brain differences in ADHD is discussed. Chapter 4 describes the SSPT technique and presents the aims and hypotheses of the current study. Chapter 5 provides details of the assessment and selection of ADHD and control participants for the study and results of the assessment for the final subject groups. The experimental methods employed in this study are presented in chapter 6, including details of the cognitive tasks, recording procedures and data analysis. The results of the study are presented in chapter 7, incorporating behavioural task performance results and SSVEP effects for the CPT-X and CPT-AX. The findings are then discussed in chapter 8 in relation to other literature. This final chapter presents the study conclusions and implications for improved understanding of the underlying neurobiological deficits in ADHD.
Chapter 2  Clinical Aspects of ADHD

This chapter presents an overview of attention-deficit/hyperactivity disorder (ADHD), specifically how it is defined, diagnosed and treated. It is not intended as a comprehensive review of the literature associated with clinical aspects of ADHD, but rather as an introduction for readers not familiar with the disorder. The concepts discussed are mostly related to American rather than European conceptualizations of the disorder, as these are most widely used in clinical assessment and treatment of ADHD in Australia. Section 2.1 provides an overview of ADHD and its history, introducing the conceptualizations of the disorder that have shaped research over the years. Section 2.2 discusses the prevalence of ADHD. The core symptoms of the disorder as it is currently defined are described in section 2.3. Comorbidity with other behavioural and learning problems is common in ADHD and is discussed in section 2.4. Section 2.5 discusses the developmental course of ADHD and the range of associated outcomes. Sections 2.6 and 2.7 discuss the diagnosis and treatment of ADHD respectively. Section 2.8 concludes the chapter with a summary of how ADHD is currently perceived.

2.1 Introduction

Children diagnosed with ADHD vary widely in the type and severity of symptoms which they demonstrate, but the disorder is generally characterized by developmentally inappropriate levels of inattention, impulsivity and hyperactivity (American Psychiatric Association, 1987, 1994; Barkley, 1997; Cantwell, 1996). These problems, which are discussed further in section 2.3, are of course seen in most children at some times, but children with ADHD are differentiated by the pervasiveness and severity of these symptoms in comparison to their peers (Barkley, 1998; Whalen, 1989).

The mechanisms involved in ADHD are not fully understood (Barkley, 1998; Cantwell, 1996; Zametkin, 1995), although several theories to explain the disorder have been suggested. Brain damage, frontal lobe dysfunction, genetic factors, developmental lag, neurotransmitter imbalance, dysfunction of the behavioural inhibition system, psychosocial influences and food allergies have all been implicated as possible causes.
of or contributing factors in the development of ADHD (Barkley, 1990; Fadely & Hosler, 1992; Gelfand et al., 1988; Whalen, 1989). As ADHD is a heterogeneous disorder there are likely to be multiple etiologies which might combine genetic predisposition, brain dysfunction and psychosocial factors (Cantwell, 1996; Tannock, 1998; Wood, 1995).

As ideas about the underlying cause and major deficits associated with problems now attributed to ADHD have changed, the disorder has undergone several changes in definition and label since its symptoms were first recognized as possibly being due to a distinct syndrome early last century (Barkley, 1990). Still (1902) described children who had attentional impairments, were overactive and displayed ‘defective moral control’. He proposed that these problems were causally related and due to an underlying neurological deficiency. The same problems were labelled ‘Minimal Brain Damage’ or ‘Minimal Brain Dysfunction’ in the 1950s and 1960s when the syndrome was thought to be caused by damage to the central nervous system (CNS) due to birth trauma, disease or head injury (Barkley, 1990). There is however no evidence of any brain damage in the majority of ADHD cases (Fadely & Hosler, 1992; Wood, 1995), although there has been some recent interest in the possibility that adverse situations during foetal development may selectively damage neurons in brain regions implicated in ADHD (Lou, 1996; Swanson & Castellanos, 1998). The disorder was then labelled ‘Hyperkinesis’ or ‘Hyperactivity’ when it was thought to be characterized primarily by excessive or inappropriate motor activity (American Psychiatric Association, 1968).

In the 1970s, research began to focus on attentional problems as the core deficit and major cause of symptoms, rather than hyperactivity (Whalen, 1989; Wood, 1995). This led to the diagnostic label of Attention Deficit Disorder (ADD), introduced by the third edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-III: American Psychiatric Association, 1980). This classification was subdivided into ADD with Hyperactivity and ADD without Hyperactivity. It remains unclear whether these two categories represent subtypes of the same disorder or two separate disorders (Dinklage & Barkley, 1992; Fadely & Hosler, 1992; Wood, 1995). Children diagnosed as having ADD without Hyperactivity were described as being withdrawn, passive, anxious and lethargic while having attention related problems (Dinklage & Barkley, 1992; Whalen, 1989). These children
may have problems with memory, speed of cognitive processing and focused attention rather than the problems of sustained attention and behavioural disinhibition seen in children diagnosed with ADD with Hyperactivity (Barkley, 1990; Wood, 1995).

The current label of the disorder, i.e. ADHD, was adopted in 1987 for the revised third edition of the DSM (DSM-III-R: American Psychiatric Association, 1987). This diagnostic scheme (described further in section 2.6) made no attempt to separate attention deficits with and without hyperactivity and used a single listing of diagnostic criteria encompassing symptoms of inattention, impulsivity and hyperactivity. This definition was revised yet again for the DSM-IV (American Psychiatric Association, 1994), which divided symptoms into two categories of ‘inattention’ and ‘hyperactivity-impulsivity’ and specified three subtypes of ADHD – predominantly inattentive type, predominantly hyperactive-impulsive type and combined type. This change reflected the growing view that poor attention may not be the core deficit responsible for the myriad of symptoms seen in children with ADHD (Barkley, 1997).

The degree of inattention displayed by children with ADHD, as with other symptoms of the disorder, is highly situationally variable (Schachar, 1991). Children with ADHD may be able to pay close attention in some circumstances, for example when watching television (Landau et al., 1992), and their attentional problems are heightened when tasks are unappealing, boring or offer no immediate reward (Dinklage & Barkley, 1992). Consequently it has been suggested that motivational rather than attentional deficits may better explain the behavioural inattention seen in ADHD (Barkley, 1990; Dinklage & Barkley, 1992). Children with a motivational deficit may be unwilling or unable to devote the attentional resources appropriate to a particular task (Barkley, 1990; Pearson and Lane, 1990). It has also been suggested that a deficit in self-regulation may better account for the symptoms of ADHD (Douglas, 1988; Sergeant, 2000; Van der Meere, 1996). Children with deficient self-regulation may have difficulties in controlling and regulating their cognitive resources and their behaviour, leading to the problem behaviours typical of ADHD.

Deficient self-regulation in ADHD has in turn been suggested to arise from a primary deficit in behavioural inhibition (Barkley, 1997). Disinhibition has come to be seen as a core deficit in ADHD, but there is disagreement about the precise nature of this deficit.
In different inhibitory dysfunction models, children with ADHD are seen as having: an underactive behavioural inhibition system leading to reduced ability to inhibit responses associated with punishment or nonreward (Quay, 1988, 1997); a reduced ability to inhibit prepotent responses due to deficient and slow inhibitory processes (Schachar et al., 1995; Schachar & Logan, 1990b); a primary deficit of behavioural inhibition leading to executive function deficits (Barkley, 1996, 1997); deviant inhibition arising from attempts to reduce the perception or experience of delay (Sonuga-Barke, 1994; Sonuga-Barke et al., 1992a, 1992b, 1996); or poor inhibition arising from an underlying dysfunction in activation and effort systems that influence motor processes and are influenced by motivational factors (Sergeant, 2000; Van der Meere, 1996).

These different ideas about the cognitive deficits associated with ADHD reflect the heterogeneity and complexity of the disorder, and highlight the need for further research aimed at understanding ADHD. ADHD is relatively common and can be associated with significant difficulties and adverse outcomes, as described in the sections below, making improved understanding of the disorder, and hopefully subsequently improved treatments, imperative.

### 2.2 Prevalence

ADHD is probably the most commonly diagnosed childhood psychiatric disorder (Castellanos, 1997; Swanson et al., 1990). Estimates of the prevalence of ADHD have varied widely, depending on the strictness of the criteria used to define the disorder and on the population studied, and have been as high as 20% (Castellanos, 1997; Barkley, 1996; Dinklage & Barkley, 1992). Many recent reviews suggest that somewhere between 3 and 10% of all school-aged children satisfy current diagnostic criteria for ADHD (American Psychiatric Association, 1994; Barkley, 1997; Castellanos, 1997; Tannock, 1998). A recent Australian survey found that 11% of children and adolescents met symptom criteria for ADHD (Birleson et al., 2000).
A consistent feature of the disorder is that it is far more common in boys than in girls. The male:female ratio for ADHD also varies depending on the definition of the disorder and the population studied, but is considered to be approximately 3:1 in the general population (Barkley, 1997; Tannock, 1998). This often rises to around 9:1 in clinic referred samples (American Psychiatric Association, 1994; Barkley, 1996; Pennington & Ozonoff, 1996), suggesting males are more likely to be referred for assessment and treatment. This gender difference may reflect a bias in the diagnostic criteria toward behaviours more commonly exhibited by boys (Barkley, 1996; Cantwell, 1996; Swanson et al., 1998b).

2.3 Symptoms

The severity and type of symptoms displayed by children with ADHD varies from child to child and also varies in individual children across different settings, times and tasks (Cantwell, 1996). The symptoms may be considered deficits in the interactions between the child’s behaviour and brain function and their environment (Fadely & Hosler, 1992; Barkley, 1990). Their task performance and social behaviours are seen as abnormal because they are inappropriate for task or environmental demands. ADHD and its symptoms can create many problems for an afflicted child. The current definition of ADHD is of a disorder generally characterized by a persistent pattern of severe inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 1994). The features of these symptoms are described in the following sections.

2.3.1 Inattention

Children with ADHD may have difficulty sustaining their attention to tasks (American Psychiatric Association, 1994; Barkley, 1990). This impairment can be observed while the child is engaged in free play or an activity which they enjoy, but is often most obvious and severe during tasks which the child finds boring, repetitive or difficult (Dinklage & Barkley, 1992; Wood, 1995). They are thus often described as having a short attention span or an inability to concentrate. They may be easily distracted and have problems with selective attention and selective processing of stimuli (American Psychiatric Association, 1994; Whalen, 1989). Their distractibility may be due to an inability, or perhaps an unwillingness, to maintain the effort required to sustain attention
to a task that has little intrinsic appeal or no immediate reward, or alternatively to a lack of inhibition of orientation of their attention to irrelevant stimuli (Barkley, 1990). Inattention may also be expressed in making careless mistakes, being disorganized, appearing not to listen, or being forgetful (American Psychiatric Association, 1987, 1994).

2.3.2 Impulsivity

Children with ADHD are often impulsive and lack self-control, problems which can be manifest in a range of behaviours. Children with ADHD often do not plan their activities and act without considering the consequences of their actions, sometimes resulting in physically dangerous situations. They may respond prematurely to instructions or to questions and may have difficulty delaying gratification and reward. They may often fail to finish set tasks and have difficulty adhering to rules and following instructions (American Psychiatric Association, 1987, 1994; Barkley, 1990; Wood, 1995). These problems in regulating responses may be due to deficient behavioural inhibition as children with ADHD seem unable to inhibit impulsive responding (Barkley, 1990; Whalen, 1989).

2.3.3 Hyperactivity

Children with ADHD may be restless and fidgety and often perform unnecessary movements (Barkley, 1990; Wood, 1995). They may exhibit levels of activity which are excessive or inappropriate for their age (American Psychiatric Association, 1994; Barkley, 1990). Many children may be described as overactive compared to others their age, but their behaviour does not have the haphazard and disorganized quality of that seen in children with ADHD (American Psychiatric Association, 1980). However, the overall level of activity in children with ADHD may in fact be normal and they may appear hyperactive because they fail to regulate their activity according to situation or task demands, or because they are constantly shifting from one task to another (Barkley, 1990; Dinklage & Barkley, 1992). Attempts to measure activity levels by having children wear devices which monitor movement or by observation have found that differences in motor activity between children with ADHD and control groups are more
likely to be apparent in structured and demanding situations than during relaxed or self-paced activities (Whalen, 1989; Wood, 1995).

### 2.3.4 Other Characteristics

There are several other characteristics common to ADHD. Children with ADHD demonstrate a greater variability of task performance and their ability can seem to fluctuate from day to day or even from moment to moment (Barkley, 1990; Whalen, 1989). Behaviour which is often in conflict with environmental demands can result in social problems and poor peer and family relationships (Whalen, 1989). Attentional deficits can often result in learning difficulties and problems in organizing and completing school work (American Psychiatric Association, 1994). Aggression, defiance and oppositional behaviour are common and can lead to further social difficulties (Dinklage & Barkley, 1992). Children with ADHD may also demonstrate greater mood lability than their normal peers (American Psychiatric Association, 1994). These other problems can be severe enough to warrant an additional diagnosis, and the most common comorbidities are discussed in the next section.

### 2.4 Comorbidity

Other psychiatric disorders and learning problems often coexist with ADHD, raising questions about the specificity of observed deficits to ADHD (Barkley, 1997), and contributing to the heterogeneous nature of the disorder (Castellanos, 1997). Between 50 and 80% of children with ADHD also meet diagnostic criteria for other disorders (Biederman et al., 1991; Cantwell, 1996; Tannock, 1998). Conduct disorder (CD), characterized by a persistent and repetitive pattern of serious antisocial behaviour, and oppositional defiant disorder (ODD), characterized by an oppositional and negative attitude toward authority figures, both commonly coexist with ADHD (American Psychiatric Association, 1980, 1987, 1994; Barkley, 1995, 1997; Biederman et al., 1991; Tannock, 1998). The overlap between oppositional behaviour, conduct problems and ADHD has been the subject of much research and debate (Banaschewski et al., 2003; Swanson et. al., 1990; Whalen, 1989). ADHD and ODD are considered risk factors for development of CD, as behavioural and social problems may lead to frustration and aggression (Swanson et al., 1990; Wood, 1995). The issue of whether
those with both ADHD and CD have a different disorder or a more severe form of the same disorder as those with ADHD alone remains unresolved (Banaschewski et al., 2003; Barkley, 1997; Schachar & Logan, 1990b).

Learning and academic difficulties are also prevalent in children with ADHD (Barkley, 1995; Castellanos, 1997; Prior, 1996; Tannock, 1998; Wood, 1995). These can include specific learning disabilities in reading, mathematics or language (Castellanos, 1997), or general academic underachievement (Prior, 1996; Wood, 1995). There may be several reasons why so many children with ADHD also have learning problems, including the influences of reduced intellectual ability, immaturity, motivational deficits, or negative reactions to the demands of school, or a common biological origin of the two disorders (Prior, 1996). In terms of diagnosis, it can be difficult to determine the primary problem as children with ADHD may develop learning difficulties as a result of their attentional problems or learning disabilities may produce secondary attention deficits (Whalen, 1989; Wood, 1995). There is also controversy over whether the same neuropsychological deficits are evident in those with ADHD and learning disability as in those with ADHD alone (Barkley, 1997; Castellanos, 1997).

Children with ADHD are also at greater risk than normal children of developing affective disorders, anxiety disorders, social difficulties, low self-esteem, aggression, and substance abuse (Barkley, 1997; Whalen, 1989; Wood, 1995). Tic disorders such as Tourette's Syndrome have also been associated with ADHD, and an estimated 70% of children with these disorders also have ADHD (Barkley, 1990). Comorbidity remains an important issue for diagnosis, treatment and research, as the presence of other disorders may alter the clinical presentation, psychological characteristics, outcome and treatment response of children with ADHD (Barkley, 1995; Cantwell, 1996; Jensen et al., 1997; Tannock, 1998; The MTA Cooperative Group, 1999b). In view of this, it has been suggested by some that new subtypes of ADHD should be delineated, including an aggressive subtype and an anxious subtype (Barkley, 1995; Jensen et al., 1997; Vance, 1998).

2.5 Developmental Course
The problem behaviours associated with the symptoms of ADHD usually appear early in a child's development and are sustained over a long period of time (Barkley, 1995; Burke, 1990; Tannock, 1998), continuing into adolescence in 50 to 80% of cases and into adulthood in 30 to 50% of these cases (Barkley, 1997).

Hyperactive and impulsive behaviours tend to diminish with age (Barkley, 1996; Castellanos, 1997; Whalen, 1989). Consequently, a young child may be diagnosed as having ADHD and may no longer meet the criteria at an older age, but this is not always the case. It was once thought that all hyperactive children ‘grew out’ of the disorder and that symptoms generally disappeared at puberty, but this view is no longer accepted (Cantwell, 1996; Dinklage & Barkley, 1992). The problem behaviours associated with ADHD often change in their nature with increasing age so that the problems persist but are not so apparent (Castellanos, 1997; Whalen, 1989). For example, the excess motor activity displayed by young children may be replaced by fidgeting and restlessness as they grow older (American Psychiatric Association, 1994; Cantwell, 1996).

Inattention related symptoms usually arise later than those related to hyperactivity, becoming more apparent as schooling becomes more challenging (Castellanos, 1997; Dinklage & Barkley, 1992). Although hyperactivity often diminishes by adolescence, inattention shows little reduction (Barkley, 1996; Castellanos, 1997; Swanson et al., 1998b; Wood, 1995).

Many children with ADHD will continue to have serious problems with inattention, impulsivity, restlessness and social difficulties throughout adolescence and adulthood (American Psychiatric Association, 1980; Barkley, 1990; Schachar, 1991; Wood, 1995). These problems can be severe and can sometimes lead to further complications. Adolescents with ADHD are at greater risk for antisocial problems, alcohol and drug abuse, and criminal behaviour, although these may be more related to comorbid CD (Barkley, 1995, 1997; Castellanos, 1997). Academic difficulties in adolescence are also more common as are frequent job changes in adulthood (Barkley, 1997; Fischer et al., 1990; Whalen, 1989). Adolescents with ADHD also remain impaired on a range of measures of academic skill, attention and inhibition in comparison to their normal peers (Fischer et al., 1990).
There appear to be several different courses of ADHD. In some individuals severe symptoms persist into adulthood, in others all symptoms disappear by late adolescence, and in others symptoms of hyperactivity disappear while attentional difficulties and impulsivity persist (American Psychiatric Association, 1980; Cantwell, 1996). The changing nature of ADHD across development raises issues for diagnosis which, as discussed in the next section, relies on the presence of symptoms much more likely to be associated with childhood.

2.6 Diagnosis

As discussed in section 2.1, a variety of diagnostic labels have been given to the disorder described by the symptoms currently attributed to ADHD. The definition and use of each of these diagnostic labels has been associated with problems and controversies, due partly to the heterogeneity of both the type and the severity of symptoms displayed by children believed to have the disorder. This heterogeneity makes definition and diagnosis of a specific disorder difficult. The frequent changes of definition and label of the disorder have been an attempt to overcome some of these difficulties as much as an attempt to reflect changes in the accepted understanding of the underlying mechanisms of the disorder (Barkley, 1998).

2.6.1 DSM-III-R Criteria

The presently used label of ADHD was adopted in 1987 for the DSM-III-R (American Psychiatric Association, 1987). The DSM-III-R criteria for ADHD are described in detail here because they were used to assess participants in this study. According to this diagnostic scheme, a diagnosis of ADHD requires an onset of symptoms before age 7, a duration of symptoms of at least 6 months, and the presence of at least eight of the following list of behavioural symptoms (at a rate considerably more frequent than that seen in most people of the same mental age):

1. Often fidgets with hands or feet or squirms in seat (in adolescents, may be limited to subjective feelings of restlessness);
2. Has difficulty remaining seated when required to do so;
3. Is easily distracted by extraneous stimuli;
4. Has difficulty awaiting turn in games or group situations;
5. Often blurts out answers to questions before they have been completed;
6. Has difficulty following through on instructions from others (not due to oppositional
behavior or failure of comprehension), e.g. fails to finish chores;
7. Has difficulty sustaining attention in tasks or play activities;
8. Often shifts from one uncompleted activity to another;
9. Has difficulty playing quietly;
10. Often talks excessively;
11. Often interrupts or intrudes on others, e.g. butts into other children's games;
12. Often does not seem to listen to what is being said to him or her;
13. Often loses things necessary for tasks or activities at school or at home (e.g. toys,
pencils, books, assignments);
14. Often engages in physically dangerous activities without considering possible
consequences (not for the purpose of thrill-seeking), e.g. runs into street without

2.6.2 Issues for Diagnosis

There was considerable controversy over the DSM-III-R diagnostic scheme for ADHD
(Swanson et. al., 1990; Whalen, 1989) and differences in interpretation of the scheme
led to poor interrater agreement for diagnosis (Prendergast et. al., 1988). Many
clinicians and researchers believed that the criteria for the severity and pervasiveness of
symptoms were not stringent enough and did not describe behaviour which is severely
deviant from normal, and that ADHD was consequently overdiagnosed (Swanson et. al.,
1990). In response to these criticisms and the emphasis shifting away from inattention
as the core deficit of all types of the disorder, the diagnostic criteria were altered again
for the DSM-IV (American Psychiatric Association, 1994). According to this latest
diagnostic scheme, a diagnosis of ADHD requires an onset of symptoms before age 7, a
duration of symptoms of at least 6 months, impairment in two or more settings, clear
evidence of significant impairment in functioning, and the presence of at least six of a
list of nine inattention symptoms and/or six of nine hyperactivity-impulsivity symptoms
(American Psychiatric Association, 1994). One of the most important changes in the
DSM-IV is the specification of the three subtypes of ADHD – predominantly
inattentive, predominantly hyperactive-impulsive, and combined type. This scheme is
generally regarded as an improvement over the DSM-III-R criteria (Barkley, 1996;
Castellanos, 1997), despite continuing limitations such as not allowing for age and
gender effects (Barkley, 1996; Wood, 1995).

In Europe, the World Health Organization’s International Classification of Diseases
(ICD-10: World Health Organization, 1993) is used for diagnosis. This manual defines
a childhood disorder with features of inattention, impulsiveness, overactivity,
restlessness and distractibility, which is labelled Hyperkinetic Disorder. The rate of
diagnosis of Hyperkinetic Disorder, as defined by ICD-10 and its predecessor ICD-9
(World Health Organization, 1978), in the UK is significantly lower than that of ADHD
in the USA (Prendergast et. al., 1988; Swanson et al., 1998b; Whalen, 1989). One of
the reasons for this inequality in prevalence is the differences between the two
diagnostic schemes. The ICD-9 and -10 generally require a greater severity of
symptoms for a diagnosis of Hyperkinetic Disorder than the DSM-III-R and -IV require
for a diagnosis of ADHD. ICD-10 criteria require the presence of all three symptom
types (inattention, impulsivity and hyperactivity), while DSM-IV criteria may be met
with just inattention or just hyperactivity symptoms. ICD criteria also recommend a
single diagnosis, whereas DSM criteria allow for diagnosis of multiple comorbid
disorders. These differences result in more positive diagnoses being made using DSM-
III-R or -IV (Prendergast et. al., 1988; Swanson et al., 1998b).

The identification and diagnosis of a homogeneous group of children with ADHD is
difficult for several reasons. It may be due in part to the lack of stringency of standard
diagnostic criteria (Swanson et al., 1990). However, the most important factor is that
children with ADHD are a heterogeneous population, varying in the type and degree of
symptoms they present and in the pervasiveness of these symptoms (Barkley, 1990;
Schachar, 1991). Other factors which add to the difficulties associated with diagnosis
include comorbidity with other disorders (Castellanos, 1997), and the possibility that
ADHD-like symptoms are secondary to emotional or learning problems (Swanson et al.,
1990). The lack of a definite etiological or causal link to ADHD further compounds
diagnostic difficulties, as does the often low correlation between assessments by parent,
teacher and clinician (Swanson et al., 1990). Accurate diagnosis is likely to be
important for determining appropriate treatment for an afflicted individual, which is the subject of the following section.

2.7 Treatment

2.7.1 Stimulant Medication

The most common treatment for ADHD, especially in the USA, is the prescription of CNS stimulant medication. The most commonly used drugs are methylphenidate (Ritalin) and dexamphetamine (Dexedrine). The efficacy of stimulants in alleviating the symptoms of ADHD has been well documented (Barkley, 1998; Erickson, 1987; Jarman, 1996; The MTA Cooperative Group, 1999a; Schachar, 1991; Solanto, 1998; Solanto et al., 2001). These drugs have been shown to improve attention, concentration and self-control, and to reduce impulsive behaviour, restlessness, motor overactivity and aggression (Barkley, 1995, 1998; Jarman, 1996; The MTA Cooperative Group, 1999a). Peer and family relationships are also often improved (Barkley, 1995; Cantwell, 1996; Jarman, 1996). Symptoms are significantly reduced by stimulants in at least 75 to 80% of children with ADHD (Barkley, 1998; Jarman, 1996; Swanson et al., 1993, 1998b).

While the benefits of the short-term action of stimulants on behaviour are well established, their long-term efficacy requires further investigation (Jarman, 1996; Swanson et al., 1998b; The MTA Cooperative Group, 1999a).

Also less well established than positive short-term behavioural effects are effects on cognitive and academic function (Jarman, 1996; Tannock et al., 1995b). Improvement on the reading achievement subtest of the Weschler Individual Achievement Test following 14 months of carefully managed medication treatment was found in the Multimodal Treatment Study of Children with ADHD (MTA: The MTA Cooperative Group, 1999a). Improvements have also been shown in some aspects of cognition and attention as measured by laboratory tasks (Van der Meere, 1996). In continuous performance tasks, children with ADHD show significantly improved performance after stimulants, achieving faster reaction times and fewer errors (Losier et al., 1996; Klorman et al., 1979, 1988; Michael et al., 1981). Improvements in working memory have also been shown (Tannock et al., 1995a).
The efficacy of amphetamines in reducing disruptive behaviour in children was first reported in the 1930's (Bradley, 1937). It was thought then that stimulants caused a 'paradoxical sedation' because although they were known to act as CNS stimulants when administered to adults, they seemingly had a sedatory effect on hyperactive children (Erickson, 1987). However, studies comparing the effects of stimulants in normal adults and children and ADHD children have found that all three groups display similar responses to these drugs, including reduced activity and improved attention (Rapoport et al., 1980; Solanto, 1998). While low doses of stimulants will improve attention and reduce activity level in everyone, the change displayed by children with ADHD may be more marked (Fadely & Hosler, 1992).

Methylphenidate and dexamphetamine act rapidly and have a short half-life, producing therapeutic effects within 20 to 60 minutes after ingestion, which then dissipate within 3 to 7 hours (Dinklage & Barkley, 1992; Jarman, 1996). These stimulants readily penetrate the blood-brain barrier and act by enhancing the actions of dopamine and noradrenaline, by facilitating their release from presynaptic nerve terminals and by blocking their reuptake (Solanto, 1998; Solanto et al., 2001). They may also inhibit the enzyme monoamine oxidase which metabolizes dopamine and noradrenaline (Solanto, 1998). As discussed further in chapter 3, dopaminergic and noradrenergic dysfunction are thought to play a significant role in ADHD. It is believed that short-term effects on these catecholaminergic systems are responsible for the improved attention, reduced motor activity and reduced impulsivity that is seen in children with ADHD treated with stimulants (Solanto et al., 2001). Noradrenaline is known to be involved in arousal, vigilance and selective attention, while dopamine is involved in sensory information processing, motivation and the regulation of motor output (Mason, 1984; Solanto, 1998). As the therapeutic effects of stimulants are observed soon after administration, they are not thought to be mediated by long-term changes in receptor sensitivity (Solanto, 1998).

Several minor side effects can occur during treatment with stimulants, including decreased appetite, insomnia, dysphoria, headaches, stomach cramps and weight loss (Barkley, 1995; Cantwell, 1996; Erickson, 1987; Jarman, 1996). These side effects are generally most pronounced when treatment begins and usually subside (Cantwell, 1996; Jarman, 1996). Tics, and very rarely Tourette’s Syndrome, may sometimes develop in
children treated with stimulants (Barkley, 1995; Jarman, 1996). There is also some evidence that long term treatment may lead to the inhibition of physical growth in children, although this effect has not been shown to be significant and is reversible with dose reduction (Jarman, 1996).

2.7.2 Other Pharmacological Treatments

Tricyclic antidepressants, which inhibit the reuptake of the catecholamines, are also used to treat ADHD, particularly in children who do not benefit from stimulants, cannot tolerate the side effects of stimulants, or have comorbid mood or anxiety disorders (Dinklage & Barkley, 1992; Jarman, 1996; Swanson et al., 1998b; Wood, 1995). Antidepressants have been shown to improve impulsivity, aggressiveness and mood and have mild effects on attention and activity level (Barkley, 1995; Cantwell, 1996; Wood, 1995). Clonidine, an antihypertensive drug, is also used to treat children with ADHD, particularly those who are aggressive or have tics that may be exacerbated by stimulants (Cantwell, 1996; Jarman, 1996; Wood, 1995). It is also sometimes used in combination with a stimulant to counteract rebound effects or side effects (Jarman, 1996).

2.7.3 Other Non-Pharmacological Treatments

Non-pharmacological treatments for ADHD include behavioural and cognitive therapies. These include positive reinforcement (rewarding children for appropriate behaviour), behaviour modification (emphasizing self-control and correcting inappropriate movements), problem solving training, social-skills training, and special education programs (Cantwell, 1996; Dinklage & Barkley, 1992; Jarman, 1996; Wood, 1995). The success of such treatments is not as well established as that of stimulant medication (Fadely & Hosler, 1992; The MTA Cooperative Group, 1999a). Parent and teacher management training is also considered important in behavioural therapies for ADHD (Cantwell, 1996; Dinklage & Barkley, 1992), and its effectiveness is enhanced when used in conjunction with medication (Jarman, 1996). Dietary treatments for hyperactivity were popularised by Feingold (1975) who blamed at least 50% of cases on artificial food additives and colourings and refined sugar. However, it is now accepted that only a very small percentage of children with ADHD may be sensitive to dietary manipulation (Jarman, 1996; Whalen, 1989). Many other as yet unproven treatments
2.7.4 The Multimodal Treatment Study of ADHD

The most comprehensive study of ADHD treatment to date is the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA: The MTA Cooperative Group, 1999a). In the MTA, 579 children with ADHD-combined type were randomly assigned to four treatment groups and assessed over a period of fourteen months. The four different treatment regimes were stimulant medication, intensive behavioural treatment, medication and behavioural treatment combined, and standard community care. All four groups showed significant reductions in ADHD symptoms, but medication and combined treatment were superior to behavioural treatment and community care. Combined treatment was also better than community care in improving oppositional/aggressive symptoms, internalizing problems, social skills, parent-child relations and reading achievement. Lower final doses of stimulants were achieved in the combined treatment group compared to the medication only group, which suggests that behavioural therapy could be a beneficial addition to medication treatment and reduce the overall exposure to stimulant drugs and their potential side effects. Two thirds of the community care group received medication, but the outcome for this subgroup was still inferior to that of the medication management group (The MTA Cooperative Group, 1999b), highlighting the importance of regular monitoring and feedback to get the best result from medication treatment (Taylor, 1999). Comorbid disorders, family resources and other individual factors were found to affect response to treatment, suggesting that treatment needs to be individually tailored. For example, for children with comorbid anxiety disorders, behavioural treatment was better than community care and equivalent to medication and combined treatments in improving ADHD and internalizing symptoms (The MTA Cooperative Group, 1999b). The MTA clearly demonstrated the effectiveness of properly managed stimulant medication treatment and its superiority over other treatments, and suggested that medication combined with intensive behavioural therapy offers the best outcome, although only slightly improved over medication alone.
Others have also recognized that ADHD is best managed using a multimodal approach, combining psychosocial and medical interventions (Cantwell, 1996; Dinklage & Barkley, 1992; Swanson et al., 1998b). Because of the heterogeneous nature of ADHD, interventions should be targeted at the individual needs of each child, considering the nature and severity of the child’s problems (Jarman, 1996; Swanson et al., 1998b).

2.8 Conclusions

As outlined in the above discussion, issues of definition, diagnosis and treatment of ADHD continue to be debated. The DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for ADHD – combined type and the ICD-10 (World Health Organization, 1993) criteria for Hyperkinetic Disorder recognize a disorder involving inattentive, hyperactive and impulsive behaviour that is developmentally inappropriate and impairs function. The overlap between the two schemes has been suggested to reflect a ‘refined phenotype’ of ADHD (Swanson et al., 1998b) and it has been this combined type that has been most widely researched. ADHD as it is currently diagnosed in Australia and elsewhere though, includes children with predominantly inattentive symptoms and children with comorbid conduct, learning, anxiety and other problems under the same umbrella. Conceptualizations of the disorder have changed as research has updated ideas about what deficits define the core problems associated with ADHD, and this has shaped changes in diagnostic schemes over the years. Deficits in attention, self-regulation and inhibition are suggested to be related to the behavioural symptoms of ADHD (Barkley, 1997; Sergeant, 2000; Swanson et al., 1998a; Van der Meere, 1996).

What causes these inhibitory, self-regulatory and attentional deficits in ADHD remains unclear, however there is some converging evidence that has shaped current thinking about the disorder. Studies of brain structure and function suggest that brain regions in frontal, striatal and parietal networks may be anatomically altered and/or dysfunctional in ADHD (Swanson et al., 1998a). The efficacy of stimulant drugs in treating ADHD suggests that abnormalities in dopaminergic and noradrenergic neurotransmitter systems are involved in ADHD (Solanto et al., 2001). Twin studies suggest a strong genetic basis for ADHD and molecular genetic studies have found associations between
polymorphisms of dopamine transporter and D4 receptor genes (Swanson et al., 2000). The evidence for neurobiological deficits in ADHD is reviewed in the next chapter, and reveals that there is still much to learn about how physiological and behavioural factors interact to produce the syndrome we label as ADHD.
Chapter 3  Neurobiological Correlates of ADHD

This chapter presents a review of the research literature on neurobiological correlates of ADHD. The previous chapter described the clinical aspects of the disorder and highlighted that there is still debate about the clinical deficits that best define the disorder. Understanding the neurobiological basis of ADHD should allow us to better define the disorder, and enable improved methods of diagnosis and treatment. Much research, especially over the last decade, has been aimed at improving this understanding and this is also the aim of the current study. This chapter begins, in section 3.1, with a discussion of research on the neurochemical correlates of ADHD. As neurochemistry is not the focus of this study, this section is not intended as a comprehensive review, but an overview of this literature. Neuropsychological research is discussed in section 3.2. While not strictly neurobiological in nature, neuropsychological research is included in this chapter because the conclusions drawn from this research have helped shape not only understanding of the cognitive deficits associated with ADHD, but also understanding of which brain regions may be involved in the disorder. Section 3.3 reviews structural and functional neuroimaging studies that have used modern brain scanning techniques to examine anatomical and functional differences in ADHD. Section 3.4 discusses electrophysiological research that has used EEG and ERP techniques to examine differences in neural activity in ADHD. The chapter concludes, in section 3.5, with an outline of the issues this study hopes to address.

3.1 Neurochemistry

The positive response of children with ADHD to treatment with stimulants, which act as dopaminergic and noradrenergic agonists, suggests catecholamine abnormalities in ADHD (Cantwell, 1996; Pliszka et al., 1996). As direct measurement of catecholamine concentrations in the brain is not possible, evidence for differences in ADHD has been sought from measurements of catecholamine metabolite concentrations in cerebrospinal fluid (CSF), blood and urine. The results of these studies are inconsistent (Cantwell, 1996; Mason, 1984; Pliszka et al., 1996; Raskin et al., 1984; Weizman et al., 1990), thus
the precise nature of catecholamine anomalies in ADHD remains unknown and several different theories have been suggested.

### 3.1.1 Dopamine

ADHD has been considered to be associated with decreased dopamine (Levy, 1991). Evidence for a dopamine deficiency in ADHD was first suggested by the observed similarity between the symptoms of ADHD and the attention and motor problems developed by children who suffered from encephalitis in the pandemic early last century (Raskin et al., 1984; Weizman et al., 1990). Adults developed Parkinsonism as a result of the same infection, which is known to be associated with dopamine deficiency. Further evidence is suggested by the therapeutic benefit of stimulants, which increase the availability of dopamine at the synapse. However, conclusive direct evidence for a dopamine deficiency in ADHD has not been found and it is now thought that this is too simplistic. The best measure of CNS dopamine levels is the concentration of homovanillic acid (HVA) in CSF (Castellanos, 1997; Raskin et al., 1984). Some early studies found reduced HVA levels in CSF in children with ADHD compared with controls, while other studies found no group differences (Pliszka et al., 1996; Raskin et al., 1984; Weizman et al., 1990).

More recent studies have attempted to determine the relationship between CSF HVA concentrations, symptom severity and drug response, and findings have not supported the theory of deficient dopamine in ADHD. A significant positive correlation between HVA levels and measures of hyperactivity was found by Castellanos et al. (1994a), and subsequently replicated (Castellanos et al., 1996a). The later study also found that higher baseline CSF HVA concentration predicted better stimulant response (Castellanos et al., 1996a). These results are consistent with findings that CSF HVA levels decrease after treatment with stimulants (Castellanos, 1997; Raskin et al., 1984; Weizman et al., 1990), and also decrease with age (Castellanos, 1997). These findings, and the assumption based on animal studies that the majority of CSF HVA originates in the striatum, led Castellanos (1997) to conclude that the motor hyperactivity in ADHD may be associated with increased HVA concentrations in the caudate, as would be found in younger children.
Methylphenidate and dexamphetamine, effective treatments for ADHD, block the reuptake of dopamine, and dexamphetamine also facilitates its release from presynaptic terminals (Malone et al., 1994; Solanto, 1998; Solanto et al., 2001). This might suggest that dopamine may be deficient at prefrontal synapses, leading to the deficits in inhibitory control, working memory and executive functions that are common in ADHD (Pliszka et al., 1996). However, this simple hypothesis is not supported by findings that dopamine agonists such as L-dopa have proven inefficient in treating ADHD, while antidepressants, which have virtually no direct effect on the dopamine system, can be an effective treatment (Pliszka et al., 1996). There are also contradictory findings regarding the effects of dopamine antagonists, with some studies showing deleterious effects and others not (Levy, 1991). As the activity of dopamine neurons is modulated by autoreceptors and feedback loops, the enhancement of synaptic dopamine activity may not be enough to explain the effects of stimulant drugs on this complex system. Dopamine autoreceptors are more sensitive to low doses of stimulants than post-synaptic receptors, suggesting that inhibition of synthesis and release of dopamine due to autoreceptor feedback mechanisms might play a role in the therapeutic effect of stimulants, and therefore that elevated pre-synaptic dopaminergic activity could be associated with ADHD (Solanto, 1998).

Further tentative evidence for dopamine system abnormalities in ADHD comes from the findings of molecular genetic studies. Some studies involving children with ADHD and their parents have found a significant association between a 10-repeat allele of the dopamine transporter (DAT1) gene and ADHD (Cook et al., 1995; Daly et al., 1999; Gill et al., 1997; Waldman et al., 1998). This allele was found to be preferentially transmitted to ADHD children. It has been speculated that this finding, along with the efficacy of dopamine transporter inhibiting drugs in treating ADHD, may suggest an overactive dopamine transporter is associated with ADHD, which would increase the reuptake of dopamine and reduce the time it has to act within the synapse (Barkley, 1998; Swanson & Castellanos, 1998). Other studies have failed to replicate this finding however (LaHoste et al., 1996; Swanson et al., 2000). In fact, Swanson et al. (2000) obtained the opposite result to previous studies, finding that the 10-repeat DAT1 allele was more often not transmitted in a sample of children with ADHD – combined type. However, these authors stated that non-replication is expected as ADHD is a complex
disorder likely to be associated with multiple genes and so did not discount the earlier findings of an association between ADHD and the DAT1 gene.

Several other studies have found an association between ADHD and a 7-repeat allele of the dopamine-4 receptor (DRD4) gene (Faraone et al., 1999; LaHoste et al., 1996; Muglia et al., 2000; Rowe et al., 1998; Smalley et al., 1998; Sunohara et al., 1997a, 2000; Swanson et al., 1998c). These studies found increased frequency of the 7-repeat DRD4 allele in samples of children and adults with ADHD compared to control groups, or preferential transmission of the allele to ADHD children. The DRD4 7-repeat allele has also been reported to be associated with novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996), a trait that shares similar characteristics with ADHD. It has been suggested that the association between ADHD and polymorphism of the DRD4 gene may be related to reduced postsynaptic responsiveness to dopamine (LaHoste et al., 1996; Swanson & Castellanos, 1998; Tannock, 1998). However, other studies have failed to replicate this association (Castellanos et al., 1998; Hawi et al., 2000; Kotler et al., 2000).

Findings of anomalies in DAT1 and DRD4 genes are consistent with models of hypodopaminergic activity and altered development of dopamine systems playing a role in ADHD (Levy & Farrow, 2001; Swanson et al., 1998b, 2000; Tannock, 1998). Brain regions rich in dopamine receptors are thought to be involved in component processes of attention including alerting and executive control (Posner & Raichle, 1996). Genetic variations in these attentional networks may result in subsensitive dopamine receptors or overactive reuptake of dopamine and may contribute to the attentional deficit that characterizes ADHD (Swanson et al., 2000). However, associations between dopamine genes and ADHD suggested by recent molecular genetic studies can only be considered preliminary given that the associations have not been strong, there have been conflicting findings and heterogeneous samples have been involved (Swanson et al., 1998b, 2000; Tannock, 1998).

Interest in dopamine system abnormalities in ADHD has also arisen from findings of brain imaging studies (discussed further in section 3.3), which implicate brain structures with rich dopamine innervation such as fronto-striatal circuits (Levy & Swanson, 2001; Tannock, 1998). Genetic or environmental factors may affect the development of
frontal lobe – basal ganglia neural networks and the dopamine systems that modulate activity in these networks (Swanson et al., 1998b). However, given the complexity of and the discrepancies amongst the findings discussed here, it seems unlikely that ADHD is related to a simple overall hypofunctioning of dopamine systems (Pliszka et al., 1996). This can be explained in part by the fact that at least five different dopamine receptors have been identified, with different anatomical distributions, different functional characteristics, and different drug responses (Levy, 1991; Pliszka et al., 1996).

To address this issue, recent reviews have attempted to explain dopaminergic abnormalities in ADHD in terms of the different dopamine systems within the brain. The response of the prefrontal cortex to input from other regions is modulated by dopaminergic innervation from the ventral tegmental area. This meso-cortical dopamine system is thought to be involved in selectively gating excitatory inputs, thereby reducing irrelevant activity and improving the signal-to-noise ratio for important stimuli (Castellanos, 1997). Reduced dopamine in this system may lead to an inability to gate inputs to the anterior attention system and to executive function deficits (Castellanos, 1997; Pliszka et al., 1996). Neurons within the meso-cortical dopamine system have few inhibitory autoreceptors, so stimulant drugs are thought to increase postsynaptic dopaminergic effects in the prefrontal cortex and promote integration of input from other cortical regions and enhance executive functions (Castellanos, 1997). Striatal regions receive dopaminergic input from the substantia nigra. Activity in this nigro-striatal dopamine system is tightly regulated by inhibitory autoreceptors and feedback from the cortex, so stimulants might produce a net inhibition of dopamine transmission in this system leading to reduced motor activity (Castellanos, 1997). Hence, Castellanos (1997) suggests that executive function deficits in ADHD might be associated with reduced activity of the meso-cortical dopamine system, while hyperactive and impulsive symptoms are associated with over activity of the nigro-striatal dopamine system. Grace (2001) has more recently suggested that hyperactivity and impulsivity might result from abnormally low tonic dopamine activity in the striatum leading to abnormally high phasic dopaminergic responses, while Levy and Swanson (2001) suggest that hypodopaminergic deficits in fronto-striatal systems might affect inhibition and working memory in ADHD. These reviews highlight the fact that
there is still much to learn about how dopamine influences normal behaviour and what role dopaminergic system dysfunction plays in ADHD.

3.1.2 Noradrenaline

Compared to dopamine, fewer studies and reviews have addressed the role of noradrenaline in ADHD, but its potential importance has been emphasized recently (Arnsten, 2000; Levy & Farrow, 2001; Pliszka et al., 1996; Solanto et al., 2001). The best indicator of central noradrenaline levels is thought to be urinary concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), the principal metabolite of noradrenaline. As with dopamine metabolite levels, there are conflicting findings for MHPG levels, with some studies finding reduced urinary MHPG in children with ADHD (Shekim et al., 1977, 1979, 1983, 1987), others finding increased levels (Khan & Dekirmenjian, 1981; Oades et al., 1998), and others finding no difference relative to controls (Rapoport et al., 1978). Some of the discrepancies among findings may be explained by subjects’ prior use of stimulants, as urinary MHPG concentrations have been found to decrease after treatment with dexamphetamine, but not after treatment with methylphenidate (Raskin et al., 1984; Weizman et al., 1990). MHPG concentrations in plasma and in CSF have also been measured in just a few studies. Castellanos et al. (1994a) found that CSF MHPG levels were positively correlated with measures of aggressive and disruptive behaviour in children with ADHD. However, they found no relationship between plasma MHPG levels and behavioural measures, a finding consistent with those of two studies by Halperin and colleagues (Halperin et al., 1993b, 1997).

As with dopamine, the strongest evidence for noradrenaline dysfunction playing a role in ADHD comes from pharmacological studies. Stimulants facilitate the release and inhibit the reuptake of noradrenaline (Mason, 1984). This is thought to inhibit the locus coeruleus via feedback loops (Malone et al., 1994; Solanto, 1998). Clonidine, which has also been found to be effective in treating ADHD, acts on presynaptic $\alpha_2$ noradrenergic receptors and inhibits noradrenaline release and locus coeruleus activity (Pliszka et al., 1996; Weizman et al., 1990). Thus excess noradrenergic activity in the locus coeruleus, where neural activity is dampened by drugs effective in the treatment of ADHD, has been postulated to play a role in this disorder (Malone et al., 1994; Pliszka et al., 1996; Solanto, 1998). This excessive noradrenergic activity might lead to
increased inhibition of cortical activity and a reduced ability to enhance the brain’s
signal-to-noise ratio appropriately for different stimuli (Pliszka et al., 1996). The
parietal cortex receives extensive noradrenergic innervation from the locus coeruleus.
This input is thought to inhibit spontaneous parietal activity, thus priming the posterior
attention system to orient to and engage novel or salient stimuli. Disruption to this
noradrenergic system in ADHD may lead to reduced selective processing of salient
stimuli and attention deficits (Pliszka et al., 1996). The prefrontal cortex also receives
noradrenergic input from the locus coeruleus, which primes the prefrontal cortex to
process task relevant stimuli, suppress task irrelevant stimuli, and inhibit behaviour.
Disruption to this system in ADHD may lead to inhibitory control and executive
function deficits and behavioural disinhibition (Arnsten, 2000; Arnsten et al., 1996).
Noradrenaline is also thought to be important for the spatial working memory and
attentional functions of the prefrontal cortex (Arnsten et al., 1996), which may also be
disrupted in ADHD (Levy & Swanson, 2001). As for dopamine, more research is
needed to clarify the role of noradrenergic dysfunction in ADHD.

3.1.3 Other Neurotransmitters

While most neurochemical research has focused on dopamine and noradrenaline, other
neurotransmitters have been suggested to play a role in ADHD, principally serotonin
and adrenaline. Serotonergic involvement in ADHD was suggested because stimulant
and antidepressant drugs have some serotonergic agonist activity (Mason, 1984;
Weizman et al., 1990). However, measures of serotonin metabolites in CSF indicate
that serotonergic systems may be normal in children with ADHD (Raskin et al., 1984;
Weizman et al., 1990). Serotonin modulation was found to be involved in the calming
effects of stimulants on hyperactive mice, whose dopamine transporter gene had been
knocked out (Gainetdinov et al., 1999). The authors of this study concluded that
serotonergic mechanisms underlie the beneficial effects of stimulants in ADHD.
However, this conclusion has been described as “erroneous” by Solanto et al. (2001), as
it relies on the myth that stimulants produce a ‘paradoxical’ calming effect in ADHD.
Solanto et al. (2001) suggest that current evidence excludes any direct role of serotonin
in the clinical effects of stimulants, and that any indirect effects are mediated by
primary effects on dopamine and noradrenaline. A polymorphism of the serotonin
HTR2A receptor gene was found to be preferentially transmitted to ADHD children in a
molecular genetic study (Quist et al., 2000). These authors suggest that complex interactions between neurotransmitter systems may be involved in mediating hyperactive behaviour and in the aetiology of ADHD.

There is some evidence for a role of adrenergic influences in ADHD (Castellanos, 1997; Pliszka et al., 1996). Deficits in both the central and peripheral adrenergic systems may lead to excessive locus coeruleus activity in ADHD (Pliszka et al., 1996). Urinary levels of adrenaline have been shown to be increased by stimulants, and it has been suggested that increased adrenaline may be part of the mechanism of drug response in ADHD (McCracken, 1991; Pliszka et al., 1996). Stimulants might increase the availability of adrenaline at synapses of central neurons, which inhibit the locus coeruleus. Alternatively, peripheral effects of increased adrenaline in the bloodstream, which are fed back to the locus coeruleus via sensory afferents, would again inhibit the locus coeruleus (McCracken, 1991; Pliszka et al., 1996).

3.1.4 Conclusions for Neurochemical Anomalies in ADHD

Given the complexity of interactions between neurotransmitters and their pharmacological effects, it seems unlikely that a simple deficiency or excess of any one neurotransmitter can account for the symptoms associated with ADHD or their improvement under drug treatment (Malone et al., 1994; Pliszka et al., 1996). Evidence suggests that dysfunctions of both noradrenergic and dopaminergic systems are involved (Levy & Swanson, 2001; Solanto et al., 2001), and several different theories have been suggested. One hypothesis is that noradrenergic deficits may be related to the cognitive and attentional problems associated with ADHD, while dopaminergic deficits may be related to hyperactivity (Malone et al., 1994). Another suggests that the central noradrenaline system may be dysregulated in ADHD, leading to inefficient priming of the posterior attention system to external stimuli, while effective mental processing is affected by deficient dopaminergic function in the executive anterior attention system (Pliszka et al., 1996). Malone et al. (1994) suggest that excessive noradrenergic activity in the locus coeruleus and deficient dopaminergic activity in frontal-mesolimbic pathways results in the symptoms of ADHD, as stimulants have a dampening effect on the locus coeruleus and facilitate the release of dopamine from the striatum. However, as stimulants produce a similar behavioural response in individuals
with and without ADHD, they may simply provide compensatory effects rather than targeting a specific neurochemical deficit (Solanto, 1998).

While the precise nature of the neurochemical deficits in ADHD remains unclear, there is growing evidence from several fields of biological research to suggest that dysfunction of frontal – basal ganglia dopamine pathways plays an important role (Castellanos, 1997; Levy & Swanson, 2001; Swanson et al., 1998b). Mutations of dopamine receptor genes within this system that innervates fronto-striatal circuits may reduce dopamine activity and alter the normal development of dopamine systems (Swanson et al., 1998b, 1998c) and may increase susceptibility for ADHD (Tannock, 1998). Children with ADHD may lack reciprocal inhibitory interactions between mesocortical and striatal dopamine neurons due to a deficit or delay in cortical development, resulting in reduced motor inhibition and goal-directed activity and increased environmentally dependant and inappropriate instinctive activity (Levy, 1991). Noradrenergic dysfunction and the effects of this on cortical function are increasingly being seen as also important in ADHD (Arnsten, 2000; Solanto et al., 2001).

3.2 Neuropsychological Research

This section presents a review of research into the neuropsychological aspects of ADHD. The most extensively studied aspects of cognition have been attention and executive functions. Studies of attention deficits in ADHD are discussed in section 3.2.1. Studies utilizing the continuous performance task (CPT) are reviewed in most detail as this task is used in the current study. Executive function studies, linking ADHD to frontal lobe deficits, are discussed in section 3.2.2. Studies using tasks designed to assess parietal lobe function, deficits of which are also suggested to be involved in ADHD, are reviewed in section 3.2.3. Neuropsychological research and its implications for cognitive deficits in ADHD are then summarized in section 3.2.4.

3.2.1 Studies of Attention
Attention has been a major focus of neuropsychological research in ADHD and deficits on various tasks designed to measure attentional aspects of performance have been found. However, task performance in children with ADHD has been found to be affected by many factors other than attention and it has been concluded that poor performance may not be attributable to a specific deficit in attention (Barkley, 1997; Schachar, 1991; Swanson et al., 1990; Van der Meere, 1996). Instead, the cognitive deficit in ADHD appears to be at the output or motor stage of information processing rather than at input or attentional stages (Barkley, 1997; Van der Meere, 1996). Studies addressing different aspects of attentional performance in ADHD are reviewed in the following sections.

3.2.1.1 Orienting and Encoding

Two basic functions involved in attentional performance are orienting, or directing attention to sensory events, and encoding, or information uptake. In his review of attentional aspects of ADHD, Van der Meere (1996) concluded that children with ADHD do not appear to differ from controls in the ability to orient or direct their attention to visual cues (Burke, 1990; Swanson et al., 1990, 1991), although they may have some difficulties in the ability to re-orient after a signal to shift their attention (Pearson & Lane, 1990). Van der Meere (1996) also concluded that studies have failed to find differences between children with ADHD and controls in information encoding ability (eg. Sergeant & Scholten, 1985a). The basic abilities of encoding and retrieval of information seem to be intact in ADHD (Douglas, 1988; Van der Meere, 1996). Encoding deficits only become apparent when task complexity increases and organisation or strategies are required, suggesting impaired self-regulatory processing in ADHD rather than impaired information processing (Douglas & Benezra, 1990).

3.2.1.2 Focused, Selective and Divided Attention

Focused attention has been defined as the ability to ignore irrelevant sensory information in favour of task-relevant information (Van der Meere & Sergeant, 1988c). Studies of focused attention have generally found that children with ADHD are not more distracted than controls by irrelevant information (eg. Van der Meere & Sergeant, 1988c; for reviews see Douglas, 1983; Van der Meere, 1996), although some studies
have found that they are more markedly affected by distracting stimuli (eg. Leung & Connolly, 1996). They may only be more distractible when the distractors used are highly salient and task intrinsic (Rosenthal & Allen, 1980).

Selective attention is similarly defined as the ability to focus on relevant information while ignoring irrelevant information (Pearson & Lane, 1990). In their review of studies of selective attention in ADHD, Pearson and Lane (1990) concluded that selective attention deficits in the visual or auditory modalities are not consistently found in children with ADHD. Poorer selective attention in children with ADHD may only be observed when more difficult discrimination between stimuli is required (eg. Loiselle et al., 1980). Pearson and Lane (1990) also suggested that the task performance of children with ADHD is affected by task complexity, the temporal structure of tasks, inefficient use of attentional strategies, motivation and developmental immaturity. These factors might explain any performance deficits, rather than selective attention deficits per se (Pearson & Lane, 1990). Some evoked potential findings do point to selective attention deficits in ADHD, however, as discussed later in section 3.4.2.1 (Klorman, 1991; Satterfield et al., 1988, 1994).

The ability to divide attention between simultaneously presented tasks has also been examined in children with ADHD and has been related to the concept of attentional capacity (Van der Meere, 1996). A deficit in divided attention or capacity could be assumed if primary task performance was affected by increased interference from a secondary task in children with ADHD to a greater extent than in controls (Van der Meere, 1996). Several studies have shown that this is not the case (Schachar & Logan, 1990a; Sergeant & Scholten, 1985a; Van der Meere & Sergeant, 1987; Van der Meere et al., 1989), although such deficits have been found in some studies (eg. Leung & Connolly, 1994). Overall, most reviewers conclude that children with ADHD cannot be said to have specific deficits in divided, selective or focused attention, suggesting that poor task performance when found is due to factors other than attention (Schachar, 1991; Pearson & Lane, 1990; Van der Meere, 1996).

### 3.2.1.3 Visuo-Spatial Attention
The covert orienting of visuo-spatial attention task (COVAT: Posner, 1980) has been used to study visuo-spatial attention in ADHD, with mixed results. This task involves responding to a target presented in either the right or left visual field (RVF or LVF) some time after a cue is presented. The cue may be valid (ie. presented in the same visual field as the following target), invalid (ie. presented in the opposite visual field to the following target), or neutral (ie. the cue is presented to both visual fields or no cue is presented). Reaction times are increased by invalid cue costs compared to reaction times associated with neutral or no cue conditions, and reaction times are reduced by valid cue benefits. Reduced invalid cue costs for LVF targets compared with RVF targets have been found in children with ADHD (Carter et al., 1995a; Swanson et al., 1990, 1991). Swanson et al. (1990, 1991) interpreted their findings as suggesting that children with ADHD showed normal orienting to the RVF cue but did not maintain attention to the cued location, thus reducing the invalid cue effect for LVF targets. They suggested that this may be related to deficits in the anterior attention system and fronto-striatal networks (Posner & Petersen, 1990), and in the left lateralized, dopamine mediated activation system (Tucker & Williamson, 1984). However, Carter et al. (1995a) suggested that deficits in right hemispheric fronto-striatal attentional mechanisms were responsible for their similar finding. In contrast to these findings, Wood et al. (1999) found an increased invalid cue cost in children with ADHD and Aman et al. (1998) found no difference in performance between ADHD and control groups. Nigg et al. (1997) found that the reaction time for uncued LVF targets was slower in children with ADHD, suggesting that right hemisphere mechanisms are underreactive to uncued stimuli, possibly due to right hemisphere noradrenergic dysfunction (Malone et al., 1994).

The presence and nature of visuo-spatial attention deficits in ADHD remain unclear due to these conflicting findings and conflicting interpretations of similar findings. One fairly consistent finding from COVAT studies of ADHD is that performance deficits in children with ADHD are observed when the cue – target interval is long (350-800 ms), but not when it is short (100-150 ms) (Burke, 1990; Swanson et al., 1990, 1991; Wood et al., 1999). These findings suggest that covert orienting to cues and the posterior attention system may be normal in children with ADHD, but that voluntary control of attention mediated by the anterior attention system may be deficient (Carter et al., 1995a; Swanson et al., 1990, 1991; Wood et al., 1999). However, Nigg et al. (1997)
found increased reaction time for uncued LVF targets at the shorter cue–target interval of 100 ms, but not at the longer interval of 800 ms. They suggest this reflects problems in the initial activation of attention, possibly due to right hemisphere dysfunction in maintaining alertness in order to detect uncued stimuli.

3.2.1.4 Sustained Attention – the Continuous Performance Task

The continuous performance task (CPT) was originally developed by Rosvold et al. (1956) as a measure of sustained attention or vigilance. The CPT has been widely used as both a research and a diagnostic instrument in the field of ADHD (Corkum & Siegel, 1993). These tasks require the subject to view sequences of randomly ordered stimuli, such as letters, and to respond to a particular infrequent stimulus, such as the letter X, or to a particular sequence of stimuli, such as X preceded by A. Omission errors (missed targets) are considered a measure of inattention, while commission errors (responses to non-targets or false alarms) are considered a measure of impulsivity (Burke, 1990; Corkum & Siegel, 1993). Reaction time (time between stimulus onset and response) to target stimuli is considered a measure of alertness (Levy, 1980).

Reactivity time is often not reported in CPT studies, which tend to concentrate on the number and/or type of errors made (Chee et al., 1989). However, children with ADHD have been found to have slower reaction times in response to target stimuli than normal controls in several studies (Chee et al., 1989; Klorman et al., 1979; Overtoom et al., 1998; Schechter & Timmons, 1985; Strandburg et al., 1996; Wood et al., 1999). This finding has been interpreted as suggesting an inability to process and respond to information quickly in children with ADHD (Wood et al., 1999). Children with ADHD also have more variable reaction times than their normal peers (Klorman, 1991; Van Leeuwen et al., 1998).

Children with ADHD have been shown to make significantly more errors of omission than normal controls in many studies (August & Garfinkel, 1989; Barkley et al., 1992; Barkley & Grodzinsky, 1994; Breen, 1989; Chee et al., 1989; Fischer et al., 1990; Halperin et al., 1990, 1993a; Harper & Ottinger, 1992; Hooks et al., 1994; Horn et al., 1989; Klorman et al., 1979; Michael et al., 1981; Overtoom et al., 1998; Schachar et al., 1988; Schechter & Timmons, 1985; Sykes, 1971, 1973; Van Leeuwen et al., 1998;
Zentall, 1986). This finding has been interpreted as evidence for inattention and deficient arousal in ADHD (Corkum & Siegel, 1993; Losier et al., 1996). Children with ADHD also make more errors of commission than their normal peers (August & Garfinkel, 1989; Barkley et al., 1990; Barkley & Grodzinsky, 1994; Chee et al., 1989; Fischer et al., 1990; Halperin et al., 1990, 1993a; Harper & Ottinger, 1992; Hooks et al., 1994; Horn et al., 1989; Klorman et al., 1979; Kupietz, 1990; Leung & Luk, 1988; Michael et al., 1981; Newcorn et al., 1989; Rapoport et al., 1980; Schecter & Timmons, 1985; Shapiro et al., 1986; Sykes, 1973; Van Leeuwen et al., 1998; Zentall, 1986).

Increased commission errors are thought to result from poor inhibition and more impulsive responding (Barkley, 1997; Halperin et al., 1993; Kupietz, 1990; Van Leeuwen et al., 1998). Losier et al. (1996) performed a meta-analytic review of error rates in CPT studies of ADHD and found that across 11 studies children with ADHD made twice as many omission errors and more than twice as many commission errors as normal controls. Both these differences were statistically significant. Increased CPT error rates in ADHD children is a fairly consistent result, although many of the studies listed above found significant group differences for only one type of error (omission or commission), and some studies have found no significant difference in either type of error between ADHD and control subjects (e.g. Werry, 1987; Wood et al., 1999).

The CPT has traditionally been used as a measure of sustained attention and increased error rates have been interpreted as indicative of a sustained attention deficit (Corkum & Siegel, 1993; Levy, 1980; Losier et al., 1996). However, a specific deficit in sustained attention in children with ADHD, suggested by diminishing performance with increasing time on task in ADHD subjects to a greater extent than in normal controls, has been demonstrated in only a few CPT studies (Seidel & Joshko, 1990; Sykes et al., 1973; Van Leeuwen et al., 1998). Furthermore, it has been argued that sustained attention has not been measured in these studies as results may have been confounded by differences in learning abilities between ADHD and control groups (Alberts & Van der Meere, 1992; Van der Meere & Sergeant, 1988a). Van der Meere and Sergeant (1988b), among others, argue that in order to demonstrate a sustained attention deficit, ADHD subjects must show a deterioration in performance with increasing time on task that is significantly greater than that shown by control subjects. In the Sykes et al. (1973) study the controls showed an improvement in task performance over time, suggesting a practice effect (Alberts & Van der Meere, 1992). In the Seidel and
Joschko (1990) study only the younger controls showed a deterioration in task performance over time. And in the Van Leeuwen et al. (1998) study the controls failed to show a decrement in error rate with increasing time, although they did show an increase in reaction time that was equivalent to that of ADHD subjects. Several other studies have found that the vigilance performance of ADHD subjects was not more adversely affected by increasing time on task than that of controls (Kupietz, 1990; Michael et al., 1981; Schachar et al., 1988; Van der Meere & Sergeant, 1988b). These findings have led to the conclusion that children with ADHD do not have a specific sustained attention deficit that is measurable by CPT performance (Corkum & Siegel, 1993; Schachar et al., 1988; Van der Meere & Sergeant, 1988b).

While performance of the CPT requires sustained attention, it also taps many other processes including arousal, motivation and inhibition (Corkum & Siegel, 1993; Klorman, 1991). Therefore, poor performance on the CPT does not necessarily reflect a specific sustained attention or vigilance deficit. Several other explanations for CPT performance deficits in children with ADHD have been proposed including momentary concentration problems (Corkum & Siegel, 1993; Oades, 1998), compromised allocation of effort (Dinklage & Barkley, 1992; Van der Meere & Sergeant, 1988b), or an inability to modulate activation according to task demands (Van der Meere, 1996). The cognitive processes measured by the CPT and therefore the nature of the deficits revealed by poor performance may also depend on task and external variables, which vary greatly between studies (Corkum & Siegel, 1993; Losier et al., 1996).

Performance on the CPT is affected by a number of variables. Developmental effects have been demonstrated, related to improvements in both sustained attention and inhibition with age (Levy, 1980; Seidel & Joshko, 1990; Sykes et al., 1971). Therefore age can be an important factor to control for, and also to consider in interpreting results (Seidel & Joshko, 1990; Werry et al., 1987). CPT performance is also affected by external variables such as whether or not feedback or rewards are given, whether instructions emphasize speed or accuracy, and the amount of practice (Corkum & Siegel, 1993). Even the presence or absence of an examiner has been shown to influence CPT performance by children with ADHD (Power, 1992).
Differences in task variables such as type of task (CPT-X or CPT-AX), stimulus rate and duration, and target probability may also influence CPT performance and the degree of performance deficits in ADHD subjects (Corkum & Siegel, 1993; Losier et al., 1996; Oades, 1998; Wood et al., 1999). Various different versions of the CPT have been used in ADHD research. Some tasks use letters while others use digits, and some require a response to a single stimulus (eg. CPT-X) while others require a response to a stimulus sequence (eg. CPT-AX). Greater performance deficits are generally observed in ADHD subjects on the more demanding CPT-AX (Corkum & Siegel, 1993; Oades, 1998).

Stimulus duration varies greatly (from 40 to 800 ms: Corkum & Siegel, 1993; Losier et al., 1996), and shorter stimulus durations are generally associated with more significant differences in error rates between ADHD and normal control groups (Chee et al., 1989; Corkum & Siegel, 1993). Inter-stimulus interval also varies between studies (600 ms to 5 seconds: Corkum & Siegel, 1993; Losier et al., 1996), as does task duration (3 to 27 minutes: Corkum & Siegel, 1993; Losier et al., 1996), and percentage of targets (10 to 25%: Corkum & Siegel; Losier et al., 1996). A higher percentage of targets has been associated with greater performance deficits in children with ADHD in comparison to controls (Corkum & Siegel, 1993).

Selection and matching of subjects may also affect the extent of differences in CPT performance between ADHD and normal control groups (Corkum & Siegel, 1993). Some researchers have emphasized the importance of controlling for group differences in age, gender and IQ (Corkum & Siegel, 1993; Werry et al., 1987). Severity of ADHD, which is affected by subject selection criteria, may also influence results, with more severely affected children likely to show more significant deficits in CPT performance (Leung & Luk, 1988; Wood et al., 1999). Heterogeneity of ADHD groups and comorbidity with other psychiatric disorders may also affect findings (Fischer et al., 1995; Halperin et al., 1992, 1993a; Losier et al., 1996). However, Wood et al. (1999) directly examined the effects of comorbidity and found no difference in CPT-X performance between pure and comorbid ADHD groups. Halperin et al. (1993a) examined CPT-AX performance in pure ADHD, pure anxiety disorders, non-ADHD disruptive behaviour disorders, and normal control groups and found that the ADHD group made significantly more errors than the other three groups, who did not differ from each other on error measures.
These findings suggest that the CPT performance deficits commonly found in children with ADHD are due to ADHD and not to the presence of comorbid symptoms (Wood et al., 1999). However, CPT performance deficits have been found in children with a number of other psychopathological conditions, including learning and reading disabilities and conduct disorder (Koelega, 1995; Oades, 1998). Some studies examining multiple subject groups find a unique pattern for ADHD subjects (Chee et al., 1989; Halperin et al., 1993a), but others do not (Robins, 1992). The issues of the effects of comorbidity and the specificity of poor performance to ADHD are difficult to resolve, as there may still be heterogeneity among ‘pure’ groups of ADHD subjects (Koelega, 1995).

Performance on the CPT has been shown to be improved by stimulants, which generally reduce reaction times and the number of errors made (Klorman, 1991; Klorman et al., 1979, 1991; Losier et al., 1996; Michael et al., 1981; Rapoport et al., 1980). Losier et al. (1996) performed a meta-analytic review of the effects of methylphenidate on the CPT performance of children with ADHD. They found that across 15 studies omission errors were reduced by 39% after methylphenidate administration, and commission errors were reduced by 29%. Klorman et al. (1991) suggested that this improved accuracy results from more efficient stimulus evaluation. Stimulants have been found to also improve CPT performance in normal children and adults (Klorman, 1991; Rapoport et al., 1980; Strauss et al., 1984), so this effect is not specific to ADHD.

### 3.2.1.5 Conclusions for Attention

Children with ADHD are consistently found to perform more poorly than normal controls on a variety of tasks designed to measure attentional processes, especially on continuous performance or vigilance tasks. As these tasks require the efficient use of a range of other cognitive processes in addition to attention, poor performance may not necessarily indicate deficits in attention (Schachar, 1991). It has been suggested that an actual deficit in attention has not been found and that task inefficiency in children with ADHD results from dysfunctional processes at the output or motor stage of information processing (Barkley, 1997; Van der Meere, 1996). Deficits in motor timing, preparation and control may better explain the poor performance of children with ADHD on attentional tasks. In terms of behavioural symptoms, children with ADHD are
consistently reported by parents and teachers to demonstrate inattention (Barkley, 1990, 1997). This behavioural inattention and distractibility might also arise from deficits in inhibition and self-regulation and the effects these deficits have on task persistence and interference control (Barkley, 1997; Schachar et al., 1995; Van der Meere, 1996). As will be explored in section 3.4, findings of evoked potential studies do suggest some evidence of attention deficits at the neural level. The ability to examine underlying brain function associated with poor attentional performance in ADHD may help to clarify at what stages of processing these attention deficits occur.

3.2.2 Studies of Frontal Lobe / Executive Functions

More recently, neuropsychological studies of ADHD have focused on measures of executive functions, or processes thought to involve the frontal lobes of the brain (Pennington & Ozonoff, 1996; Sergeant et al., 2002; Tannock, 1998). Performance deficits on various measures of executive functions have been found in ADHD subjects using a variety of tasks. Adults with prefrontal lobe injuries are also found to perform poorly on these same tasks, and brain imaging studies have found frontal activation during performance of these tasks. This has led to the suggestion that poor performance on executive function tasks by children with ADHD indicates frontal lobe deficits (Barkley, 1997).

In their reviews of studies of executive functions in ADHD, Pennington and Ozonoff (1996) and Sergeant et al. (2002) concluded that executive function deficits in ADHD were found in the majority of studies, but not all. Measures of motor inhibition (discussed further in section 3.2.2.1) consistently found differences between ADHD and normal control groups, e.g. the go – no-go task (Shue & Douglas, 1992) and the stop task (Aman et al., 1998). The executive function deficit in ADHD does not appear to be exclusively in motor inhibition however, as studies of other executive function tasks also find group differences, e.g. working memory tasks such as self ordered pointing (Shue & Douglas, 1992). Pennington and Ozonoff (1996) concluded that executive function deficits in ADHD have been consistently found in well controlled studies and do not appear to be a factor of IQ, age or comorbidity. Apart from measures of vigilance, non-executive function measures including verbal and visuo-spatial tasks are far less consistent in demonstrating deficits in ADHD (Pennington & Ozonoff, 1996).
Executive function deficits are not specific to ADHD, however, as they are also found in other disorders (Sergeant et al., 2002). Findings from some of the most commonly used executive function tasks are discussed in section 3.2.2.1, followed by a discussion of findings from tasks designed to look specifically at motor inhibition in section 3.2.2.2.

3.2.2.1 Executive Function Tasks

The Wisconsin card sort task (WCST) involves sorting stimuli according to number, colour or shape and requires stopping an ongoing response when feedback signals that a change in the sort criterion is required (Barkley, 1997; Berman et al., 1995). Patients with frontal lobe lesions, particularly lesions of the dorso-lateral prefrontal cortex (DLPFC), perform poorly on this task (Arnett et al., 1994; Berman et al., 1995). Performance of the WCST has been associated with prefrontal cortex activation in normal adults in a positron emission tomography (PET) study (Berman et al., 1995) and in a steady-state visually evoked potential (SSVEP) study (Silberstein et al., 1995). Berman et al. (1995) interpreted their finding of DLPFC activation as indicating working memory involvement in the WCST. Silberstein et al. (1995) found increased prefrontal activation at the time when a new sort criterion had to be determined, suggesting prefrontal mediation of changing the card sort strategy.

Children with ADHD have been shown to perform more poorly than controls on the WCST in several studies, making more perseverative or non-perseverative errors or completing fewer categories (Boucugnani & Jones, 1989; Chelune et al., 1986; Gorenstein et al., 1989; Klorman et al., 1999; Seidman et al., 1995b; Shue & Douglas, 1992). However, Sergeant et al. (2002) concluded that almost a third of studies reviewed failed to show significant group differences. Findings of poor performance in children with ADHD have generally been interpreted as indicative of frontal lobe dysfunction and in particular disinhibition (Barkley, 1997; Barkley & Grodzinsky, 1994; Boucugnani & Jones, 1989; Chelune et al., 1986). In addition to poor inhibition, these findings suggest problems with using feedback about errors to modify responses (Barkley, 1997; Shue & Douglas, 1992) and may also reflect deficiencies in working memory and its influence on motor control (Barkley, 1997). However, Sergeant et al. (2002) argue that non-perseverative errors are more likely to discriminate ADHD...
children from controls than perseverative errors, and this may reflect a general inaccuracy rather than deficits in cognitive flexibility.

The Stroop colour-word interference task involves naming the colour of the letters that form a word representing a different colour, eg. the word RED written in green, and so requires inhibition of the automatic response of reading the word (Bench et al., 1993; Vendrell et al., 1995). Patients with frontal lobe lesions, particularly lesions of the right prefrontal cortex, perform poorly on this task (Vendrell et al., 1995). Performance of the Stroop has also been associated with right orbito-frontal cortex and right anterior cingulate activation in normal adults in PET studies (Bench et al., 1993; Pardo et al., 1990). Children with ADHD have been shown to make more errors on the Stroop and complete the task more slowly than controls (Boucugnani & Jones, 1989; Carter et al., 1995b; Gorenstein et al., 1989; Grodzinsky & Diamond, 1992), suggesting a deficiency in the control of interference from prepotent responses (Barkley, 1997; Carter et al., 1995b). These findings have been interpreted as indicative of right prefrontal dysfunction in ADHD (Barkley, 1997).

The Tower of London (TOL) task requires arranging objects to match a given arrangement using the fewest possible moves and is used as a measure of problem solving and planning ability (Morris et al., 1993). Patients with injuries to the prefrontal cortex have difficulties on the TOL (Goel & Grafman, 1995) and its performance has been associated with left prefrontal cortex activation in a PET study (Morris et al., 1993). Poor performance on the TOL has been found in children with ADHD and interpreted as indicative of frontal lobe and executive dysfunction (Aman et al., 1998; Klorman et al., 1999; Pennington et al., 1993). However, 2 of 7 studies reviewed by Sergeant et al. (2002) found no difference in performance between ADHD and control groups. The TOL taxes several executive functions including working memory, problem solving, planning and inhibition (Goel & Grafman, 1995; Pennington et al., 1993). Poor performance in ADHD may reflect problems in any or all of these functions or their interactions (Barkley, 1997).

The matching familiar figures test (MFFT) requires choosing a picture that matches the target picture exactly from a number of similar pictures. Children with ADHD are found to make more errors and spend less time searching for and deciding on the
response than normal controls (De Hass, 1986; Pennington et al., 1993; Robins, 1992; Rosenbaum & Baker, 1984; Sonuga-Barke et al., 1994). These findings have been interpreted as evidence of deficient impulse control and an inability to inhibit responding while searching for the correct response in children with ADHD. However, Sonuga-Barke et al. (1994) found that children with ADHD responded more impulsively only when faster responding led to shorter trials, but not when the trial length was fixed, suggesting delay aversion rather than deficient inhibitory control. As with other executive function tasks the MFFT probably involves complex interactions between several cognitive processes in addition to inhibition (Barkley, 1997; Schachar & Logan, 1990a; Tannock, 1998). Findings of increased commission errors on the CPT have also been interpreted as suggesting poor motor inhibition in children with ADHD (Barkley, 1997). Commission errors on the CPT are thought to index impulsive responding, as are increased errors on the MFFT. However, performance on the MFFT and CPT may be affected by attentional capacity and strategies used as well as impulsivity, and increased errors may not be due to one specific deficit (Schachar & Logan, 1990a; Sonuga-Barke et al., 1994; Tannock, 1988).

### 3.2.2.2 Inhibition Tasks

Deficient performance by children with ADHD on frontal lobe tasks such as the WCST, the Stroop and the MFFT has been interpreted as being a consequence of poor response inhibition in ADHD (Barkley & Grodzinsky, 1994). However, these tasks rely on the effective use of many executive functions in addition to inhibition of prepotent responses, as discussed above. More direct evidence comes from purer measures of motor inhibition, which fairly consistently demonstrate deficient inhibition in children with ADHD (Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant et al., 2002). The go – no-go task requires inhibiting a motor response to the ‘no-go’ stimuli. Children with ADHD have been found to have difficulties inhibiting responding and to make more errors on this task, suggesting motor control difficulties similar to those reported for patients with frontal lobe lesions (Iaboni et al., 1995; Shue & Douglas, 1992; Trommer et al., 1988).

The Stop task requires stopping an already initiated motor response when a ‘stop signal’ is presented during a choice reaction time task. Children with ADHD are consistently
found to demonstrate difficulties inhibiting responses in this task and to have slower inhibitory processes (Aman et al., 1998; Oosterlaan & Sergeant, 1996; Oosterlaan et al., 1998; Rubia et al., 1999; Schachar & Logan, 1990b; Schachar et al., 1995, 2000). These findings have been interpreted as indicating less efficient inhibitory control in ADHD (Quay, 1997; Schachar & Logan, 1990b). The involvement of frontal lobe inhibitory mechanisms in the stop task is suggested by findings of ERP differences in stop trials compared with go trials at frontal recording sites (De Jong et al., 1990) and by frontal activation in neuroimaging studies (Rubia et al., 1999). In a current study at the Brain Sciences Institute, we have also shown poor inhibitory control and reduced prefrontal activity in boys with ADHD during the stop task (Carter et al., in preparation).

In a variation of the stop task, the Change task, which requires making an alternative response to the stop signal, children with ADHD also perform more poorly than controls (Oosterlaan & Sergeant, 1996; Schachar et al., 1995). The Change task requires the inhibition of an on-going action and rapid shifting to an alternate action, abilities which are both found to be deficient in children with ADHD, suggesting impairments in response re-engagement in addition to response inhibition (Oosterlaan & Sergeant, 1998; Schachar et al., 1995).

### 3.2.2.3 Conclusions for Executive Functions

Poor performance on executive function tasks has been found in ADHD children in the majority of studies (Pennington & Ozonoff, 1996; Sergeant et al., 2002). These tasks often involve a number of complex cognitive functions including inhibition, set shifting, working memory, planning and use of feedback. Interpretation of slower and/or less accurate task performance can therefore be difficult. As these tasks have been shown to involve the prefrontal cortex in lesion and imaging studies, poor performance in ADHD is thought to reflect prefrontal deficits (Barkley, 1997; Tannock, 1998). Measures of motor inhibition such as the stop task may be most consistent in distinguishing ADHD children from controls and suggest inhibitory dysfunction in ADHD (Oosterlaan & Sergeant, 1996; Sergeant et al., 2002). Deficits in inhibition and other executive functions are not specific to ADHD, but occur in other disorders including ODD, CD and autism (Sergeant et al., 2002). The relationship between performance deficits and
3.2.3 Studies of Parietal Lobe Functions

A small number of studies have used neuropsychological tasks to examine parietal lobe function in children with ADHD. The idea of parietal lobe involvement in ADHD arose from observations that children with ADHD and patients with right parietal lobe damage showed similar symptoms of inattention and hypoarousal (Aman et al., 1998; Voeller & Heilman, 1988). Children with ADHD were found to make more errors of omission and more left-sided errors than controls on the letter cancellation task, suggesting deficits similar to those of adults with right hemisphere dysfunction (Voeller & Heilman, 1988). Mental rotation tasks have also shown deficits in children with ADHD (Aman et al., 1998; Snow, 1990), similar to those reported for patients with right parietal lesions (Ditunno & Mann, 1990).

The right parietal cortex has been shown to be involved in visuo-spatial attention in PET studies (Corbetta et al., 1993) and in lesion studies (Posner & Raichle, 1996). The pattern of performance exhibited by patients with right parietal lesions on visuo-spatial attention tasks such as the COVAT is an increased invalid cue effect for LVF targets, suggesting difficulties in disengaging attention from invalid cues presented to the RVF (Posner & Raichle, 1996). However, with one exception (Wood et al., 1999) this pattern of COVAT performance has not been found in children with ADHD (Aman et al., 1998; Swanson et al., 1991). Aman et al. (1998) did find deficits in children with ADHD on two other measures of right parietal function, the turning task and spatial relations. They suggested that these findings may reflect the presence of right parietal dysfunction in ADHD, and that this dysfunction may be too subtle to produce deficits on the COVAT which may be sensitive only to more severe parietal deficits. As they found stronger evidence for frontal lobe deficits in ADHD, Aman et al. (1998) also suggested an alternative explanation that their findings may reflect the influence of frontal lobe deficits on parietal lobe function.

3.2.4 Conclusions for Neuropsychological Deficits in ADHD
While parietal lobe function in ADHD has not been extensively studied, some evidence does exist for possible right parietal dysfunction in children with ADHD (Aman et al., 1998). There is stronger evidence for deficits in frontal lobe function in ADHD children, who are fairly consistently found to have difficulties with aspects of task performance thought to be mediated by the frontal lobes, including motor control, problem solving, formulating and testing hypotheses, using feedback to modify responding, organizing responses, and adhering to task constraints (Barkley, 1997; Barkley & Grodzinsky, 1994; Boucugnani & Jones, 1989; Gorenstein et al., 1989; Pennington & Ozonoff, 1996; Shue & Douglas, 1992). This combination of deficits is similar to that found for patients with frontal lobe lesions and suggests that ADHD may be associated with comprehensive frontal lobe deficits in planning, hypothesis testing and inhibitory control (Shue & Douglas, 1992).

One of the most consistent findings from neuropsychological studies is that of deficits in response inhibition in children with ADHD, providing compelling evidence that ADHD involves impaired behavioural inhibition (Barkley, 1997; Barkley & Grodzinsky, 1994). However, inhibitory deficits may not be sufficient to explain the range of executive dysfunction in children with ADHD, who are also found to have difficulties in problem solving, effective use of feedback, and generation and use of strategies (Shue & Douglas, 1992). The integrative function of the frontal lobes may be impaired in ADHD as it is in patients with frontal lobe lesions, and impairment of higher order cognitive processing may result from difficulties in integrating information (Shue & Douglas, 1992). Alternatively, these other deficits may arise from the influence of deficient inhibition on other executive functions as suggested by Barkley (1997). Another alternative interpretation of poor performance by ADHD children on motor inhibition tasks was offered by Sergeant (2000), who suggests that successful or failed inhibition is dependent on the energetic state of the subject and that there is inadequate activation of inhibitory mechanisms in ADHD.

While the majority of studies do find executive function deficits in children with ADHD, there are conflicting findings for most of the frontal lobe tasks that have been used (Pennington & Ozonoff, 1996; Sergeant et al., 2002). Some of the inconsistencies in the results of neuropsychological studies of ADHD may be due to methodological
differences such as selection criteria and type of tests used, or to heterogeneity of ADHD subject groups (Barkley & Grodzinsky, 1994; Seidman et al., 1995a).

These inconsistencies in methodology and results also plague the literature on studies of attention in ADHD. While many studies find that children with ADHD perform poorly on attentional tasks, it is often concluded that this poor performance cannot be explained by attention deficits (Barkley, 1997; Schachar, 1991; Swanson et al., 1990; Van der Meere, 1996). Studies that isolated various aspects of information processing failed to find deficits in orienting of attention, encoding of information, selective attention or divided attention, but have found deficits in motor processes (Sergeant & Scholten, 1983, 1985a, 1985b; Van der Meere & Sergeant, 1987, 1988c). These findings suggest that the inattention that is characteristic of ADHD may also be related to deficits in inhibition and self-regulation (Barkley, 1997; Van der Meere, 1996). Children with ADHD fairly consistently demonstrate performance deficits on continuous performance or vigilance tasks in terms of slower and more variable reaction times and increased errors of omission and of commission. These findings have been interpreted as reflecting concentration problems (Corkum & Siegel, 1993; Oades, 1998), compromised regulation of effort or activation (Dinklage & Barkley, 1992; Van der Meere, 1996; Van der Meere & Sergeant, 1988b), and poor inhibition (Barkley, 1997). So, executive function deficits may also be related to the poor performance of children with ADHD on the CPT. This is further supported by evidence that the frontal lobes are involved in vigilance tasks (Pardo et al., 1991).

### 3.3 Neuroimaging Research

Various brain imaging methodologies have been applied to ADHD research in an attempt to find the underlying neurobiological basis of the disorder. These have included both structural and functional imaging methods, revealing some differences in both brain anatomy and brain function in subjects with ADHD. Structural neuroimaging studies are reviewed in section 3.3.1 and functional neuroimaging studies are reviewed in section 3.3.2.

#### 3.3.1 Structural Imaging
3.3.1.1 Computerized Tomography

Computerized tomography (CT) uses X-rays to scan the brain or other body structures and relies on the different absorption rates of X-radiation by tissues of different densities. Images of the scanned tissue are reconstructed from X-ray intensity measures. Fine structural details of soft brain tissues are not well resolved with this technique however.

Early studies that utilized CT to image brain structure in children and adults with ADHD revealed few significant differences from controls. In a comparison between children with ADHD and a control group who required CT scans for various clinical indications, no group differences were found in lateral ventricular size or in frontal lobe width, but the frontal lobes were found to be more symmetric in the ADHD group (Shaywitz et al., 1983). These authors concluded that if anatomic abnormalities exist in ADHD, they were not distinguishable using CT techniques available at that time. In a study of young adult males, no group differences were found in ventricular or hemispheric areas between an ADHD group and a group who required CT scans for evaluation of head trauma (Nasrallah et al., 1986). This study did find a 58% prevalence of mild to moderate cortical atrophy in the ADHD group, but the authors concluded that this finding may be due as much to coexisting psychiatric diagnoses or alcohol abuse as to the presence of ADHD (Nasrallah et al., 1986). The use of ionizing radiation in CT has limited its use in studies involving children, and therefore in studies of ADHD (Filipek et al., 1992; Tannock, 1998).

3.3.1.2 Magnetic Resonance Imaging

More recently magnetic resonance imaging (MRI), which offers better spatial resolution than CT and uses non-ionising radiation, has been used to study anatomical differences between ADHD and normal control groups. This technique uses rapidly changing high strength magnetic fields and relies on the different time taken for absorbed energy to be emitted from (usually hydrogen) nuclei within different types of tissue. These different relaxation times allow reconstruction of images of the brain, with much better tissue resolution than can be achieved with CT.
Using MRI, ADHD subjects have consistently been found to have a significantly smaller right frontal cortex than normal controls (Castellanos et al., 1996b; Filipek et al., 1997; Hynd et al., 1990; Pueyo et al., 2000). Because of this reduced right prefrontal lobe size, ADHD subjects also failed to demonstrate the normal right > left frontal asymmetry found in control subjects (Castellanos et al., 1996b; Hynd et al., 1990; Pueyo et al., 2000), which may be consistent with the greater frontal symmetry in ADHD subjects found using CT (Shaywitz et al., 1983). These findings have been interpreted as suggestive of right prefrontal deficits in ADHD (Castellanos et al., 1996b; Hynd et al., 1990). However, it was suggested by one reviewer that this assumed right-sided dysfunction is actually on the left and that these findings could reflect a lack of age-appropriate synaptic pruning in the left prefrontal cortex in children with ADHD (Oades, 1998).

Some researchers have speculated that the observed abnormal frontal symmetry and proposed frontal dysfunction in ADHD might be related to differences in the size of the corpus callosum (Giedd et al., 1994; Hynd et al., 1991). Various regions of the corpus callosum have been reported to be smaller in ADHD subjects. In several studies, anterior regions of the corpus callosum (rostrum, rostral body or genu) were found to be significantly smaller in ADHD subjects compared with normal controls (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991). Other studies found that posterior regions (splenium or isthmus) were significantly smaller in ADHD groups (Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). However, Castellanos et al. (1996b), whose sample included the subjects who participated in the study by Giedd et al. (1994), reported no significant difference between the larger ADHD and control groups in the total midsagittal area of the corpus callosum, nor in the area of any of the seven subregions measured. Overmeyer et al. (2000) reported no differences in total or regional corpus callosum areas between boys with ADHD and male siblings of children with ADHD and concluded that diagnosis should not be based on abnormality of callosal development. Some of the discrepancies between results for the corpus callosum may be due to differences in the selection of the subregions measured, the MRI procedures used, and the characteristics of the groups studied (Castellanos et al., 1996b; Semrud-Clikeman et al., 1994; Tannock, 1998). The known anatomy of cortical interconnections via the corpus callosum suggests that, if they exist, differences in the
anterior regions of this structure could be related to frontal dysfunction in ADHD (Giedd et al., 1994; Hynd et al., 1991), while differences in posterior regions might be related to visuo-spatial, math or sustained attention deficits that are sometimes seen in ADHD (Hynd et al., 1991; Semrud-Clikeman et al., 1994).

Other MRI studies of ADHD have focused on the basal ganglia, due to its connections with frontal cortex and suggestions of fronto-striatal deficits underlying ADHD symptoms. Castellanos and colleagues found a right > left asymmetry of the caudate nucleus in normal control subjects (Castellanos et al., 1994b; Castellanos et al., 1996b). This asymmetry was absent in ADHD children who had a significantly smaller right caudate nucleus than controls. These studies also found that age-related reductions in caudate volume that occurred in normal controls were diminished in ADHD subjects. This might be consistent with later findings that 14-16 year old adolescents with ADHD had a larger right caudate area than normal controls and reversed asymmetry (right > left), which were suggested to be related to a failure of the normal maturational processes of synaptic pruning that result in caudate volume reduction (Mataro et al., 1997; Pueyo et al., 2000). However, several other studies have found a left > right caudate asymmetry in normal control children, which was reversed in ADHD subjects who were found to have a significantly smaller left caudate (Filipek et al., 1997; Hynd et al., 1993; Semrud-Clikeman et al., 2000). Aylward et al. (1996) found no group differences in caudate asymmetry. Castellanos et al. (1996b) discounted the contrasting earlier finding of left > right normal caudate asymmetry (Hynd et al., 1990), stating that right > left caudate asymmetry had been found in three independent samples of normal adults (Breier et al., 1992; Flaum et al., 1995; Peterson et al., 1993) in addition to their paediatric sample. They also suggested that the strengths of their study included a larger sample size and better characterized subjects. However, subsequent studies have again shown the opposite left > right asymmetry in children (Filipek et al., 1997; Semrud-Clikeman et al., 2000), so this issue remains unresolved. Most recently, both the left and right caudate of ADHD girls were found to be smaller compared to control girls, but only the left caudate difference remained significant after covariance for total brain volume and IQ (Castellanos et al., 2001). Gender, age and diagnostic differences between samples might account for some of these contradictory findings. The discrepancies between results for the caudate nucleus may also be due in part to methodological differences in the way this structure was measured, such as whether the
head and body were included or just the head, or whether axial or coronal slices were used (Castellanos et al., 1994b, 1996b).

The globus pallidus and putamen, other nuclei forming the basal ganglia, have also been examined in MRI studies. The globus pallidus has been found to be smaller and to differ from normal asymmetry in ADHD subjects. Singer et al. (1993) found that the left globus pallidus was smaller in children with Tourette’s Syndrome with comorbid ADHD than in normal controls. This finding was replicated by Aylward et al. (1996), who also found reduced total globus pallidus volume, which was predominant on the left, in 10 children with ADHD only. In contrast, Castellanos and colleagues (1996b; 1996c) found that the right globus pallidus was smaller and that the normal right > left asymmetry was reversed in ADHD subjects. The putamen has not been found to be significantly different between ADHD and normal control groups (Aylward et al., 1996; Castellanos et al., 1996b, 1996c).

In an exploratory analysis of cerebellar volume, this measure was found to be decreased in ADHD boys (Castellanos et al., 1996b). In later studies that specifically examined the cerebellum, the posterior inferior lobe of the cerebellar vermis (lobules VIII to X) was found to be significantly smaller compared to healthy controls in boys with ADHD (Berquin et al., 1998; Mostofsky et al., 1998) and in girls with ADHD (Castellanos et al., 2001). These findings suggest that dysfunction of a cerebello-thalamo-prefrontal circuit may be involved in the motor control and executive function deficits in ADHD (Berquin et al., 1998). Further evidence that patients with cerebellar lesions show executive function deficits (Fiez et al., 1992), that methylphenidate increases metabolism in the cerebellum (Volkow et al., 1997), and that the cerebellum has projections to the prefrontal cortex (Middleton & Strick, 1994), support this hypothesis. Further research is needed to clarify the specific anatomical connections between regions of the cerebellum and regions of the cerebral cortex, and the nature of abnormalities of these connections in ADHD (Mostofsky et al., 1998; Castellanos et al., 2001).

Some studies have reported a smaller total brain volume in children with ADHD, and this measure was accounted for when reporting regional volume or area differences (Castellanos et al., 1994b, 1996b, 2001). The lateral ventricles have also been measured...
in several MRI studies of ADHD, yielding conflicting results. One study found a larger posterior lateral ventricle compared with psychiatric controls (Lyoo et al., 1996), another found a smaller left lateral ventricle compared with normal controls (Castellanos et al., 1996b), and a third found no significant group differences (Filipek et al., 1997). Other brain structures found to be smaller in ADHD subjects include frontal white matter (Filipek et al., 1997; Semrud-Clikeman et al., 2000) and parieto-occipital white matter (Filipek et al., 1997).

Some attempts have been made to correlate anatomical measures found to be deviant in ADHD with behavioural measures of ADHD symptoms. Areas of anterior regions of the corpus callosum (rostrum and rostral body) found to be smaller in boys with ADHD were negatively correlated with parent and teacher ratings of hyperactivity/impulsivity, suggesting a role for abnormal frontal lobe circuitry in ADHD (Giedd et al., 1994). Casey et al. (1997a) found that task performance on response inhibition tasks was significantly correlated with anatomical measures of fronto-striatal circuitry found to be abnormal in children with ADHD (prefrontal cortex, caudate and globus pallidus) in a previous study (Castellanos et al., 1996b), but not with the size of normal structures (putamen). As the correlations between task performance and measures of prefrontal cortex and caudate nuclei were predominantly in the right hemisphere, the authors suggested that these findings indicate the involvement of right fronto-striatal circuitry in response inhibition and in ADHD (Casey et al., 1997a). However, other studies have not found greater relationships between behaviour and right hemispheric structures. ADHD and control subjects with higher scores on the externalizing scale of the Child Behaviour Checklist were found to have smaller left and right frontal white matter volumes and smaller left caudate head volumes (Semrud-Clikeman et al., 2000). Smaller frontal white matter volume was also correlated with slower performance on a colour naming task and smaller left caudate volume was correlated with poorer performance on the Stroop task in this study. In another study, larger right and left caudate nucleus areas were associated with higher ratings on the Conners Teachers Rating Scale and poorer performance on tests of attention in control and ADHD adolescents (Mataro et al., 1997), suggesting further evidence of caudate involvement in the deficits found in ADHD, but in contrast with most other findings of smaller caudate size in ADHD. In contrast to all these findings, Castellanos et al. (1994b) found no significant correlations between caudate volumes or asymmetry and continuous
performance task errors or teacher and parent hyperactivity and conduct ratings. In their study of ADHD girls, Castellanos et al. (2001) found that smaller total brain volume was associated with lower full scale IQ scores and higher Child Behaviour Checklist attention problems scores, and that smaller posterior inferior cerebellar vermal volume was associated with more severe Child Behaviour Checklist anxiety-depression ratings.

3.3.1.3 Conclusions for Structural Imaging

Structural brain imaging studies, especially MRI studies, have revealed some anatomical brain differences in children with ADHD. In a recent review, Rapoport et al. (2001) concluded that ADHD is characterized by 4% smaller total brain volume, 15% smaller posterior inferior cerebellar vermal volume, and inconsistent basal ganglia abnormalities, changes that do not appear to progress with age. Others have concluded that regions of the frontal lobes and basal ganglia are about 10% smaller in ADHD groups than in controls (Swanson et al., 1998b). These findings point to possible fronto-striatal system differences, consistent with biological theories of ADHD that implicate fronto-striatal dopamine pathways in the pathophysiology of ADHD (Castellanos, 1997; Levy, 1991; Swanson et al., 1998b) and with neuropsychological theories that see ADHD as resulting from frontal lobe deficits, in particular deficits in response inhibition (Barkley, 1997; Casey et al., 1997a). Findings of decreased volumes in other regions such as the cerebellum (Berquin et al., 1998) and parieto-occipital white matter (Filipek et al., 1997), suggest that some ADHD children might show altered structure outside fronto-striatal systems, including areas that subserve components of attention and cognition (Hale et al., 2000). The majority of studies suggest that right hemisphere abnormalities are predominant in ADHD. This is especially so for the frontal cortex (Castellanos et al., 1996b; Filipek et al., 1997; Hynd et al., 1990), although the laterality of basal ganglia abnormalities is less clear (Castellanos et al., 1994b; Hynd et al., 1993). Despite some concordance between results, there are inconsistencies between findings for normal controls as well as for children with ADHD, which may be due to differences between studies in subject selection criteria or in MRI methods and image analysis (Tannock, 1998). In addition, structural MRI studies have failed to identify consistent structural landmarks associated with ADHD diagnosis, limiting the diagnostic potential of this technique (Overmeyer et al., 2000; Overmeyer & Taylor, 2001; Vaidya & Gabrieli, 1999).
3.3.2 Functional Imaging

3.3.2.1 Positron Emission Tomography

Positron emission tomography (PET) measures the abundance of injected radioactive isotopes in different brain regions to determine task related metabolic activity and/or blood flow. As the radioactive isotopes decay to their non-radioactive stable state, they emit a positron, which then interacts with an electron to produce two photons that are emitted in opposite directions. These photons are detected and the location from which they were emitted is determined. This provides an image of patterns of blood flow or metabolism, as more active regions will have higher rates of radioactive emission. PET studies of ADHD have been restricted to older subjects due to ethical concerns about exposing children to the radioactive isotopes necessary for this technique (Lou, 1992; Zametkin et al., 1990, 1993). The studies that have been conducted have yielded rather inconsistent results.

Using the radiotracer [18F]fluoro-deoxyglucose (FDG) to measure glucose metabolism, Zametkin et al. (1990) found that reduced global metabolism and reduced regional metabolism in 30 of the 60 areas examined was associated with performance of an auditory CPT in adults with a history of childhood ADHD, when compared with normal controls. The greatest differences in metabolism occurred in premotor and superior prefrontal cortex, areas associated with control of motor activity and attention, suggesting a relationship between reduced frontal metabolic activity and ADHD symptoms (Zametkin et al., 1990). Reduced metabolism in ADHD subjects was also found in the striatum and the thalamus. In a subsequent study of adolescents with ADHD (Zametkin et al., 1993), no significant group differences were found for global or absolute regional cerebral glucose metabolism. However, reduced normalized (regional/global) metabolism in ADHD subjects was found in six regions including the left anterior frontal cortex, where significantly reduced glucose metabolism was also found in adults with ADHD in the previous study (Zametkin et al., 1990). Left anterior frontal metabolism was significantly correlated with ADHD symptom severity in the adolescent sample, providing further evidence of a link between reduced frontal metabolism and deficits in motor and attentional control (Zametkin et al., 1993).
In both the adult (Zametkin et al., 1990) and adolescent (Zametkin et al., 1993) studies, a trend toward stronger group differences in metabolism in female subjects than in males was observed (Ernst et al., 1994a; Zametkin et al., 1993). When the adolescent sample was expanded, no group differences in global or absolute regional metabolism were found across the entire groups (Ernst et al., 1994a). However, global glucose metabolism was 15% lower in girls with ADHD than in normal girls, and significant regional metabolism reductions occurred in premotor, orbito-frontal and temporal cortex in girls with ADHD. No significant differences were found between boys with ADHD and normal boys. A subsequent study which included a larger independent sample of adolescent girls failed to replicate this finding, as no differences in global or regional metabolism between girls with ADHD and normal girls were found (Ernst et al., 1997a). Differences in sample characteristics and data analysis techniques were discussed as possible reasons for the conflicting results (Ernst et al., 1997a). Lateralization of normalized metabolism was significantly different between groups in the later study, with lower metabolism in the left hemisphere in girls with ADHD and in the right hemisphere in controls (Ernst et al., 1997a). Gender effects were also found in another FDG PET study of adults (Ernst et al., 1998b). In this study, the effects of age on glucose metabolism during an auditory CPT were examined in 18 to 56 year olds. Increased age was associated with reduced global glucose metabolism in women with ADHD, but there were no significant correlations for control women, ADHD men or control men. CPT performance improved with age in the ADHD women, but again not in any of the other groups. The authors suggested that the roles of behavioural, hormonal and genetic factors on brain function abnormalities should be examined in future research (Ernst et al., 1998b).

In the few PET studies that have examined pharmacological effects, neither methylphenidate nor dexamphetamine have been shown to alter global glucose metabolism in adults with ADHD (Ernst et al., 1994b; Matochik et al., 1993, 1994). In a FDG PET study of 8 ADHD adults, intravenous infusion of dexamphetamine did not significantly affect global or regional metabolism but did improve CPT scores (Ernst et al., 1994b). In a later similar study of 13 healthy adults, significant increases in regional glucose metabolism occurred in subcortical, limbic, frontal and cerebellar regions, while metabolism decreased in the temporal cortex (Ernst et al., 1997b). The authors
concluded that the observed changes in metabolism reflect effects on neurotransmitter systems and enhanced activation of networks involved in CPT performance, but the findings have yet to be replicated in ADHD subjects. When the acute effects of single oral doses of methylphenidate and dexamphetamine on ADHD adults were examined using FDG PET, both drugs produced inconsistent patterns of increases and decreases in regional metabolism and neither drug altered global metabolism (Matochik et al., 1993). A later study examining chronic effects after six weeks of treatment again found that neither drug altered global metabolism, and that methylphenidate altered metabolism in just two of sixty regions sampled while dexamphetamine did not affect regional metabolism (Matochik et al., 1994). Both drugs improved behavioural self-report measures of restlessness and attention, suggesting they were effective in treating adult ADHD. Perhaps the lack of significant findings of altered brain metabolism in these studies might be due to heterogeneity amongst the adult samples.

Two recent studies used PET with the radiotracer $[^{18}F]$flourodopa to examine presynaptic dopaminergic function in adults and adolescents with ADHD. This tracer is transported into presynaptic terminals, converted to $[^{18}F]$flourodopamine by the enzyme dopa decarboxylase, and stored in storage vesicles. Hence the data obtained reflect dopa decarboxylase activity and dopamine storage processes (Ernst et al., 1998a, 1999). In both studies, brain areas high in dopamine including the prefrontal cortex, striatum (caudate and putamen) and midbrain (ventral tegmentum and substantia nigra) regions were examined. For adults, only the prefrontal cortex showed significantly lower DOPA decarboxylase activity in ADHD subjects, with medial and left prefrontal areas showing the largest differences (Ernst et al., 1998a). Given this and previous PET findings of discrepancies between adults and adolescents with ADHD, the authors hypothesized that a prefrontal dopaminergic dysfunction underlies ADHD symptoms in adults and that this dysfunction is secondary to subcortical dopaminergic deficits and their interactions with maturational processes. For adolescents, dopa decarboxylase activity in the right midbrain region was greater in ADHD subjects and was correlated with symptom severity (Ernst et al., 1999). However, the increase in midbrain enzyme activity in ADHD subjects did not remain significant after correction for multiple comparisons, and control subjects were unaffected siblings of children with ADHD (as mandated by ethics committees). So while these results are interesting, they require replication in independent and larger samples. Increased levels of dopamine synthesis
could result from any combination of abnormalities in a number of processes affecting enzyme activity, which increases in response to low extracellular levels of dopamine, or from increased density of dopaminergic neurons (Ernst et al., 1999). Further research is needed to help clarify which components of the dopamine system are abnormal in ADHD and how these abnormalities interact with development. Given the ethical concerns of radiation exposure in this type of research, especially with children, this remains problematic.

Another PET study of adult ADHD used the radiotracer \([^{15}\text{O}]\text{H}_2\text{O}\) to examine regional cerebral blood flow changes related to working memory (Schweitzer et al., 2000). In healthy men, blood flow was increased in a paced auditory serial addition task compared to a number generation task in right frontal and left temporal regions, suggesting activation in the working memory task reflecting retrieval and subvocal rehearsal. In men with ADHD, activations were more widespread and were largest in precuneus and left inferior parietal regions, suggesting diminished retrieval and use of visual imagery. The ADHD men performed worse on the working memory task and reported using visual imagery. The authors suggested that these findings reflect the use of compensatory strategies in ADHD subjects, but acknowledged that they need confirmation in larger samples (Schweitzer et al., 2000).

3.3.2.2 Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) detects single photons emitted from radioactive decay, and hence has poorer spatial resolution than PET. It uses a different type of radioactive agent to those employed in PET to produce an image of the pattern of blood flow at the time of injection.

Studies using SPECT have revealed reduced cerebral blood flow in the frontal lobes and striatum in children with ADHD, although the findings are somewhat inconclusive (Amen & Carmichael, 1997; Lou et al., 1984, 1989; Sieg et al., 1995). In the first, small study using the radiotracer Xenon-133, cerebral blood flow was reduced in frontal lobe white matter regions and in the caudate nuclei in ADHD subjects (Lou et al., 1984). These findings were replicated in subsequent studies which found hypoperfusion in the striatum, especially on the right, and hyperperfusion in the occipital lobes and left
sensori-motor and primary auditory regions (Lou et al., 1989, 1990a). The reduced activity in frontal and striatal regions and increased activity in primary sensory regions were partly reversible with administration of methylphenidate (Lou et al., 1984, 1989). Kim et al. (2001) have also shown increased regional cerebral blood flow after methylphenidate treatment in boys with ADHD in frontal, caudate and thalamic areas. Lou et al. (1989) postulated a primary dysfunction of striatal structures in ADHD, which leads to disinhibition and hyperfunction of primary sensory and sensori-motor cortices. Lower striatal perfusion was also found in pre-school children compared to older children in a normal developmental study (Lou et al., 1990b), suggesting a neurobiological correlate to the behavioural immaturity seen in children with ADHD (Lou, 1992). These findings of reduced striatal activity in children with ADHD are consistent with the known anatomical connections between the caudate nuclei and prefrontal cortex (O’Tuama & Treves, 1993) and suggest that dysfunction in these pathways might be associated with the symptoms of ADHD (Dinklage & Barkley, 1992). One problem with the Lou et al. (1984, 1989) studies is that many of their ADHD subjects suffered from some type of early neurological insult such as hypoxia or encephalitis, raising the question of whether the findings are applicable to more typical groups of children with ADHD whose development was free of potentially damaging traumas (O’Tuama & Treves, 1993). Another problem is that metabolism was measured at rest, and so the results provide no information about function associated with specific cognitive processes.

In a more recent SPECT study using the radiotracer N-Isopropyl I-123 IMP, Sieg et al. (1995) found greater hemispheric I-123 IMP uptake asymmetry in ADHD subjects, with reduced blood flow in left frontal and left parietal regions, in comparison to psychiatric controls. The authors suggested their results, in addition to other PET and SPECT findings, might reflect a maturational lag resulting from delayed myelinization in ADHD, especially in the frontal lobes (Sieg et al., 1995). Reduced frontal activation was also found by Amen and Carmichael (1997) using high-resolution SPECT in children and adolescents with ADHD under resting and “intellectual stress” conditions. Under intellectual stress, i.e. when performing a concentration task, 65% of ADHD subjects showed reduced perfusion compared to the resting condition in the prefrontal cortex. Only 5% of control subjects showed the same reduction in prefrontal activation.
Gustafsson et al. (2000) used factor analysis of their SPECT data to examine the relationship between regional cerebral blood flow patterns and EEG, behavioural and cognitive measures. Low blood flow in temporal and cerebellar regions with high blood flow in the basal ganglia was correlated with motor impairment and lower intelligence scores. Low blood flow in frontal and parietal regions, especially the right frontal lobe, was correlated with higher parent rating scale scores. They did not find any meaningful relationships between blood flow and EEG power spectra measures. The authors interpreted these results as suggesting two functional disturbances in ADHD, one of the frontal lobes related to behaviour deviance, and one of the integration of the temporal lobes, cerebellum and subcortical structures related to motor planning and cognition. In contrast to this study’s finding of hypoperfusion of right frontal areas, Spalletta et al. (2001) found that regional cerebral blood flow in the left DLPFC was reduced compared to the right DLPFC in children with ADHD. In addition, higher right relative blood flow and lower left relative blood flow were predictors of higher symptom severity and attentional impairment as measured by the Stroop task. These discrepant findings are most likely due to differences in methodology and subject selection. So while SPECT studies have revealed some evidence of reduced metabolism in ADHD, the regions most affected and the relationship to cognitive function remains unclear.

3.3.2.3 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) measures task related brain blood flow changes by detecting increased levels of oxyhemoglobin that occur as a result of a brain region becoming more active. As deoxyhemoglobin is washed away, the MR signal is increased due to the different magnetic properties of oxy- and deoxyhemoglobin. This technique offers better temporal and spatial resolution than PET or SPECT. There have been only a handful of studies of ADHD using fMRI to date.

A study of adolescents with ADHD found that, compared with normal peers, they showed reduced activation predominantly in right hemisphere cortical regions during inhibitory tasks (Rubia et al., 1999). In a stop signal task, involving motor response inhibition, activation was reduced in the ADHD group in the right inferior frontal lobe, right mesial frontal cortex and left caudate nucleus. In a delay task, involving motor timing, ADHD subjects showed less activation than controls in the right mesial frontal
cortex and posterior cingulate, and greater activation in the supplementary motor area. The authors concluded that ADHD is associated with deficits in higher order attentional regulation of motor output, related to reduced mesial frontal (anterior cingulate) activity, and deficits in inhibitory control, related to reduced frontal and caudate activity during motor inhibition (Rubia et al., 1999). A subsequent study also found reduced right prefrontal activation in ADHD adolescents compared to controls during tasks requiring inhibition and delay management, but not during a simple sensori-motor task, confirming the relationship between frontal dysfunction and inhibition deficits (Rubia et al., 2001). Another study of ADHD adults found reduced anterior cingulate activation compared to healthy controls during the counting Stroop (Bush et al., 1999). In this study, ADHD subjects did activate fronto-striatal regions, suggesting specific dysfunction of the anterior cingulate, which is involved in stimulus and response selection and therefore perhaps in the inattention and impulsivity that characterize ADHD.

Another fMRI study examined fronto-striatal function in children with ADHD and matched controls during the performance of go – no-go tasks (Vaidya et al., 1998). Compared to the controls, the ADHD group had significantly reduced striatal activation during a stimulus-controlled (more difficult) task and significantly increased frontal activation during a response-controlled (easier) task. The authors suggested that the finding of increased frontal activation, which differs from previous reports of frontal hypometabolism in ADHD (Sieg et al., 1995; Zametkin et al., 1990), might reflect greater inhibitory effort. The finding of reduced striatal activation is consistent with other functional imaging studies finding reduced metabolism in this region (Lou et al., 1984, 1989) and with structural imaging studies that have reported associations between anatomical abnormalities of the striatum and poor performance on inhibitory tasks in ADHD subjects (Casey et al., 1997a; Mataro et al., 1997). The authors concluded that activation in children with ADHD may be abnormally high or low depending on the specific demands of inhibitory control imposed by the task (Vaidya et al., 1998).

A pilot study of 10 ADHD subjects aged from 14 to 51 years found that activation was predominant in the right middle frontal gyrus during a visual vigilance task (Sunshine et al., 1997). No comparison group was included in this study, but the authors reported that similar areas of activation were found in a previous study of normal subjects using
the same task (Lewin et al., 1996). Some additional areas of activation not seen in normal subjects were found in the ADHD group in right and left frontal, left precentral and left parietal regions. The authors concluded that this result might represent true regions of abnormality in the ADHD subjects during visual vigilance, perhaps related to attempted compensation for their disorder, or alternatively may be due to artifacts (Sunshine et al., 1997).

Some of the disparate results of these fMRI studies may be due to effects of the different cognitive tasks and subject age ranges used. Areas of reduced or increased activation in ADHD subjects might depend on the specific demands of the cognitive tasks employed (Vaidya et al., 1998). In a developmental study using go–no-go tasks, Casey et al. (1997b) found that both healthy children and adults activated dorso-lateral and orbital prefrontal cortical regions, but the volume of activation was greater for children. The authors related this finding to reduced efficiency of inhibitory and working memory processes in children compared to adults. Rubia et al. (2000) compared healthy young adults and adolescents and found increased prefrontal activation in adults during response inhibition and motor timing tasks, with apparently different networks being recruited by the two groups to achieve similar inhibitory performance. These findings highlight developmental effects which make comparisons between studies of children, adolescents and adults with or without ADHD difficult.

3.3.2.4 Conclusions for Functional Imaging

In agreement with many of the findings of anatomical differences in children with ADHD, functional brain imaging studies suggest that dysfunction of fronto-striatal networks may be involved in ADHD. However, the findings of functional imaging studies of ADHD have been inconsistent in terms of the precise nature of this fronto-striatal system dysfunction. These inconsistencies may be due in part to differences in the age groups and methodologies employed. Many of the studies discussed above used small, heterogeneous samples with wide age ranges, some included subjects with comorbid developmental learning disabilities or early neurological insult (Lou et al., 1984, 1989), some used children with other psychiatric disorders or siblings of ADHD subjects as controls (Lou et al., 1984, 1989; Sieg et al., 1995), and within each imaging modality a variety of imaging and analysis methodologies have been used. These
limitations and methodological differences mean that future studies using larger samples, more specific subject selection criteria, and comparable imaging and analysis techniques are needed to verify the nature of functional abnormalities in ADHD, how they are affected by developmental changes, and their specificity to ADHD (Tannock, 1998). This will not be a simple task given that these imaging studies are limited by the difficulties associated with getting young children, especially those that may be hyperactive, to comply with the demands of the scanning procedures. In addition, studies have examined function averaged over the course of attentional or inhibitory tasks, and the findings therefore provide no information regarding differences in activation in ADHD associated with specific task events or transient cognitive processes. As techniques for event-related fMRI improve, this may be able to be addressed, however the significant problem of movement artifact in this technique would remain.

3.4 Electrophysiological Research

Electrophysiological techniques, in particular event related potentials (ERPs), do provide the opportunity to examine transient task-related processes as they have millisecond temporal resolution. These techniques have been applied to examine differences in neural processing in ADHD in a variety of studies. Investigations of EEG power spectra differences in ADHD are reviewed in section 3.4.1. ERP studies of ADHD are reviewed in section 3.4.2.

3.4.1 EEG Studies

The electroencephalogram (EEG) measures the electrical activity of cortical neurons, recording this activity usually from electrodes on the scalp. The EEG is composed of activity over a range of frequencies and is classified into frequency bands known as delta (1 – 3.5 Hz), theta (3.5 – 7.5 Hz), alpha (7.5 – 12.5 Hz) and beta (12.5 – 40 Hz). The lower frequency bands are most associated with rest or low levels of activity, while the higher frequency bands are most associated with active states.
EEG studies have tended to find slower cortical electrical activity in children with ADHD (i.e. more low frequency or less high frequency activity), although there have been conflicting findings. Increased theta activity in ADHD subjects compared with normal controls has been found in several studies, particularly in frontal regions (Bresnahan et al., 1999; Clarke et al., 1998, 2001b; Mann et al., 1992; Matsuura et al., 1993; Chabot & Serfontein, 1996). Increased delta activity, especially in posterior regions, has also been observed (Clarke et al., 1998). These findings of increased slow EEG activity suggest a general cortical underactivity in ADHD children. Mann et al. (1992) found that frontal theta power was increased in children with ADHD compared to controls during a resting condition and increased further during cognitive tasks. As theta activity in children decreases with increasing age (Clarke, 2001a; Gasser et al., 1988), the findings for children with ADHD resemble those of younger children, suggesting a possible maturational delay in children with ADHD (Mann et al., 1992). Matsuura et al. (1993) also related their findings of increased frontal theta to brain immaturity in children with ADHD. Chabot & Serfontein (1996) also found increased theta in ADHD children, which was greatest in frontal regions, but concluded that this represented a deviation from normal development rather than a maturational lag. Clarke et al. (1998) found increased theta power in ADHD children in all regions including midline frontal. Frontal theta was greater for the ADHD-combined type group than for the ADHD-inattentive type group. The authors suggested this finding may be related to an association between frontal dysfunction and the overt behavioural problems exhibited by children with the combined type (Clarke et al., 1998).

Reduced or slower (i.e. lower frequency) alpha activity has been found in children with ADHD (Callaway et al., 1983; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001b; Dykman et al., 1982; Matsuura et al., 1993; Shetty, 1971), as has reduced or slower beta activity (Bresnahan et al., 1999; Callaway et al., 1983; Caresia et al., 1984; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001b; Dykman et al., 1982; Mann et al., 1992; Oades, 1987). Mann et al. (1992) found reduced beta activity in children with ADHD in posterior and temporal regions during cognitive tasks, and related this finding to maturational delays in brain systems involved in attention. Clarke et al. (1998) also found less beta activity in posterior regions in children with ADHD, and in addition found decreased alpha in all regions with the greatest difference in posterior regions. As fast frequency activity increases with development (Clarke et al., 2001a; Gasser et
al., 1988), they suggested that their findings support the idea of a maturational lag in ADHD.

These findings of increased slow EEG activity (delta and theta) and decreased fast EEG activity (alpha and beta) suggest EEG slowing in children with ADHD and have been interpreted in terms of cortical underarousal and less active information processing (Ackerman et al., 1994; Chabot & Serfontein, 1996; Lubar, 1991; Mann et al., 1992; Oades, 1998; Tannock, 1998). This is supported by findings of increased deficits when the EEG is recorded during reading or drawing (Lubar, 1991; Mann et al., 1992). Some researchers have suggested that increased EEG slowing reflects delayed brain maturation in children with ADHD (Clarke et al., 1998; Matsuura et al., 1993; Ucles & Lorente, 1996; Tannock, 1998), while others suggest that development is deviant from normal rather than delayed (Callaway et al., 1983; Chabot & Serfontein, 1996). Some studies have addressed the effects of age on EEG differences in ADHD subjects. Bresnehan et al. (1999) found increased theta activity and reduced beta activity in groups of children, adolescents and adults with ADHD compared to age matched controls. While the increase in theta was similar for all ages, the reduction in beta decreased with increasing age. Given that symptoms of hyperactivity reduce with age in ADHD while symptoms of impulsivity persist, the authors hypothesized that decreased beta activity may be linked to hyperactivity and increased theta activity to impulsivity. Clarke et al. (2001b) examined age effects in 8 to 12 year olds and found that EEG differences between controls and ADHD-inattentive type subjects remained fairly constant over the 5 year range, while theta activity reduced with age more rapidly in ADHD-combined type subjects. They suggested that this difference might reflect diminishing hyperactive/impulsive symptoms and persistent inattention symptoms.

Gender effects on EEG differences in ADHD have also been examined in some studies. Clarke et al. (2001b) found that control vs. ADHD group differences in theta and beta activity were larger in males than females. Baving et al. (1999) found that alpha-1 activity (8 – 10 Hz) was increased in the right frontal region in ADHD boys compared to control boys, and in the left frontal region in ADHD girls compared to control girls. The authors related these findings to right frontal deficits in boys, consistent with MRI findings of a smaller right frontal cortex in ADHD (Castellanos et al., 1996b; Filipek et al., 1997; Hynd et al., 1990), and to gender differences in PET studies where reductions
in left frontal metabolism were greater in females than males (Ernst et al., 1994a; Zametkin et al., 1993).

While increased slow EEG activity is found in most studies, there have been some conflicting findings. Kuperman et al. (1996) found increased beta activity in children with ADHD compared with normal controls, and suggested that this finding indicated elevated mental activity and overarousal in children with ADHD, which might contribute to sustained attention difficulties. Their subjects were drawn from a community rather than a clinical sample, but met DSM-III-R criteria for ADHD according to teacher reports. Chabot and Serfontein (1996) found increased beta activity, especially in frontal regions, in a subgroup of their ADHD subjects (13%), suggesting hyperarousal of fronto-striatal systems in these children, in contrast to the hypoarousal found in the majority of ADHD subjects. Clarke et al. (1998) excluded four ADHD subjects from their analyses because they had much higher levels of beta activity (> 3 SD above mean) than the rest of the group. They concluded that this subset of subjects in their study and in Chabot and Serfontein (1996) suggested there may be a subtype of ADHD characterised by increased beta activity.

A subsequent study also found increased beta activity in a subset (20%) of ADHD subjects (Clarke et al., 2001c). This study found reduced alpha and increased theta activity compared to controls in the total group of 184 children with ADHD-combined type, consistent with many other findings of studies comparing group means. In addition, three subgroups with distinct EEG profiles were identified by cluster analysis. 42% of ADHD subjects were characterized by increased theta and decreased delta and beta. 38% had increased theta and central/posterior beta and decreased alpha and frontal/central beta. 20% had increased beta and decreased alpha and frontal/central delta. As all subjects met criteria for ADHD-combined type, the authors suggested that different aetiologies, which could be reflected in the different EEG profiles, may lead to the same behaviour profiles. They concluded that children with ADHD are not homogeneous in terms of their EEG profiles and that this variability needs to be recognized in any efforts to use EEG as a diagnostic tool (Clarke et al., 2001c). Another issue which raises questions about the assumption that EEG slowing characterizes ADHD is that EEG slowing has been found for other clinical populations, especially learning disabled children (Ackerman et al., 1994; Lubar et al., 1985).
3.4.2 Event Related Potential Studies

Event related potentials (ERPs) are EEG changes that are time locked to the onset of a particular stimulus. Epochs of EEG following stimulus presentation are usually averaged over multiple trials, and the resulting ERP waveform is thought to reflect aspects of the subject’s perception, processing and decision making related to that stimulus. Negative and positive waves of the ERP occurring at specific latencies after stimulus onset have been related to various aspects of information processing and cognition. Two components of the ERP thought to be related to attentional processes have been most studied in ADHD. The early negative waves, N1 and N2, are discussed in section 3.4.2.1, and the later positive peak, the P3, is discussed in section 3.4.2.2. One of the most used tasks in ERP studies of ADHD is the CPT and these studies are reviewed in section 3.4.2.3.

3.4.2.1 N1 and N2 in ADHD

Two early negative ERP waves, the N1 and N2, have been examined in several ADHD studies. The N1, occurring at a latency of around 100 ms, is generally larger to attended than to non-attended stimuli and is thought to reflect an attentive division between concurrent stimulus channels (Loiselle et al., 1980). The N2 occurs at a latency of around 200 ms, is generally larger to novel than to frequent stimuli, and is thought to reflect automatic orienting to deviant stimuli (Robaey et al., 1992; Satterfield et al., 1988). N2 has also been related to stimulus comparison and categorization (Oades, 1998; Robaey et al., 1992), and to inhibition (Overtom et al., 1998; Pliszka, 2000). The increased negativity to rare versus frequent stimuli is termed mismatch negativity (MMN), while the difference between attended and non-attended stimulus ERPs is termed processing negativity (PN). These early negative components of the ERP have predominantly been studied in ADHD during selective attention tasks, often using simultaneously presented visual and auditory oddball paradigms and requiring the subject to attend to one modality or the other.

The N1 to attended auditory targets in a selective attention task using simultaneously presented visual and auditory oddball paradigms was found to be significantly smaller
in children with ADHD than in normal controls (Satterfield et al., 1994). The 6 year old ADHD subjects in this study also showed a smaller difference in N1 amplitude between attended and non-attended stimuli than controls. A similar finding has been obtained for older ADHD subjects (12 to 14 years old) using an auditory selective attention task (Loiselle et al., 1980). These results have been interpreted as reflecting a selective attention dysfunction in children with ADHD (Klorman, 1991; Loiselle et al., 1980). In an auditory oddball task that did not require selective attention, no group differences in N1 amplitude were found (Winsberg et al., 1997).

A smaller N2 amplitude to auditory targets in children with ADHD has been found in some studies (Satterfield & Braley, 1977; Satterfield et al., 1988, 1994). In addition, children with ADHD have been found to have a smaller difference in N2 amplitude between attended and non-attended stimuli (Satterfield et al., 1994) and between target and non-target stimuli (Satterfield et al., 1988). These findings of reduced N2 amplitude have been suggested to reflect deficiencies in children with ADHD in preferential processing of attended stimuli and in orienting to target or novel stimuli (Satterfield et al., 1988, 1994). In contrast, using visual categorization tasks, Robaey et al. (1992) found that ADHD boys had a larger N2 amplitude than normal controls, as did Prichep et al. (1976) using an auditory guessing paradigm. Robaey et al. (1992) suggested that the parieto-occipital N2 was related to stimulus classification and was larger in ADHD subjects due to enhanced automatic processes, which were associated with inadequate higher order controlled processes (indexed by smaller P3 amplitude) and did not leave additional resources to adapt information processing according to task demands. Prichep et al. (1976) related their finding of larger N2 amplitude to low arousal levels in children with ADHD, as N2 amplitude was reduced after administration of methylphenidate. In other studies, no differences in N2 amplitude were found between ADHD subjects and normal controls using an auditory oddball task (Winsberg et al., 1997), visual feature detection tasks (Holcomb et al., 1985; Taylor et al., 1993) or the continuous performance task (Overtoom et al., 1998). Johnstone and Barry (1996) found that frontal N2 amplitude to non-targets in a tone discrimination task was smaller for children with ADHD compared to normal controls, and that posterior N2 amplitude was larger in children with ADHD, perhaps consistent with the findings of Robaey et al. (1992).
Overtoom et al. (1998) did find that N2 amplitude was smaller in a subgroup of children with ADHD and comorbid ODD. They suggested that the fronto-central N2 component to non-targets in the CPT-AX (A followed by notX) was related to inhibitory processes and that deficiencies in these processes or increased impulsivity may be restricted to the comorbid group. Other recent studies have also found N2 differences related to inhibition. Using the stop signal task, Pliszka et al. (2000) found that the N2 to stop signals recorded over the right inferior frontal cortex was reduced in ADHD children compared to controls and that N2 amplitude was correlated with inhibition task performance. They also found that a right frontal slow positive wave to go stimuli was reduced in ADHD subjects on trials when they subsequently failed to inhibit a response. They related these findings to right frontal deficits associated with inhibitory control deficits as also found using fMRI (Rubia et al., 1999).

Mismatch negativity (MMN), an enhancement of early negativity in the ERP to infrequent target stimuli compared to that to frequent standard stimuli, is thought to be related to automatic orienting to novel stimuli and to be a process which is not under voluntary control (Satterfield et al., 1988). MMN was found to be smaller in children with ADHD in selective attention tasks (Rothenberger et al., 2000; Satterfield et al., 1988), but was found to be normal using an auditory oddball task (Winsberg et al., 1997). In the Rothenberger et al. (2000) study, only the ADHD group with comorbid CD showed a significantly reduced MMN, suggesting a greater deficit in automatic information processing in these children than those with ADHD only. Children with ADHD are often said to be less responsive to target stimuli, but this is more frequently linked with smaller P3 than with smaller MMN. Oades et al. (1996) found that MMN was left lateralized in children with ADHD but right lateralized in normal controls, which in conjunction with a similar finding for P3 laterality was interpreted as suggesting right hemisphere impairment in ADHD.

Processing negativity (PN) is an enhancement of early negativity in the ERP to attended compared to non-attended stimuli and is thought to reflect attentional processes that are under voluntary control (Satterfield et al., 1988). PN has been found to be smaller in children with ADHD in several studies using selective attention tasks (Jonkman et al., 1997; Satterfield et al., 1988, 1990, 1994). These findings have been interpreted as suggesting poor discrimination and poor preferential processing of attended stimuli and
are consistent with deficits in selective attention (Klorman, 1991; Satterfield et al., 1988, 1994).

As the above discussion indicates, the results for N1, N2, MMN and PN vary from study to study. Methodological differences between studies make it difficult to directly compare these results. Some of the discrepancies between results for N1 and N2 may be due to differences in the tasks and modalities used to elicit the ERP (Klorman, 1991), to differences in the age groups studied and developmental effects (Levy & Ward, 1995; Oades, 1998; Satterfield et al., 1990), to heterogeneity of subject groups and comorbidity in ADHD subjects, or to differences in the electrode sites used to record the ERP. Many studies do not report regions in which effects are most prominent. Findings of posterior/anterior differences (Johnstone & Barry, 1996) and laterality differences (Oades et al., 1996) suggest that topography may be important for these early ERP components. Smaller negative ERP components in children with ADHD are most consistently found in the auditory rather than the visual modality (Tannock, 1998), and when selective attention tasks are used that include a set of stimuli to be ignored and place greater demand for selective attention (Klorman, 1991).

Latencies for the early negative ERP peaks have not often been reported, and in those studies that have discussed latency the results are inconsistent. Using visual feature detection tasks Sunohara et al. (1997b) found that N2 latency was longer in children with ADHD than normal controls, while Taylor et al. (1993) found no group difference in N2 latency. For a visual choice reaction time task, the latencies of early anterior components including N1 and N2 were slower in ADHD boys compared to controls (Karayanidis et al., 2000). However, the latency of the auditory N1 component was found to be shorter in children with ADHD in two other studies (Oades et al., 1996; Satterfield et al., 1994). This finding may suggest that children with ADHD process perceptual information faster than their normal peers (Oades, 1998; Oades et al., 1996). In contrast, Loiselle et al. (1980) found no group difference for auditory N1 latency. These disparate findings suggest that group differences in early negative component latencies may depend on task demands and stimulus modality.

3.4.2.2 P3 in ADHD
In studies of ADHD, the most commonly examined ERP component is the P3 (also labelled P300 or P3b), which is a late positive wave with a latency of 300 to 800 ms (Klorman, 1991). The amplitude of the P3 is influenced by stimulus probability, relevancy or novelty (Klorman, 1991; Levy & Ward, 1995), and the latency of the P3 is influenced by cognitive, perceptual or memory load (Klorman, 1991). Because of these effects on its amplitude and latency, the P3 component is thought to reflect allocation of attention and to mark the end of stimulus evaluation processes which precede response selection and execution (Klorman, 1991). It has also been related to updating of internal representations and to working memory (Tannock, 1998).

The majority of studies examining the P3 have found that the amplitude of this component is smaller in children with ADHD than in normal controls (Frank et al., 1994; Holcomb et al., 1985; Jonkman et al., 1997; Kemner et al., 1996; Klorman et al., 1979; Loiselle et al., 1980; Michael et al., 1981; Novak et al., 1995; Overtoom et al., 1998; Robaey et al., 1992; Satterfield et al., 1990, 1994; Strandburg et al., 1996; Van der Stelt et al., 2001; Van Leeuwen et al., 1988; Verbaten et al., 1994). These studies have shown that reduced P3 amplitude in children with ADHD can be found in both auditory and visual modalities and in response to both target and non-target stimuli (Tannock, 1998). There are contradictory findings however, as some studies have reported no significant group differences in P3 amplitude (Frank et al., 1998; Rothenberger et al., 2000; Satterfield et al., 1988; Taylor et al., 1993; Winsberg et al., 1997).

Smaller P3 amplitude in ADHD subjects has been interpreted in different ways. It may reflect a general underarousal or underreactivity to task relevant stimuli (Satterfield et al., 1990; Tannock, 1998), cognitive and information processing difficulties (Frank et al., 1994; Klorman, 1991; Satterfield et al., 1994; Van der Stelt et al., 2001), or deficits in selective or sustained attention (Holcomb et al., 1985; Loiselle et al., 1980; Michael et al., 1981; Overtoom et al., 1998). The reduction in P3 amplitude in children with ADHD is generally associated with poorer performance on the task used to elicit the ERP, leading to the suggestion that it is likely to reflect deficient cognitive processing (Klorman, 1991; Levy & Ward, 1995).
The specific cognitive deficits associated with smaller P3 amplitude in children with ADHD are dependent on the tasks used to elicit the ERP. Visual CPTs consistently elicit smaller P3 to target stimuli in children with ADHD compared to controls (Klorman et al., 1979; Michael et al., 1981; Overtoom et al., 1998; Strandburg et al., 1996), as discussed further in the next section. This result is generally interpreted as reflecting attention deficits (Klorman et al., 1979; Michael et al., 1981; Overtoom et al., 1998). One study that used visual target detection or oddball tasks, similar to the CPT, also found smaller P3 amplitude in ADHD subjects (Holcomb et al., 1985), but other studies using similar tasks found no significant group differences for P3 amplitude (Kemner et al., 1996; Taylor et al., 1993). Holcomb et al. (1985) interpreted their findings of reduced P3 amplitude and reduced difference between P3 amplitude to targets and to non-targets as reflecting inappropriate allocation of attentional resources by their ADHD group.

Using auditory oddball or tone discrimination tasks, smaller P3 amplitude to target tones in children with ADHD has been found in some studies (Frank et al., 1994; Holcomb et al., 1986; Kemner et al., 1996), but not in others (Frank et al., 1998; Winsberg et al., 1997). Kemner et al. (1996) found that reduced P3 to deviant auditory stimuli occurred irrespective of the task relevance of the stimulus and concluded that smaller P3 amplitude in ADHD is due to abnormal processing of deviant stimuli. Frank et al. (1994) suggested that the reduced P3 amplitude in their ADHD with LD group reflects cognitive and processing difficulties rather than an attention deficit.

In selective attention tasks, smaller visual and/or auditory P3 amplitude has been found in several studies (Jonkman et al., 1997; Satterfield et al., 1990, 1994), but not in others (Satterfield et al., 1988). Jonkman et al. (1997) concluded that children with ADHD have a deficit in the activation of P3 processes. Satterfield et al. related their results to a deficit in preferential processing of attended stimuli (Satterfield et al., 1994) and to insufficient locus coeruleus activity that is normally triggered by attended, task-relevant stimuli (Satterfield et al., 1990). Both groups also found group differences in earlier ERP components. While Satterfield et al. (1994) suggested that abnormalities in different ERP components reflect deficiencies in independent cognitive processes, Jonkman et al. (1997) suggested that reduced P3 amplitude may be secondary to deficits in earlier aspects of attentional processing. While both groups used similar paradigms...
and found smaller P3 amplitude in children with ADHD, Jonkman et al. (1997) found smaller P3 to non-target attended stimuli and Satterfield et al. (1994) found smaller P3 to attended targets, differences which most likely led to the differing interpretations of their results. Selective attention has also been examined using an auditory task requiring subjects to attend to tones presented to one ear or the other (Loiselle et al., 1980) and this study found smaller P3 amplitude to attended target tones in children with ADHD and related their findings to selective attention dysfunction in ADHD.

Other visual tasks employed in ERP studies that have resulted in findings of smaller P3 amplitude in children with ADHD include categorization (Robaey et al., 1992), spatial orienting (Novak et al., 1995), selective attention to colour (Van der Stelt et al., 2001), and delayed-go tasks (Brandeis et al., 1998). Smaller P3 amplitude in children with ADHD has been found in a variety of different task conditions and modalities. However, the P3 to target stimuli consistently shows the greatest reduction in amplitude, in particular when task performance is also deficient (Brandeis et al., 1998; Klorman, 1991). This common finding is therefore likely to reflect deficits in cognitive processing of task-relevant stimuli in children with ADHD.

Many studies have used only a few electrodes to record the ERP and have discussed overall P3 amplitude reductions in terms of cognitive processes but not in terms of topography. The P3 to visual targets is generally found to have a maximum amplitude over parietal regions (Klorman, 1991; Satterfield et al., 1988). Differences in topography in children with ADHD may be as important as overall differences in amplitude. Some recent studies have used larger numbers of electrodes and have examined the topography of the P3 in children with ADHD. Using 17 electrodes and an auditory tone discrimination task, Johnstone & Barry (1996) found that P3 amplitudes to target stimuli were smaller in the posterior region but larger in the frontal region for children with ADHD compared with normal controls. They suggested that the ADHD group utilized an additional frontally distributed cognitive process when processing task-relevant stimuli, which might reflect an attentional compensation mechanism (Johnstone & Barry, 1996). Van der Stelt et al. (2001) found that the reduction in P3 amplitude in ADHD boys in a colour selective attention task was maximal at left temporal sites. They also found an early frontal positivity in controls that was absent in the ADHD group. These authors suggested that ADHD boys’ deficits in attention to
colour were associated with reduced activation of a neural network involving prefrontal and occipito-temporal cortex. The laterality of the P3 component may also differ in children with ADHD. Oades et al. (1996) used 19 electrodes and an auditory tone discrimination task and found a right-biased P3 asymmetry in normal controls that was absent in their ADHD group, suggesting a right hemisphere impairment in terms of stimulus processing in children with ADHD.

Other researchers have used ERP microstates and source localization techniques to examine the topography of the ERP in children with ADHD and controls (Brandeis et al., 1998, 2002; Steger et al., 2000; Van Leeuwen et al., 1998). Microstates are successive ERP segments with stable topographies that vary in duration and are related to different stages of information processing (Brandeis & Lehmann, 1986). The global field power (GFP), defined as “the spatial standard deviation over all voltages in a map” (Van Leeuwen et al., 1998, p. 100) can be calculated for each microstate and is similar to an amplitude measure. Van Leeuwen et al. (1998) recorded the ERP at 30 electrode sites while children performed the CPT-AX. They found no significant group differences in the topography of ERP microstates, but found reduced GFP in a CNV/P3 microstate to cues (the A) in the ADHD group. The topography of this microstate was defined by a posterior positivity in both the ADHD and control groups. Source localization analysis using low resolution electromagnetic tomography (LORETA: Pascual-Marqui et al., 1994) identified posterior sources for this microstate that were less right biased in the ADHD group. The authors concluded that their results suggest impaired orienting to cues in children with ADHD, possibly involving the posterior attention system (Van Leeuwen et al., 1998). Similar results were found by the same group in a later multicentre study (Brandeis et al., 2002). Using a delayed-go task, Brandeis et al. (1998) also found reduced GFP in late P3 type microstates in their ADHD group and related this finding to less efficient posterior orienting mechanisms. These results are consistent with findings of reduced parietal P3 amplitude in children with ADHD and suggest that possible deficits in parietal brain mechanisms in ADHD and their relationship to well established frontal deficits should not be overlooked (Brandeis et al., 1998; Van Leeuwen et al., 1998). Steger et al. (2000) examined ERP microstates in unilateral and bilateral stimulus presentation and response conditions. They found that the GFP of a P3 microstate was reduced in ADHD boys for bilateral targets, especially at occipital sites. They suggested that this might reflect deficits in
coping with the coordination demands of the bilateral condition and that this was consistent with previous findings of reduced P3 amplitude suggesting reduced resource allocation to targets in ADHD. Steger et al. (2000) also found reduced GFP in ADHD boys in the left unilateral condition, which they suggest reflects right hemisphere deficits in ADHD as the left hand response RT was also increased in the ADHD group compared to controls.

Reduced P3 amplitude has also been found in several other clinical populations including children with autism, learning disabilities and schizophrenia, so this effect is not specific to ADHD (Klorman, 1991; Levy & Ward, 1995; Oades, 1998). A recent study addressed the issue of the specificity of abnormal ERPs to ADHD using auditory and visual oddball tasks, and found that only the parietal P3 amplitude to deviant auditory stimuli was smaller in children with ADHD than in groups of autistic and dyslexic children (Kemner et al., 1998). In an earlier study, Kemner et al. (1994) found that visual P3 amplitude in autistic children did not differ from that of children with ADHD or dyslexia. Frank et al. (1994) found that auditory P3 amplitude was smaller in children with learning disabilities (LD) and in children with LD and ADHD than in normal controls. They suggested that smaller P3 amplitude in children with LD and/or ADHD is due to cognitive processing difficulties rather than an attention deficit. In a later study (Frank et al., 1998), they found significantly smaller auditory P3 amplitude than controls in a LD group and a LD + ADHD group, but not in an ADHD only group. They again suggested that P3 abnormalities in children with learning and attentional problems reflect processing rather than attentional deficits.

Abnormalities in P3 latency in children with ADHD have also been reported. Some studies that examined P3 latency to visual stimuli found it to be longer in ADHD subjects than in normal controls (Holcomb et al., 1985; Strandburg et al., 1996; Sunohara et al., 1997b; Taylor et al., 1993). This finding has been interpreted as suggesting that stimulus evaluation and attentional processes are slower and more difficult for children with ADHD (Holcomb et al., 1985; Klorman, 1991; Tannock, 1998; Taylor et al., 1993). Holcomb et al. (1985) also found that P3 latency in their ADHD group increased across blocks of their visual target detection task, suggesting a deterioration of these processes over time. In contrast, shorter P3 latencies in children with ADHD have been reported for a visual categorization task (Robaey et al., 1992)
and an auditory selective attention task (Loiselle et al., 1980), while other studies have found no significant group differences in P3 latency (Holcomb et al., 1986; Michael et al., 1981; Satterfield et al., 1988, 1994). Loiselle et al. (1980) found that P3 latency to attended tones was significantly longer than to non-attended tones in their control group and suggested that this reflected extra processing time required for signal detection and response. Shorter P3 latencies in their ADHD group might then suggest that they did not devote this extra time to processing task relevant information. Robaey et al. (1992) suggested that shorter P3 latencies in children with ADHD reflected faster processing of the physical attributes of the visual stimuli, which might account for the increased number of errors in ADHD subjects. Some of the discrepancies in findings for P3 latency may be due to the different tasks employed. Visual target detection tasks may produce longer P3 latencies in children with ADHD due to slowed evaluation processes (Holcomb et al., 1985; Strandburg et al., 1996; Sunohara et al., 1997b; Taylor et al., 1993), while tasks requiring selective attention or categorization may produce shorter P3 latencies due to less efficient modulation of processing speed according to task demands (Loiselle et al., 1980; Robaey et al., 1992).

3.4.2.3 ERP Studies of the CPT in ADHD

The CPT has been used in several studies to examine attentional processes and the associated visual ERP. Klorman et al. (1979) found reduced P3 amplitude at Cz (a midline central electrode site) in hyperactive children compared with controls when they performed the CPT-X. P3 amplitude to both targets and non-targets was reduced in the hyperactive group, and their task performance was significantly worse. These results were replicated in a subsequent study (Michael et al., 1981), which found reduced P3 amplitude at both Cz and Pz (a midline parietal electrode site) and deficient task performance in hyperactive children during a B-X version of the CPT (similar to CPT-AX, using B as the cue rather than A). The P3 to both targets and non-targets was significantly smaller in the hyperactive group for the CPT-X, while only the P3 to targets was reduced for the CPT-BX. These findings of reduced P3 amplitude in hyperactive children during the CPT were concluded to reflect deficits in sustained attention (Klorman et al., 1979; Michael et al., 1981).
More recently, Overtoom et al. (1998) recorded the ERP at Fz (midline frontal), Cz, Pz and Oz (midline occipital) during the CPT-AX. They suggested that the parietal P3 to targets (X preceded by A) could be used as a measure of attentional processes, while the fronto-central N2 to non-targets (not-X preceded by A) could be used as a measure of inhibitory processes. The ADHD group had a smaller parietal P3 amplitude to targets, indicating attention deficits. But there were no group differences in fronto-central N2 to non-targets, indicating a lack of expected inhibition deficits in the ADHD group. These results were consistent with task performance results, as the ADHD group performed significantly worse on an inattention score but not on an impulsivity score. The authors concluded that deficient processing in the ADHD group was related to attention rather than to response inhibition (Overtoom et al., 1998). Similar results were obtained by Strandburg et al. (1996) for two versions of the CPT. These authors concluded that their findings of reduced P3 amplitude and longer P3 latency reflect processing problems in children with ADHD that occur in later rather than early stages, as ERP components related to earlier stages of processing were normal.

In an ERP microstate study of the CPT-AX, Van Leeuwen et al. (1998) found reduced GFP in a CNV/P3 microstate (277-605 ms) to the cue (A) in children with ADHD, but not to the target (X). The authors concluded that impaired orienting to cues involving a posterior attention system, rather than impaired target processing involving frontal executive processes, was involved in ADHD children’s deficient CPT performance (Van Leeuwen et al., 1998). Brandeis et al. (2002) also found reduced GFP in a P3 microstate following the cue in the CPT-AX in ADHD children. Cue P3 amplitude was also correlated with the speed and accuracy of response to the subsequent target, suggesting that this represents a measure of attentional orienting to potential targets in a critical but behaviourally silent period of the task. Insufficient phasic activation of the posterior attention system in the ADHD subjects was suggested by reduced posterior sources for P3 in this group. The reduced P3 was preceded by a larger N1 compared to controls. The authors concluded that children with ADHD respond to cues with increased initial orienting (suggested by increased N1 amplitude) and then insufficient resource allocation (suggested by reduced P3 amplitude) (Brandeis et al., 2002).
These findings of reduced P3 amplitude in response to both cue and target stimuli in different versions of the CPT suggest reduced allocation of attention to task relevant stimuli in children with ADHD.

3.4.2.4 Conclusions for ERP Research

Several differences in cognitive ERPs between children with ADHD and normal controls have been found. The most consistent of these is reduced amplitude of the P3 component to attended target stimuli recorded from the parietal region. This is generally associated with poorer task performance and smaller differences are found for the P3 to non-attended or non-target stimuli, suggesting that reduced target P3 amplitude in children with ADHD is related to specific cognitive deficits (Brandeis et al., 1998; Klorman, 1991). This finding suggests that children with ADHD are under-reactive to task-relevant stimuli and may have deficits in allocation of attention and later stages of stimulus processing (Klorman, 1991; Tannock, 1998). However, the finding of reduced P3 amplitude in children with ADHD may have limited value in explaining the specific deficits associated with ADHD as it is also commonly found in other clinical populations (Brandeis et al., 1998).

Findings for earlier ERP components associated with the initial orienting of attention are less consistent. Findings of reduced amplitude of N2 and MMN in children with ADHD have been related to deficits in a basic orienting response and in the locus coeruleus noradrenergic system which enhances responsiveness to important signals (Satterfield et al., 1988, 1994). Findings of reduced frontal PN suggest deficits in preferential processing of attended stimuli and are thought to be consistent with reduced frontal metabolism in ADHD (Satterfield et al., 1988, 1994). These findings also suggest deficits in selective attention (Klorman, 1991). However, there are conflicting findings for these early negative ERP components and behavioural studies of selective attention have failed to demonstrate a specific deficit in this aspect of cognition (Pearson & Lane, 1990; Van der Meere & Sergeant, 1988c).

ERP studies suggest that deviant processing in children with ADHD appears to be most pronounced for relevant target stimuli and to be associated with later, controlled stages of processing, indexed by reduced P3 amplitude (Brandeis et al., 1998; Klorman, 1991).
This appears consistent with neuropsychological research that suggests deficits in response selection and organization and motor processes in children with ADHD (Klorman, 1991; Schachar et al., 1995; Tannock, 1998; Van der Meere, 1996).

3.5 Conclusions and Unresolved Issues

In most recent reviews, ADHD is characterized behaviourally as a disorder of self-regulation and executive functioning, and physiologically as a dysfunction of brain circuits including the basal ganglia and frontal cortex (e.g. Barkley, 1997; Castellanos, 1997; Van der Meere, 1996). Neuropsychological findings, as reviewed in this chapter, suggest poor performance on a range of cognitive tasks in ADHD, especially measures of sustained attention (the CPT) and inhibition. Task inefficiency is a main characteristic of children with ADHD, but whether this is due to deficits in attention, executive functions or motor control, or a combination of deficits, remains unclear.

In his review of studies of attention in ADHD, Van der Meere (1996) concluded that various attention related abilities have been found to be normal in children with ADHD, and that task inefficiency is caused by dysfunctional processes at the output side of information processing, affecting timing, preparation and control of motor processes. He suggests that a non-optimal activation state accounts for poor attentional task performance and behavioural inattention in ADHD. Activation is said to be affected in CPTs involving a slow event rate and few working memory processes (Van der Meere, 1996). In CPT studies using a slow event rate, ADHD children showed a greater decrement in performance over time than controls, suggesting a sustained attention deficit and deficient activation (Van der Meere et al., 1995a, 1995b). In studies with a fast event rate this was not the case. Van der Meere (1996) suggests that ERP findings of an abnormal P3 component in ADHD may also reflect activation state and motor output deficits. Neuroimaging findings of abnormalities in the basal ganglia are also suggested to be associated with activation deficits as this region is involved in the organization of motor behaviour and in the activation system (Sanders, 1983). Dopamine and noradrenaline fronto-striatal pathways play important roles in these mechanisms (Tucker & Williamson, 1984) and dysfunction of these neurotransmitters is implicated in ADHD (Levy, 1991; Pliszka et al., 1996), providing further evidence for a
deficit in the regulation of activation in ADHD (Van der Meere, 1996). Despite neuropsychological evidence against an attention deficit in ADHD, behavioural inattention is a common feature of the disorder and ERP studies have shown evidence of deviant attentional processes in ADHD. Whether these findings can all be explained in terms of state regulation deficits involving fronto-striatal dysfunction requires further research.

Others have suggested that disinhibition best characterizes ADHD. Various models of behavioural inhibition dysfunction as a core deficit in ADHD have been put forward and all assume frontal lobe involvement. Some suggest that ADHD children suffer from an inability to withhold responses, while others suggest that they are instead delayed in response related processes and that this better accounts for the loss of motor control in these children and their poor task performance. In a model suggested by Quay (1997), dysfunction is linked to the behavioural inhibition system, which is located in the septo-hippocampal system and its connections to the frontal cortex and is dependant on noradrenergic input from the locus coeruleus. In Barkley’s model, dysfunction is linked to the orbito-frontal cortex and its connections with the striatum and is thought to arise from genetic and developmental factors (Barkley, 1997). In Sergeant and Van der Meere’s effort-activation model, fronto-striatal dopaminergic system dysfunction is implicated and children with ADHD are thought to be delayed in response related processes and to show inadequate activation of inhibitory mechanisms due to a state regulation deficit (Sergeant, 2000; Van der Meere, 1996). Despite obvious links between deficient inhibition and frontal lobe dysfunction in ADHD, whether these can account for the attention problems associated with the disorder, as suggested by Barkley (1997), remains unclear.

Techniques that measure aspects of brain activity allow investigation of the underlying brain function during the performance of tasks involving attention and inhibition, and therefore may help test these models linking cognitive deficits to specific brain regions. Converging evidence from neuroimaging studies reviewed in this chapter suggests smaller and less active fronto-striatal network regions in ADHD, suggesting abnormalities in the neural networks that affect attention and executive function (Swanson & Castellanos, 1998). However, questions remain about the specificity of these abnormalities to ADHD, their aetiology, and their functional significance in terms
of cognitive processes (Tannock, 1998). Structural and functional imaging studies have allowed examination of non-specific brain differences in ADHD, and findings have been of enormous benefit in adding to our knowledge of underlying biological abnormalities. Functional imaging studies have shown evidence of reduced activation in ADHD, especially in frontal regions, during tasks involving attention and inhibition. However, these studies do not provide a link between overall fronto-striatal deviations and specific cognitive processes, because activation is averaged over the course of a task that most likely requires involvement of many cognitive functions for efficient performance.

Electrophysiological studies investigating EEG power spectra activity in ADHD suggest increased slow frequency and reduced high frequency activity, but again provide little information about task related processes. The ERP however, provides the temporal resolution required to examine brain function during specific task components. ERP studies reviewed in this chapter have found reduced responses to task relevant stimuli in ADHD. The most consistent finding is that of reduced P3 amplitude, thought to reflect reduced allocation of attentional resources (Brandeis et al., 2002; Klorman, 1991). This effect has been found for the response to targets in CPT and similar tasks and to cues in the CPT-AX. Most studies have used only a few electrode sites and so have not examined which brain regions are involved in these reduced responses. Those that have used multiple electrodes suggest that posterior sources are involved in P3 processes in controls and are reduced in ADHD children (Brandeis et al, 2002; Van Leeuwen et al., 1998).

While functional neuroimaging findings suggest predominantly frontal involvement in ADHD, ERP studies suggest deficits in parietal processes. In neurobiological models of attention, the frontal lobes are associated with executive control of attention, the parietal lobes with orienting of attention, and the right frontal and right parietal regions with alerting and vigilance (Posner & Raichle, 1996). Given the behavioural symptoms of the disorder, it is feasible that problems in all three attention networks might be associated with ADHD. While most reviewers suggest that the executive network, and to a lesser extent the vigilance network, is most affected in ADHD, ERP findings suggest possible involvement of the orienting network as well. Swanson et al. (1998a) suggest that the alerting network is tapped by CPT performance, the executive network
is tapped by tasks requiring inhibition of automatic responses, e.g. the stop task, and the orienting network is tapped by visuo-spatial orienting tasks, e.g. the COVAT.

The aim of the current study is to address the issue of frontal and parietal contributions to attentional dysfunction in ADHD. It may be that deficits in both regions and in interactions between them are involved in deviant attentional processing in ADHD. This study will use the CPT-X and CPT-AX to examine the dynamic sequence of patterns of cortical activity during task components related to heightened attention, namely target and cue – target intervals. Vigilance tasks have been shown to activate the alerting network in imaging studies (Pardo et al., 1991), but these CPTs also involve executive control of attention and orienting to stimuli, so allow investigation of several aspects of attention and the associated brain networks. This study will use the technique of steady-state probe topography (SSPT), which is described in the next chapter, to investigate brain activity during the CPT. SSPT provides the temporal resolution required to examine cortical activity associated with transient processing of specific stimuli, as well as the temporal continuity required to examine dynamic patterns of cortical activity during relevant task intervals. This technique will provide the opportunity to examine not only overall differences in activation or extent of response to important stimuli, but also any differences in the timing of these effects between ADHD and control groups. It is therefore hoped that this study will provide new information about deficits in brain function associated with attentional processes in ADHD.
NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the Swinburne Library.
Chapter 5  
Assessment and Selection of Participants

5.1  Introduction

This chapter outlines the methods applied in this study to recruit potential participants, assess them for ADHD and related problems, and select the final groups of ADHD and control subjects who met all inclusion criteria. The characteristics of these final groups will then be described. As this study involves a comparison between a clinical and a normal population, it was considered important to carefully assess each participant before including them in either the ADHD or control group, and to have data that describes the diagnostic status and cognitive ability of the groups. As discussed in chapter 2, ADHD can be associated with a range of additional problems, so several measures were included in this assessment, as described in the following sections.

This study was conducted in conjunction with the Australian Twin ADHD Project (ATAP), which was being conducted by colleagues Professor David Hay and Associate Professor Florence Levy. This project involved assessing ADHD and learning difficulties in twins all over Australia. Recruitment of participants for the current study through the ATAP and other avenues is discussed in section 5.2. The measures of ADHD symptoms, psychiatric comorbidities, IQ and learning problems used in the current study were the same as those used by the ATAP and are described in section 5.3. Section 5.4 then describes the criteria that were applied to exclude several potential participants and arrive at the final subject groups. The results of the assessment of ADHD, comorbidities, IQ and learning for these final groups are detailed in section 5.5, as well as the medication status of participants.

5.2  Recruitment

Recruitment was restricted to boys aged between 7 and 14 years, due to the much greater prevalence of diagnosed ADHD in boys and possible gender differences in development of the brain processes under investigation. Seventy-seven children were recruited to participate in the study.
Fifty-five boys were recruited through the Australian National Health and Medical Research Council (NHMRC) Twin Registry. This included fifty-two twins (26 pairs) and three singleton siblings. Families were selected who had twin boys in the appropriate age range who displayed either many (>6) or few (<4) DSM-III-R (American Psychiatric Association, 1987) ADHD symptoms. Singleton brothers of these twins were included if they also met these criteria. These initial symptom scores were determined from parental reports obtained as part of the ATAP on inattention and other problem behaviours in school-aged twins and their siblings. The ATAP involved a mass screening of all twins and their siblings in Australia who were aged from 4 to 12 years and were enrolled with the Australian NHMRC Twin Registry. The methods employed in this screening are described in detail by Levy et al. (1996). Briefly, a screening questionnaire, the Australian Twin Behaviour Rating Scale (ATBRS: Levy & Hay, 1991), was mailed to all eligible families. This questionnaire comprised items based on the DSM-III-R criteria for ADHD, ODD, CD and SAD, items assessing other attentional, behavioural and emotional symptoms, as well as items assessing parameters such as speech and reading problems and handedness. This questionnaire was found to have high reliability and to give conservative ratings compared to diagnostic interview (Levy et al., 1996). Parents completed the initial ATBRS 2 to 3 years prior to the recruitment of their family for this study. Those children identified as displaying few ADHD symptoms according to the initial screening were recruited for this study as potential control subjects and those identified as displaying many symptoms were recruited as potential ADHD subjects. An updated version of the ATBRS was administered at the time of the boys involvement in this study to update their symptom ratings, as described in the next section. In addition to meeting diagnostic criteria according to the ATBRS, all boys included in the final ADHD group were required to have been given a clinical diagnosis of ADHD by a paediatrician.

A further nineteen children were recruited through the Centre for Community Child Health at Melbourne’s Royal Children’s Hospital. Children were selected who had been given a primary diagnosis of ADHD by their paediatrician. Three children were recruited through the parent support group, ACTIVE, who had also been diagnosed with ADHD by paediatricians.
5.3 Assessment Methods

Each of the children recruited underwent an initial assessment to determine their diagnostic status related to ADHD and other commonly comorbid problems, as well as their IQ and reading/spelling ability. This assessment was generally conducted at the participant’s home and involved interviewing the child’s mother about their medical and schooling history, and conducting standardized tests of IQ and reading with the child, as described in the following sections. At this visit the parent and teacher questionnaires were given to the participant’s mother for later return to the researcher.

5.3.1 Parent and Teacher Questionnaires

All participants were assessed for ADHD as well as Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and Separation Anxiety Disorder (SAD). ADHD subjects were assessed for each of these disorders to ensure they met criteria for a DSM-III-R diagnosis of ADHD and to determine the presence of comorbid symptoms of the other disorders. As discussed in section 2.3, comorbidity is common in ADHD, especially with the other disruptive behaviour disorders (ODD and CD). Control subjects were assessed to ensure they were free of ADHD and other problems. As this study was commenced just prior to the publication of the DSM-IV (American Psychiatric Association, 1994), DSM-III-R criteria were used throughout to classify the participants. ATBRS questionnaires were completed by the mother and the teacher of each participant at the time of the child’s involvement in the study. These questionnaires are included in Appendix One. As the questionnaires were designed for the ATAP, not all items on the questionnaires were assessed for the purposes of this study. Those items that were used in the current study and the methods of assessment are described below.

The mother of each subject was asked to complete an updated version of the ATBRS (Levy & Hay, 1991; Levy et al, 1996). This questionnaire incorporated items related to the DSM-III-R diagnostic criteria for ADHD, ODD, CD and SAD (American Psychiatric Association, 1987). Parents were asked to circle a number (0, 1, 2 or 3) to indicate how applicable each item was for their child. For the purposes of this study, a
response of 2 or 3 (2 = pretty much/often, 3 = very much/very often) was considered a positive response indicating the presence of that symptom, while a response of 0 or 1 (0 = not at all, 1 = just a little/sometimes) was considered a negative response. This was true for all symptoms of ADHD, ODD and SAD and three of the thirteen symptoms of CD. For the remaining ten symptoms of CD, which relate to seriously deviant actions that do not need to occur often for them to be considered symptomatic, a response of 1, 2 or 3 was considered positive. The number of positive responses was then summed to give a symptom score for each disorder that could be compared with the number of symptoms required to meet diagnostic criteria. Responses to items related to symptom duration, age of onset and degree of disruption caused by the symptoms were also taken into consideration when deciding whether diagnostic criteria for each disorder were met.

The mother of each participant was also given a questionnaire to be passed on to their child’s teacher. The teacher was then asked to return the questionnaire by mail to ensure their responses would remain confidential. The teacher questionnaire included only the ADHD items of the ATBRS. As for the parent questionnaire, teachers were asked to circle a number (0, 1, 2 or 3) to indicate how applicable each item was for their student. The teachers’ responses were analysed in the same way as for the parent questionnaire to give a symptom score for ADHD.

Subjects with ADHD symptom scores of 8 or more on either questionnaire were included in the ADHD group, provided they also met the other DSM-III-R criteria (i.e. age of onset, etc.). Subjects with scores of less than 4 on both questionnaires were included in the control group, provided they did not meet criteria for any of the other disorders assessed.

5.3.2 Wechsler Intelligence Scale for Children - Third Edition

All participants were administered five subtests of the Wechsler Intelligence Scale for Children - third edition (WISC-III: Wechsler, 1992). Coding, Arithmetic and Digit Span were included as measures of attention and distractibility (Kaufman, 1994). Block Design and Vocabulary were included as measures of general intelligence and were used to estimate IQ (Sattler, 1992). Table 5.1 briefly describes the procedures for administration, the abilities measured and some of the influences that may affect an
individual’s performance for each subtest. The subtests are listed in Table 5.1 in the order of administration that was used for all subjects.

The raw scores obtained on each subtest were converted to a scaled score to correct for age, using the conversion tables provided in the WISC-III manual (Table A.1, pp. 217-249; Wechsler, 1992). Each subtest has an average scaled score of 10 and a standard deviation of 3. The Freedom from Distractibility Index (FDI) for each subject was determined by summing their scaled scores for Arithmetic and Digit Span, and looking up the corresponding index score equivalent from the WISC-III manual (Table A.7, p. 257; Wechsler, 1992). The estimated IQ for each subject was determined by summing their scaled scores for Block Design and Vocabulary, and looking up the estimated Full Scale IQ equivalent from Sattler’s *Assessment of Children* (Table L-12, p. 1171; Sattler, 1992). Sattler (1992) recommends this combination of subtests as the best short-form pair for estimating Full Scale IQ, as both tests correlate highly with the Full Scale IQ, have good reliability and are good measures of general intelligence. The FDI and IQ have an average of 100 and a standard deviation of 15. Subjects whose estimated IQ was less than 80 were excluded from the final subject groups, due to potential influences of low intelligence on the cognitive functions being assessed by this study.

Table 5.1 (following page): WISC-III subtests

<table>
<thead>
<tr>
<th>SUBTEST</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coding</td>
<td>A series of shapes (Coding A, for 6-7 year olds) or numbers (Coding B, for 8-16 year olds), each of which is paired with a symbol in a given code. For Coding A, the child draws inside each shape its corresponding symbol, and for Coding B draws under each number its corresponding symbol, completing as many items as possible in 2 minutes. Measures visual-motor speed and coordination, as well as short-term memory and learning, and is influenced by distractibility.</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>A series of arithmetic problems of increasing difficulty, ranging from simple counting to complex problems involving multiple mathematical functions. The child solves each problem mentally and responds orally. Each item is timed, and bonus points are awarded for fast completion on later items. Measures numerical reasoning and speed of computation and is influenced by attention and prior learning.</td>
</tr>
<tr>
<td>Block Design</td>
<td>A series of two-dimensional red and white geometric patterns modelled by the examiner or printed in a booklet, which the child replicates by arranging red and white cubes in the same pattern. Each item is timed, and bonus points are awarded for fast completion. Measures spatial perception and problem solving and is influenced by individual cognitive style.</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>A series of words presented orally by the examiner for which the child is required to give an oral definition. No time limits are imposed, and each item is scored according to the quality of the response. Measures word knowledge and verbal expression and is influenced by prior learning and cultural opportunities.</td>
</tr>
<tr>
<td>Digit Span</td>
<td>A series of number sequences of increasing length presented orally by the examiner and repeated orally by the child. For Digits Forward each sequence is repeated verbatim, and for Digits Backwards each sequence is repeated in reverse order. Measures short-term auditory memory and sequencing and is influenced by attention and distractibility.</td>
</tr>
</tbody>
</table>

97
5.3.3 Boder Test of Reading-Spelling Patterns

All participants were administered the Boder Test of Reading - Spelling Patterns (Boder & Jarrico, 1982) in order to assess the presence and extent of any reading difficulties, which have been found to be prevalent in children with ADHD (Biederman et al, 1991; Levy et al, 1996; Prior, 1996). The Boder comprises an oral reading test and a written spelling test. The reading test uses graded word lists of twenty words each, half of which are phonetic and half non-phonetic. Each child’s reading level was determined as the highest grade level at which the child could read on sight at least half the words in the list. The Reading Quotient (RQ) was then calculated according to the following formula:

\[ \text{RQ} = \left( \frac{\text{reading age}}{\text{chronological age}} \right) \times 100 \]

where reading age was obtained by adding 5 to the reading level, as children begin school at age 5.

After administration of the reading test, two word lists were prepared for the spelling test. Ten Known Words, half phonetic and half non-phonetic, were selected from words at or below the child’s reading level which were read on sight in the reading test and were therefore within the child’s sight vocabulary. The Known Words were used to tap the child’s ability to revisitualize words in their sight vocabulary, ie. the visual processes required for spelling.

Ten Unknown Words, half phonetic and half non-phonetic, were selected from words at or above the child’s reading level that the child was not able to read at all. The Unknown Words were used to tap the child’s phonetic word-analysis skills in spelling, ie. the auditory processes required for spelling. The spelling lists were dictated and the child was asked to write the Known Words “as well as you can” and the Unknown Words “the way they sound”. The Known Words score (KW) was calculated as the percentage of words spelled correctly and the Unknown Words score (UW) was calculated as the percentage of words spelled either correctly or as good phonetic equivalents. That is, the Known Words were scored for correctness only, while the Unknown Words were scored for their phonetic equivalence to the dictated words.
The RQ, KW and UW scores were then used to identify the child’s reading - spelling pattern. The reading - spelling pattern is considered normal when the KW and UW scores are both greater than 50% and the RQ is at least 100, and deviations from the normal pattern are categorised into five reading disability subtypes (Boder & Jarrico, 1982). The patterns of scores for identifying the different reader subtypes and descriptions of the abilities reflected by each category are summarised in Table 5.2.

Table 5.2: Boder reading-spelling patterns
Criteria for identifying the different Boder reading-spelling pattern subtypes (Boder & Jarrico, 1982).

<table>
<thead>
<tr>
<th>READING SUBTYPE</th>
<th>SCORES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>KW &gt; 50  UW &gt; 50  RQ ≥ 100</td>
<td>Reflects strengths in both auditory and visual processes and their integration.</td>
</tr>
<tr>
<td>Non-specific Reading Disability</td>
<td>KW &gt; 50  UW &gt; 50  RQ &lt; 100</td>
<td>Reflects a non-specific reading retardation.</td>
</tr>
<tr>
<td>Dysphonetic (Group I)</td>
<td>KW ≤ 50  UW ≤ 50  RQ ≥ 67</td>
<td>Reflects strengths in visual function and weaknesses in auditory function.</td>
</tr>
<tr>
<td>Dyseidetic (Group II)</td>
<td>KW ≤ 50  UW &gt; 50  RQ ≤ 80</td>
<td>Reflects strengths in phonic analysis and weaknesses in visual function.</td>
</tr>
<tr>
<td>Mixed (Group III)</td>
<td>KW ≤ 50  UW ≤ 50  RQ &lt; 67</td>
<td>Reflects weaknesses in both visual and auditory functions.</td>
</tr>
<tr>
<td>Undetermined</td>
<td>KW &lt; 50  UW &gt; 50  RQ &gt; 80</td>
<td>Reflects remediated dysphonetic or dyseidetic type.</td>
</tr>
</tbody>
</table>
5.3.4 Learning History

Parents were asked, in items on the ATBRS, whether their child had ever had remedial reading. They were also asked in an interview whether their child had ever experienced any learning difficulties, had ever received extra help for learning difficulties or had ever repeated a grade. Learning history was divided into four categories (remedial reading, other intervention, repeated grade and diagnosed learning disability) and simple yes or no responses were recorded for each category for each subject. This brief assessment of learning problems was included to obtain a general idea of their incidence in each group, and no attempt was made to quantify the extent of learning difficulties in individual subjects.

5.4 Participant Exclusions

On the basis of their results from the assessments described above, several potential participants were excluded from the study. Six children (three sets of twins) completed only the initial assessment but did not have questionnaires returned and did not participate any further. One twin subject was excluded due to meeting criteria for ODD, but not ADHD, according to the parent ATBRS. Three twin subjects were excluded as they met criteria for ADHD according to parent and/or teacher reports but had not been clinically diagnosed. Two twin subjects were excluded who had low symptom scores according to reports obtained in this study but had symptom scores of 8 or more from the original ATBRS questionnaire. A further nine twin subjects were excluded who did not meet diagnostic criteria for ADHD but had ADHD symptom scores of 4 or more, which was above the cut-off set for inclusion in the control group.

Three subjects were excluded due to having a diagnosis of neurological problems (two twin subjects and one diagnosed ADHD subject). Eight subjects were excluded due to having an estimated IQ of less than 80 (four twin subjects and four diagnosed ADHD subjects). Three control subjects and two ADHD subjects were excluded as they were left handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Only right handed children were included in the study, due to possible influences of laterality effects on the SSVEP measures.
A further five control subjects were excluded on the basis of data from their electrophysiological recording session. One had extremely slow reaction times for the cognitive tasks, two had EEG data which failed to pass artifact rejection criteria (see section 6.6.2), and two did not complete all three tasks. A further ADHD subject was also excluded, who had EEG data which failed to pass artifact rejection criteria.

5.5 Final Subject Groups

After these exclusions, the final sample comprised 34 male subjects aged between 89 months (7 years 5 months) and 168 months (14 years). All were right handed and had normal or corrected to normal vision. The ADHD group comprised 17 boys, with a mean age of 129 months (SD=24). Two were recruited through the Australian NHMRC Twin Registry, twelve were recruited through the Centre for Community Child Health at Melbourne’s Royal Children’s Hospital, and three were recruited through the parent support group ACTIVE. Those children who were taking stimulant medication for ADHD (n = 15) remained medication free for at least 24 hours prior to their electrophysiological testing session. All ADHD subjects had been diagnosed by a paediatrician and also met criteria for a DSM-III-R diagnosis according to responses on the parent and/or teacher questionnaires.

The control group comprised 17 normal boys, with a mean age of 132 months (SD=19). There was no significant difference in age between the groups. All control participants were recruited through the Australian NHMRC Twin Registry. All had symptom scores of 3 or less from the DSM-III-R criteria for ADHD on both the parent and teacher questionnaires, and none met criteria for any of the other disorders assessed by the parent questionnaire. All had no known history of neurological or psychiatric problems, and all had no significant academic or behavioural problems.

The results of the various assessment measures described in section 5.3 are detailed in the following sections, for these final subject groups.

5.5.1 ADHD Ratings
As described in section 5.3.1, parent and teacher questionnaires were completed for each participant. For the final group of 34 subjects, all parent questionnaires were completed and returned but four teacher questionnaires were not returned (two control and two ADHD subjects). The group mean numbers of DSM-III-R symptoms of ADHD from each measure are shown in Table 5.3. The groups were clearly distinguished by the number of symptoms exhibited, according to both parent and teacher reports. Although the mean number of symptoms exhibited by ADHD subjects from the teacher reports was below the DSM-III-R diagnostic cut-off of 8, it was still significantly higher than that for normal subjects (p<.0001). The most probable reason for the lower rates of symptoms in ADHD subjects reported by teachers than by mothers is the fact that the majority of these children were on medication at school and teachers did not see the full extent of their problem behaviours.

Table 5.3: Group ADHD symptoms
Mean number of ADHD symptoms (standard deviations in parentheses), from the 14 behaviours listed in the DSM-III-R diagnostic criteria (American Psychiatric Association, 1987), reported by subjects’ mothers and teachers for the ADHD and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Parent Questionnaire</th>
<th>Teacher Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.2 (0.8) range 0-3</td>
<td>0.3 (0.7) range 0-2</td>
</tr>
<tr>
<td>ADHD</td>
<td>11.2 (2.7) range 5-14</td>
<td>5.1 (3.3) range 0-12</td>
</tr>
</tbody>
</table>

All ADHD subjects met diagnostic criteria for the disorder on the parent questionnaire except one, but this subject did meet criteria on the teacher questionnaire. One other ADHD subject met criteria on the teacher questionnaire. None of the control subjects displayed any more than 3 symptoms according to either measure.

5.5.2 Comorbidity Ratings

In addition to ADHD, the presence of symptoms of other psychiatric disorders was reported by parents of thirteen (76%) ADHD subjects. The rates of comorbidity for
ODD, CD and SAD determined from parental responses on the questionnaire are shown in Table 5.4. The most common comorbid diagnosis was for ODD, but five of the subjects who met criteria for ODD also had comorbid CD and/or SAD.

Table 5.4: Comorbidity rates in the ADHD group
Numbers of ADHD subjects who met criteria for other psychiatric disorders assessed by the parent questionnaire.

<table>
<thead>
<tr>
<th>Oppositional Defiant Disorder</th>
<th>Conduct Disorder</th>
<th>Separation Anxiety Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (71%)</td>
<td>6 (35%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

Seven ADHD subjects met criteria for comorbid ODD only, one subject met criteria for CD only, four subjects met criteria for ODD and CD, and one subject met criteria for ODD, CD and SAD. Four ADHD subjects did not meet criteria for any comorbid disorders. In addition to being free of ADHD, none of the control subjects met criteria for any of these other disorders. No subjects had tic disorders or Tourette’s syndrome.

5.5.3 WISC-III Results

The group mean scaled scores for the five WISC-III subtests administered are shown in Table 5.5. Group differences for each of the scores examined were assessed using one-way analyses of variance. The ADHD group performed more poorly than the control group on all subtests, significantly so on Coding (p<.005), Arithmetic (p<.01), Block Design (p<.005) and Digit Span (p<.05). Estimated IQ and Freedom from Distractibility scores are shown in Table 5.6. As expected, the FDI, which was calculated from scores on WISC-III subtests influenced by concentration and distractibility (Kaufman, 1994), was significantly lower for children with ADHD than control children (p<.01). The estimated IQ, which was calculated from WISC-III subtests considered to be good measures of general intelligence (Kaufman, 1994) and to give the best estimate of full scale IQ (Sattler, 1992), of ADHD subjects was also significantly lower than that of the control group (p<.005), although it was within the
‘average’ IQ range of 85 to 115. All subjects included in both groups had an estimated IQ of at least 80, but no restriction was placed on FDI scores as these were expected to be compromised in ADHD subjects.

**Table 5.5: WISC-III subtest scores**
Group mean scaled scores for WISC-III subtests (standard deviations in parentheses) for control and ADHD groups. Results of ANOVAs to assess the significance of the group differences are also presented.

<table>
<thead>
<tr>
<th></th>
<th>Coding</th>
<th>Arithmetic</th>
<th>Block Design</th>
<th>Vocabulary</th>
<th>Digit Span</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>10.7 (3.1)</td>
<td>11.1 (3.3)</td>
<td>13.3 (3.5)</td>
<td>10.4 (3.7)</td>
<td>11.8 (4.0)</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td>7.6 (3.2)</td>
<td>8.3 (3.0)</td>
<td>9.8 (3.0)</td>
<td>8.9 (1.5)</td>
<td>9.4 (3.2)</td>
</tr>
<tr>
<td>$F_{(1,32)}$</td>
<td>8.38</td>
<td>6.88</td>
<td>9.75</td>
<td>2.34</td>
<td>3.58</td>
</tr>
<tr>
<td>$p$</td>
<td>&lt;0.005</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
<td>0.07</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 5.6: IQ and Freedom from Distractibility scores**
Group mean estimated Full Scale IQ and Freedom from Distractibility Index (standard deviations in parentheses). IQ = estimated Full Scale IQ calculated using the Vocabulary and Block Design short-form (Sattler, 1992). FDI = Freedom from Distractibility Index calculated using Arithmetic and Digit Span scores (Wechsler, 1992). Results of ANOVAs to assess the significance of the group differences are also presented.

<table>
<thead>
<tr>
<th></th>
<th>IQ</th>
<th>FDI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>111 (18)</td>
<td>109 (17)</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td>96 (10)</td>
<td>95 (14)</td>
</tr>
<tr>
<td>$F_{(1,32)}$</td>
<td>8.45</td>
<td>7.24</td>
</tr>
<tr>
<td>$p$</td>
<td>&lt;0.005</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**5.5.4 Boder Test Results**
The results of the Boder reading and spelling test are shown in Table 5.7. The reading quotient is the ratio of reading age to chronological age, multiplied by 100, where reading age is determined from the highest grade level at which the child can read at least half the words presented. The ADHD group were observed to have greater reading difficulties than the control group, having a significantly lower average reading quotient (p<.05). The number of known words (i.e. words read correctly at first glance during the reading test) spelled correctly was lower in the ADHD group and this difference approached significance. The number of unknown words (i.e. words that the child was unable to read at all) spelled correctly or as good phonetic equivalents was significantly less for the ADHD than the control group (p<.005), suggesting relatively weak phonetic skills in the ADHD group.

**Table 5.7: Boder test scores**

Group mean scores from the Boder test of reading and spelling (standard deviations in parentheses). Reading Quotient = (reading age / chronological age) x 100. Known Words = percentage of 10 readable words spelled correctly. Unknown Words = percentage of 10 non-readable words spelled correctly or written as good phonetic equivalents. Results of ANOVAs to assess the significance of the group differences are also presented.

<table>
<thead>
<tr>
<th></th>
<th>Reading Quotient</th>
<th>Known Words</th>
<th>Unknown Words</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>118 (27)</td>
<td>70 (26)</td>
<td>65 (21)</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td>96 (30)</td>
<td>54 (28)</td>
<td>39 (27)</td>
</tr>
<tr>
<td>$F_{(1,32)}$</td>
<td>4.99</td>
<td>2.85</td>
<td>9.61</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>0.05</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

According to the Boder classification of these test scores, three control subjects had reading-spelling patterns suggestive of developmental dyslexia (two dysphonetic and one undetermined), twelve ADHD subjects had reading-spelling patterns suggestive of developmental dyslexia (seven dysphonetic, one dyseidetic, two mixed and two undetermined), and one ADHD subject had a reading-spelling pattern suggestive of non-specific reading disability. Fourteen control and four ADHD subjects had normal reading-spelling patterns.
5.5.5 Learning Interventions

Learning difficulties were found to be far more prevalent in the ADHD group than the control group. The rates of learning interventions in the two subject groups are shown in Table 5.8. While the only intervention reported for control subjects was one case of remedial reading, fifteen ADHD subjects had a history of learning problems of varying severities, ranging from needing remedial reading to having a diagnosed learning disability. Five ADHD subjects had also repeated a grade at school.

Table 5.8: Learning intervention rates

Numbers of subjects with a history of interventions for learning problems and with a diagnosed learning disability for the two subject groups. Other interventions include tutoring, modified school courses and attendance at special schools.

<table>
<thead>
<tr>
<th></th>
<th>Remedial Reading</th>
<th>Other Intervention</th>
<th>Repeated Grade</th>
<th>Learning Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ADHD</td>
<td>12 (71%)</td>
<td>6 (35%)</td>
<td>5 (29%)</td>
<td>4 (24%)</td>
</tr>
</tbody>
</table>

Of the four ADHD subjects who achieved normal scores on the Boder, one had had remedial reading and repeated a grade, one had had remedial reading and tutoring, and two had no history of learning difficulties. The three control subjects whose Boder scores suggested developmental dyslexia had no history of interventions for learning problems and were reported not to be having any reading or learning difficulties and so were not excluded. The control subject who had had remedial reading achieved a normal score on the Boder.

5.5.6 Medication Status

Fifteen ADHD subjects were being treated by their paediatricians with stimulant medication, and six of these were concurrently taking clonodine, at the time of their participation in the study. Six subjects were taking methylphenidate only, five were
taking methylphenidate and clonidine, three were taking dexamphetamine only, and one was taking dexamphetamine and clonidine. One ADHD subject had never been prescribed medication for the disorder, and one had previously taken methylphenidate for three years but ceased treatment approximately six months prior to his involvement in the study. Where clonidine was prescribed in combination with a stimulant, it was intended to assist with controlling aggressive behaviour and/or minimizing sleep disturbance (Jarman, 1996). It was not prescribed for controlling tics, which were not present in any of the participants of this study.

Each participant refrained from taking their stimulant medication for at least 24 hours prior to their electrophysiological recording session. This was considered a sufficient minimum washout period given that the serum half-life and duration of behavioural effects of oral therapeutic doses of stimulants are at most 5 hours (Greenhill, 1998; Solanto, 2000; Swanson & Volkow, 2002). While longer minimum washout periods are sometimes used, similar periods of 12 to 30 hours have been used in several published studies that have investigated brain electrical activity in children with ADHD, including our own (Baving et al., 1999; Brandeis et al., 2002; Farrow et al., 1996; Monastra et al., 1999; Pliszka et al., 2000; Silberstein et al., 1998; Strandburg et al., 1996; Sunohara et al., 1999). Due to potential dangers associated with abruptly ceasing clonidine and its much longer half-life, participants were not asked to alter their normal use of this drug. These methods of drug withdrawal were recommended by our collaborating paediatrician, Dr Frederick Jarman, who referred most of the ADHD participants.

None of the control subjects had ever been treated with stimulants or other psychoactive medication. The only other regular medication taken by any participant, ADHD or control, was for asthma.

5.5.7 Summary of Assessment Findings

The ADHD group were clearly distinguished from the control group on a range of behavioural and cognitive measures in addition to the DSM-III-R ADHD symptoms. As expected for a clinical ADHD sample, they had more behavioural problems, as shown by the high rates of symptoms of the disruptive behaviour disorders (ODD and CD) reported by parents. They did not have a high level of anxiety problems however,
with only one subject meeting criteria for SAD. They did have significantly more
cognitive and learning problems, as shown by their poor performance on the WISC-III
and the Boder and their high rates of interventions for learning difficulties. The results
highlight the fact that many related problems can be associated with ADHD, affecting
academic and social functioning. This ADHD group represents a population with
relatively severe ADHD and a range of comorbid behavioural and learning difficulties.
Chapter 6  Methods

6.1  Introduction

Behavioural inattention is considered a core deficit in ADHD, as outlined in the discussion of the symptoms and diagnosis of the disorder in chapter 2. Despite conclusions by several reviewers that research has been unable to pinpoint a deficit in specific aspects of attention in ADHD, performance deficits and reduced brain activity during attentional tasks have been shown in ADHD, as reviewed in chapter 3. The CPT is a widely used measure of attention that is sensitive to attentional dysfunction (Riccio et al., 2002). As discussed in chapter 3, performance deficits on the CPT are consistently found for children with ADHD as are deficits in evoked potential responses to relevant stimuli in the CPT. The CPT therefore seems an appropriate task to use to examine attention related brain function in children with and without ADHD, as this study aims to do. As discussed in chapter 4, as a measure of brain function SSPT provides the temporal resolution required to examine dynamic patterns of brain activity during specific task components associated with heightened attention, and the spatial resolution required to examine topographic patterns of cortical activity at these times. SSPT therefore appears to be an ideal technique to study the temporal and spatial patterns of brain activity associated with attentional processes during the CPT, and how these may be disturbed in children with ADHD.

This chapter describes the experimental methods employed to test the hypotheses that were presented at the end of chapter 4. Section 6.2 details the computerized cognitive tasks that were performed by participants, their structure, timing, and the method of presentation. The methods associated with recording the EEG are described in section 6.3 and those associated with the presentation of the steady-state probe stimulus are described in section 6.4. The recording session procedure is outlined in section 6.5. Finally, section 6.6 details the signal processing procedures applied to the recorded electrophysiological data to investigate the SSVEP correlates of task performance, and compare this between ADHD and control groups.

6.2  Cognitive Tasks
All subjects performed a baseline and two continuous performance tasks (CPTs) while their brain electrical activity was recorded. For all tasks the rate of presentation was one stimulus per 3.5 s, the stimulus duration was 2 s and there was a 1.5 s inter-stimulus interval during which the screen was blank. For each task a total of 80 stimuli were presented and the total task time was 280 s. The presentation of each task is summarized in Figure 6.1. Each stimulus letter or number was presented in the centre of the computer monitor screen and subtended a horizontal and vertical angle of approximately 1° when viewed by the subject who sat at a fixed distance of 1.3 m from the screen. Stimuli were coloured white and had an average illuminance of 13.0 Cd/m² against the monitor background of 1.2 Cd/m², measured using a Tektronix J16 narrow angle digital photometer.

The tasks were presented in the same order for all subjects. Subjects first performed a low demand vigilance task which required them to view the numbers 1, 2, 3, 4 and 5, presented sequentially, and to respond by pressing buttons with both thumbs on each appearance of the 5. This sequence of numbers was repeated sixteen times. This task was termed the ‘baseline task’. Subjects were instructed that they did not have to respond quickly, but should relax, keep watching the numbers on the screen and press the buttons when they saw the target 5.

Subjects then performed the CPT-X, which required them to view letters presented randomly and to respond to the unpredictable appearance of an X. This task included twenty targets and sixty non-targets. Non-target letters were any letter of the alphabet other than X and each was presented between one and five times. Subjects were instructed to respond as quickly as possible after detecting a target X. This version of the task had previously been shown to discriminate ADHD children from controls (Levy & Hobbes, 1981).
Finally, subjects performed the CPT-AX, which required them to view letters presented randomly and to respond on each appearance of an X which had been preceded by an A. This task included fifteen target A-X sequences. The task also included As that were followed by a letter other than X, so that not all As validly cued a target. It included Xs that were preceded by a letter other than A, so that not all Xs were targets. And it included non-target sequences of two letters that were not A or X. Non-cue and non-target letters included D, E, G, J, K, L, O, P, S, V, W, Y and Z. Subjects were again instructed to respond as quickly as possible after detecting a target X.
The baseline task was incorporated in order to provide a measure of baseline SSVEP activity, so that activity during the tasks under investigation, the CPT-X and CPT-AX, could be referenced to this baseline level. All three tasks involved the same sensory and motor components. However, while passive viewing of stimuli and regular responses to a predictable target were required for the baseline task, the CPTs with unpredictable targets required attention to and evaluation of each stimulus. In order to investigate the SSVEP activity associated with this additional cognitive processing, a subtractive method was employed in order to isolate the cognitive processes of interest from the sensory and motor processes occurring in parallel. That is, baseline activity was subtracted from CPT related activity, as explained further in section 6.6.4.

Incorporating a baseline or reference task in this way is a commonly used and well established method of separating task components and identifying related activity in specific brain regions, and is used in PET, fMRI and electrophysiological mapping (Friston, 1996). This separation of task components is considered important for the appropriate interpretation of results, ensuring that the resulting brain function images provide information directly related to the cognitive processes of interest (Cherry & Phelps. 1996; Gevins, 1996; Posner & Abdullaev, 1996).

For all three tasks, responses were made using a hand held button box designed to minimize movement while responding. The response apparatus consisted of a small rectangular box with two buttons of 1.5 cm diameter mounted on the top surface, which could be held comfortably in the hands while they rested in the lap with the thumbs resting on the buttons. Participants were instructed to press the buttons simultaneously with both thumbs on the presentation of targets. A bimanual button press was used so that motor effects on the SSVEP would also be bilateral.

Reaction times (time between presentation of stimulus and subject response) were recorded automatically for each button press to an accuracy of 1 ms, thus enabling calculation of mean reaction time for correct responses (MRT), number of errors of omission (CPTO; missed targets) and number of errors of commission (CPTC; responses to non-targets, and CPTC(B); responses to blanks) for each task. In the calculation of MRT, response times of less than 100 ms and greater than 1500 ms were excluded. Group differences in these behavioural measures were assessed using one-way analyses of variance.
In order to familiarize subjects with task performance requirements and ensure that task instructions were fully understood, a one minute practice version of each task was performed prior to the full task. No performance data were recorded for these practice tasks. The task instructions given to participants are provided in Appendix Two.

6.3 EEG Recording

Brain electrical activity was recorded from 64 scalp electrodes while subjects performed the cognitive tasks. The Ag/AgCl electrodes were mounted in a helmet designed and constructed at the Brain Sciences Institute, Swinburne University of Technology (Ciorciari et. al., 1987), and were spring loaded to allow them to be held comfortably in position on the scalp. The 64 electrode sites included all International 10-20 positions (Jasper, 1958) and additional sites located midway between the 10-20 positions, as illustrated in Figure 6.2. The average inter-electrode separation was 3.2 cm. Linked earlobe electrodes were used as a reference and a nose electrode served as a ground. The recorded brain electrical activity was amplified, bandpass filtered (3 dB down at 0.1 Hz and 30 Hz), digitized to 12 bit accuracy at a rate of 208 Hz, and saved to hard disk for subsequent off-line analysis (Silberstein et al., 1990; Silberstein et al., 1995).
6.4 Steady-State Probe Stimulus

The stimulus used to evoke the SSVEP was a 13 Hz sinusoidal flicker superimposed over the visual field. The flicker subtended a horizontal angle of 160° and a vertical angle of 90°. When viewed against the task monitor background, the luminance of the peak of the stimulus waveform was 3.2 Cd/m², and that of the minimum point of the waveform was 1.2 Cd/m². The flicker was presented using a set of glasses mounted on the front of the recording helmet. The glasses comprised two sets of red light emitting diode (LED) arrays viewed through half silvered mirrors, allowing the flicker to be superimposed over the subject’s viewing field and therefore over the cognitive task stimuli. The LED arrays were housed in a small Faraday cage to prevent electrical contamination of the EEG. The light intensity of the LED arrays was controlled by a 13 Hz sinusoidal voltage waveform, with a non-linearity of less than 0.5% between voltage input and light intensity.
Task presentation and data acquisition were time locked to the steady-state stimulus presentation, such that the cognitive task and EEG data acquisition commenced simultaneously at a positive zero-crossing of the 13 Hz stimulus waveform. Sixteen EEG data points were sampled for each steady-state stimulus cycle, and samples were acquired at the same points in each stimulus cycle. This meant that during subsequent data analysis, epochs of SSVEP data associated with specific components of the cognitive tasks could be easily and accurately extracted. It also meant that information could be obtained about phase or latency differences between the 13 Hz stimulus and the SSVEP. The experimental set up is summarized in Figure 6.3.

![Experimental recording arrangement](image)

**Figure 6.3: Experimental recording arrangement**

Equipment used in recording EEG data and presenting the steady-state stimulus and cognitive tasks.

### 6.5 Procedure

This study was approved by the human research ethics committees of Swinburne University of Technology, the Australian NHMRC Twin Registry and the Royal
Children’s Hospital. A parent of each participant gave informed consent for their child to participate. (This study was conducted prior to the introduction of current Australian National Health and Medical Research Council guidelines requiring children to give written consent in addition to their parent/guardian.)

Recording sessions were of approximately 1 hour duration. The subject and their accompanying parent/s were first familiarized with the laboratory and the recording equipment and procedures. Parents were then asked to complete the consent form. The subject was then seated 1.3 m in front of the task computer monitor and prepared for the recording – reference leads and helmet were fitted, EEG signals were checked, and glasses for delivering the steady-state stimulus were fitted and checked. Instructions for the baseline task were then given and the practice baseline task was presented. Provided the subject performed the practice task correctly, the full baseline task was then presented while brain electrical activity was recorded. These procedures were then repeated for the CPT-X and CPT-AX. For the baseline task subjects were instructed to simply press the buttons after seeing the target 5, while speed and accuracy of performance were equally emphasized for the CPT-X and CPT-AX.

6.6 Signal Processing

6.6.1 SSVEP Calculation

The 13 Hz component of the recorded EEG data (i.e. the SSVEP) for each task was extracted using Fourier analysis techniques, in order to determine the variations in amplitude of the SSVEP and the phase difference between the 13 Hz stimulus waveform and the SSVEP. Coherent demodulation, involving multiplication of the EEG signal by the stimulus waveform to calculate the sine Fourier coefficients, and by the stimulus waveform shifted by 90° to calculate the cosine Fourier coefficients, was used to obtain the coefficients for each stimulus cycle (Regan, 1989).

The 13 Hz cosine and sine Fourier coefficients were then averaged over an integration period equivalent to 10 stimulus cycles. This 10 cycle integration window was then repeatedly shifted 1 stimulus cycle (i.e. 1/13 s) and the Fourier coefficients were
recalculated for this overlapping period. This averaging resulted in a new set of averaged Fourier coefficients for each stimulus cycle, with an improved signal-to-noise. Using an integration period of 10 stimulus cycles resulted in a temporal resolution of 769 ms (10/13 s). This period was chosen as a compromise between long integration periods improving noise rejection and short integration periods allowing tracking of rapid changes in SSVEP amplitude and phase (Silberstein et al., 1990). For each task this process was repeated until the entire 280 s of data were analyzed. An identical procedure was applied to data recorded from each of the 64 electrodes.

The amplitude and phase of the SSVEP at each time point were calculated from the corresponding Fourier coefficients using the following equations:

\[ \text{SSVEP amplitude} = \sqrt{a_n^2 + b_n^2} \]
\[ \text{SSVEP phase} = \tan^{-1}(b_n/a_n); \]
where \( a_n \) = cosine Fourier coefficient, \( b_n \) = sine Fourier coefficient.

This yielded 64 amplitude and phase time series for each task for each subject.

### 6.6.2 Artifact Detection and Compensation

As explained in section 4.2, the SSVEP is relatively insensitive to corruption by artifacts such as EMG or EOG because these artifacts have power spread over a range of frequencies while the steady-state stimulus and resultant SSVEP have their power focused at 13 Hz (Silberstein et al., 1990). The relative insensitivity of the SSVEP to common artifacts permits the relaxation of the rejection criteria for artifact contamination that are typically employed when evaluating EEG power spectra. Nevertheless, both the raw EEG and SSVEP data were subjected to tests to determine whether data had been contaminated by artifact above predetermined threshold levels and to identify the specific electrodes at which this had occurred (Silberstein et al., 1995).

In the first test, the amplitude distribution of the recorded EEG was determined for each electrode during each of the cognitive tasks. The amplitude of the EEG has a Gaussian distribution (McEwen & Anderson, 1975), and so the amplitude distribution of the
recorded data was correlated with a Gaussian function. This technique detects data exceeding the input voltage range of the analogue to digital converter, which might occur due to intermittent contact between an electrode and the scalp. Electrodes with a signal with a correlation coefficient of less than 0.75 were classified as unacceptable.

In the subsequent test, the SSVEP time series at each electrode was correlated with the mean time series of its’ four nearest neighbouring electrodes. Electrodes where data were significantly different from that of the nearest neighbours were more likely to be suspect as data from the closely spaced electrodes used in the 64-channel system are expected to be highly correlated (Nunez, 1981). This technique detects artifact such as EMG and 50 Hz mains interference, which display a Gaussian-like amplitude distribution and may therefore pass the first test described above. For this test, electrodes were considered unacceptable if the correlation coefficient was less than 0.6. Subject data were included in the analysis if no more than seven suspect electrodes were identified by these tests. Contaminated data was then replaced by a weighted average of the data from the four nearest electrodes that had passed all test criteria.

6.6.3 Event Averaging

To examine changes in the SSVEP associated with specific components of the cognitive tasks, 10 s epochs of SSVEP data centred on the appearance of a target stimulus were averaged for all occurrences of that stimulus. As with traditional ERP techniques, this averaging across repeated presentations of the same stimulus improves the signal-to-noise for the response of interest. Only those targets to which a correct behavioural response was made were included in the average, i.e. target stimuli were included only if a button press occurred between 100 and 1500 ms after presentation. This yielded averaged SSVEP amplitude and phase time series, of 10 s duration, associated with specific correctly identified targets for each of the 64 electrodes for each subject.

For the baseline task, the average was centred on the presentation of the target 5. The mean values of these SSVEP amplitude and phase time series centred on presentation of the 5 in the baseline task were then calculated. For the CPT-X, the average time series was centred on the presentation of the X and for the CPT-AX, the average time series was centred on the presentation of each X preceding an A.
6.6.4 Group Averaging

Before group effects could be examined by averaging each time series and the baseline mean across subjects, individual data were first normalized to account for inter-subject variations in the absolute magnitude of the SSVEP. This was done by calculating the mean SSVEP amplitude for the 10 s epoch centred on presentation of the 5 in the baseline task for each electrode, giving 64 values for each subject. The mean of these 64 values was then calculated and used as the normalization factor for that subject. All individual amplitude time series data were then divided by their normalization factor prior to inclusion in the cross subject average.

Cross subject averaging was then performed, yielding two sets of group data, one for the 17 ADHD subjects and one for the 17 control subjects. Each set of group averaged data included the SSVEP amplitude and phase time series for the CPT-X and CPT-AX target conditions and the mean amplitude and phase for the baseline target condition, for all 64 electrodes. In all subsequent group comparisons, for each group time series from the CPT-X and CPT-AX were compared with the mean of the time series centred on the 5 in the baseline task. This was done by subtracting the baseline mean values from the CPT time series values at each point in the 10 s epoch, providing a measure of SSVEP amplitude and phase variations at relevant points during the CPT in reference to a baseline task with equivalent sensori-motor components. SSVEP differences between these baseline and activated states could then be interpreted as responses associated with the attentional processing demands of the CPT, as previously outlined in section 6.2. This method of subtracting activity measured during a control condition from that measured during an activation task is commonly used in functional imaging studies (e.g. Bush et al., 1999; Rubia et al., 1999) and is considered very effective for mapping activity associated with specific cognitive processes and identifying the corresponding functionally specific brain regions (Friston, 1996).

SSVEP amplitude differences from the baseline mean were expressed in terms of normalized units, while phase differences were expressed in terms of latency variations. Given that the period of the stimulus and therefore of the SSVEP is 1/13 s and
corresponds to a phase difference of $2\pi$ radians, a phase difference of 1 radian corresponds to a change in latency of 12.24 ms.

6.6.5 Topographic Mapping and Statistical Comparisons

Differences between the baseline task mean and the amplitude and latency time series associated with targets in the CPT-X and CPT-AX were calculated and two-dimensional topographic maps of these differences were produced. Inter-electrode values were calculated using a spherical spline interpolation procedure (Cadusch et al, 1992). These maps were constructed to illustrate the topography of the SSVEP amplitude and latency differences between the baseline task and the more demanding CPT tasks for each group. Effectively, the baseline values were set to zero and CPT related changes were expressed as deviations from this zero level. Equating the control and ADHD groups’ baseline activity in this way takes into account any group differences in function associated with sensori-motor processing and therefore allows a direct comparison of their CPT activity associated with the attentional processing that this study aimed to investigate. A 256 colour scale was used for the topographic maps, such that reductions in amplitude and latency compared to the baseline were displayed as warmer colours, and increases as cooler colours.

Significance Probability Mapping (SPM) based on the Hotelling’s $T^2$ parameter was used to illustrate the topography of the statistical strength of the amplitude and latency differences between the two conditions (Silberstein et al., 1995). The Hotelling’s measures were based on multiple bivariate T tests of the difference between the mean SSVEP in the baseline task target condition and the SSVEP time series data for the CPTs. These bivariate tests account for the fact that the SSVEP time series are expressed as complex numbers with real and imaginary components, representing the amplitude and latency of the SSVEP response (Silberstein et al., 1995). Topographic maps of the square root of the Hotelling’s $T^2$ parameter were produced for each comparison. The $T$ value rather than the $T^2$ parameter itself was mapped because small areas could contain very large $T^2$ values which would dominate the scale, so mapping the $T$ values allowed for much smoother contours. Higher Hotelling’s $T$ values reflect more consistent differences in amplitude and latency between the two conditions. On
the SPM maps, iso-T contours were used to illustrate the regions where the value of T corresponded to single comparison p values of 0.01, 0.005 and 0.001.

A p value of 0.05 is normally considered the threshold for statistical significance. In circumstances involving multiple comparisons, such as the SPM maps which include comparisons at the 64 recording sites, this p value needs to be adjusted. This is usually done by way of a Bonferroni correction, whereby the p value is adjusted by dividing by the number of independent comparisons (Abt, 1983). The straightforward application of this criterion to the case of 64 recording sites would yield an adjusted p value of 0.05/64, however, this overlooks the high correlation between neighbouring scalp sites which are in fact not independent (Nunez, 1981; Silberstein et al., 1995). Spatial principal components analysis suggests that a value of 5 more accurately represents the degree of independence for 64 separate but correlated recording sites (Silberstein & Cadusch, 1992). Therefore, a p value of 0.01 on the Hotelling’s T maps was used as the threshold for statistical significance. Where multiple time points were examined, for example in the CPT target sequences, this value needs to be further divided by the number of time points sampled.
Chapter 7 Results

This chapter details the findings of this study. Section 7.1 describes the behavioural results for the cognitive tasks performed by subjects. Mean reaction times and errors for the ADHD and control groups are given for the baseline task, CPT-X and CPT-AX. The results of statistical tests examining group differences for each measure are also presented. Section 7.2 describes the electrophysiological results. To investigate brain function associated with cognitive processing during the target intervals in the CPT, SSVEP amplitude and latency patterns during these intervals were examined for both the control and ADHD groups. Changes in SSVEP amplitude and latency relative to the baseline in the CPT-X are illustrated in section 7.2.1, and results for the CPT-AX are illustrated in section 7.2.2.

7.1 Behavioural Results

Mean reaction times and numbers of errors for the three cognitive tasks performed by subjects while their brain electrical activity was recorded are shown in Table 7.1. The ADHD group reacted to targets more slowly and made more errors than the control group in all three tasks, although not all group differences were significant. In the baseline task, ADHD subjects were significantly more likely than controls to fail to respond to the target 5 (p<.005) and to make a response during the blank between stimuli (p<.001). They also completed fewer correct trials (p<.01). In the CPT-X, the ADHD group made significantly more errors of commission than controls, both to non-target stimuli (p<.01) and to blanks between stimuli (p<.01), and had significantly slower reaction times (p<.05). Only sixteen ADHD subjects were included in the average for the CPT-X. One subject had extremely slow reaction times and made many errors of omission, leaving too few correct trials to average, and so was excluded due to his poor performance on this task. His baseline task and CPT-AX performance were similar to the rest of the participants however, so he was not excluded from analyses for these tasks. In the CPT-AX, the ADHD group made significantly more commission errors (p<.05) and responded to more blanks between stimuli (p<.05).
Table 7.1: Mean reaction times, number of correct responses and numbers of errors for ADHD and control groups

Group means and standard deviations (in parentheses) for behavioural measures for the three tasks. Results of Anovas performed for group comparisons are also shown. MRT = mean reaction time for correct responses to targets (in ms). Correct trials = number of correct responses included in average accounting for omission errors and reaction times of less than 100 ms (out of a maximum 16 targets in baseline task, 20 in CPT-X and 15 in CPT-AX). CPTO = number of omission errors (missed targets). CPTC = number of commission errors (responses to non-target stimuli). CPTC(B) = number of commission errors on blanks (i.e. responses made during 1.5 s inter-stimulus interval).

<table>
<thead>
<tr>
<th>TASK</th>
<th>MRT (ms)</th>
<th>Correct trials</th>
<th>CPTO</th>
<th>CPTC</th>
<th>CPTC(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE TASK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>427 (105)</td>
<td>15.8 (0.8)</td>
<td>0.1 (0.2)</td>
<td>0.6 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ADHD</td>
<td>499 (165)</td>
<td>14.9 (1.1)</td>
<td>0.8 (0.9)</td>
<td>1.7 (3.5)</td>
<td>1.2 (1.3)</td>
</tr>
<tr>
<td>F(1,32)</td>
<td>2.31</td>
<td>6.59</td>
<td>9.68</td>
<td>1.58</td>
<td>16.56</td>
</tr>
<tr>
<td>p</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CPT-X</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>599 (115)</td>
<td>19.9 (0.2)</td>
<td>0.1 (0.2)</td>
<td>0.5 (0.8)</td>
<td>0.1 (0.5)</td>
</tr>
<tr>
<td>ADHD</td>
<td>691 (165)</td>
<td>19.7 (0.8)</td>
<td>0.3 (0.8)</td>
<td>1.8 (1.9)</td>
<td>0.8 (0.9)</td>
</tr>
<tr>
<td>F(1,31)</td>
<td>3.46</td>
<td>1.58</td>
<td>1.58</td>
<td>6.31</td>
<td>7.61</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
<td>0.11</td>
<td>0.11</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>CPT-AX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>528 (117)</td>
<td>14.8 (0.5)</td>
<td>0.2 (0.5)</td>
<td>1.1 (1.1)</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>ADHD</td>
<td>587 (154)</td>
<td>14.5 (0.8)</td>
<td>0.5 (0.8)</td>
<td>2.6 (3.4)</td>
<td>1.5 (2.9)</td>
</tr>
<tr>
<td>F(1,32)</td>
<td>1.34</td>
<td>2.42</td>
<td>1.60</td>
<td>2.91</td>
<td>4.35</td>
</tr>
<tr>
<td>p</td>
<td>0.13</td>
<td>0.07</td>
<td>0.11</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Mean reaction times for both groups were slowest in the CPT-X, faster in the CPT-AX which provides a cue to a potential subsequent target, and fastest in the baseline task in which there is no uncertainty about when the target will appear. Reaction times of less than 100 ms were excluded from all averages as they would indicate an anticipatory response rather than a true reaction time. These only occurred during the baseline task, in one control and four ADHD subjects.

The ADHD group had higher standard deviations for all group averages of reaction time and number of errors, suggesting a greater degree of performance variability within the ADHD group than the control group.

### 7.2 Electrophysiological Results

This section describes the findings of the investigation of SSVEP amplitude and latency responses related to cognitive processing of task relevant stimuli in the CPT-X and CPT-AX, for the ADHD and control groups. Section 7.2.1 details the CPT-X findings, beginning in section 7.2.1.1 with a description of the topography of SSVEP effects in the 2 s interval between the disappearance of the stimulus preceding the target X to 500 ms after target presentation. The topographic maps provide the opportunity to examine the brain regions that are most activated during this interval of heightened attention in normal controls, and which regions may be deviant in the ADHD boys. The dynamics of the SSVEP amplitude (section 7.2.1.2) and latency (section 7.2.1.3) changes during this interval are then presented as time series illustrations at specific electrode sites. The electrode sites depicted were chosen to be representative of the SSVEP effects in regions where group differences in activity were observed in the topographic maps for both the CPT-X and CPT-AX. This was done in order to further investigate the temporal nature of the SSVEP responses in these regions of interest. The CPT-AX findings are presented in the same fashion in section 7.2.2. For the CPT-AX, SSVEP amplitude and latency changes are examined in the 4 s interval from the presentation of the cue A to 500 ms after the presentation of the target X.

#### 7.2.1 CPT-X Results
The entire control group of 17 subjects was included in the cross subject average of the CPT-X related SSVEP responses described in the following sections. However, only 16 ADHD subjects were included in this group’s average. One ADHD subject was excluded from analysis because of anomalies in his behavioural data for the CPT-X, as described in section 7.1.

7.2.1.1 SSVEP Topography in the CPT-X

The topographic distribution of the SSVEP amplitude and latency differences at specific points in time around the presentation of the target X in the CPT-X are illustrated in Figure 7.1 for the control group and Figure 7.2 for the ADHD group. As explained in section 6.6.4, SSVEP amplitude and latency changes during the CPT-X are expressed as the difference from the mean amplitude and latency calculated from the 10 s epoch centred on the presentation of the target 5 in the baseline task. Reductions in amplitude and latency in the CPT-X, relative to the baseline task mean, are indicated by warmer colours, while cooler colours indicate increases in amplitude or latency. The maps on the right in Figures 7.1 and 7.2 are the significance probability maps of the Hotelling’s T comparison between the baseline mean and the CPT-X time series. Higher T values are indicated by warmer colours and suggest greater consistency of SSVEP differences across the group. As explained in section 6.6.5, the three iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001.

Four points in time around the presentation of the target X are illustrated in Figures 7.1 and 7.2. In both figures, the maps in the top row represent the SSVEP amplitude difference, the SSVEP latency difference and the Hotelling’s T values indicating the statistical strength of these differences at the disappearance of the stimulus preceding the X (at 3.5 s in the averaged 10 s epoch). The maps in the second row represent the same SSVEP measures one second later (at 4.5 s) when the screen is blank. The maps in the third row represent the SSVEP at the appearance of the target X (at 5 s). And the final row of maps represent the SSVEP 500 ms after target presentation (at 5.5 s), which would be just prior to the response that occurred on average at 599 ms for controls and 691 ms for the ADHD group. At this time the X is still on the screen.
Applying the Bonferroni corrections for multiple comparisons described in section 6.6.5, the threshold for significance of the baseline – CPT-X SSVEP differences presented in Figures 7.1 and 7.2 would be a p value of 0.0025. The normal value of 0.05 would need to be divided by 5, to correct for multiple recording sites, and by 4, to correct for the multiple time points examined. In the Hotelling’s T maps therefore, areas inside the iso-T contour representing an uncorrected p value of 0.001 would be regions of significant SSVEP differences, and areas inside the iso-T contour representing a p value of 0.005 would be regions of SSVEP differences approaching significance.

In the control group (Figure 7.1), a diffuse amplitude reduction, relative to the baseline task mean, coincides with the interval leading up to and following the appearance of the target X. At the disappearance of the stimulus preceding the X, participants would be expected to begin preparing for the next stimulus, which as far as they know may or may not be a target. At this time point (3.5 s), large amplitude reductions are apparent in the control group in fronto-central and parieto-occipital regions. One second later (at 4.5 s), during the blank interval leading up to the appearance of the X, the large parieto-occipital amplitude reduction is still apparent, while there are smaller amplitude reductions in other regions. At the appearance of the target X (5 s), there are large amplitude reductions in occipital, left and medial frontal and left temporal regions. There are still large amplitude reductions in these regions 500 ms later (at 5.5 s), leading up to the response, as well as further reductions in the right frontal region.

The ADHD group (Figure 7.2) showed smaller and more restricted frontal and temporal amplitude reductions at these times. Furthermore, in parieto-occipital regions there are amplitude increases, relative to the baseline task mean, rather than the decreases seen in controls. The largest group differences in CPT-X related SSVEP amplitude were observed in the parieto-occipital region where, apart from a large left occipital amplitude reduction at the disappearance of the stimulus preceding the X (3.5 s), there are large increases in amplitude in the ADHD group, in contrast to the large and sustained parieto-occipital amplitude reductions in the control group.

In control subjects (Figure 7.1), small SSVEP latency reductions relative to the baseline task mean occur in frontal and temporal regions on and following the disappearance of
the stimulus preceding the X (at time points 3.5 and 4.5 s). Following the presentation of the target X (at 5 and 5.5 s), latency reductions in control subjects are more restricted to left and right prefrontal regions.

In ADHD subjects (Figure 7.2), a prefrontal latency reduction is associated with the disappearance of the stimulus preceding the X (at 3.5 s), while latency is increased at other frontal and central sites. On and following the appearance of the target (at 5 and 5.5 s), there is a large frontal latency reduction in ADHD subjects, predominantly in the right frontal region. The latency in parietal and occipital regions is slightly increased compared to the baseline mean in both groups for most of the illustrated interval around presentation of the target X. The main group difference in CPT-X related SSVEP latency appears to be in the dynamic pattern of frontal latency changes. In controls, latency was reduced over widespread frontal areas prior to the appearance of the X, with only prefrontal latency reductions and latency increases in other frontal areas following the target appearance. In the ADHD group, the opposite temporal pattern was observed with more widespread frontal latency reductions occurring after presentation of the X.
Figure 7.1: Topography of baseline – CPT-X differences for the control group
(Note: The legend for Figure 7.1 appears on the following page.)
**Figure 7.1 (previous page):** Topography of baseline – CPT-X differences for the control group

Topographic differences for SSVEP amplitude (normalized units) and latency (ms) between baseline mean and CPT-X time series. Warmer colours (pink/red) indicate reduced amplitude and latency in the CPT-X relative to the baseline, cooler colours (blue) represent increases. Hotelling’s T maps indicate the statistical strength of these differences, warmer colours indicate higher T values. Iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001. Four time points are shown. 3.5 s is the time of the disappearance of the preceding stimulus. 4.5 s is during the blank between stimuli. 5 s is the presentation of the target X. 5.5 s is 500 ms into target presentation, just prior to response which occurred at an average of 599 ms for controls.

The Hotelling’s T maps for control subjects (Figure 7.1) show that the most significant baseline – CPT-X differences in the SSVEP occurred at the disappearance of the stimulus preceding the X (3.5 s), where T values correspond to uncorrected p values of less than 0.005 in almost all regions. Amplitude and latency differences are most significant in frontal and right parieto-temporal regions leading up to the appearance of the target (at 4.5 s). Significant effects are evident at prefrontal, left and right temporal and right parietal regions following the appearance of the target X (at 5 and 5.5 s).

These statistical results suggest a high degree of consistency in SSVEP effects across the control group during the CPT-X target interval.

As shown in Figure 7.2, the ADHD group baseline – CPT-X differences were less significant than those of controls, suggesting less consistent effects in the clinical group. Significant effects were observed in right frontal and right parietal regions at the disappearance of the stimulus preceding the X (3.5 s). Around the presentation of the target (at 4.5, 5 and 5.5 s), the differences in frontal regions are the most significant.
Figure 7.2: Topography of baseline – CPT-X differences for the ADHD group
(Note: The legend for Figure 7.2 appears on the following page.)
Figure 7.2 (previous page): Topography of baseline – CPT-X differences for the ADHD group

Topographic differences for SSVEP amplitude (normalized units) and latency (ms) between baseline mean and CPT-X time series. Warmer colours (pink/red) indicate reduced amplitude and latency in the CPT-X relative to the baseline, cooler colours (blue) represent increases. Hotelling’s T maps indicate the statistical strength of these differences, warmer colours indicate higher T values. Iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001. Four time points are shown. 3.5 s is the time of the disappearance of the preceding stimulus. 4.5 s is during the blank between stimuli. 5 s is the presentation of the target X. 5.5 s is 500 ms into target presentation, just prior to response which occurred at an average of 691 ms for the ADHD group.

7.2.1.2 SSVEP Amplitude Dynamics in the CPT-X

Figure 7.3 illustrates the variations with time in the cross-subject averages of the SSVEP amplitude around the presentation of targets in the CPT-X at a midline frontal site, electrode 16 (Fz), in control subjects (red lines) and ADHD subjects (blue lines). The dashed horizontal line illustrates the mean value of the averaged SSVEP amplitude for the 10 s epoch centred on the appearance of the target 5 during the baseline task. This is set to zero for both populations and hence the amplitude of the CPT-X time series is expressed as the difference in amplitude from this baseline.

At this frontal site in both subject groups, the SSVEP amplitude is reduced compared to the baseline leading up to the presentation of the target, although there is a greater amplitude reduction in controls at the disappearance of the preceding stimulus. The response to the target X differs between the groups. In the control group, the amplitude reduces further on and after the appearance of the X, and is most reduced at around the time the response is made (600 ms after stimulus presentation). Following the response there is a sharp increase in amplitude. In the ADHD group however, there is an amplitude increase on and after the appearance of the target.
Figure 7.3: SSVEP amplitude time series in the CPT-X at electrode 16 (medial frontal, Fz)

SSVEP amplitude time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 16 (Fz). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-X related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.

As described in section 4.3, reductions in SSVEP amplitude at times of heightened attention have previously been associated with increased regional cortical activation (Silberstein et al., 1990, 1996). Applying this interpretation to the current data suggests greater medial frontal activation in response to the target stimulus in controls than in the ADHD boys. This group difference in target processing related medial frontal activation is also evident in the topographical maps (see Figures 7.1 and 7.2).

Figure 7.4 illustrates the amplitude variations in the CPT-X target interval at a right parietal site, electrode 57 (midway between P4 and O2). At this site, there is a
reduction in amplitude compared to the baseline in controls leading up to the appearance of the target, while the amplitude is around the baseline level during this interval in ADHD subjects. In the control group, there is a slight amplitude increase at the presentation of the target, but the amplitude remains reduced compared to the baseline until a sharp increase occurs at around the time of response. In contrast, in the ADHD group the amplitude increases sharply much earlier, on the presentation of the X, and is increased compared to baseline during the post-target interval.

Figure 7.4: SSVEP amplitude time series in the CPT-X at electrode 57 (right parietal)
SSVEP amplitude time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 57 (midway between P4 and O2). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-X related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
A very similar pattern was observed at an occipital site, electrode 61 (Oz) (Figure 7.5). At this site, the amplitude is reduced compared to the baseline in the control group both before and after target presentation. In the ADHD group there is a small reduction in amplitude on the disappearance of the preceding stimulus, but this quickly reverses to an amplitude increase, and the amplitude then increases further after target presentation. These SSVEP amplitude effects at parieto-occipital sites are also evident in the topographic maps (Figures 7.1 and 7.2), with controls showing a sustained parieto-occipital amplitude reduction in contrast to amplitude increases in the ADHD group. As with the medial frontal amplitude differences, these results suggest reduced CPT-X related parieto-occipital activation in the ADHD boys.

**Figure 7.5:** SSVEP amplitude time series in the CPT-X at electrode 61 (occipital, Oz)
SSVEP amplitude time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 61 (Oz). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-X related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
7.2.1.3 SSVEP Latency Dynamics in the CPT-X

Figure 7.6 illustrates the variations with time in the cross-subject averages of the SSVEP latency around the presentation of the X at a right prefrontal site, electrode 4. In control subjects there are small, brief latency reductions compared to the baseline following the disappearance of the preceding stimulus and following the presentation of the target X. Following the response, latency increases sharply in the controls. The latency for the ADHD group follows a somewhat similar pattern to that of the control group, but is more reduced compared to the baseline at the appearance of the X. Following the response however, latency decreases sharply in the ADHD group in contrast to the latency increase in controls at this time.

![SSVEP latency time series in the CPT-X at electrode 4 (right prefrontal)](image)

**Figure 7.6:** SSVEP latency time series in the CPT-X at electrode 4 (right prefrontal)

SSVEP latency time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 4 (right prefrontal). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-X related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
Figure 7.7 illustrates the latency at a midline frontal site, electrode 16 (Fz). In the control group there is little variation from the baseline in the latency in this region. In the ADHD group there is an increase in latency at the disappearance of the stimulus preceding the X, followed by a reduction in latency after the appearance of the target X. The group differences in prefrontal and frontal SSVEP latency responses are also evident in the topographic maps (Figures 7.1 and 7.2), which show more widespread latency reductions over frontal areas before target presentation in controls, but after target presentation in the ADHD boys.

**Figure 7.7: SSVEP latency time series in the CPT-X at electrode 16 (medial frontal, Fz)**

SSVEP latency time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 16 (Fz). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-X related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
Figure 7.8 illustrates the CPT-X related changes in latency at a right parietal site, electrode 57, midway between P4 and O2. As can also be seen in Figures 7.1 and 7.2, during the interval from the disappearance of the preceding stimulus through to about 500 ms after target presentation, right parietal latency is around the baseline level or slightly increased in both groups. It is only after the response is made that latency changes are evident, with a latency increase in controls and a latency decrease in the ADHD group. This is similar to the latency effects observed in the right prefrontal region in the CPT-X (Figure 7.6).

Figure 7.8: SSVEP latency time series in the CPT-X at electrode 57 (right parietal)
SSVEP latency time series in the CPT-X target interval for the control group (red) and the ADHD group (blue) at electrode 57 (midway between P4 and O2). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-X related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.1 and 7.2. The first vertical line at 3.5 s represents the point in time at which the preceding stimulus disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
7.2.1.4 Summary of CPT-X Findings

In the control group, reductions in SSVEP amplitude relative to the baseline mean, suggesting increased levels of regional cortical activation (Silberstein et al., 1990, 1995), were associated with the interval preceding and following presentation of the target X. These amplitude reductions were largest and most sustained in medial frontal and parieto-occipital regions. In the ADHD group, smaller medial frontal amplitude reductions and parieto-occipital amplitude increases were associated with this target interval, suggesting reduced activation in response to CPT-X demands in the clinical group compared to controls.

Transient reductions in right prefrontal and frontal SSVEP latency, indexing increased processing speed in these regions (Silberstein et al., 1996, 1998), were associated with the interval around the appearance of the target X in both the control and ADHD groups. However there were group differences in the timing of these latency reductions. In the control group, latency reductions were more prominent before the appearance of the X, while in the ADHD group they were more prominent after the target was presented. At parietal and occipital sites, the latency was generally at the level of the baseline or slightly increased in both groups for the interval surrounding the presentation of the X. Group differences in right parietal latency were observed only after the time of response.

7.2.2 CPT-AX Results

All 17 control subjects and 17 ADHD subjects were included in analysis of the CPT-AX results described in the following sections.

7.2.2.1 SSVEP Topography in the CPT-AX

The topographic distribution of the SSVEP amplitude and latency differences at four points in time during the A – X target sequence in the CPT-AX are illustrated in Figure 7.9 for the control group and Figure 7.10 for the ADHD group. SSVEP amplitude and latency changes during the CPT-AX are expressed as the difference from the mean amplitude and latency calculated from the average target epoch in the baseline task. As
for the CPT-X, reductions in amplitude and latency in the CPT-AX, relative to the baseline, are indicated by warmer colours. In the Hotelling’s T maps, which depict the statistical strength of the baseline – CPT-AX differences, higher T values are indicated by warmer colours and suggest greater consistency of SSVEP differences across the group. As explained in section 6.6.5, the three iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001. As for the CPT-X, as explained in section 7.2.1.1, Bonferroni correction for multiple comparisons would result in a threshold p value for statistical significance of 0.0025.

In both Figures 7.9 and 7.10, the maps in the top row represent the SSVEP amplitude difference, the SSVEP latency difference and the Hotelling’s T at the appearance of the cue A (at 1.5 s in the 10 s epoch). The maps in the second row represent the same SSVEP measures at the disappearance of the A two seconds later (at 3.5 s). The maps in the third row represent the SSVEP at the appearance of the target X (at 5 s). And the final row of maps represent the SSVEP around 500 ms after target presentation (at 5.5 s), which would be just prior to the response that occurred on average at 528 ms for controls and 587 ms for the ADHD group.

In control subjects (Figure 7.9), the appearance of the A (at 1.5 s) is associated with amplitude reductions, relative to the baseline task mean, at frontal and occipital sites. At the disappearance of the A (3.5 s) there is a diffuse amplitude reduction in the controls in most cortical regions, which is maximum in the parieto-occipital region. This parieto-occipital amplitude reduction is sustained through to the appearance of the target X (at 5 s). During this time, participants would be expected to be preparing for the possible appearance of a target, following being cued by the A. Around 500 ms after target presentation (5.5 s), there are further amplitude reductions in frontal and left temporal regions in the controls.
Figure 7.9: Topography of baseline – CPT-AX differences for the control group
(Note: The legend for Figure 7.9 appears on the following page.)
Figure 7.9 (previous page): Topography of baseline – CPT-AX differences for the control group

Topographic differences for SSVEP amplitude (normalized units) and latency (ms) between baseline mean and CPT-AX time series. Warmer colours (pink/red) indicate reduced amplitude and latency in the CPT-AX relative to the baseline, cooler colours (blue) represent increases. Hotelling’s T maps indicate the statistical strength of these differences, warmer colours indicate higher T values. Iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001. Four time points are shown. 1.5 s is the time of the appearance of the cue A. 3.5 s is the time of the disappearance of the A. 5 s is the presentation of the target X. 5.5 s is 500 ms into target presentation, just prior to response which occurred at an average of 528 ms for controls.

In ADHD subjects (Figure 7.10), small amplitude reductions in several areas coincide with the appearance of the A (1.5 s). At the disappearance of the A (3.5 s), there are small frontal and central amplitude reductions but amplitude increases in other areas, in contrast to the diffuse amplitude reductions seen in controls at this time. At the appearance of the target X (5 s), there are large amplitude increases in central, parietal and occipital regions. The largest amplitude increase in the ADHD group at target presentation is in the right parietal region where there is, in contrast, a large amplitude reduction in controls at this time. A diffuse amplitude increase is also apparent 500 ms after target presentation (at 5.5 s) in ADHD subjects. As for the CPT-X, the largest group differences in CPT-AX related SSVEP amplitude were observed in the parieto-occipital region, where there is a large and sustained amplitude reduction during the A – X interval in the control group, but only a smaller and very brief parieto-occipital amplitude reduction at the appearance of the A in the ADHD group. These findings suggest reduced activation in the ADHD boys, especially in posterior cortex, in response to a cueing stimulus.
Figure 7.10: Topography of baseline – CPT-AX differences for the ADHD group
(Note: The legend for Figure 7.10 appears on the following page.)
Figure 7.10 (previous page): Topography of baseline – CPT-AX differences for the ADHD group

Topographic differences for SSVEP amplitude (normalized units) and latency (ms) between baseline mean and CPT-AX time series. Warmer colours (pink/red) indicate reduced amplitude and latency in the CPT-AX relative to the baseline, cooler colours (blue) represent increases. Hotelling’s T maps indicate the statistical strength of these differences, warmer colours indicate higher T values. Iso-T contours represent uncorrected p values of 0.01, 0.005 and 0.001. Four time points are shown. 1.5 s is the time of the appearance of the cue A. 3.5 s is the time of the disappearance of the A. 5 s is the presentation of the target X. 5.5 s is 500 ms into target presentation, just prior to response which occurred at an average of 587 ms for the ADHD group.

In the control group (Figure 7.9), transient SSVEP latency reductions relative to the baseline task mean occurred during the A – X interval. At the appearance of the A (1.5 s), there is a large latency reduction in the right prefrontal region. As for amplitude, the largest latency reductions in control subjects occur at the disappearance of the A (3.5 s) and are evident across frontal and temporal regions. The appearance of the target X (at 5 s) is associated with right prefrontal and right parietal latency reductions. Around 500 ms after the presentation of the target X (at 5.5 s), latency reductions occur across the frontal region in controls and are maximum in prefrontal regions.

In ADHD subjects (Figure 7.10), latency increases relative to the baseline task mean predominate during the A – X interval, in contrast to the large latency reductions seen in controls. The right prefrontal latency reductions associated with the cue A (at 1.5 and 3.5 s) in controls are absent in the ADHD group, who show prefrontal latency reductions only after target presentation (at 5 and 5.5 s). Latency reductions in the right centro-parietal area are evident throughout the A – X interval in controls, but latency is increased in this region in the ADHD group. These findings suggest increased processing speed in the control group during the critical target interval, which does not occur in the ADHD boys.

The Hotelling’s T maps for control subjects (Figure 7.9) show that the most significant baseline – CPT-AX differences in the SSVEP occur at the disappearance of the A
(at 3.5 s), where T values reflect uncorrected p values of less than 0.001 at most sites. This suggests a highly consistent SSVEP effect in the control group at the time when the cue disappears, which is likely to involve processes associated with preparation for a potential target. At the appearance of the A (1.5 s), the most significant effects in controls are in the right prefrontal region where latency was reduced at this time. At the appearance of the X (5 s), the most significant area is the right parietal region where amplitude and latency reductions occur. And just prior to response (5.5 s), the amplitude and latency reductions in the medial frontal region appear to be the most significant effects.

The ADHD baseline – CPT-AX SSVEP differences (Figure 7.10) are less significant than those of controls, suggesting less consistency in the clinical group. The most significant differences occur at temporal sites throughout most of the A – X interval. There is a significant effect in the medial frontal region at the appearance of the A (1.5 s), possibly associated with the small amplitude reduction at this time. A significant effect is also evident in the right parietal region at the disappearance of the A (3.5 s), which may be associated with the large increase in latency at this time.

7.2.2.2 SSVEP Amplitude Dynamics in the CPT-AX

Figure 7.11 illustrates the group averaged SSVEP amplitude as a function of time around the presentation of targets in the CPT-AX at a midline frontal site, electrode 16 (Fz), in control subjects (red) and ADHD subjects (blue). The dashed line represents the mean value of the averaged SSVEP amplitude for the 10 s epoch centred on the appearance of the target 5 during the baseline task. This is set to zero for both populations. In controls, the SSVEP amplitude in the interval between the A and X at frontal sites is generally reduced compared to the baseline, apart from a brief amplitude increase just before the target X appears. The amplitude begins to decrease when the cue A is presented and an amplitude reduction is then sustained till after the A disappears. A further decrease then follows target presentation.
Figure 7.11: SSVEP amplitude time series in the CPT-AX at electrode 16 (medial frontal, Fz)

SSVEP amplitude time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 16 (Fz). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.

The SSVEP amplitude responses to the cue A and the target X at this medial frontal site in the ADHD group differed markedly from those of controls. In the ADHD group, a very brief amplitude reduction occurs at the appearance of the A, but this is not sustained through the 2 s presentation of the A as it is in controls. At the appearance of the target X, there is an amplitude increase in ADHD subjects, in contrast to the amplitude reduction in controls. These group differences in medial frontal SSVEP amplitude are also evident in the topographic maps (Figures 7.9 and 7.10) and suggest reduced medial frontal activation in the ADHD boys in response to both cues and targets.
Figure 7.12 illustrates the SSVEP amplitude time variations at a right parietal site, electrode 57, midway between P4 and O2. In the control group, following the appearance of the A there is a large reduction in amplitude, peaking around 500 ms before the A disappears. The amplitude then increases slightly but the reduction compared to the baseline is sustained through to the appearance of the X, where there is another decrease. In the ADHD group, right parietal amplitude is increased compared to the baseline throughout the A – X interval, in contrast to the sustained amplitude reduction in controls. There is a relative reduction in amplitude at the disappearance of the A in the ADHD group, but this is a transient effect. These right parietal SSVEP amplitude effects suggest sustained activation during the A – X interval in this region in controls, but reduced activation in the ADHD boys. Amplitude changes following target presentation also differ between the groups, with amplitude increasing in controls but decreasing in the ADHD group.

Figure 7.13 illustrates the amplitude at an occipital site, electrode 61 (Oz). In this region there is a large reduction in amplitude in the control group, sustained throughout the A – X interval and after the presentation of the target, which is maximum between the disappearance of the A and the appearance of the X. In contrast, amplitude is increased compared to the baseline in the ADHD group throughout the A – X interval. There are relative amplitude reductions at the appearance and disappearance of the A in the ADHD group, but none of the sustained effects seen in controls.
Figure 7.12: SSVEP amplitude time series in the CPT-AX at electrode 57 (right parietal)

SSVEP amplitude time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 57 (midway between P4 and O2). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
Figure 7.13: SSVEP amplitude time series in the CPT-AX at electrode 61 (occipital, Oz)
SSVEP amplitude time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 61 (Oz). The dashed horizontal line represents the mean normalized amplitude for the baseline task and is set to zero for both groups. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.

7.2.2.3 SSVEP Latency Dynamics in the CPT-AX

Figure 7.14 illustrates the SSVEP latency differences with respect to the mean latency during the baseline task at a right prefrontal site, electrode 4. In controls, the appearance of the A, the disappearance of the A and the appearance of the X coincide with transient reductions in SSVEP latency. This latency reduction is largest at the time of the disappearance of the A. The ADHD group however, show only very small latency reductions at the disappearance of the A and at the appearance of the X. Group
differences in SSVEP latency changes in this right prefrontal region appear to be most associated with the cue A.

**Figure 7.14: SSVEP latency time series in the CPT-AX at electrode 4 (right prefrontal)**

SSVEP latency time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 4 (right prefrontal). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-AX related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
Figure 7.15 illustrates the latency at a midline frontal site, electrode 16 (Fz). In the control group, prominent latency reductions compared to the baseline occur at the disappearance of the A and following the appearance of the target X. In the ADHD group, latency increases occur at these times and there is increased SSVEP latency compared to baseline at this frontal site throughout the A – X interval. Group differences in latency in the medial frontal region are evident in the response to both the A and the X and suggest increased frontal processing speed at these critical times in controls, but an absence of such effects in the ADHD boys.

**Figure 7.15:** SSVEP latency time series in the CPT-AX at electrode 16 (medial frontal, Fz) SSVEP latency time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 16 (Fz). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-AX related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
Right parietal latency effects in the CPT-AX are illustrated in Figure 7.16. At this site there are relative latency reductions in the control group during the presentation of the A and again following the appearance of the X, in contrast to latency increases in the ADHD group. Figures 7.9 and 7.10 show that this effect is even more pronounced in more anterior areas of the right parietal region, where there are large latency reductions relative to the baseline in controls but latency increases in the ADHD boys.

Figure 7.16: SSVEP latency time series in the CPT-AX at electrode 57 (right parietal)
SSVEP latency time series in the CPT-AX target interval for the control group (red) and the ADHD group (blue) at electrode 57 (midway between P4 and O2). The dashed horizontal line represents the mean latency for the baseline task and is set to zero ms for both groups. CPT-AX related latency changes are therefore expressed as differences from the baseline. The four vertical lines indicate the time points represented in the topographical maps of Figures 7.9 and 7.10. The first vertical line at 1.5 s represents the point in time at which the A is presented. The second vertical line at 3.5 s represents the point in time at which the A disappears and the screen goes blank. The third vertical line at 5 s represents the time at which the X appears.
7.2.2.4 Summary of CPT-AX Findings

In the control group, reductions in SSVEP amplitude relative to the baseline mean, suggesting increased levels of regional cortical activation (Silberstein et al., 1990, 1995), were associated with the A – X interval. These amplitude reductions in controls were most apparent in medial frontal and parieto-occipital regions. It was also in these regions where the most prominent group differences in amplitude were observed. In the ADHD group, smaller medial frontal amplitude reductions and parieto-occipital amplitude increases were associated with this interval, suggesting reduced activation in response to both the cue and target stimuli in the CPT-AX in the clinical group compared to controls.

Transient reductions in right prefrontal and medial frontal SSVEP latency, indexing increased processing speed in these regions (Silberstein et al., 1996, 1998), were associated with the A – X interval in the control group. Much smaller right prefrontal latency reductions were observed in the ADHD group, and these were associated with presentation of the target X, whereas they were larger for the cue A in controls. In the medial frontal region, latency was increased compared to baseline throughout the A – X interval and following the appearance of the target in the ADHD group. There were also group differences in the right parietal region where latency reductions occurred in controls and latency increases occurred in the ADHD group during presentation of the A and of the X.

7.3 Summary of Results

The ADHD group performed poorly in comparison to controls on the three cognitive tasks, having slower reaction times and making more errors of omission and of commission. Some of these group differences were statistically significant, including errors of commission in the CPT-X and the CPT-AX and reaction time in the CPT-X. Although performance was worse in the ADHD group, it was at a similar level to that of the control group. That is, the ADHD subjects were able to perform the tasks with a reasonable level of accuracy and with response times that were only around 10 to 15% slower than controls. The number of correct trials that were able to be included in
analyses was also very similar for both groups. Within the ADHD group, performance was more variable than in the control group, with the ADHD group having higher standard deviations on all measures of reaction time and number of errors.

In addition to group differences in behavioural measures, the electrophysiological data demonstrated group differences in SSVEP amplitude and latency changes during the CPT-X and CPT-AX. The target X in both tasks was associated with diffuse amplitude reductions, suggesting increased cortical activation, in the control group. In the ADHD group however, frontal amplitude reductions associated with target processing were much smaller, and parieto-occipital amplitude was increased compared to the baseline level, suggesting decreased activation. In addition, the cue A in the CPT-AX was associated with reductions in SSVEP amplitude and latency in the control group. Sustained parieto-occipital amplitude reductions were observed in the control group, while amplitude was increased in this region in the ADHD group. Large frontal latency reductions were observed in controls, while latency increases occurred in frontal regions in the ADHD group. The SSVEP response to both cue and target stimuli was characterized by increased regional activation and processing speed in the control group. These effects were largely absent in the ADHD group, suggesting a reduced SSVEP response to task relevant stimuli in this group.
Chapter 8 Discussion

This chapter presents a discussion of the study’s findings which were detailed in the previous chapter. The behavioural results are discussed in section 8.1 with respect to other findings for the CPT. Group differences in performance measures of reaction time and errors are interpreted in terms of cognitive theories of ADHD. The electrophysiological results are discussed in section 8.2 with respect to other research findings and neurobiological theories of ADHD. Group differences in SSVEP amplitude and latency are interpreted in terms of previous SSPT findings and related to other neuroimaging and electrophysiological findings for ADHD. The chapter concludes in section 8.3 with the major conclusions relating to this study and suggestions for future research.

8.1 Behavioural Findings

Consistent with many previous findings of poor performance on CPTs (for reviews see Corkum & Siegel, 1993; Losier et al., 1996), the ADHD group reacted to targets more slowly and made more errors than the control group in all three tasks (see section 7.1), although not all these differences were statistically significant.

8.1.1 Reaction Time

Reaction times were on average around 60-90 ms slower for the ADHD group, suggesting a slowness in processing and responding to important information (Wood et al., 1999). This result is consistent with other findings of slower CPT RT in children with ADHD (Barkley & Grodzinsky, 1994; Chee et al., 1989; Harper & Ottinger, 1992; Klorman et al., 1979; Overtoom et al., 1998; Schechter & Timmons, 1985; Strandburg et al., 1996; Wood et al., 1999). The group difference in reaction time was greatest and was only significant for the CPT-X, which suggests that this slowness is more pronounced when there is no warning or cue that a target may appear, as there is in both the baseline task and CPT-AX. As expected due to the different degrees of warning of impending target stimuli in the different tasks, mean reaction times for both groups were slowest in the CPT-X, faster in the CPT-AX and fastest in the baseline task. This
suggests that both groups took advantage of the knowledge of when targets were likely
to occur to speed their responses and is consistent with an earlier finding that ADHD
children did not benefit less than psychiatric and normal controls from the opportunity
to prepare attention (Schachar et al., 1988). In fact in this study ADHD subjects appear
to have gained greater advantage than controls from the warning stimulus in the CPT-
AX. The control group’s average reaction time was 71 ms faster in the CPT-AX
compared to the CPT-X, while the ADHD group’s was 104 ms faster.

The slower RT of ADHD subjects in the CPT-X may in part be explained by the long
inter-stimulus interval of 3.5 seconds employed in this study. Previous studies have
shown that the RT of ADHD subjects is more sensitive to increases in inter-stimulus
interval than that of controls (Van der Meere et al., 1992; Zahn et al., 1991). Van der
Meere et al. (1992) suggested that these findings reflect motor preparation problems in
ADHD. However, Chee et al. (1989) found that the RT of ADHD subjects was not
more greatly affected than that of controls by inter-stimulus interval or display time,
once time on task was controlled for. Evoked potential studies have found longer P3
latencies to CPT targets in ADHD children, suggesting slower stimulus evaluation
processes (Holcomb et al., 1985; Strandburg et al., 1996; Sunohara et al., 1997b; Taylor
et al., 1993). Klorman et al. (1991) used P3 latency as a measure of the proportion of
RT that involves stimulus evaluation prior to motor processes. Using a CPT that
required responses to both targets and non-targets, they found that RT and P3 latency
for targets were faster, while for non-targets P3 latency was faster and motor processing
time (RT – P3 latency) was longer after methylphenidate compared with placebo in
ADHD adolescents. The authors suggested that methylphenidate improves the ability to
allocate attentional capacity to stimuli and speeds stimulus evaluation processes, leading
to faster RT and reduced omission errors. So whether slower evaluation processes,
slower motor processes, or perhaps a combination of both leads to slowed RT in ADHD
remains unclear. The amplitude of the P3 to CPT targets is commonly found to be
reduced in ADHD children, suggesting underarousal and information processing
difficulties for task relevant stimuli (Klorman, 1991; Satterfield et al., 1990, 1994;
Tannock, 1998). It seems feasible that the reduced arousal and reduced efficiency of
information processing associated with ADHD might slow both evaluation and motor
processes and therefore RT. The results of the current study also suggest reduced
cortical activity in response to task relevant CPT stimuli in ADHD boys, as discussed below in section 7.2, which may explain their slower RTs.

8.1.2 Omission Errors

The ADHD group made more errors of omission than controls in all tasks, significantly so in the baseline task in which ADHD subjects on average missed 5% of targets. Increased omission errors in the baseline task might reflect lapses of concentration due to the task being very easy, having a long interval between targets requiring a response, and perhaps being too boring to sustain the attention of children with ADHD who reportedly have difficulty with mundane tasks (American Psychiatric Association, 1994; Barkley, 1997). As discussed in section 3.2.1.4, many previous studies have found increased omission errors in ADHD children compared to controls (e.g. Halperin et al., 1993a; Van Leeuwen et al., 1998), but others have found no significant difference (e.g. Wood et al., 1999). In their meta-analysis of studies, Losier et al. (1996) found that ADHD subjects on average made twice as many omission errors as controls, and that these errors were reduced by 39% by methylphenidate.

Findings of increased errors of omission in ADHD have been related to inattention and deficient arousal (Corkum & Siegel, 1993; Losier et al., 1996). In their review of CPT studies, Corkum and Siegel (1993) concluded that group differences in omission errors suggest a difference in the level of vigilance and provide evidence for a constant arousal deficit in ADHD, rather than a sustained attention deficit. Van der Meere and Sergeant (1988b) also suggest that ADHD children are not impaired in terms of maintaining attention, but are compromised in allocating effort at any given moment. So increased omission errors may result from deficient arousal, effort or motivation, rather than simple inattention. However, other researchers have found relationships between omission errors and other measures of inattention. Using a CPT-AX, the number of omission errors plus slow RT commission errors to X not preceded by A was found to be correlated with inattention scores from two different rating scales (Halperin et al., 1988). This error measure has been used as an “inattention score” in subsequent studies, while the number of fast RT commission errors to letters other than X following an A plus the number of slow RT commission errors to an A has been used as an “impulsivity score” (Halperin et al., 1990, 1993a). These measures were also used in an
ERP study of the CPT-AX, which in addition used the parietal P3 to the target X as an attentional measure and the frontal N2 to letters other than X preceded by an A as an inhibitory measure (Overtoom et al., 1998). This study found that compared to controls the inattention score was greater in ADHD children and the amplitude of their parietal P3 to targets was reduced. In contrast the ADHD group’s impulsivity score and frontal N2 to letters other than X preceded by an A did not differ from those of controls. The authors concluded that deficient processing in ADHD children in the CPT-AX was attentional in nature and not related to deficits in inhibition.

In the CPT-AX and CPT-X in this study the rates of omission errors were low for both groups, but were around three times greater for the ADHD group than the control group. These group differences were not statistically significant however, perhaps due to the low number of errors and the relatively easy nature of the tasks. Greater CPT performance differences between ADHD and control groups are generally found when the attentional demands of the task are high, i.e. for tasks using short display times and short inter-stimulus intervals (Corkum & Siegel, 1993). The number of omission errors was greater for both groups in the more demanding CPT-AX than the CPT-X, but was still relatively low.

8.1.3 Commission Errors

The ADHD group also made more errors of commission than controls in all tasks, both to non-target stimuli and to blanks between stimuli. Many other studies have also found greater commission errors in ADHD groups (e.g. Barkley & Grodzinsky, 1994; Van Leeuwen et al., 1998), while some studies have found no significant group difference (e.g. Wood et al., 1999). In a meta-analysis of studies, Losier et al. (1996) found that ADHD subjects made more than twice as many commission errors than controls, and that these errors were reduced by 29% by methylphenidate. When compared to other neuropsychological tasks, CPT commission errors have been found to distinguish ADHD subjects from normal controls better than any other measure (Barkley & Grodzinsky, 1994). Another study of the CPT found that age normalized commission errors and age normalized mean RT best discriminate ADHD (Levy & Hobbes, 1997).
Commission errors that are false responses are often reported as a measure of impulsivity (Riccio et al., 2002). Findings of increased commission errors in ADHD have often been related to deficient inhibition and increased impulsivity (Barkley, 1997; Halperin et al., 1993a; Van Leeuwen et al., 1998). However, Van der Meere (1996) has suggested that as children with ADHD are slow-inaccurate performers, impulsivity defined by fast-inaccurate performance does not explain their deficient task performance, which might be due to any combination of hasty scanning of stimuli, rapid decision making, poor planning and/or response inhibition problems. He further suggests that this slow-inaccurate performance results from a non-optimal activation state, which causes slow motor preparation and execution and perhaps slow motor inhibition. Sergeant (2000) likewise suggests that activation, reflected by tonic changes in physiological activity, is necessary for response inhibition and that inhibition deficits in ADHD may be modulated by an inability to adjust the activation state. The type of error made may also be important in the interpretation of poor CPT performance (Riccio et al., 2002). For the CPT-AX, Halperin et al. (1988) found that slow RT commission errors to X not preceded by A were associated with inattention, while fast RT errors to letters other than X following an A were associated with impulsivity and hyperactivity.

In this study, ADHD subjects made significantly more errors of commission in both the CPT-X and CPT-AX. As for omission errors, more commission errors were made by both groups in the more demanding CPT-AX than in the CPT-X. However, the number of commission errors made by both groups was very low, with many subjects making none at all. The data do not therefore allow an analysis of the average RT of errors or of subtypes of errors, in order to determine whether they were more likely to be impulsive or inattentive errors. So whether the increased commission errors in the ADHD group means that they responded more impulsively than controls, or is due to deficient inhibition, reduced activation, slow motor and/or inhibition processes, other information processing deficits, or some combination of effects, remains unclear.

The ADHD group responded during blanks between stimuli significantly more often than controls in all three tasks, suggesting that they were less able to inhibit inappropriate motor responses. While the rate of commission errors to blanks for the control group was extremely low, some ADHD subjects appeared to ‘play’ with the response buttons during the tasks, i.e. they performed the tasks correctly but pressed the
buttons between stimuli for no apparent reason. This behaviour may not be specifically related to task performance but might reflect generally hyperactive or disinhibited behaviour. One study that looked at motor and visual activity during vigilance task performance concluded that this hyperactivity may help prevent deterioration of task performance through self-stimulation (Alberts & Van der Meere, 1992). Another study found that ADHD subjects did not differ from controls in the number of impulsive errors made in a high stimulation active response condition, but did respond more impulsively in a passive response condition (Zentall & Meyer, 1987). These findings support the optimal stimulation theory of ADHD (Zentall & Zentall, 1983), and suggest the possibility that this self-stimulating behaviour might account in part for the high number of commission errors to blanks made by the ADHD group in this study.

8.1.4 Conclusions

Consistent with previous findings, the ADHD group on average showed a general performance deficit on the CPTs employed in this study. They responded more slowly, missed more targets and made more false alarms than controls in all three tasks, although not all group differences were statistically significant. As discussed, previous research suggests that this performance deficit may be due to slower and less efficient information evaluation and motor processes, resulting from inattention, deficient inhibition, reduced activation, underarousal, or some combination of deficits. Despite their poorer performance than controls, the ADHD group still performed the tasks adequately, i.e. they were able to understand the task instructions and perform the tasks correctly with relatively low error rates. Given also that only target trials for which a correct response was made were included in SSVEP event averages, the observed differences in brain electrical activity, discussed in the following section, are unlikely to be due to group differences in level of understanding or competency in basic performance of the tasks.

8.2 Electrophysiological Findings

Previous neuroimaging research reviewed in chapter 3 suggests that ADHD is associated with neurobiological deficits involving, in particular, the frontal lobes of the
brain. These findings provide evidence consistent with theories of ADHD as a disorder involving primary deficits in executive functions, especially inhibition. However, several issues including the use of small sample sizes and adult or adolescent samples and conflicting findings among many imaging studies mean that there is still much regarding the brain regions involved in ADHD that requires clarification. Although inattention is no longer seen as the core feature of ADHD, much electrophysiological research suggests possible underlying deficits in orienting and maintaining attention and attention deficits remain an important behavioural component of the disorder. This study aimed to examine differences in cortical activity in children with ADHD during attentional task performance in an effort to help clarify the nature of the relationship between functional brain differences and attentional dysfunction in ADHD. It was hypothesized that attentional task performance would be associated with increased frontal and parietal cortical activity in control subjects, consistent with previous imaging findings and attention network theories, and that frontal regions in particular would be underactive in ADHD subjects, consistent with the frontal deficits associated with this disorder.

This section discusses the electrophysiological findings of this study with respect to these hypotheses and to other research findings. Results for the CPT-X are first briefly summarized and interpreted, in section 8.2.1. The findings for the CPT-AX are then summarized in section 8.2.2. Section 8.2.3 presents a discussion of the relationship of the findings for frontal regions to other research, and section 8.2.4 discusses the posterior region findings. Section 8.2.5 discusses the relationship of the findings in specific brain regions to proposed networks of attention. Finally, the findings of group differences in phasic and sustained activation are discussed in relation to the idea of state regulation deficits in ADHD in section 8.2.6.

### 8.2.1 CPT-X Findings

For the CPT-X, SSVEP amplitude and latency changes associated with target presentation were examined. During the 2 s interval between the disappearance of the stimulus preceding a target X and 500 ms following the appearance of the X, amplitude reductions were observed in most cortical regions in the control group. These were largest and most sustained in medial frontal and parieto-occipital regions. SSVEP
amplitude reductions have previously been associated with regional cortical activation in response to increased cognitive demand (Silberstein et al., 1990, 1995). The amplitude reductions in controls in the current study suggest increased cortical activation during this important interval, which involves preparation of visual and motor processes for the possible appearance of a target, target detection, and response preparation and execution. This result suggests that activation in frontal and parietal regions is associated with performance of this vigilance task in normal boys. In contrast to the findings for controls, smaller medial frontal amplitude reductions and parieto-occipital amplitude increases occurred during this same interval in ADHD boys. This suggests reduced activation in this group compared to controls, most prominently in parieto-occipital and frontal regions, leading up to and following target presentation.

The group differences in parieto-occipital activation appear to be a sustained effect. While the time course of SSVEP amplitude changes around target presentation was similar for both groups, there was a sustained amplitude reduction compared to the baseline level in the control group but an amplitude increase compared to the baseline in the ADHD group. This suggests a sustained increase in parieto-occipital activation during the critical target interval of the CPT-X in the control group, consistent with increased visual attention during the more demanding task. The ADHD group however failed to demonstrate this effect, instead showing reduced parieto-occipital activation compared to the baseline, suggesting a diminished attentional response to increasing task demands in comparison to controls.

Group differences in medial frontal activation were of a more transient nature, with time courses varying on and after target presentation. Target presentation was associated with a further frontal amplitude reduction in the control group, perhaps related to motor response preparation and execution. By contrast, there was an amplitude increase in the ADHD group, suggesting reduced frontal activation following target presentation when a response must be made.

Group differences in SSVEP latency during the target interval in the CPT-X were also evident in the medial frontal region. In the control group, latency was reduced prior to the appearance of the X and increased on and after target appearance, although these latency changes were small. The opposite dynamic pattern was observed in the ADHD
group, who showed increased latency prior to the X and reduced latency after the X. Reductions in SSVEP latency have previously been associated with faster neural processing and increased excitatory processes (Silberstein et al., 1996, 2000). This suggests faster frontal processing in controls, leading up to stimulus presentation when frontal processes might be expected to be involved in preparation for the possible appearance of a target. This was followed by increased frontal activation, indexed by the SSVEP amplitude reduction described above, after target presentation when a response needed to be initiated. In the ADHD group however, slower frontal processes preceded target presentation, which was then followed by reduced frontal activation, indexed by an amplitude increase. This may reflect inefficient attentional processes associated with preparation leading up to stimulus presentation and with response planning and execution in the ADHD group. This suggestion is further supported by the significantly increased reaction times to targets in the CPT-X in the ADHD group in comparison with controls. Greater medial frontal latency reductions leading up to and after presentation of the target X in a CPT-AX study of normal adults were associated with faster reaction times (Silberstein et al., 1996). Slower reaction times in the CPT have also been associated with longer P3 latency in ERP studies (Riccio et al., 2002). The medial frontal SSVEP latency reduction after target presentation in the ADHD group may have occurred too late to benefit task performance.

Small right prefrontal latency reductions were observed in both groups during the target interval in the CPT-X, especially following the disappearance of the preceding stimulus and the appearance of the X. For the controls these latency reductions were restricted to the medial right prefrontal area, while they were more lateral in the ADHD group. These latency reductions suggest increased processing speed and excitation in areas of right prefrontal cortex in both groups. There was generally little change in posterior latency in either group during this interval.

These results for the CPT-X indicate group differences in cortical processes associated with attentional task performance, both in preparatory processes and in the response to a target stimulus. This may indicate that the ADHD boys were less able than controls to increase levels of cortical activation in response to task demands. Deficient preparatory processes following the disappearance of the preceding stimulus, which acts as a
warning to prepare for a possible upcoming target, and deficient allocation of attention and processing to the target in the ADHD boys are both implicated by these results.

8.2.2 CPT-AX Findings

For the CPT-AX, changes in SSVEP amplitude and latency were examined during the 4 second interval between the appearance of a cue A and 500 ms after the appearance of a target X. During this interval, SSVEP amplitude reductions were observed in the control group that were largest and most sustained in medial frontal and parieto-occipital regions, the same regions most activated in the CPT-X. Prefrontal amplitude reductions were also evident in controls during the presentation of the A. This suggests that as for the CPT-X, increased frontal and parietal activation is associated with CPT-AX performance in normal boys. In the ADHD group, however, only small prefrontal amplitude reductions occurred during the A – X interval and parieto-occipital amplitude was increased compared to the baseline, except briefly at the appearance of the A. This suggests reduced frontal and parietal activation in ADHD boys compared to controls.

The largest group difference in SSVEP amplitude was in the right parieto-occipital region, especially at the time of presentation of the target X. At this time controls demonstrated increased right posterior activation in response to the target, while in the ADHD group there was a large amplitude increase, suggesting reduced activation compared to the baseline. Also in the right parietal region, SSVEP latency was reduced compared to the baseline in controls, especially at the appearance of the X. By contrast, right parietal latency increases were observed in the ADHD group. These findings of reduced activation and slower processing in right parietal cortex in ADHD boys in response to the cue A and even more so in response to the target X suggest reduced activity in posterior attention systems in comparison to controls. As for the CPT-X, parieto-occipital activation in the control group was of a sustained nature, with reduced SSVEP amplitude compared to the baseline throughout the A – X interval.

Changes in frontal activity during the A – X interval were, as for the CPT-X, more transient than the sustained posterior activity. Latency reductions in the control group were predominant at right prefrontal sites at the appearance and disappearance of the
cue A. Much smaller prefrontal latency reductions were evident in the ADHD group and were most prominent after the appearance of the target X.

In the medial frontal region, controls displayed an amplitude reduction during the 2 s presentation of the A and another amplitude reduction following presentation of the X, suggesting increased frontal activation in response to the cue and the target. By contrast, ADHD subjects showed frontal amplitude increases at the same times. Controls also displayed large medial frontal latency reductions at the appearance of the A, disappearance of the A and appearance of the X. Much smaller frontal latency reductions were observed in the ADHD group at these times. These results suggest that increased activation and faster processing in frontal regions is associated with control boys’ response to the cue A and the target X, perhaps reflecting enhanced anterior attention system processes at crucial times in the task. The results also suggest deficits in these processes in ADHD boys.

The CPT-AX task results indicate striking group differences in the response to a priming stimulus, i.e. the cue A. The findings suggest that ADHD subjects were less able than controls to increase levels of cortical activation in response to the cue, indicating a reduced priming effect of the A. The largest effects were observed at the time of the disappearance of the A, which would act as a warning that an upcoming target may be imminent. Widespread activation and increased processing speed occurred in the control group at this time, but not in the ADHD group.

Group differences in activation were more evident in the CPT-AX than in the CPT-X. This might be due to the increased cognitive demand associated with the CPT-AX, or it may indicate an incapacity in ADHD subjects to maintain activation over the duration of the recording session, as the CPT-AX was performed last. It is also possible that both factors are involved. SSVEP latency differences were also more apparent in the CPT-AX, especially in the right prefrontal region where latency reductions were smaller and occurred later in the ADHD group compared to controls. This suggests that ADHD boys may have been unable to utilize frontal neural networks efficiently to take advantage of the priming effect of the A.
In both the CPT-X and CPT-AX, cortical activation was more variable in the ADHD group, as suggested by their lower Hotelling’s T values and smaller area of significant difference between activity in the baseline and cognitive tasks, in comparison to the control group. Their task performance was also more variable, as indicated by greater standard deviations of reaction times and number of errors in the ADHD group compared to controls. This increased variability within the ADHD group is consistent with other similar findings and with the idea that ADHD is a heterogeneous disorder.

8.2.3 Frontal Region Effects

In the current study, group differences in SSVEP amplitude and latency changes associated with processing cue and target stimuli provide evidence of reduced activation and slowed processing in frontal regions in children with ADHD. As discussed in chapter 3, frontal dysfunction is regarded as a core feature of ADHD. Frontal activation was reduced in the ADHD group compared to controls in both the CPT-X and CPT-AX, especially in the medial frontal region. In addition, frontal latency was increased in the ADHD group compared to controls, especially in the right prefrontal region in the CPT-AX. These results appear consistent with a range of previous findings and with executive function / frontal lobe deficit theories of ADHD.

Increased theta (i.e. low frequency EEG) activity in frontal regions in children with ADHD has been reported in several EEG studies (Bresnahan et al., 1999; Clarke et al., 1998, 2001b; Mann et al., 1992; Matsuura et al., 1993; Chabot & Serfontein, 1996). These findings have been interpreted as suggesting underarousal and immaturity of frontal processes in children with ADHD (Mann et al., 1992; Matsuura et al., 1993; Tannock, 1998). While the EEG is most often recorded at rest in these studies, frontal theta activity was found to be further increased in ADHD subjects during cognitive tasks (Mann et al., 1992). This suggests less frontal activation in response to information processing demands in children with ADHD, and appears consistent with the reduced frontal activation in ADHD subjects at times of preparation for and response to target stimuli in the CPT-X and CPT-AX in the current study. This increased slow EEG activity might also be related to the increased frontal latency observed in the ADHD group. Although, latency reductions were observed in the ADHD group after target presentation rather than before as in the controls. This
highlights the importance of high temporal resolution techniques, as timing of processes may be different in ADHD, rather than overall effects.

Previous ERP studies also suggest deficits in frontal activity in ADHD. The amplitude of the frontal N2 component following non-target stimuli or stop signals has been found to be smaller in children with ADHD (Johnstone & Barry, 1996; Overtoom et al., 1998; Pliszka et al., 2000). These findings have been related to problems of inhibition. Other studies have found a smaller frontal PN (i.e. smaller difference between the response to attended versus unattended stimuli) in ADHD subjects (Jonkman et al., 1997; Satterfield et al., 1988, 1990, 1994). These findings have been interpreted as suggesting poor discrimination and poor preferential processing of attended stimuli and deficits in selective attention (Klorman, 1991; Satterfield et al., 1988, 1994). Slower latencies of anterior N1 and N2 components in a choice reaction time task have also been reported (Karayanidis et al., 2000). These findings suggest reduced and slower frontal responses to inhibitory and attentional task demands in ADHD, although there have been some conflicting findings for these ERP components. The current findings of reduced frontal activation and increased frontal latency at critical times in the CPT, in children with ADHD compared to controls, are also consistent with the idea that ADHD is associated with deficient activation of frontal processes according to task demands.

Reduced frontal metabolic activity in ADHD has been suggested by brain imaging studies. In a PET study of ADHD adults, reduced glucose metabolism during an auditory CPT was found in premotor, superior prefrontal and left anterior frontal regions (Zametkin et al., 1990). However, later PET studies revealed conflicting findings and age and gender effects on metabolic differences (Ernst et al., 1994a, 1997a, 1998b; Zametkin et al., 1993). SPECT studies have revealed reduced cerebral blood flow in ADHD subjects in frontal regions including left frontal cortex (Sieg et al., 1995; Spalletta et al., 2001), right frontal cortex (Gustafsson et al., 2000), frontal white matter (Lou et al., 1984), and prefrontal cortex (Amen & Carmichael, 1997). While the precise nature of frontal metabolic differences in ADHD differs, these findings may also be consistent with the finding of reduced frontal activation in the current study.

Reduced activity in medial frontal and anterior cingulate cortex has been found in ADHD adults and adolescents in fMRI studies, suggesting deficits in attentional
regulation of response selection and motor output (Bush et al., 1999; Rubia et al., 1999). Bush et al. (1999) found reduced anterior cingulate activation in adults with ADHD during the interference condition in a counting Stroop task, but not during a neutral condition. Rubia et al. (1999) found reduced right medial frontal lobe activation during inhibitory tasks in adolescents with ADHD. Both authors suggested that dysfunction in medial frontal regions and their connections with fronto-striatal networks may be involved in the inattention and disinhibition that characterize ADHD. Comparison of these results with those of the current study are problematic given the differing cognitive tasks and methods used, and the older age of subject groups. However, medial frontal differences in activity between ADHD and control groups were prominent in both the CPT-X and CPT-AX in the current study. Together these findings may suggest deficits in ADHD in executive control of information processing and motor preparation mediated by this region.

The anatomical size of frontal brain regions in children with ADHD has been examined using MRI. In some studies, anterior regions of the corpus callosum (rostrum, rostral body or genu) were found to be significantly smaller in ADHD subjects compared with normal controls (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991). Frontal white matter volume has also been found to be smaller in ADHD (Filipek et al., 1997; Semrud-Clikeman et al., 2000). ADHD subjects have consistently been found to have a significantly smaller right frontal cortex than normal controls (Castellanos et al., 1996b; Filipek et al., 1997; Hynd et al., 1990; Pueyo et al., 2000). These findings provide further evidence of frontal deficits in ADHD.

Frontal lobe deficits in ADHD are also suggested by poor performance on neuropsychological tasks known to involve the frontal lobes. Imaging and lesion studies have shown prefrontal lobe involvement in tasks such as the WCST (Arnett et al., 1994; Berman et al., 1995; Silberstein et al., 1995), the TOL (Goel & Grafman, 1995; Morris et al., 1993) and the Stroop (Bench et al., 1993; Pardo et al., 1990; Vendrell et al., 1995). Poorer performance on these tasks has been found in ADHD subjects, suggesting deficits in executive functions mediated by the prefrontal cortex, including working memory, inhibition and use of feedback (Aman et al., 1998; Boucugnani & Jones, 1989; Chelune et al., 1986; Shue & Douglas, 1992). While executive function deficits are not specific to ADHD (Sergeant et al., 2002), they
provide strong evidence that frontal deficits are associated with the disorder. Deficits in the higher order or executive components of CPT performance might therefore be associated with the differences in frontal activity between ADHD and control groups in this study.

Other SSPT studies have examined the brain activity associated with CPT-AX performance in normal adults and schizophrenics. The finding of increased frontal activation in control boys at critical points in the CPT in the current study is consistent with the frontal amplitude and latency reductions at the appearances of the A and X found in normal adults (Silberstein et al., 1996). This study also found that faster RTs were associated with greater frontal latency reductions, suggesting that more efficient processing within frontal neural networks was associated with improved task performance (Silberstein et al., 1996). In a subsequent study, prefrontal latency reductions following the appearances of the A and X were found for controls, but not for schizophrenics (Silberstein et al., 2000). In addition, frontal latency following the appearance of the target X was correlated with MRT in both groups, further suggesting increased frontal activation is associated with improved performance. The results are also consistent with a proposed hypofrontality in schizophrenia (Silberstein et al., 2000) and highlight the fact that frontal deficits are not specific to any one disorder. Taken together with these findings, the lack of frontal latency reductions in ADHD boys in the current study, during preparatory intervals when latency reductions were prominent in controls, suggests slower and less efficient frontal neural network processes in this group.

Electrophysiological, imaging and lesion studies also suggest frontal involvement in normal performance of the CPT. Increased errors and slower reaction times have been found for patients with frontal lesions (Rueckert & Grafman, 1996). In normal adults, CPT performance was found to be associated with increased frontal beta activity, suggesting increased alertness and attentiveness (Valentino et al., 1993). CPT performance has been associated with increased frontal metabolic rate in normal adults in several PET studies (Buchsbaum et al., 1990; Cohen et al., 1988; Hazlett et al., 1993; Mansour et al., 1996; Rezai et al., 1993). Using MRI, Sax et al. (1999) found that CPT performance was correlated with prefrontal cortex volume in bipolar patients. These
findings further suggest that the reduced frontal activation in ADHD boys in this study reflects frontal deficits associated with CPT performance.

Other research findings relate specifically to the right frontal region, where differences in SSVEP latency were most prominent in the current study. ADHD subjects have consistently been found to have a significantly smaller right frontal cortex than normal controls in MRI studies (Castellanos et al., 1996b; Filipek et al., 1997; Hynd et al., 1990; Pueyo et al., 2000). These findings have been interpreted as suggestive of right prefrontal deficits in ADHD (Castellanos et al., 1996b; Hynd et al., 1990). Using SPECT, Gustafsson et al. (2000) found that low blood flow in frontal and parietal regions, especially the right frontal lobe, was correlated with higher parent ADHD rating scale scores. In an ERP study, Oades et al. (1996) found that frontal MMN was left lateralized in children with ADHD but right lateralized in normal controls, which in conjunction with a similar finding for P3 laterality was interpreted as suggesting right hemisphere impairment in ADHD.

Some imaging studies have found a relationship between the right frontal region and inhibition deficits in ADHD. Casey et al. (1997a) found that task performance on response inhibition tasks was significantly correlated with anatomical measures of fronto-striatal circuitry found to be abnormal in children with ADHD, including right prefrontal cortex. This finding suggests the involvement of right fronto-striatal circuitry in response inhibition and in ADHD (Casey et al., 1997a). An fMRI study found reduced right prefrontal activation in ADHD adolescents compared to controls during tasks requiring inhibition and delay management, but not during a simple sensorimotor task, confirming the relationship between frontal dysfunction and inhibition deficits (Rubia et al., 2001). Using the stop task, Pliszka et al. (2000) found that the N2 to stop signals recorded over the right inferior frontal cortex was reduced in ADHD children compared to controls and that N2 amplitude was correlated with inhibition task performance. They also found that a right frontal slow positive wave to go stimuli was reduced in ADHD subjects on trials when they subsequently failed to inhibit a response. They related these findings to right frontal deficits associated with poor inhibitory control. The reduced right frontal SSVEP effects in ADHD boys in this study suggest that attentional processing is also associated with right frontal dysfunction in ADHD.
The Stroop task has been shown to depend on right frontal lobe activity in lesion and PET studies (Bench et al., 1993; Pardo et al., 1990; Vendrell et al., 1995). Deficient performance on this task has been found in ADHD subjects and this has been interpreted as evidence of right prefrontal dysfunction in ADHD (Barkley, 1997; Boucugnani & Jones, 1989; Carter et al., 1995a; Gorenstein et al., 1989; Grodzinsky & Diamond, 1992).

While some of these imaging and neuropsychological findings do not relate specifically to the findings for the CPT in the current study, they do suggest right prefrontal deficits in ADHD, consistent with the current findings. Right frontal activity has been associated with the CPT in non-ADHD studies. In a study comparing the effects of left and right frontal lesions on CPT performance, patients with right frontal lesions were found to have slower reaction times, make more omission errors and have a greater vigilance decrement than those with left frontal lesions or controls (Rueckert & Grafman, 1996). Rightward asymmetry of frontal activation during CPT performance has also been found using fMRI (Hager et al., 1998) and PET (Buchsbaum et al., 1990; Benedict et al., 1998). The involvement of right frontal cortex in control boys in the CPT in this study seems consistent with these findings, and reduced activity in this region in ADHD boys suggests deficits in these right frontal processes.

8.2.4 Posterior Region Effects

In addition to differences in frontal activity in the current study, group differences in SSVEP amplitude and latency changes were also observed in parieto-occipital regions. Parieto-occipital activation was reduced in the ADHD group compared to controls in both the CPT-X and CPT-AX, and parietal latency was increased in the ADHD group compared to controls. The largest group differences were observed in the right parietal region. Parietal effects in ADHD have not been nearly so extensively studied as frontal effects, but there are some other findings suggesting parietal deficits consistent with the findings of this study.

The amplitude of the P3 component of the ERP, which is maximal over parietal cortex, is often reported to be smaller in ADHD groups (e.g. Jonkman et al., 1997; Kemner et al., 1996; Novak et al., 1995; Overtoom et al., 1998; Strandburg et al., 1996; Van der
In the CPT-AX, reduced parietal P3 amplitude to targets (Michael et al., 1981; Overtoom et al., 1998) and to cues (Brandeis et al., 2002; Van Leeuwen et al., 1998) has been found. Posterior beta (fast EEG) activity has also been shown to be reduced in children with ADHD (e.g. Clarke et al., 1998; Mann et al., 1992). These findings of reduced parietal electrophysiological activity have been interpreted as representing cortical underarousal and information processing difficulties in ADHD related to attention deficits. Studies examining ERP microstates have also found reduced power in P3 microstates in posterior regions, suggesting less efficient orienting and possible involvement of the posterior attention system in ADHD (Brandeis et al., 1998, 2002; Van Leeuwen et al., 1998). Findings of reduced P3 amplitude suggest reduced responsiveness and allocation of attention to task relevant stimuli. The findings of the current study are consistent with this, but in addition suggest deficient preparatory processes before stimuli are presented as the intervals leading up to target presentation in both the CPT-X and CPT-AX were associated with reduced parieto-occipital activation in the ADHD group. In fact this group difference was sustained throughout the intervals investigated.

Imaging studies have generally focused on fronto-striatal regions and few differences in parietal activation have been reported. Using SPECT, Sieg et al. (1995) found greater hemispheric I-123 IMP uptake asymmetry in ADHD subjects, with reduced blood flow in left parietal and also left frontal regions, in comparison to psychiatric controls. In another SPECT study, low blood flow in parietal and frontal regions, but especially the right frontal lobe, was correlated with higher parent ADHD rating scale scores (Gustafsson et al., 2000). Some MRI studies have found posterior regions of the corpus callosum (splenium or isthmus) to be significantly smaller in ADHD groups and have related this finding to parietal deficits involving visuo-spatial and attention problems that can be associated with ADHD (Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). Parieto-occipital white matter volume was also found to be reduced in ADHD (Filipek et al., 1997), which may be noteworthy given the reciprocal connections between prefrontal and posterior parietal cortex (Himelstein et al., 2000).

Deficits in right parietal lobe function in ADHD have been shown in a few neuropsychological studies. On tasks such as letter cancellation and mental rotation, children with ADHD demonstrate deficits similar to those seen in patients with right
parietal lesions (Aman et al., 1998; Snow, 1990; Voeller & Heilman, 1988). These neuropsychological and neuroimaging studies of ADHD provide only minimal evidence for parietal deficits in ADHD, which has probably contributed to the focus that is generally given to the role of frontal deficits in the disorder.

In normal adults, CPT performance has been shown to involve the right parietal region. Decreased parietal alpha and theta (i.e. slow EEG) activity was found during CPT performance (Valentino et al., 1993). Parietal activation during the CPT is also seen in ERP studies with normal adults, with the prominent component being the P3 to target stimuli, which is maximal at parietal sites (Roberts et al., 1994; Schupp et al., 1994). Parietal P3 latency has also been found to be correlated with reaction time (Wagner et al., 1989). In the current study, parietal latency effects were small in the CPT-X, but large latency reductions occurred in controls in the CPT-AX in the right anterior parietal region that were not observed in the ADHD group.

PET studies of activation associated with CPT performance suggest that involvement of parietal areas may depend on sensory modality. Increased glucose metabolism in right frontal and right temporo-parietal regions was found to be associated with visual CPT performance in healthy controls, and was reduced in both regions in schizophrenics (Buchsbaum et al., 1990). However, only an anterior attention network involving the cingulate and medial frontal lobe was activated during an auditory CPT (Benedict et al., 1998). Parietal effects in the current study might therefore be associated with visual attention processes, and deficits in these processes in ADHD.

Other SSPT studies suggest parietal involvement in CPT-AX and vigilance tasks. In normal adults during a visual vigilance task, centro-parietal amplitude reductions occurred during anticipation of the target and parieto-occipital amplitude reductions occurred at the presentation of the target. This parietal activation was greatest on the right (Silberstein et al, 1990). During the CPT-AX, prefrontal and parietal latency reductions followed the appearances of the A and X in controls, but not in schizophrenics (Silberstein et al., 2000). This suggests that, as for frontal effects, parietal attentional deficits may not be specific to ADHD.
Reduced occipital activation in the ADHD group was also found in the current study, perhaps consistent with a recent report of reduced power in a P3 microstate at occipital sites associated with a choice reaction time task (Steger et al., 2000). These authors suggested that this is consistent with previous findings of reduced P3 amplitude suggesting reduced resource allocation to targets in ADHD. In a PET study of normal adults, a correlation between occipital lobe metabolic rate and visual CPT performance was found (Buchsbaum et al., 1992). Occipital SSVEP amplitude reductions were also found to occur at the presentation of the target during a visual vigilance task (Silberstein et al, 1990). These findings suggest a role for occipital cortex in visual attention. Visual attention deficits may therefore be associated with the reduced parieto-occipital activation in ADHD boys in the current study.

8.2.5 Networks of Attention

Posner and Raichle (1996) have localized three different aspects of attention to specific networks of interconnected brain regions. The ‘executive control’ network involves areas of medial frontal cortex, including the anterior cingulate and the supplementary motor area, and basal ganglia regions, especially the caudate. This network is involved in the control of goal directed behaviour, inhibition of automatic responses and target detection. It is also involved with control of working memory via connections with the prefrontal cortex, control of visual orienting via connections with the posterior parietal cortex, and control of processing of visual features via connections with the occipital cortex. The ‘alerting’ network involves right frontal and right parietal cortical regions. This network is involved in establishing and maintaining an alert or vigilant state and readiness to act. It works to maintain attention to input information and involves noradrenaline activity and connections from the locus coeruleus. The ‘orienting’ network involves posterior parietal cortex and occulo-motor areas. This network is involved in covert orienting to sensory, particularly visual, stimuli and serves to select and enhance relevant visual input.

Attention is thought to involve complex interactions between these functional systems, which work together to regulate attentional processes, via interconnections between the brain regions involved. The orienting network selects and enhances relevant information, which is then transmitted to anterior regions. The executive control
network uses this information to coordinate detection and processing of targets and response selection, while exerting control over the orienting network via connections between medial frontal and posterior parietal cortex. And the vigilance network influences activity in the orienting and executive networks in order to maintain alertness to relevant input information (Posner & Raichle, 1996).

Swanson et al. (1998a) have suggested that the DSM-IV ADHD symptoms of inattention can each be related to activity in these three networks. Symptoms of sustained attention are said to be related to deficits in the alerting network, symptoms of selective attention are related to deficits in the orienting network, and symptoms of memory organization are related to executive network deficits. Swanson et al. (1998a) further suggest that CPTs link symptoms of sustained attention to activity in the alerting network, visuo-spatial tasks link symptoms of selective attention to the orienting network, and conflict tasks involving inhibition of automatic responses link symptoms of impulsivity to the executive network. The relationship of the findings of the current study to these networks of attention is discussed below.

8.2.5.1 Executive Control Network

As discussed in sections 8.2.1 and 8.2.2, activation in medial frontal cortex was observed in controls and was reduced in ADHD boys in the current study. This could be related to involvement of the executive attention network in CPT performance in controls and deficits in these processes in ADHD children. Greater medial frontal amplitude reductions were observed in controls than in the ADHD group. In the CPT-X, differences were apparent at the disappearance of the preceding stimulus and for around 1 s after appearance of the target X. In the CPT-AX, amplitude differences were associated with the 2 s presentation of the cue A and again for around 1 s after appearance of the target X. As the executive network is involved in detection and recognition of a stimulus and its’ task relevance (Posner & Raichle, 1996), increased medial frontal activation at these times of cue and target processing in controls seems consistent with activation of executive attention. In addition, the supplementary motor area would be expected to be activated at target presentation in preparation for a motor response, and the post-target amplitude reductions in controls may be related to this. Reduced medial frontal activation at these times in the ADHD group suggests deficits in
processes of executive attention and motor preparation. In addition, a large medial frontal latency reduction was observed in controls at the disappearance of the A, but increased latency was observed at this time in the ADHD group. Recognition of this event as a cue to a potentially imminent target would be expected to activate the executive attention system, and these latency differences therefore provide further evidence of reduced activation of this system in ADHD boys.

Of the three networks of attention described above, the executive network involving fronto-striatal systems is the one most often suggested to be associated with deficits in ADHD. Barkley (1997) suggests that symptoms of inattention in ADHD can be explained by a primary deficit in inhibition and executive functions, related to frontal lobe deficits. Poor sustained attention may represent impaired goal-directed persistence that is a result of poor inhibition and its effects on self-regulation. And distractibility may arise from poor interference control that allows irrelevant internal or external events to disrupt self-control and task persistence. Inattention is then seen as a consequence of impaired behavioural inhibition and interference control and the resulting deficits in the self-regulation or executive control of behaviour. Sustained attention or task persistence can be affected by external task factors such as novelty, immediacy and reinforcement, or by internally generated regulation of motivation and goal-directed behaviour. It is the latter, self-regulated form of sustained attention that is most likely to be deficient in children with ADHD as they show greater deficits in tasks or settings that demand goal-directed responses in the absence of any immediate reinforcement (Barkley, 1997; Van der Meere; 1996). The CPT used in the current study would fall into this category of task, and reduced frontal activation in the ADHD boys seems consistent with an executive function deficit.

8.2.5.2 Alerting Network

Group differences in the right prefrontal region were also observed in this study, especially for SSVEP latency in the CPT-AX. In the CPT-X, right prefrontal amplitude and latency were slightly reduced in both groups. In the CPT-AX, there was again little change in amplitude, but much larger right frontal latency reductions occurred in controls than in the ADHD group, especially at the appearance and disappearance of the A. This region is thought to be involved in a vigilance network responsible for
maintaining alertness (Posner & Raichle, 1996). Increased alertness associated with these cueing events in the CPT-AX might therefore be associated with the latency reductions in controls. The lack of these effects in the ADHD group suggests deficits in this alerting process.

The right parietal region is also implicated in the alerting network and group differences in SSVEP latency in the CPT-AX were observed here also. Right parietal latency was reduced during the A – X interval in controls but increased in ADHD boys. These latency effects were most apparent in the anterior right parietal region and coincided with right frontal latency reductions in controls, suggesting they are possibly related to activity in the alerting network. Increased excitation in right frontal and right parietal regions associated with the appearance and disappearance of the cue may help to establish and maintain alertness in anticipation of a potential target. The absence of this effect in ADHD boys suggests they may fail to take advantage of the cue in the same way as controls.

The prefrontal cortex is of course involved in many cognitive functions in addition to attention. The dorso-lateral prefrontal cortex (DLPFC) for example has been shown to be involved in holding cognitive goals in working memory and allocating attention to appropriate processing systems to meet these goals (Luks et al., 2002). The right prefrontal latency reductions in controls associated with the cue in the current study may be related to increased right DLPFC activity. This region has strong connections to medial frontal and parietal cortex, both also found to be active during CPT performance in control boys.

Swanson and Castellanos (1998), among others, propose that neuroimaging findings in ADHD suggest abnormalities in neural networks affecting input/output processing and attention. These models of ADHD concentrate on fronto-striatal dopaminergic system abnormalities. They include only perhaps a minor role for the right parietal cortex, described as being important for tasks of sustained attention or vigilance along with the right frontal cortex (Pardo et al., 1991; Posner & Raichle, 1996). Pardo et al. (1991) localized a system for sustained attention using PET, finding regional increases in blood flow in the prefrontal and superior parietal cortex, primarily in the right hemisphere, regardless of the modality or laterality of sensory input. As already pointed out, this
activity has been related to the alerting network of attention (Posner & Raichle, 1996). Pardo et al. (1991) related this neural system activated during vigilance tasks to the ‘on-line’ analysis of the stimuli for relevant target properties. They pointed out that work on the monkey (Fuster 1989; Goldman-Rakic, 1987) has identified somatosensory and visual cortical fields in these regions specialized for attentive analysis of sensory features. In the CPT-AX, these processes may be involved in the maintenance of activation in the A – X interval, allowing a working retention of the parameters necessary for correct task performance.

Further evidence for this frontal – parietal network playing a role in this working memory type process of on-line retention comes from a study by LaBar et al. (1999), which demonstrated an overlap of neuroanatomical networks involved in spatial attention and in working memory. A verbal working memory task and a covert spatial attention task were administered to the same subjects in an fMRI study. Frontal and parietal sites were active in both tasks, which the authors suggest share common cognitive features related to dynamic shifting of attentional resources. Levy and Farrow (2001) recently reviewed the roles of anterior and posterior attention systems and reciprocal frontal – parietal networks in ADHD and concluded that these are important for working memory and the ability to maintain representations of important stimuli and of appropriate behavioural responses. In the CPT-AX, continuous on-line monitoring of the most recently presented letter and of the response requirements of the task is required and therefore may involve these fronto-parietal circuits.

Frontal – parietal networks may therefore be involved in a range of cognitive processes, including maintaining vigilance, maintaining on-line representation of task goals, and dynamic shifting of attentional resources. Of course, these could all be seen as different conceptualizations of the one process, i.e. controlling attentional processing to meet task demands. However this is defined, the current study provides evidence that a right prefrontal – right parietal network is activated, particularly in response to salient cueing events, in the CPT in control boys, and suggests deficits in this process in ADHD boys. This finding is consistent with cognitive and behavioural deficits in ADHD involving problems with maintaining and adjusting attention appropriate to task demands and required responses. It may also be consistent with the idea of working memory deficits in ADHD (Barkley, 1997; Levy & Farrow, 2001). Working memory plays a pivotal
role in the organization of behaviour to generate and maintain representations of input stimuli, and to access and maintain representations of appropriate behavioural responses. Deficits in working memory might lead to the disorganized behaviour, distractibility, stimulation seeking, and frequent rapid shifts in activity that are seen in ADHD (Levy & Farrow, 2001).

8.2.5.3 Orienting Network

SSVEP amplitude effects were observed in the right parietal region in this study. These were more posterior than the latency effects discussed above, suggesting they may be more likely to involve the orienting network, as the alerting network discussed above is thought to involve more anterior areas of right parietal cortex (Posner & Raichle, 1996). In the CPT-X, a sustained right parietal amplitude reduction was observed from the disappearance of the preceding stimulus through to around 1 s after the appearance of the target X. In the ADHD group, right parietal amplitude was increased in the same interval, especially after target appearance. In the CPT-AX, a similar effect was observed, with reduced amplitude throughout the A – X interval in controls and increased right parietal amplitude in the ADHD group. These findings might suggest deficits in orienting to both cues and targets in the ADHD boys. Control boys may maintain activation in this network in order to direct and enhance attention to important stimuli, while ADHD boys are unable to do so.

Evidence for differences in orienting responses in ADHD is also suggested by other findings of altered ERP responses to cues in the CPT-AX. Van Leeuwen et al. (1998) found reduced parieto-occipital P3 global field power to cues in ADHD children in an ERP microstate study. As posterior sources were identified for this ERP component, they related this finding to impaired orienting to cues involving the posterior attention system, which is modulated by noradrenergic projections from the locus coeruleus and is known to be involved in orienting and vigilance. Brandeis et al (2002) more recently found a larger frontal N1 and smaller parietal P3 following the cue in the CPT-AX in ADHD children in a multicentre study. They suggested that ADHD children attend to cues with increased initial orienting followed by insufficient resource allocation. The cue P3 amplitude was correlated with speed and accuracy of response to the subsequent
target, suggesting the P3 represents a measure of attentional orienting to potential
targets in a critical but behaviourally silent period of the task (Brandeis et al., 2002).

Posterior sources were again found for the P3 and were reduced in ADHD subjects,
suggesting insufficient phasic activation of the posterior attention system in this group
(Brandeis et al., 2002). While reduced sustained parieto-occipital activation was
observed in the ADHD group in this study, phasic effects were also evident following
the cue in the CPT-AX. In this region, SSVEP amplitude in the control group began to
decrease around 300 to 500 ms after the appearance of the A and this increased
activation was then sustained until the appearance of the X some 3 s later. However, in
the ADHD group, SSVEP amplitude increased following the appearance of the A,
suggesting decreased parieto-occipital activation at this time. This finding appears
consistent with that of Brandeis et al. (2002) that ADHD children fail to allocate
sufficient attentional resources in orienting to the cue.

Given that frontal dysfunction is more often associated with ADHD than parietal
deficits, Brandeis et al. (2002) also speculated about the relationships between frontal
and posterior and tonic and phasic deficits in ADHD. They suggested that sustained
frontal regulation deficits might mediate deficient phasic posterior activation, or phasic
frontal hypoactivation might be associated with preparatory processes following the P3.
The relationship of the current findings of reduced tonic and phasic activation in ADHD
boys to deficits in activation and arousal are discussed below in section 8.2.6.

8.2.5.4 Conclusions for Attention Networks

The findings of the current study suggest possible involvement of the executive, alerting
and orienting attention networks in the CPT performance of control boys. While
activation potentially associated with the executive control and orienting networks was
observed in controls in both the CPT-X and CPT-AX, activation of the alerting network
regions of right frontal and right parietal cortex were most associated with the cue A in
the CPT-AX. The absence of these activations in the ADHD boys suggests deficits in a
range of attentional processes in this group’s CPT performance. As previously
discussed in sections 8.2.3 and 8.2.4, other ADHD research has produced findings
consistent with deficits in these brain regions. ERP findings suggest abnormalities in
parietal regions and the orienting network. SPECT, PET and fMRI findings implicate dysfunction in frontal regions and the alerting and executive control networks. And structural MRI findings suggest structural abnormalities in the basal ganglia and frontal lobes, again implicating the alerting and executive attention networks. The use of SSPT in the current study has allowed investigation of dynamic patterns of activity in these networks and the findings suggest a role for both tonic and phasic effects in the reduced activity seen in the ADHD boys. It may be that dynamic interactions between networks and processes of attention are deficient in ADHD, rather than there being a simple inactivation of a particular brain region or network.

8.2.6 Tonic/Phasic Effects and State Regulation

Sergeant (2000) and Van der Meere (1996) have suggested that ADHD is characterized by deficits in the regulation of activation, leading to slow and inaccurate responding on attentional and inhibitory tasks. The poor CPT performance and the lack of sustained activation in regions involved in anterior and posterior attention systems observed in the ADHD group in this study appear consistent with this conceptualization of ADHD. In addition, reduced phasic changes in cortical activity were observed in the ADHD group, which may be more related to deficits in arousal, as explained below.

According to the information processing models of Sanders (1983) and others, short-term processing operations that mediate between a stimulus and the appropriate response are modulated by variations in the states of activation, arousal and effort. As reviewed in chapter 3, research suggesting that basic information processing operations such as orienting and encoding are intact in children with ADHD suggests that their inefficient task performance and behavioural symptoms may be related to deficits in the regulation of these states (Sergeant, 2000; Van der Meere, 1996). Activation is associated with tonic changes in physiological activity and a behavioural tonic readiness to respond, while arousal is related to phasic responses time locked to stimulus processing (Pribram & McGuiness, 1975; Sanders, 1983). Activation is also associated with fronto-striatal dopaminergic systems and control of motor readiness, while arousal is related to noradrenergic systems and alerting (Tucker & Williamson, 1984). These states are in turn modulated by effort, which has been defined as the energy required to meet task demands, and evaluation, which involves monitoring task performance and
making appropriate adjustments to effort, activation and arousal (Sanders, 1983). As deficits are more likely to be found in ADHD children in output or motor stages of task processing rather than earlier information processing stages, it has been concluded that deficits in the regulation of activation and effort are responsible for this motor dysfunction (Van der Meere, 1996).

For the CPT and similar tasks, arousal is thought to be most affected by a fast event rate and high demand on working memory, while activation is most affected by a slow event rate and few working memory demands (Van der Meere & Sergeant, 1988b). Children with ADHD are generally found to perform more poorly in conditions of a slow event rate (Chee et al., 1989; Scheres et al., 2001; Van der Meere et al., 1992, 1995b), suggesting that their slow and inaccurate performance on these tasks is associated with problems in adjusting their state of activation (Scheres et al., 2001; Sergeant, 2000; Van der Meere, 1996).

For the control group in the current study, tonic increases in frontal activation in the CPT-X and CPT-AX compared to the baseline were evident from the SSVEP amplitude reductions which were sustained for 1 to 2 s following cue and target presentation in the medial frontal region. In the ADHD group however, much smaller frontal amplitude reductions were evident at the same times. The absence of tonic increases in cortical activity in the CPT suggests reduced activation in response to task demands in the ADHD group. This difference occurred in regions discussed above as being involved in the executive control network of attention. As activation is associated with tonic responses and control of motor readiness, reduced sustained activity in the medial frontal region in ADHD boys seems consistent with a non-optimal activation state associated with deficits in executive control of task performance.

Reduced phasic changes in activity at critical times in the CPT were also observed in the ADHD group, especially in the CPT-AX in regions discussed above as being involved in the alerting network of attention, particularly the right frontal region. While the control group demonstrated phasic SSVEP latency reductions, that were time locked to the appearance and disappearance of the cue A and the appearance of the target X, the ADHD group demonstrated much smaller latency reductions or latency increases at these times. As arousal is associated with phasic responses to stimuli and alerting, this
lack of phasic increases in right frontal excitatory processes suggests reduced arousal in the ADHD group.

The tonic and phasic changes in activity associated with CPT performance in controls are unlikely to be independent, given the strong interconnections between parietal, lateral frontal and medial frontal cortical regions (Goldman-Rakic, 1988). These anatomical connections are thought to be associated with complex interactions between the different networks of attention (Posner & Petersen, 1990; Posner & Raichle, 1996). In control boys, phasic responses to critical task events, especially the presentation of a cue, were observed in regions associated with the alerting network. These might act to maintain activation in connected regions of the executive control network, creating a tonic readiness to respond to expected targets, and also in the orienting network, in order to enhance visual attention to the target location. Alternatively, activation in the executive network may influence the working memory type processes associated with the alerting network, previously discussed in section 8.2.5.2, in order to reinforce task goals in response to important events. Both these interactions, and probably others, between the observed tonic and phasic activity are potentially important for efficient task performance. Given these interactions, it also seems unlikely that the reduced tonic and reduced phasic effects in ADHD boys would be independent. Perhaps reduced activation and reduced arousal in connected brain regions feedback on each other contributing to the range of deficits in attentional performance associated with ADHD.

While, based on previous research, deficits in the regulation of activation are thought to be predominant in ADHD (Sergeant, 2000; Van der Meere, 1996), deficits in arousal are suggested by the results of some ERP studies. Early negative ERP components, the N1 and N2, are thought to be related to early information processes of orienting and encoding. They are larger in response to attended than non-attended stimuli (processing negativity, PN) and to target than non-target stimuli (mismatch negativity, MMN). These information processing operations are modulated by arousal according to the Sanders (1983) model. Some studies have found reduced amplitude of these early negative ERP components in children with ADHD (e.g. Jonkman et al., 1997; Satterfield et al., 1988, 1994), suggesting selective attention and arousal deficits (Klorman, 1991; Van der Meere, 1996). However, other studies have not found differences in ADHD (Holcomb et al., 1985; Taylor et al., 1993; Winsberg et al., 1997).
Rothenberger et al. (2000) found that only their ADHD group with comorbid CD showed a significantly reduced MMN, suggesting a greater deficit in automatic information processing in these children than in those with ADHD only. Similarly, Overtoom et al. (1998) found that N2 amplitude to non-targets was reduced in children with ADHD and comorbid ODD, but not those with ADHD only. These authors suggested that the fronto-central N2 to non-targets was related to inhibitory processes and that deficiencies in these processes or increased impulsivity might be greater in the comorbid group. As described in chapter 5, comorbidity with ODD and CD were high among the ADHD group in this study. The previous findings just described could suggest that this comorbidity may in part explain the deficits in arousal suggested by reduced phasic SSVEP changes in response to task relevant stimuli. However, Banachewski et al. (2003) recently found that the P3 to the cue in the CPT-AX, related to attentional orienting, was attenuated in ADHD only and CD/ODD only groups but not in a comorbid group. The relationship of comorbidity to these effects therefore remains unclear.

As discussed earlier in section 8.2.5.3, deficits in attentional orienting mechanisms in ADHD are also suggested by reduced posterior P3 effects following the cue in the CPT-AX (Brandeis et al., 2002; Van Leeuwen et al., 1998) and by reduced activation of posterior cortex in the current study. Whether these deficits are due to deficient orienting mechanisms per se, or to deficits in the modulation of these mechanisms by arousal, is not possible to determine from the electrophysiological data. The neuropsychological findings of intact orienting mechanisms in ADHD (Van der Meere, 1996) suggest the involvement of arousal, consistent with the idea of state regulation deficits in ADHD. The lack of arousal in the ADHD group, associated with reduced phasic activity in the alerting network, might therefore have influenced the lack of tonic activation in the orienting network. This would be consistent with the known interconnections between these regions (Posner & Petersen, 1990; Posner & Raichle, 1996) and might play a role in the deficits in visual attention performance commonly observed in ADHD.

In conclusion, both activation and arousal deficits in ADHD are suggested by the findings of this study. Sustained effects in the medial frontal region in both the CPT-X
and CPT-AX suggest deficits in activation related to fronto-striatal dopaminergic systems and deficient executive control and motor preparation. Phasic effects in right frontal and right parietal regions in the CPT-AX suggest deficits in arousal in response to a cue related to noradrenergic systems and alerting. Sustained effects in the parieto-occipital region might then be related to deficits in visual attention and orienting as a result of influences on this system from reduced activation and arousal in connected attention networks.

8.3 Conclusions, Limitations and Future Directions

This study used SSPT to investigate regions of cortical activity associated with attentional dysfunction in ADHD. SSVEP effects associated with attentional processing were examined at times of heightened attention during the CPT in boys with ADHD and normal controls. Specifically, SSVEP amplitude and latency changes associated with cue and target processing in the CPT-X and CPT-AX were evaluated. It was hypothesized that reduced activation, indexed by reduced changes in SSVEP amplitude and latency, would be observed in frontal and parietal regions in children with ADHD compared to controls, in line with previous neuroimaging and electrophysiological findings.

For the CPT-X, it was hypothesized that SSVEP changes in these regions, associated with increased vigilance and motor preparation in response to the target, would be reduced in ADHD children. The interval leading up to and following the appearance of the target X in the CPT-X was found to be associated with reduced activation in the ADHD group. In frontal regions, smaller amplitude reductions occurred in ADHD boys than controls, especially after target presentation, suggesting reduced activation related to executive attention processes and motor preparation. In parieto-occipital regions, sustained activation was observed in controls during this interval, but activation was reduced compared to the baseline in the ADHD group, suggesting deficits in visual attention processes perhaps related to orienting and alerting.

For the CPT-AX, it was hypothesized that processing of both the cue A and the target X would be associated with reduced frontal and parietal activation in ADHD children, and
that this would be most evident in the interval between the A and the X when attentional processes would be expected to be maximally enhanced in anticipation of a potential target requiring a response. Reduced activation in response to the cue and target were found in the ADHD group compared to controls. The A – X interval was associated with sustained reductions in amplitude in controls in medial frontal and parieto-occipital regions, but predominantly amplitude increases in the ADHD boys, suggesting reduced sustained activation in executive attention and orienting networks. In addition, phasic SSVEP latency reductions time locked to the appearance and disappearance of the cue A and the appearance of the target X were observed in controls in right prefrontal and right parietal regions associated with an alerting network. SSVEP latency reductions were in contrast much smaller or absent in the ADHD group, suggesting deficits also in this aspect of attention.

The order and timing of tasks are important factors in the interpretation of these results. All CPT related SSVEP changes were referenced to the low demand baseline task undertaken first by all subjects. When undertaking the CPT-X around 5 minutes later and the CPT-AX some 10 minutes later, the findings suggest that control subjects were able to increase levels of activation and arousal to meet increasing task demands. The ADHD subjects, however, failed to show these increases and often demonstrated a decrease compared to the baseline. Whether this is a consequence of an inability to increase activation and arousal for the more demanding tasks, or an inability to sustain attention or motivation over time cannot be determined, although it is conceivable that both factors may have played a role in the observed ADHD deficits.

A limitation of the current study is the lack of a direct statistical comparison of SSVEP effects between the two groups. Statistics were only examined for the baseline – CPT differences within groups. Software to enable statistical tests between groups for SSVEP measures is currently in development, but unfortunately was not available for this study. While the group differences in brain activation reported here appear sizeable and consistent across two different tasks, it is not possible to say whether they are statistically significant. However, preliminary results for the CPT-AX with smaller subject groups demonstrated the same group differences in frontal and parietal SSVEP amplitude during the A – X interval (Farrow et al., 1996). In a separate analysis of the data presented here that was conducted for publication (Silberstein et al., 1998), we
examined SSVEP effects in the CPT-AX with respect to the mean SSVEP amplitude and latency in the CPT-X rather than the baseline task, at the suggestion of a reviewer. Once again, the group differences in SSVEP amplitude and latency during the A – X interval described here remained, even when using a different reference task. So despite the lack of a direct statistical test, the findings of reduced task-related activation in ADHD boys seem robust.

Another possible limitation in the interpretation of the current findings is the high degree of variability of SSVEP responses in the ADHD group. The Hotelling’s T maps examining the statistical strength of the baseline – CPT differences in the two groups suggest that generally the task related effects observed in controls were consistent across the group, however this was not the case for the ADHD group. Increased variability of task performance is also commonly found in ADHD groups, but this raises the question of whether the observed deficits in the ADHD group are applicable to all ADHD children.

A related issue is that of the high degree of comorbidity with the other behavioural disorders and learning problems in the ADHD group. High rates of comorbidity with ODD and CD and with learning difficulties are common in clinical samples of children with ADHD, but relatively little is known about the effects of comorbidity on the type and severity of cognitive deficits found in ADHD. Given the small sample size and the high rates of comorbidity in this study (only two subjects had pure ADHD without oppositional, conduct or learning problems), it was not possible to subdivide the ADHD group into those with and without comorbid problems. Hence it is impossible to say to what extent the electrophysiological and behavioural findings may have been affected by comorbidity issues, and whether the findings can be extended to children with ADHD without comorbidity. In a study that involved some of the participants of this study, CPT performance was found not to be affected by comorbidity when comorbid and pure ADHD groups were compared (Wood et al., 1999).

To have excluded ADHD subjects with comorbid symptoms from this study would have resulted in a biased sample not representative of children clinically diagnosed with ADHD. However, determining the specificity of research findings to ADHD may benefit from future studies restricting subjects to a refined phenotype of ADHD, as
suggested by Swanson et al. (1998b), involving children only with ADHD – combined type and no comorbid problems. Future SSPT studies examining differences in brain activity between comorbid and pure ADHD groups might also help to resolve how comorbidity affects function and dysfunction in ADHD.

As already stated, when we examined SSVEP effects in the CPT-AX using the CPT-X as the reference task, the group differences described here remained (Silberstein et al., 1998). In this publication we addressed the issue of the significant difference in IQ between the control and ADHD groups, by assessing SSVEP effects in IQ matched subgroups. Group differences in SSVEP amplitude and latency were evaluated for the total groups and for the IQ matched subgroups. These were found to be highly correlated at all electrode sites, with mean correlation coefficients of 0.86 for amplitude differences and 0.88 for latency differences (Silberstein et al., 1998, p. 1108). The group differences in CPT related activation in this study are therefore not thought to be related to the lower IQ of the ADHD group.

Reduced activity in brain regions associated with functional networks of attention was observed in ADHD boys. Some of these effects were sustained through critical task intervals, while others were more phasic. While it has been speculated here that these effects are unlikely to be independent, it would be interesting to examine in future research the degree of correlation between them. Coherence analysis, which allows measurement of the correlation of activity recorded at pairs of electrodes, could be employed to investigate the relationships between activity in the separate brain regions associated with attention networks. Similar analysis techniques could potentially be developed to examine the relationship between activity of varying temporal structure, i.e. tonic or phasic. Further investigation in this way of the findings reported here might provide improved knowledge about how these relationships differ in ADHD.

Despite some limitations, the findings of this study are thought to be consistent with neuropsychological findings suggesting cognitive deficits in tasks known to involve frontal and parietal cortical regions, with neuroimaging findings of dysfunction and structural abnormalities in fronto-striatal regions, with electrophysiological findings of slower EEG activity and reduced ERP responses in frontal and parietal regions, and with neurochemical hypotheses of dopaminergic and noradrenergic system dysfunction.
in ADHD. The findings also support the association of ADHD with dysfunction in networks of attention (Swanson et al., 1998a) and deficits in state regulation (Sergeant, 2000; Van der Meere, 1996).

Attention and the control it exerts on task performance is a multifaceted process, involving allocation of attention toward the processing of task-relevant stimuli and responses in order to meet the goals of the task. It also involves self-monitoring mechanisms to determine whether behavioural goals are met, or whether additional efforts are required. These processes are thought to be mediated by attention networks involving the frontal lobes, parietal lobes, basal ganglia and thalamic nuclei. Attentional control also overlaps with working memory and the maintenance of an active representation of information and task requirements. The deficits in activation and arousal of attention networks observed in ADHD boys in this study therefore suggests they may have problems in a wide range of cognitive processes.

The SSPT technique appears to offer a useful measure of brain activity which is complementary to PET, fMRI and ERP measures. In particular, the combination of high temporal resolution and the capacity to study time extended task components such as cue – target intervals offers the opportunity of examining the dynamics of brain activity associated with cognitive tasks. This has been shown in the current study to be especially useful in the investigation of the neurophysiological mechanisms underpinning attentional dysfunction in ADHD. Investigations of the effects of methylphenidate on SSVEP deficits in ADHD children, and of SSVEP changes related to inhibitory dysfunction in the stop task are currently being undertaken by our group. It is hoped that, along with the study reported here, these will shed further light on the neurobiology of ADHD.
NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the Swinburne Library.
References


Daly, G., Hawi, Z., Fitzgerald, M. & Gill M. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Molecular Psychiatry, 1999, 4: 2192-2196.


Nigg, J., Swanson, J.M. & Hinshaw, S. Covert visual spatial attention in boys with ADHD. Neuropsychologia, 1997, 35: 165-176.


Papanicolaou, A.C., Deutsch, G., Bourbon, W.T., Will, K.W., Loring, D.W. & Eisenberg H.M. Convergent evoked potential and cerebral blood flow evidence of task-


NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the Swinburne Library.
Appendix One

Parent and Teacher Questionnaires
COVER SHEET FOR PARENTS

Family ID:_____________________________________________________

Name:________________________________________________________

Address:_______________________________________________________

___________________________________________________________

Telephone number:____________________________________________

Child’s name:_________________________________________________

Date of birth:__________________________________________________

Age:___________________________________________________________

Grade/year at school:___________________________________________

If any of the above details are incorrect, please write in the appropriate information.
The questionnaire is asking for information about your first born twin. Where possible, the questionnaire should be completed by the twins’ mother. If this is not possible, please have someone complete the questionnaire who knows all the children in your family well.

Where possible we have provided the name and date of birth of this child below. This information was added by you when you completed our initial survey. If the child’s name or date of birth is incorrect or space is blank, could you please write the appropriate information.

First name:  2
Date of Birth  3

Please indicate the person completing this form. (Mother if possible)

☐ Mother
☐ Father
☐ Other (please specify the relationship e.g. elder sister)

Today’s Date: __/__/__

BEHAVIOUR QUESTIONS

Below are descriptions of children’s behaviour or the problems that they sometimes have. Please circle how applicable you think each item is for this child now or within the time period specified (e.g. months) when compared to other children of the same age.

Circle the 0 if the item does not apply to your child at all. Circle the 1 if the item applies just a little or sometimes. Circle the 2 if the item applies pretty much or often. Circle the 3 if the item applies very often.

Not at all 1 = Just a little/Sometimes 2 = Pretty much/Often 3 = Very much/Very often

Compared to other children of the same age, how applicable are the following items (1 to 41) for this child or within the past six months?

Please circle the appropriate response.

Is easily distracted by external stimuli (e.g. noise or conversation).

Has trouble following through on instructions and fails to finish school work, chores or duties.

Has difficulty keeping attention on work or games.

Does not seem to listen

a. to what is said to him/her.

b. when spoken to directly.

Loses things necessary for tasks or activities at home or school (e.g. pencils, toys or tools).

Breaks things necessary for tasks or activities at home or school (e.g. toys or tools).
<table>
<thead>
<tr>
<th>Item</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has difficulty organising tasks and activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shifts from one uncompleted activity to another.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fails to give close attention to details in schoolwork, work or other activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makes careless mistakes in schoolwork, work or other activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is &quot;on the go&quot; or acts as if &quot;driven by a motor&quot;.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acts before thinking.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaves seat in classroom or other situations in which remaining seated is expected.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is absent minded.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulty awaiting his/her turn.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurs out answers to questions before they have been completed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulty playing or engaging in leisure activities quietly.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has trouble focussing attention on tasks or play activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Runs about or climbs excessively in situations where it is inappropriate.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is lazy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engages in physically dangerous activities without considering consequences (e.g. running onto street without looking).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fidgets with hands or feet or squirms in seat.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is underactive, slow moving or lacks energy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interrupts or intrudes on others (e.g. butts into conversations or games).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shows a lack of persistence.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talks excessively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stares into space and daydreams.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is forgetful in daily activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appears to be low in energy, sluggish, or drowsy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is confused or lost in thought.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is &quot;vague&quot; or internally preoccupied.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoids, dislikes or is reluctant to engage in tasks that require prolonged concentration (e.g. schoolwork or homework).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appears to be apathetic, or unmotivated to engage in goal directed activities (e.g. schoolwork or chores).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is motivated to engage in passive activities or things he/she enjoys doing (e.g., watching television or listening to music).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Please circle the appropriate response.*
Fails to sustain attention in tasks or play activities.
0 1 2 3
Is poorly coordinated or clumsy.
0 1 2 3
Talks excessively in situations where it is socially inappropriate.
0 1 2 3
Gets tired too much (other than because of illness).
0 1 2 3

To what extent is the child’s behaviour, as described by items 4 to 41, distressing or disruptive:

a. at home?
0 1 2 3
b. at school?
0 1 2 3
c. elsewhere?
0 1 2 3

For the above questions (4 to 41) circled “1”: how old was the child when you first noticed any one of these behaviours?

For the above questions (4 to 41) circled “2 or 3”: how old was the child when you first noticed any one of these behaviours?

pared to other children of the same age, how applicable are the following items (45 to 57) for this now or within the past six months? Please circle the appropriate response.

Cries a lot.
0 1 2 3
Appears unhappy, sad or depressed.
0 1 2 3
Feels too guilty.
0 1 2 3
Does not feel like eating; his/her appetite is poor.
0 1 2 3
Argues with you, teachers and other adults.
0 1 2 3
Loses his/her temper or throws tantrums when he/she does not get his/her own way?
0 1 2 3
Actively defies or refuses to comply with adults’ requests or rules.
0 1 2 3
Deliberately annoys people.
0 1 2 3
Blames others for his/her own mistakes or misbehaviour.
0 1 2 3
Is touchy or easily annoyed by others.
0 1 2 3
Is angry and resentful.
0 1 2 3
Is spiteful or vindictive.
0 1 2 3
Swears or uses obscene language.
0 1 2 3

pared to other children of the same age, how applicable are the following items (58 to 74) for this now or within the past 12 months? Please circle the appropriate response.

Lies or makes up stories to get out of trouble.
0 1 2 3
Lies or breaks promises to obtain goods or favours, or to avoid obligations (e.g. ‘cons’ others).
0 1 2 3
Has stolen:

a. items of nontrivial value without confronting a victim (e.g. shoplifting but without breaking and entering; forgery)?

b. with confrontation of a victim (e.g. mugging, purse-snatching, extortion)?

Has been physically cruel to animals.

Has deliberately lit fires with the intention of causing serious damage.

Has been suspended from school?

Has been absent from school without permission.

Initiates physical fights.

Has run away from the parental home overnight at least twice (or once without returning for a lengthy period).

Has broken into someone else’s house, building or car.

Has deliberately destroyed other people’s property (not by lighting fires).

Has forced someone into sexual activity.

Has used a weapon that can cause serious physical harm to others (e.g. bat, brick, broken bottle, knife or gun).

Has been physically cruel to people.

Stays out at night against parental instruction.

Bullies, threatens or intimidates others.

Has used alcohol or other drugs.

For the above questions (58 to 74) circled "1":

a. did any of the behaviour described occur in the past 6 months? (Tick if yes)

b. How old was the child when you first noticed any one of these behaviours?

For the above questions (58 to 74) circled "2 or 3":

a. did any of the behaviour described occur in the past 6 months? (Tick if yes)

b. How old was the child when you first noticed any of these behaviours?

Compared to other children of the same age, how applicable are the following items (77 to 88) for this child now or within the past four weeks? Please circle the appropriate response.

Shows excessive distress when away from home or family members.

Shows excessive distress when anticipating being away from home or family members.
Refuses or is reluctant to go to preschool or school:
- because of fear of separation. 0 1 2 3
- in order to stay at home. 0 1 2 3

Does this child:
- need a parent or other close person nearby to fall asleep? 0 1 2 3
- persistently refuse to sleep away from home? 0 1 2 3
- frequently get up during the night to check on, or sleep near, a parent or family member? 0 1 2 3

Worries about something bad happening to his/her parents or other family members. 0 1 2 3
Worries about death or dying. 0 1 2 3
Worries that something bad will separate him/her from his/her parents (e.g. getting lost or kidnapped). 0 1 2 3

Follows you around from room to room to avoid being alone. 0 1 2 3
Is scared or reluctant to be alone at home or elsewhere without significant adults. 0 1 2 3

Complains of headaches, stomach aches, nausea or vomiting:
- on school days. 0 1 2 3
- when separated from parents or family members. 0 1 2 3
- when anticipating separation from parents. 0 1 2 3

Has recurrent bad dreams or nightmares about separation from the family. 0 1 2 3
Distressed when away from home (e.g. wants to return home or telephone parents). 0 1 2 3

For the above questions (77 to 88) circled “1”: how old was the child when you first noticed any one of these behaviours? [ ]

For the above questions (77 to 88) circled “2 or 3”: how old was the child when you first noticed any one of these behaviours? [ ]

Compared to other children of the same age, how applicable are the following items (91 to 111) for this child now or within the past six months? Please circle the appropriate response.

This child:
- shows excessive anxiety and worry about events or activities (e.g school or work performance). 0 1 2 3
- finds it difficult to control his/her excessive worry about events/activities. 0 1 2 3

The excessive anxiety and worry is associated with the following complaints.
- restlessness, feeling "keyed up", or "on edge". 0 1 2 3
- easily fatigued. 0 1 2 3
c. difficulty concentrating or mind "going blank".
  0 1 2 3

d. irritability.
  0 1 2 3

e. muscle tension.
  0 1 2 3

f. sleep disturbance.
  0 1 2 3

The excessive worry, anxiety or complaints cause significant distress or problems in everyday life (e.g. school or social).
  0 1 2 3

Is afraid of being embarrassed or humiliated when in group or performance situations with unfamiliar people (peers and adults).
  0 1 2 3

Gets on well with children and adults that he/she knows well.
  0 1 2 3

Cries, panics, gets upset or tense in situations where there are unfamiliar people (children or adults).
  0 1 2 3

Realises that his/her fears of unfamiliar situations are unreasonable.
  0 1 2 3

Avoids feared situations that make him/her distressed or becomes very upset if forced to stay.
  0 1 2 3

The distress associated with the feared (social or performance) situations interferes significantly with this child’s everyday life.
  0 1 2 3

Starts fights with peers.
  0 1 2 3

 Strikes back when teased.
  0 1 2 3

 Teases and name calls.
  0 1 2 3

 Breaks rules in games.
  0 1 2 3

 Gets others to gang up on a peer.
  0 1 2 3

 Gets into verbal arguments.
  0 1 2 3

 Blames others in fights.
  0 1 2 3

 Uses physical force to dominate.
  0 1 2 3

 Over-reacts angrily to accidents.
  0 1 2 3

 Is quick to fight when frustrated.
  0 1 2 3

 Responds negatively when fails.
  0 1 2 3

 Threatens and bullies others.
  0 1 2 3

If you feel one or more of your children has a behavioural problem, to what extent is this:

 a. distressing at home?
   0 1 2 3

 b. distressing at school?
   0 1 2 3
Have you sought professional help for any behaviour problems? (tick for yes)

If yes, from whom:

Please state the person's profession
(e.g. psychiatrist, psychologist, school counsellor.) ________________________________

Has this child ever had (tick for yes): Is this child still having (tick for yes):

Remedial reading: [ ] 117. Remedial reading: [ ]
Speech therapy: [ ] 118. Speech therapy: [ ]

If your child is not having any remedial assistance, do you think he/she should have had (tick for yes):

Remedial reading: [ ] 119. Remedial reading: [ ]
Speech therapy: [ ] 120. Speech therapy: [ ]

MEDICATION QUESTIONS

Has this child ever been on any medication for hyperactivity or attention / learning problems? (Tick the box if yes.) [ ]

If yes, what was the name of the medication?

Ritalin (methylphenidate) [ ]
Dexamphetamine [ ]
Clonidine [ ]
other please specify ________________________________ [ ]

At what age did this child begin taking this medication?

a. Age (years / months): [  /  ]
b. For how long? (years / months): [  /  ]

Is this child currently on any medication for hyperactivity or attention problems? (Tick the box if yes.) [ ]

If yes, what is the name of the medication?

Ritalin (methylphenidate) [ ]
Dexamphetamine [ ]
Clonidine [ ]
other please specify ________________________________ [ ]
Questions 1 to 24 are missing as this form is a part of a larger questionnaire.

Name: __________________________ Year at School: ____________

**BEHAVIOUR QUESTIONS**

Below are descriptions of children’s behaviour or the problems that they sometimes have. Please decide how applicable you think each item is for this child now or within the past 6 months, compared to other children of his/her age group. Circle the 0 if the item does not apply to your child at all. Circle the 1 if the item applies just a little. Circle the 2 if the item applies pretty much. Circle the 3 if the item applies very much.

Not at all. 1 = Just a little / sometimes. 2 = Pretty much / often. 3 = Very much / very often.

*circle the appropriate response.*

- Is easily distracted by external stimuli (e.g., noise or conversation).
  - 0
  - 1
  - 2
  - 3

- Has trouble following through on instructions without close supervision (e.g., fails to finish school work, chores or duties).
  - 0
  - 1
  - 2
  - 3

- Has difficulty keeping attention on tasks or play activities.
  - 0
  - 1
  - 2
  - 3

Does not seem to listen

- a. to what is said to him/her.
  - 0
  - 1
  - 2
  - 3

- b. when spoken to directly.
  - 0
  - 1
  - 2
  - 3

- Loses things necessary for tasks or activities at home or school (e.g., pencils, toys or tools).
  - 0
  - 1
  - 2
  - 3

- Breaks things necessary for tasks or activities at home or school (e.g., toys or tools).
  - 0
  - 1
  - 2
  - 3

- Has difficulty organising tasks and activities.
  - 0
  - 1
  - 2
  - 3

- Shifts from one uncompleted activity to another.
  - 0
  - 1
  - 2
  - 3

- Is "on the go" or acts as if "driven by a motor".
  - 0
  - 1
  - 2
  - 3

- Fails to give close attention to detail in schoolwork, work or home tasks.
  - 0
  - 1
  - 2
  - 3

- Makes careless mistakes in schoolwork, work or other activities.
  - 0
  - 1
  - 2
  - 3

- Acts before thinking.
  - 0
  - 1
  - 2
  - 3

- Leaves seat in classroom or other situations in which remaining seated is expected.
  - 0
  - 1
  - 2
  - 3

- Has difficulty awaiting his/her turn.
  - 0
  - 1
  - 2
  - 3

- Blurs out answers to questions before they have been completed.
  - 0
  - 1
  - 2
  - 3
FAMILY INFORMATION

151. Child’s grade/year level at school: [ ]

152. Nowadays family structure is often more complex (e.g. blended families). If the children in your family are not from the same biological parents, could you please describe your family structure. This information will be kept completely confidential. 

The following questions refer to the mother and father of the child.

Mother | Father

153. Name: ____________________________

154. Date of birth: ______________________

155. Mother’s current occupation: ____________________________

156. Father’s current occupation: ____________________________

For the following code:

1 Primary 2 High school 3 High school 4 Apprentice/ 5 Diploma 6 University 7 University
0 - 7 yrs 8 - 10 yrs 11 - 12 yrs technical degree postgrad

157. Please write the number corresponding to mother’s highest level of education: [ ]

158. Please write the number corresponding to father’s highest level of education: [ ]

Thank you for your time and assistance with this study.
COVER SHEET FOR TEACHERS

Family ID : ____________________________________________

Child's name : _________________________________________

Date of birth : _________________________________________

Age : _________________________________________________

Grade/year at school : __________________________________

Person completing form : ________________________________
<table>
<thead>
<tr>
<th>Behavior</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has difficulty playing quietly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Runs about or climbs excessively in situations where it is inappropriate.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Engages in physically dangerous activities without considering consequences (e.g., running onto street without looking).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fidgets with hands or feet or squirms in seat.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Interrupts or intrudes on others (e.g., butts into conversations or games).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Talks excessively.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stares into space and daydreams.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Is forgetful in daily activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Appears to be low in energy, sluggish, or drowsy.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Is confused or lost in thought.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Is &quot;spacey&quot; or internally preoccupied.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Avoids, dislikes or is reluctant to engage in tasks that require prolonged concentration (e.g., schoolwork or homework).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Appears to be apathetic, or unmotivated to engage in goal directed activities (e.g., schoolwork or chores).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Motivated to engage in passive activities or things he/she enjoys doing (e.g., watching television or listening to music).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fails to sustain attention in tasks or play activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Talks excessively in situations where it is socially inappropriate.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>To what extent is the child’s behaviour, as described by the above items, distressing or disruptive:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. at home:</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b. at school:</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c. elsewhere:</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
The twin Registry is involved in several international studies including ones on asthma and on factors associated with cleft lip (also called harelip) and palate in twins. Your responses to the following questions would greatly assist us with this work.

Check the appropriate box if the answer is yes to any of these questions. Please answer these questions if you have previously reported these conditions to the Australian Twin Registry.

Check the appropriate box if yes.

Which of your twins have:

- Cleft lip (harelip)?
- Cleft palate?
- Has a doctor ever diagnosed asthma in this child?
- Has a doctor ever diagnosed asthma in mother?
- Has a doctor ever diagnosed asthma in father?

Some people experience repeated movements in the form of jerks, jumps or spasms called motor tics. Common motor tics may be exaggerated eye-blinking, twitching of the face, nods of the head, jerks of the shoulder. Tics may affect any part of the body and to some degree are not in the person’s control.

- Has this child ever experienced any motor tics? (Tick if yes)
- At what age in years did these symptoms begin?

Some people are known to produce sounds or to say things in response to an urge, despite their wishes not to do so. This may take the form of repeated throat clearing, sniffing or grunting in the absence of a cold or other irritation, a single or a few words uttered repeatedly through the day. We call these behaviors vocal tics.

- Has this child ever had vocal tics as described above? (Tick if yes)
- At what age in years did these vocal tics begin?
Appendix Two

Task Instructions
ADHD PROTOCOL TASK INSTRUCTIONS

Explain baseline task:

"The first task is a number game. You will see the numbers 1, 2, 3, 4 and 5 come up on the screen one at a time. And they come up in the right order, first 1, then 2, then 3, and so on. When it gets to 5, it starts at 1 again and keeps going. What you have to do is keep looking straight ahead at the screen and wait until you see a 5 appear on the screen. Each time you see the 5, I want you to press the buttons. You don't have to do it fast, so just wait till you see the 5 and then press the buttons so that I will know that you've seen it. You can have a short practice first."

Ask child if he has any questions about task.
Present practice sequence, make sure child understands instructions and performs task correctly.

"Now you can do the proper task. It goes for a few minutes. Remember to keep looking straight ahead, sit still and don't talk until it's finished."

Run BASELINE task.

Explain CPT-X:

"The second task is a letter game. You will see letters of the alphabet come up on the screen one at a time. They are not in order though, they are all jumbled up. What you have to do is keep looking straight ahead at the screen and wait until you see an 'X' appear. Each time you see an 'X', I want you to press the buttons quickly, as soon as you see the 'X'. Don't press the buttons for any other letters. Don't worry if you make a mistake though, just keep going. You can have a short practice first."

Ask child if he has any questions about task.
Present practice sequence, make sure child understands instructions and performs task correctly.

"Now you can do the proper task. This one goes for a few minutes too. Remember to keep looking straight ahead, sit still and don't talk until it's finished."

Run CPT-X.

Explain CPT-AX:

"This is another letter game, very similar to the last one. The difference is that this time you have to press the buttons when you see an 'X', only if the 'X' comes after an 'A'. If the 'X' comes after a different letter than 'A', don't press the buttons. And if a different letter than 'X' comes after an 'A', don't press the buttons. Only press when you see an 'X' that comes straight after an 'A', and try to press the buttons quickly, as soon as you see the 'X'. Don't worry if you make a mistake, just keep going. You can have a practice first."

Ask child if he has any questions about task.
Present practice sequence, make sure child understands instructions and performs task correctly.

"Now you can do the proper task. This one goes for a few minutes too. Remember to keep looking straight ahead, sit still and don't talk until it's finished."

Run CPT-AX.
Publications by the author

Journal Articles


Published Abstracts


**Conference Presentations**


Carter JD, Farrow M, Silberstein RB, Tucker A, Stough C & Pipingas A. The stop-signal task: a comparison of auditory and visual stop-signals set proportional to mean
reaction time. Presented at the 10th World Congress of the International Organisation of Psychophysiology, 8-13 February, 2000, Sydney, Australia.


