Changes in Brain Electrical Activity of Boys with ADHD Following Neurotherapy

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a pervasive developmental disorder reported to affect between 2-20% of children. The disorder is characterised by inappropriate levels of inattentiveness, impulsivity, and hyperactivity. Genetic and electrophysiological studies have suggested dysfunction in dopamine-mediated frontal and norepinephrine-mediated parietal attentional systems. The mainstream treatment for ADHD has been stimulant medication, which blocks the reuptake of Dopamine. Stimulants have short-term benefits for around 60% of children with ADHD, however, long-term benefits have not been demonstrated, and adverse side effects are often intolerable.

Since the 1970s, Neurotherapy (EEG-Biofeedback) has shown promise as a safe treatment for children with ADHD. Several recent controlled studies have compared Neurotherapy with stimulant medication, and found Neurotherapy to be as effective as stimulants in redressing symptoms in around 70%-80% of children with ADHD, without adverse side effects.

The purpose of this thesis was to investigate changes in the brain electrical activity of seventeen boys with ADHD aged 7 - 15 years (mean 10.35), before, and after Neurotherapy Treatment. The dependent variables were pre- and post-Neurotherapy changes in: (a) Steady-state Visually Evoked Potentials (SSVEP), while performing the CPT-AX version of the continuous performance task; (b) behavioural measures of attention, derived from analysis of key-presses during the CPT-AX task; (c) parent and teacher reports of DSM-IV ADHD symptoms, as assessed by the Australian Twin Behaviour Rating Scale (ATBRS); and (d) performance on a Continuous Performance Task, the Test of Variables of Attention (TOVA).

Following Neurotherapy, changes in the amplitude and latency of the steady-state visually evoked potential (SSVEP) indicated that the functioning of medial frontal, right pre-frontal, and right parietal regions significantly improved, suggesting increased
activation and speed of neural processing. These changes in brain electrical activity were associated with normalisation of TOVA scores and DSM-IV ADHD symptoms.

This research is the first to demonstrate that Neurotherapy resulted in the dynamic neuromodulation of the dopamine-mediated frontal and norepinephrine-mediated parietal components of the attentional system, as proposed by Tucker and Williamson’s (1984) model of the attentional system. It provides further support to the recent controlled studies and metaanalysis that suggest that Neurotherapy is an effective and efficacious treatment for ADHD. Given that, treatment effects are expected to be permanent and devoid of adverse side effects, Neurotherapy should be considered as the primary treatment for ADHD. Further research should focus on how to improve Neurotherapy protocols and service delivery for ADHD and other brain based disorders.
Acknowledgements

I thank my wife Carmen for her faith in me and her support over the years while I juggled studies, a busy clinical practice, and family life. I also thank my family who has encouraged me to finish the writing of this thesis.

I thank my supervisor, Professor Richard Silberstein, for his ongoing encouragement and for sharing his knowledge and experience with me. I am grateful to Dr. Maree Farrow PhD, who initially set up the methodology for this research, modeled on the methodology used of her own studies at the Brain Sciences Institute. I also thank Dr. Geoff Nield PhD, of the Brain Sciences Institute for his assistance in processing the SSVEP data.

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Finally, I would like to thank the families and the children who participated in this research. Without them, there would have been no study and no thesis.

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Dr. Sigfried Othmer, (EEG-Info) for the donation of a Procomp+ with Biograph software
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 and acknowledgment is made.

Jacques Duff

November 2009
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<tbody>
<tr>
<td>ABA</td>
<td>Applied Behaviour Analysis</td>
</tr>
<tr>
<td>ACCcd</td>
<td>Anterior Cingulate Cortex Cognitive Division</td>
</tr>
<tr>
<td>ADD</td>
<td>Attention Deficit Disorder</td>
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<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>
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<tr>
<td>ATBRS</td>
<td>Australian Twin Behaviour Rating Scale</td>
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<tr>
<td>BA</td>
<td>Brodmann area</td>
</tr>
<tr>
<td>BASC</td>
<td>Behaviour Assessment System for Children</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>Centimeter</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COVAT</td>
<td>Covert orienting of visuospatial 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>Computed 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 pre-frontal cortex</td>
</tr>
<tr>
<td>D2</td>
<td>Dopamine - 2 receptor</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>DSM-IV 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>[18F]flouro-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>GABA</td>
<td>Gamma amino butyric acid</td>
</tr>
<tr>
<td>GFP</td>
<td>Global field power</td>
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<tr>
<td>HVA</td>
<td>Homovanillic acid</td>
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<tr>
<td>Hz</td>
<td>Hz</td>
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<tr>
<td>IBI</td>
<td>Intensive Behaviour Intervention</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<tr>
<td>I.Q.</td>
<td>Intelligence quotient</td>
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<tr>
<td>IVA</td>
<td>Integrated Visual and Auditory Continuous Performance Test</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>KO</td>
<td>Knocked out</td>
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<tr>
<td>LD</td>
<td>Learning disability or Learning Difficulties</td>
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<tr>
<td>LED</td>
<td>Light emitting diode</td>
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<tr>
<td>LVF</td>
<td>Left visual field</td>
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<tr>
<td>m</td>
<td>Metre</td>
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<tr>
<td>MFFT</td>
<td>Matching Familiar Figures test</td>
</tr>
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<td>MHPG</td>
<td>3-methoxy-4-hydroxyphenylglycol</td>
</tr>
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<td>MMN</td>
<td>Mismatch negativity</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MRT</td>
<td>Mean reaction-time</td>
</tr>
<tr>
<td>ms</td>
<td>Millisecond</td>
</tr>
<tr>
<td>MTA</td>
<td>Multimodal treatment study of children with attention deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National health and medical research council</td>
</tr>
<tr>
<td>nRt</td>
<td>Nucleus Reticularis Thalami (nRt)</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive Compulsive Disorder</td>
</tr>
<tr>
<td>ODD</td>
<td>Oppositional Defiant Disorder</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PN</td>
<td>Processing negativity</td>
</tr>
<tr>
<td>RQ</td>
<td>Reading quotient</td>
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<tr>
<td>RT</td>
<td>reaction-time</td>
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<td>RVF</td>
<td>Right visual field</td>
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<tr>
<td>s</td>
<td>Second</td>
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<tr>
<td>SAD</td>
<td>Separation anxiety disorder</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>SPM</td>
<td>Significance probability mapping</td>
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<td>SSPT</td>
<td>Steady-state Probe Topography</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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<tr>
<td>SSVEP</td>
<td>Steady-state Visually-Evoked Potentials</td>
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<tr>
<td>TOL</td>
<td>Tower of London task</td>
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<tr>
<td>TOVA</td>
<td>Test of Variables of Attention</td>
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<tr>
<td>VB</td>
<td>Ventro basal (nuclei of the thalamus)</td>
</tr>
<tr>
<td>WCST</td>
<td>Wisconsin Card Sort Test</td>
</tr>
<tr>
<td>VRT</td>
<td>Variability In reaction-time in CPT</td>
</tr>
<tr>
<td>WISC-III</td>
<td>Wechsler intelligence scale for children - third edition</td>
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<td>WISC-IV</td>
<td>Wechsler intelligence scale for children - fourth edition</td>
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<tr>
<td>°</td>
<td>degrees</td>
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<tr>
<td>π</td>
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<tr>
<td>5-HTP</td>
<td>5 Hydroxy Tryptophan</td>
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Chapter 1. Introduction

This research is the first to examine, with high surface spatial and temporal resolution, the changes in Steady-state Visually Evoked Potentials (SSVEP) of children with Attention Deficit/Hyperactivity Disorder (ADHD) during the course of a high-demand Continuous Performance Task (CPT-AX) after Neurotherapy Treatment. The Research also examines the improvements in attentional parameters associated with Neurotherapy Treatment.

The dependent variables were pre- and post-Neurotherapy changes in: (a) Brain electrical activity, as measured by Steady-state Visually Evoked Potentials (SSVEP), while performing the CPT-AX version of a high attentional demand Continuous Performance Task (CPT); (b) behavioural measures of attention derived from analysis of key-presses during the CPT-AX task; (c) Australian Twin Behaviour Rating Scale (ATBRS) (Levy & Hay 1991), consisting of parent and teacher reports of DSM-IV ADHD symptoms; and (d) performance on a high attentional demand Continuous Performance Task, the Test of Variables of Attention (TOVA).

Prevalence of ADHD

ADHD has been described as a relatively common behavioural disorder that substantially interferes with a child’s ability to function normally at home and in school (American Psychiatric Association 1994). The disorder is characterised by difficulties in a number of areas, including paying attention, sustaining mental effort, concentration,
distractibility, forgetfulness, fidgetiness, poor impulse control and hyperactivity (American Psychiatric Association 1994). It is generally accepted that the disorder occurs in 5 to 10% of children (American Psychiatric Association 1994; Barkley 1997b; Schneider & Tan 1997). However, estimates of the occurrence of ADHD in the research literature range from 2 to 20% of school-age children (Cohen, Riccio & Gonzalez 1994). The increasing prevalence of ADHD over the past thirty years has prompted considerable research into its aetiology, and there have been several revisions of the classification of the disorder in subsequent issues of the American Psychiatric Association’s Diagnostic and Statistical Manual for Mental Disorders over that period (American Psychiatric Association 1980, 1987, 1994). Despite an extensive body of research from various disciplines, there is little cross disciplinary dialogue in the literature that has elucidated the relationships between nutritional and metabolic anomalies, brain morphology, neurochemistry, neurophysiology and behavioural manifestations of the disorder. There has been no single aetiology proposed for the disorder and there has not been any laboratory tests found that can identify ADHD amongst the range of childhood behavioural disorders (Barkley 1991). While ADHD generally continues to be viewed as a disorder which affects attention and/or hyperactivity and impulsive behaviours, theories of ADHD are beginning to focus more on poor inhibition and deficient self-regulation as being central to the disorder (Barkley 2003). However, the diversity of the proposed causal factors and the range of core and associated behaviours suggest that ADHD may be a catch-all acronym for a range of underlying disorders with a wide range of behavioural manifestations (Goodman & Poillion 1992). Nonetheless, studies from various disciplines have
attempted to elucidate the relationships between morphological and functional systems in ADHD, as discussed next.

**Neuropsychological Studies**

Neuropsychological studies of children with ADHD have revealed consistent deficits in: executive function which are thought to be associated with frontal lobe deficits; motor inhibition; and deficits in subcortical and parietal brain regions (Barkley 1997b; Faraone & Biederman 1998; Klorman et al. 1999b). It has been suggested, that inefficiency of a range of cognitive processes in ADHD may affect speed of processing, and that dysfunctional processes at the later motor stages of information processing are responsible for these errors, rather than processes in earlier attentional stages (Barkley 1997b; Sergeant 2000). Findings of studies using a Continuous Performance Task (CPT), the Test of Variables of Attention (TOVA) are consistent with these suggestions (Greenberg & Waldman 1993). Children with ADHD perform poorly on the TOVA, which measures four variables of attention: sustained attention, impulse control, response time and variability in the response time (Forbes 1998; Lubar et al. 1995c; Manor, Sever & Weizman 1999). In the TOVA, the “attention measure” may reflect a combination of orienting to stimulus and executive functions, the “impulse control measure” may reflect inhibition and self-regulation, the “response time measure” may reflect efficiency of neuronal processes and the “variability in the response time measure” may reflect the consistency and repeatability of neuronal processes (Greenberg & Waldman 1993).
**Structural Neuroimaging Studies**

Structural neuroimaging studies have found inconsistent or conflicting results among different research groups in the morphology of frontal sub-cortical areas in ADHD, possibly resulting from cohort effects or differences in neuroimaging equipment and methodologies (Castellanos 1999; Castellanos et al. 2001). Despite controversial findings, there is a general consensus that anatomic ADHD is associated with dysfunction of fronto-striatal networks and that the relevant regulatory circuits include the pre-frontal cortex and the basal ganglia, which are modulated by dopaminergic enervation from the midbrain (Castellanos 1999; Castellanos et al. 2001).

**Functional Electrophysiology and the use of SSVEP in ADHD**

Functional electrophysiology such as Event Related Potentials (ERP) studies, and functional neuroimaging, such as PET, SPECT and fMRI studies have been used to investigate the differences between ADHD and normal subjects in the function of cortical and other specific areas of the brain associated with various cognitive tasks (Castellanos 2002; Castellanos et al. 1996a). Functional neuroimaging techniques can evaluate changes in blood flow related to changes in brain activity in cortical and sub-cortical regions with relatively high spatial resolution, but with poor temporal resolution. On the other hand, functional electrophysiology can evaluate changes in brain activation with high temporal resolution but is limited to investigating cortical areas. Since the temporal resolution is in the order of milliseconds, small transient changes in brain electrical activity evoked by a stimulus can be resolved and studied in
addition to more sustained changes.

Electrophysiological studies are of two types: First, ERP studies that measure the evoked potentials, by averaging the electrical activity from 50 or more (typically one- second trials) following a stimulus presentation; second, Quantitative EEG (QEEG) studies, which measure averages of brain electrical activity over an observation period of several minutes (Chabot et al. 2001). QEEG research has shown that ADHD is characterised by excessive slow brainwave activity in the theta (4-7 Hz) frequency band (Barry, Clarke & Johnstone 2003; Barry et al. 2009a; Chabot et al. 2001) and that ADHD can be identified with high specificity through the use of an index of the theta/beta power ratios at the apex of the head (location Cz) (Monastra, Lubar & Linden 2001).

The most consistent finding from Event Related Potential studies has been reduced amplitude of the parietal P300 component when ADHD subjects attend to target stimuli (Alexander et al. 2008; Brandeis et al. 2002; Hermens et al. 2005a; Johnstone & Barry 1996; Klorman 1991a; Lazzaro et al. 1997; Overtoom et al. 1998b). This has been interpreted as suggesting that the brains of children with ADHD may be less reactive than normal to stimuli under task conditions, and may reflect diminished deployment of attentional capacity and deficits in the allocation of attentional resources in later stages of stimulus processing (Klorman 1991a). Findings of other ERP studies have found differences in initial orienting and in the allocation of attentional resources to a cued task between ADHD and controls (Alexander et al. 2008; Frank, Seiden & Napolitano 1994; Johnstone & Barry 1996; Klorman et al. 1990; Ozdag et al.
2004).

Functional MRI and PET neuroimaging studies have found less activation in the frontal lobes and the basal ganglia of subjects with ADHD compared to controls during tasks requiring attention and inhibition. The few MRI and PET studies conducted to date have been conducted with adolescent or adult subjects, mostly because of the difficulties in getting children with ADHD to remain still while they perform a cognitive task in an MRI or PET scanner. Since QEEG, PET and fMRI studies provide an averaged representation of activation over minutes, they are unable to measure potentially important transient effects. Furthermore, these studies do not inform us whether the reduced activation observed in ADHD is sustained during task or is a response to specific tasks. They also do not elucidate whether reduced activation is associated with specific stimuli over brief intervals or whether it is associated with the execution of a response. Similarly, ERP studies have typically not at evoked responses over time intervals longer than one second and may also be missing critical instantaneous information related to mental control during demanding tasks requiring varying effort and lasting several seconds.

These limitations are overcome in the current research thesis which uses SSVEP at 64 electrodes to provide much higher spatial resolution than usual in ERP studies and the steady-state probe topography (SSPT) technique which enabled the examination of much longer time intervals, in this case a 10-seconds period examined on a millisecond basis.
Stimulant Medication and public concerns

The mainstream treatment for the symptoms of ADHD has been stimulant medication which has been used since the 1940s (Barkley 1990a). Although it was commonly promoted and thought that stimulant medication may provide children with a window of opportunity to learn, reviews of the literature have found that the best that parents can expect is an improvement in attention and a reduction in hyperactivity, but no long-term academic output or long-term improvement in inappropriate behaviours or cognitive skills could be expected (Swanson et al. 1993b).

Stimulant medication may be effective in helping around 60% of children with ADHD, but the effects are transient, lasting around 4 hours, often requiring several doses each day. In addition, some children experience unacceptable side effects, such as exaggerated or aggressive behaviours, difficulties sleeping, less than expected weight gain, TIC disorders, Tourettes Syndrome and cardiovascular events (Barkley 1990a). Following world-wide concerns, the Federal Drug Administration (FDA) directed the manufacturers of all drug products approved for the treatment of ADHD to develop patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise patients of precautions that can be taken (FDA 2006).

Results of a national survey conducted in 2000 revealed that 11% of Australian children and adolescents would meet the diagnostic criteria for ADHD (Birleson, Sawyer & Storm 2000; Sawyer et al. 2001). In Western Australia, public concerns about
excessive use of stimulant medication have sparked ongoing Senate enquiries with the view of finding a solution to that state’s high stimulant prescription rates for ADHD (Senate 2003).

These concerns may be eased through the use of Neurotherapy which has been found to be “Efficacious and Specific” in the treatment of ADHD, with no adverse side effects and with treatment outcomes expected to be permanent (Arns et al. 2009).

**Neurotherapy (EEG Biofeedback)**

Neurotherapy is EEG biofeedback, an operant conditioning paradigm which was originally used in sleep studies by Sterman at UCLA to train cats to increase the frequency of occurrence of alpha spindles, or Sensorimotor Rhythm (SMR) bursts (bursts of EEG alpha waves of 12-15Hz), over the sensorimotor cortex. Later it was found that these cats became resistant to chemically induced seizures, prompting Sterman to investigate the effectiveness of Neurotherapy in treating epileptics (Sterman 1973a). Unexpectedly, along with amelioration of seizure disorder, subjects reported better concentration and reduced hyperactivity (Sterman 1973a; Sterman 2000b). Early experimentation to reduce theta and promote beta or Sensorimotor Rhythm (SMR) activity, mostly by Lubar at Tennessee University with hyperactive and inattentive children, found that these children could improve their symptoms considerably (Lubar 1991b; Lubar & Shouse 1976a; Lubar & Shouse 1977). A number of studies have since demonstrated that Neurotherapy can be used to train the theta/beta ratio towards normal and that concurrently in around 70-80% of cases
ADHD symptoms have been reported to have improved to the point where stimulant medication was no longer necessary (Arns et al. 2009; Fuchs et al. 2003; Gevensleben et al. 2009; Lubar & Lubar 1984; Rossiter 2004a, b; Rossiter & La Vaque 1995; Tansey 1990; Thompson & Thompson 1998b).

Neurotherapy has been used to treat a number of conditions, using a number of different electrode placements and training frequencies. Generally, as applied to ADHD, subjects are rewarded for suppressing theta (4-7Hz) while concurrently increasing beta (15-18Hz) or SMR (12-15Hz) over the sensory motor cortex, in an attempt to improve the theta/beta ratio or promote SMR (Sterman 2000a). Electrodes on the scalp of the subject are connected through an electroencephalograph to a computer which represents the electrical activity in the form of a game. Based on the principles of operant conditioning and Applied Behaviour Analysis, the computer software provides contingent audiovisual reward feedback whenever the theta, SMR and beta amplitudes meet the reward criteria set by the therapist. After around 40 sessions, approximately 70-80% of children are reported to be able to change their theta/beta ratios towards normal. Research to-date suggests that improvements in theta/beta ratios are correlated with improvements in concentration, attention and in academic output; as well as reduced hyperactivity, fidgetiness and undesirable behaviours (Arns et al. 2009; Fuchs et al. 2003; Gevensleben et al. 2009; Lubar & Lubar 1984; Rossiter 2004a, b; Rossiter & La Vaque 1995; Tansey 1990; Thompson & Thompson 1998b). A number of studies have investigated the specificity of the training protocols used in altering brain electrical activity and associated behavioural changes.
However, although there are many studies with apparently favourable outcomes, there are only a few well-designed effectiveness controlled studies and no efficacy studies to-date.

Effectiveness studies that have compared the effects of Neurotherapy to those of stimulant medication on ADHD symptoms have found the therapeutic effects of Neurotherapy to be comparable to those of stimulant medication (Fuchs et al. 2003; Rossiter 2004a, b; Rossiter & La Vaque 1995). Several more studies have examined the specificity of Neurotherapy protocols in normalising theta/beta ratios, ERPs and ADHD symptoms. A recent Meta-analysis of ADHD studies has found that, in line with the guidelines for rating clinical efficacy, Neurotherapy treatment for ADHD can be considered “Efficacious and Specific” (level 5) with a high effect size (ES) for inattention and impulsivity and a medium ES for hyperactivity (Arns et al. 2009).

However, there has been no studies to-date that has systematically examined the changes in brain electrical activity following Neurotherapy, on a millisecond basis, over an extended period of time and with high spatial resolution.

**SSPT**

Steady-state Probe Topography (SSPT) technology has the potential to allow for the examination of brain electrical activity on a millisecond basis with high surface spatial resolution. The SSPT technique developed by Silberstein and colleagues has been used in a number of studies at Swinburne University of Technology. The technique has been used to examine the effects of cognitive task performance on the
steady-state visually evoked potential (SSVEP) generated by an irrelevant probe, a 13 Hz sinusoidal visual flicker, at 64 electrode sites (Ellis, Silberstein & Nathan 2006; Farrow 2003; Farrow et al. 1996; Gray et al. 2003; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 2001; Silberstein et al. 1990). The SSPT also provides the temporal resolution and continuity necessary for the investigation of dynamic patterns of activity associated with task components. SSVEP amplitude and latency variations have been shown to be sensitive to a range of cognitive processes, including attention in ADHD (Farrow 2003; Farrow et al. 1996; Silberstein et al. 1996).

The aim of the current research was to use SSPT to examine the effectiveness of Neurotherapy in the treatment of ADHD. Specifically changes in SSVEP associated with attentional task performance in children with ADHD following 40+ sessions of Neurotherapy were examined. Attention performance and SSVEP were investigated during target components of the CPT-AX task before and after Neurotherapy. During this task, the target (X) is cued by the prior appearance of the letter (A). The cue to target (A-X) interval in the CPT-AX task provided the opportunity to examine processes of brain electrical activity during this period of increased attention. The SSVEP was calculated for a period of 10 seconds centered on the appearance of the X and was examined across the 64 electrodes used in the recording. Changes in TOVA and Australian Twin Behaviour Rating Scale (ATBRS) scores were used to evaluate behavioural changes.

The present study adds further credence to the growing literature supporting the effectiveness of Neurotherapy in the treatment of ADHD by elucidating the
temporal changes in SSVEP brain electrical activity after Neurotherapy in children with ADHD.

This thesis is presented over eight chapters: In chapter 2, the clinical aspects of ADHD are described. Literature related to how the disorder is defined, diagnosed and treated is reviewed and an overview of its neurobiological underpinnings is provided. In chapter 3, the literature on EEG and Neurotherapy for ADHD is reviewed. The rationale for Neurotherapy, its clinical use and the specificity of Neurotherapy Protocols are discussed. In chapter 4, the SSPT technique and the main aims and hypotheses of the Thesis are presented. In chapter 5, the methods section is outlined. The selection and particulars of participants and the experimental methods are identified. These include CPT-AX cognitive task, the TOVA, the SSPT recording procedures and the data analysis. In chapter 6, the results are presented, including changes in TOVA scores, behavioural task performance results, SSVEP effects for the CPT-AX task and ATBRS behavioural reports from parents and teachers. In chapter 7, the experimental findings, their relationship to existing literature and conclusions are presented. Suggestions are made for better diagnosis of subtypes of ADHD based on dysfunction in arousal and activation in the attentional system. In chapter 8, conclusions, limitations and future directions are discussed.
Chapter 2. Overview of Clinical and Neurobiological aspects

This chapter provides the reader with an overview of ADHD, its definition, diagnosis, neurobiology, electrophysiology and the advantages and disadvantages of stimulant medication as the prevalent treatment for ADHD. However, since ADHD aetiology is not the focus of this thesis, this chapter is not intended as an in-depth review of all aspects of ADHD aetiology. The chapter is divided as follows:

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2.13.2 ERP Studies of the CPT

2.1 Historical Perspective on ADHD

The first medical reference to symptoms of ADHD can be traced back to 1902, when an article by British Paediatrician Sir George Frederick Still appeared in the *Lancet* describing children who had attentional difficulties, were overactive and distractible (Still 1902). Still ascribed their impaired “inhibitory volition” and “marked inability to concentrate and sustain attention” to “defects of moral control”, which he felt was associated with neurological deficits (Still 1902).

In the 30s and 40s, the concept of minimal brain dysfunction (MBD) was used to explain observations that there was a group of disorders in children which manifested primarily as disruptiveness, hyperactivity and impulsivity associated with poor attention span (Strause & Lehtinen 1947). The terms ‘Minimal Brain Damage’ and ‘Minimal Brain Dysfunction’ were used in the 50s and 60s when the disorders of attention and motor control were thought to result from central nervous system damage associated with birth trauma, infectious diseases or head injuries (Barkley 1990a). In the late 60s and early 70s, the focus of research was on the hyperactivity displayed by children. This was reflected in the terms “Hyperkinesis or Hyperactivity Syndrome” that were used to describe the disorder. In the 70s, the research focus switched to the attentional problems rather than hyperactivity as the core deficit and primary drive for the symptoms (Barkley 1990a; Whalen 1989; Woods & Ploof 1997).

The acknowledgment that it was possible for a child to have attentional
difficulties without hyperactivity symptoms was first reflected in the third edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association 1980), where the disorder was labeled “Attention Deficit Disorder” (ADD). The DSM-III diagnostic criteria differentiated between two classifications: ADD with hyperactivity and ADD without hyperactivity. Children diagnosed as having Attention Deficit Disorder without hyperactivity were described as withdrawn, passive, anxious and lethargic (Whalen & Henker 1998) and seemed to have difficulties with short-term memory, processing speed and focused attention. On the other hand, children with hyperactivity seemed to have difficulties with sustained attention and behavioural disinhibition (Barkley 1990a). It was not until 1987 that the disorder was relabeled “Attention Deficit/Hyperactivity Disorder” in the DSM-IIIR, the revised third edition of the DSM-III (American Psychiatric Association 1987). This diagnostic system is still currently used in the DSM-IV, the fourth edition of the DSM, which combines attention deficits with hyperactivity into a single classification that includes the combined symptoms of inattention, impulsivity and hyperactivity (American Psychiatric Association 1994).

### 2.2 Prevalence of ADHD

Estimates of the occurrence of ADHD in the research literature range from 2 to 20% of school-age children (Cohen, Riccio & Gonzalez 1994); the wide range of prevalence reported may vary depending on the diagnostic perspective employed by the clinician (Cohen, Riccio & Gonzalez 1994). However, it is generally accepted that
the disorder occurs in 5 to 10\% of children (American Psychiatric Association 1994; Barkley 1997b; Schneider & Tan 1997). Results of a US national survey indicated that the number of office-based visits documenting a diagnosis of ADHD increased from 947,208 in 1990, to 2,357,833 in 1995, and there was a 2.3-fold increase in the population-adjusted rate of office-based visits documenting a diagnosis of ADHD (Robison et al. 1999). A Mental Health Survey in Australia in 2000 found that 11\% of Australian children and adolescents met the criteria for ADHD and 23\% had one of the childhood mental disorders surveyed: Depressive Disorder, Conduct Disorder and Attention-Deficit/Hyperactivity Disorder (Birleson, Sawyer & Storm 2000; Sawyer et al. 2001). The majority of children with ADHD referred to mental health clinics are referred for assistance with aggression and other forms of misbehaviours, which are more common in boys, producing an apparently higher prevalence of boys with ADHD than girls (Brown, Madan Swain & Baldwin 1991). ADHD children without hyperactivity are frequently shy, socially withdrawn, and moderately unpopular. Consequently children with ADHD who are predominantly inattentive are believed to be under-reported (Lahey & Carlson 1991). Longitudinal studies have found that many of the symptoms of ADHD persist into adulthood, affecting work, social and familial situations (Weiss & Hechtman 1993).

Studies into the distribution of ADHD have found that boys are 4 to 6 times more likely to be diagnosed than girls are. However, when hyperactivity is not included in the comparison, the difference between boys and girls is smaller (Brown, Madan Swain & Baldwin 1991; Strause & Lehtinen 1947). In the 1990 US survey, mentioned
above, the number of visits by girls diagnosed with ADHD rose 3.9-fold between 1990 and 1995 (Robison et al. 1999). In the Australian Twin Study, 2,391 twins, and sibling pairs from Australia, ages 3-18 were studied. The magnitude of familial influences was similar for boys and girls, although there were shared environmental influences on ADHD in girls but not in boys; and dominance genetic influences on ADHD in boys but not in girls (Rhee et al. 1999). Despite showing considerably less aggressive behaviours than boys, girls with ADHD tended to have more problems with mood, affect and emotions, tended to be more socially withdrawn and to show more internalising symptoms such as depression and anxiety (Barkley 1990a). A major long-term study of girls diagnosed with ADHD in elementary school, found that they were at greater risk for substance abuse, emotional problems and academic difficulties in adolescence than their non-ADHD counterparts (Hinshaw et al. 2006). A 5-year long prospective study that followed girls with ADHD, along with a matched comparison sample found that the childhood-diagnosed ADHD group displayed moderate to large deficits in executive/attentional performance on childhood neuropsychological assessments and rapid naming tasks, relative to the comparison group at follow-up. Overall, the neuropsychological and executive deficits identified in childhood persisted for at least 5 years in girls with ADHD (Hinshaw et al. 2007).

### 2.3 **Diagnostic Criteria and Subtypes**

In the USA and Australia, the current criteria for diagnosing ADHD is that proposed in the Diagnostic and Statistical Manual for Mental Disorders of the
American Psychiatric Association, fourth edition (DSM-IV) (American Psychiatric Association 1994), which differentiates between three subtypes of ADHD according to predominant features: (a) A **predominantly hyperactive impulsive type** characterised by fidgetiness, squirming in or leaving assigned seat, excessive running or climbing, difficulty engaging or playing in activities quietly and talking excessively, difficulty waiting in line or waiting for own turn, often interrupting others and blurting out answers; (b) A **predominantly inattentive type** characterised by distractibility, forgetfulness, difficulty sustaining attention or mental effort, difficulty following through on instructions, organising tasks or activities and paying close attention to details or schoolwork; and (C) A **combined type** with features of both previous subtypes.

The use of the DSM–IV's descriptive approach to ADHD subtyping may not be the most clinically useful definition of the disorder since this method does not enlighten treatment needs nor predict treatment response (Pelham 2001). In addition, the DSM-IV subtypes do not consider the underlying neurophysiology that may be associated with the various subtypes. An adjunctive method of classifying ADHD children may be according to their brainwave patterns, which are more likely to reflect CNS anomalies (Loo & Barkley 2005).

### 2.4 Symptoms Associated with Specific ADHD Subtypes

Children with ADHD have been reported as presenting with considerable
variation in both the occurrence and in the severity of the symptoms displayed, with symptoms sometimes waxing and waning over time and varying between settings (Barkley 1991; Cantwell 1996). While most children display some inattention and hyperactivity at some time or another; children with ADHD have a persistent pattern of more severe inattention and/or hyperactivity and impulsivity (American Psychiatric Association 1994). Some children appear unaffected in some circumstances when there is minimal demand for mental effort or self-control; but in demanding task conditions, their resources seem overwhelmed and they display inappropriate behaviours. Overall there are four core areas of concern in the behaviours of ADHD children: attention deficits, distractibility, impulse control (poor inhibition) and hyperactivity (American Psychiatric Association 1994).

2.4.1 Attention Deficits and Distractibility

Children with ADHD are reported to experience difficulties sustaining attention mostly during tasks that they find boring, repetitive, or requiring mental effort. These deficits may not be observed when they are engaged in free play or in activities which they find enjoyable (American Psychiatric Association 1994). However, the difficulties that they experience in sustaining mental effort may be responsible for their short attention span, their inability to concentrate for extended periods, their distractibility and selective attention (American Psychiatric Association 1994). The inattentiveness displayed by children with ADHD also results in careless mistakes, forgetfulness, poor
organisational skills and appearing not to listen when spoken to (American Psychiatric Association 1994).

2.4.2 Impulse control

Children with ADHD are reported to be often impulsive, appearing to respond spontaneously to environmental stimuli and failing to think first and consider the impact and consequences of their actions (Farmer & Peterson 1995). It has been observed that they do not seem to think ahead, have poor organisational skills, and often expose themselves to high-risk situations. Children with ADHD suffer more injuries than controls, and it has been shown that they anticipate less severe consequences following risky behaviour and report fewer active methods of preventing injury than children without ADHD (Farmer & Peterson 1995). They are often reported to blurt out answers to questions, jump queues and as having difficulties delaying gratification, preferring smaller immediate rewards and stimulation to larger delayed rewards (Schweitzer & Sulzer Azaroff 1995).

2.4.3 Hyperactivity and fidgetiness

Most children display fidgetiness and over activity from time to time. However, children with ADHD exhibit restlessness, fidgetiness and age-inappropriate levels of motor activity which interferes with their daily lives (American Psychiatric Association
1994). In some ADHD children it is not so much that they are overactive all the time, but rather that they seem unable to appropriately regulate their activity to match the situation (Barkley 1997a).

2.5 Progress of the Disorder from Childhood to Adulthood

Many children with ADHD have difficulties with their academic performance at school. As many as 23% to 30% do not achieve the results that would be expected of children of their age and general intelligence (Frick & Lahey 1991). Between 40% and 60% of children diagnosed with ADHD have repeated a grade at school by adolescence (Brown & Borden 1986). Many are performing below grade level or have borderline academic performance. Children with ADHD typically have impaired concentration and attention. This results in poor self-organisation, poor self-regulation, and difficulty with time management, which in turn lead to the poor academic performance that is frequently observed (Searight, Nahlik & Campbell 1995).

Children with ADHD typically have difficulty forming and maintaining friendships with other children. They frequently misread social cues and as a result may act in an inappropriate manner (Barkley 1990a). Studies have indicated that the inattentive, disruptive, off-task, often provocative, immature behaviours of these children result in their peers being controlling and directive towards them during group tasks (Barkley 1990a). Because of combined difficulties and perceived failures in various life areas such as sport, academia, and social activities, children with ADHD
frequently experience low self-esteem. While lack of self esteem can be clearly observed in some children with ADHD, in others it may be hidden behind a brash, and apparently confident exterior (Wallace 1996).

Aggressive and antisocial behaviours such as fighting, stealing, and truancy are considered the most significant problems associated with ADHD. Estimates are that between 30% to 90% of children with ADHD exhibit conduct problems (Hinshaw 1987). Apart from the immediate impact of conduct problems on the child’s interactions with others, the presence of these problems has been shown to place children with ADHD at risk for drug or alcohol abuse, and for displaying other antisocial and delinquent behaviours as adolescents and young adults (Aylward 1979; Mannuzza et al. 1989).

Studies indicate that most children with ADHD continue to experience difficulties into adolescence (Weiss 1990; Weiss & Hechtman 1993). The changes and stresses to which all teenagers are subjected during this stage of their development, are frequently sufficient to lead to a re-emergence of symptoms which may have been controlled in childhood (Quinn 1997). Several studies that have followed children with ADHD through their development have found that symptoms that were predominant during childhood, such as hyperactivity, were no longer such a serious problem in adolescence (Weiss 1990; Weiss & Hechtman 1993). The studies have found that the hyperactivity often abates somewhat during teenage years, and that issues such as distractibility, restlessness and difficulty with relationships were reported to be the main source of problems (Quinn 1997). In their clinical sample, Hart and colleagues found that, whilst hyperactivity declined with passing years, there were no age-related
changes in inattentive behaviours (Hart et al. 1995). Academic problems, where present, can continue at the same level over the transition from childhood to adolescence.

Academic difficulties can become evident at this stage as a result of general expectation at school that children have acquired a great deal of general knowledge during their primary school years which is immediately and automatically available to them (Levine 1989). However, children with ADHD frequently do not have this fund of readily available knowledge, as a result of not having attended when the information was originally presented (Levine 1989).

Many of those with ADHD continue to experience symptoms well into adulthood. While symptoms may not present during highly interesting or motivating tasks, attentional deficits are likely to show during tedious or uninteresting tasks. Without the structure provided by the school environment, or parents to assist with organising activities, the adult with ADHD may have difficulties meeting the organisational demands of everyday life (Weiss & Hechtman 1993). Long-term studies that have followed children with ADHD treated with psycho-stimulant medication (Methylphenidate or dexamphetamine) through to adulthood, have reported that these adults experience less stability and satisfaction in areas such as employment, educational achievement, interpersonal relationships and mental health (Weiss & Hechtman 1993). For example, one study revealed that ratings of the social-skills and self-esteem of ADHD children, which were only slightly different between ADHD and non-ADHD early in the study, became progressively worse over time (Weiss &
Hechtman 1993). The measures showed that the social-skills and self-esteem of the ADHD group had deteriorated significantly by the 10-year follow-up, and much more by the 15 year follow-up. As adults, this group reported significantly higher levels of anxiety, depression and other psychiatric disorders (Weiss & Hechtman 1993). Adults with ADHD frequently reported feelings of failure, frustration, underachievement, and guilt (Green & Chee 1997).

2.6 Co-morbidities and Differential Diagnosis of ADHD

Children with ADHD belong to a heterogeneous population with varying symptom range, severity and pervasiveness (Barkley 1990b). ADHD studies reflect variations in diagnostic criteria, measurement sampling and designs which confound diagnosis and study results (Cohen, Riccio & Gonzalez 1994; Schacher 1991). It is very difficult to find a group of children who exhibit purely ADHD symptoms, as co-morbidity with other disorders is common in ADHD (Castellanos 1997), and children with emotional or learning problems can also appear to suffer from attention deficits (American Psychiatric Association 1994; Cantwell 1993). It has been estimated that 4% to 6% of school-age children also suffer from some form of Learning Disorder. Although ADHD and Learning Disorders are thought of as distinct neuropsychiatric entities, there is considerable co-morbidity between the two disorders (American Psychiatric Association 1994; Riccio & Jemison 1998). As many as 20-30% of children with ADHD are estimated to have learning disabilities (Bender 1997; Biederman, Newcorn & Sprich 1991; Rutter 1982). Attempts to differentiate children with ADHD from normal controls or from psychiatric controls on measures of cognitive and/or
neuropsychological function, neurotransmitter activity, genetic factors, and neuroanatomy have yielded inconsistent results (Barkley, Grodzinsky & DuPaul 1992). Precise and accurate determination of the presence of ADHD versus Learning Disorders can be of critical importance for effective treatment to avoid the potentially devastating impact of these disorders on children and their families.

Up to 50% of children with ADHD may warrant a co-morbid diagnosis of Oppositional Defiant Disorder, Obsessive Compulsive Disorder or Conduct Disorder as a result of the presence of severe externalising behaviours (Bender 1997; Biederman, Newcorn & Sprich 1991; Rutter 1982). A further 25-35% may have co-morbid anxiety and 15% may have mood disorders with associated internalising symptoms (Bender 1997; Biederman, Newcorn & Sprich 1991; Rutter 1982).

Deficits in the ability to sustain attention may be common in children with other psychiatric disorders, making the task of differential diagnosis difficult (Swaab Barneveld et al. 2000). Sub-groups of children with ADHD delineated based on the disorder's co-morbidity with other disorders may have differing risk factors, clinical courses, and pharmacological responses. Thus, their proper identification and differentiation may lead to refinements in preventative and treatment strategies (Biederman, Newcorn & Sprich 1991).

Children with ADHD and co-morbid Obsessive Compulsive Disorder (OCD) may have obsessive thoughts and/or compulsions. A NIH study, found that twice as many boys than girls were diagnosed with OCD, and that boys had an earlier onset than girls,
with an average age of onset of around 7 to 9 years of age as opposed to an age of onset of around 11 for girls (Swedo et al. 1989). The less severely affected children and those attempting to hide their symptoms make this group more difficult to diagnose. The most common symptoms include: long unproductive hours doing homework; excessive erasing, sometimes to the point of tearing the paper; retracing over letters and words; re-reading paragraphs over and over; excessive laundry or toilet paper usage; insistence on using some clothes or towels only once; unusual bedtime rituals; unduly worrying about germs or about a small cut or pimple; exaggerated need for reassurance; rigid bedtime rituals and hoarding of useless objects (Leonard et al. 1990). These are not always obvious symptoms and OCD co-morbidity may be missed when the child also presents as hyperactive, oppositional and with behavioural problems (Leonard et al. 1990).

The diversity of symptoms and co-morbidities has led Goodman and Poillion to suggest that ADHD may be an acronym for a range of underlying factors (Goodman & Poillion 1992). Following an extensive review of the literature, they found that there had been 69 different characteristics attributed to children labeled ADHD along with 38 possible aetiologies suggested for the disorder (Goodman & Poillion 1992). The psychological nature of these symptoms has led to the use of cognitive and behavioural interventions for this group, and these are the subject of the next section.

2.7 **Behavioural and Cognitive Interventions for ADHD**
Numerous studies have documented the relative effectiveness of a wide range of interventions for children with ADHD. The majority of these are based on contingency management, but several deal with antecedents, in particular, modifications of the task and of the physical environment of the classroom (Abramowitz & O'Leary 1991). Interventions involve: contingency management; manipulation of consequences; token economies; reinforcement and response cost; home-school reward/punishment contingencies; time-out from positive reinforcement and cognitive-behavioural interventions (Abramowitz & O'Leary 1991).

2.8 Psycho-stimulant Treatment of ADHD

Psycho-stimulants (Methylphenidate and Dexamphetamine) are the most commonly used medical treatment for children with ADHD. The drug Methylphenidate is responsible for a high percentage of the psycho-stimulant medication market for ADHD (Bender 1997). Dosage of stimulant medication varies from one individual to the next, but is usually begun at the lowest recommended dose, and is usually given two or three times daily. Dosage is increased gradually to achieve a state of maximum symptom relief with minimal side effects. The effects of Methylphenidate can be observed 30 minutes after ingestion, and the peak efficiency is reached between one and three hours later, with the efficacy wearing off after four to six hours (Bender 1997). The benefits of psycho-stimulant medication in the treatment of children with ADHD are firmly established. However, few studies have extended beyond 24 months (Greenhill, Halperin & Abikoff 1999).
According to Barkley, psycho-stimulant medications have been reported to reduce the problematic hyperactive symptoms of ADHD in approximately 60-70% of children with ADHD (Barkley 1990a). In a review of stimulant use in ADHD, the pooled results of the treatment of 5,899 children participating in 161 randomised controlled trials, found that 65-75% of children treated with psycho-stimulant medication showed clinical improvement, while the rates for clinical response from the placebo groups ranged from 4% to 30% (Greenhill, Halperin & Abikoff 1999). Research and clinical findings indicate that the ability to attend increases, social behaviours improve, and impulsivity decreases with the use of psycho-stimulants (Barkley 1990a). Frequently parents report not only that behaviours improve significantly, but also that relationships between the child and the rest of the family, as well as with peers, improve markedly once the child is placed on medication (Bender 1997).

In 1992, the National Institute of Mental Health and 6 teams of investigators began a multi-site clinical trial: “The Multimodal Treatment of Attention-Deficit Hyperactivity Disorder (MTA) Study” (Jensen et al. 2001). Five hundred and seventy nine children were randomly assigned to either one of four treatment conditions, each designed to reflect best-known practices within each treatment approach and each lasting 14 months. These were: (a) Routine community care; (b) Monthly medication management follow-up, following initial weekly titration; (c) Intensive behavioural treatment and (d) The combination of behavioural treatment and medication management.

Medication management combined with behavioural treatment were
substantially superior to behavioural and community care interventions on their own for symptoms of ADHD. Results also suggested slight advantages of combined interventions over medical management, behavioural treatment and community care for social skills, academic performance, parent-child interactions, oppositional behaviours, anxiety and depression (Jensen et al. 2001). The MTA study results indicated that high quality medication management characterized by careful and adequate dosing, Methylphenidate administration three times daily, along with weekly initial titration and monthly follow-up visits, and communication with schools conveyed substantial benefits to those children that received Methylphenidate (Jensen et al. 2001). In addition, children with parent-defined co-morbid anxiety disorders, particularly those with overlapping disruptive disorder, showed preferences for the behavioural and combined interventions. Parental attitudes and disciplinary practices mediated improved response to the behavioural and combined interventions (Jensen et al. 2001). Reduced final doses of stimulant medications were achieved in the combined treatment group compared with the medication management group. The explanation offered for this was that behavioural therapy is a useful adjunct to medication and may reduce the overall consumption of stimulant drugs and their side effects (Jensen et al. 2001).

The superior effectiveness of optimally managed stimulant medication treatment over community care and behaviour intervention was demonstrated in the MTA study (Jensen et al. 2001). The study confirmed what previous smaller studies and reviews had already found, namely, that combined medication and intensive
behaviour therapy offered the best treatment options for ADHD (Jensen et al. 2001). However the MTA study was not without its critics, as described in the next section (Greene & Ablon 2001).

### 2.9 Concerns Relating to Psycho-stimulant Medication for ADHD

Greene and Ablon (2001) criticised the MTA study and raised the following concerns (a) whether the medication management and behavioural arms of the MTA were assessed to comparable degrees. Medication management was individually optimised with initial weekly titration of medication and monthly reviews and assessment were carried out while on medications. On the other hand, behavioural interventions were not optimised based on individual needs, and post-treatment assessment was made months after termination of treatment. Hence it is questionable whether: (a) cognitive-behavioural interventions were incorporated to an adequate extent and tailored to individual needs, (b) whether core ADHD symptoms, attention, distractibility and impulse control, which were responsive to medication, were overemphasized relative to other important functional domains both as treatment targets and as outcome measures; and (c) whether parent and teacher characteristics warranted more emphasis than they were given in the research, as such an emphasis would represent parent-teacher reports of behavioural interventions more fairly (Greene & Ablon 2001).

Pelham also criticised what he described as misinterpretations and premature
reporting of findings of the MTA study, and bias towards drug prescription in the
design of the MTA study (Pelham 1999).

Pelham (1999) remarked that medication management was superior to
behaviour treatment on parent and teacher ratings of inattention and teacher ratings
of hyperactivity, but not on any of the other 16 measures. These included, classroom
observed behaviours, parent- and teacher-rated social skills, parent-rated parent-child
relationships, peer sociometric ratings, and academic achievement. Hence, medication
management was superior to behaviour treatment on only two of the 19 measures
assessed, yet published results focused on attention and hyperactivity measures alone.
In addition, Pelham made a strong case for methodological bias in favour of
medication management on the basis that behaviour treatment was assessed 4-6
months after cessation of treatment while medication management was assessed in its
acute and most active stage. In contrast to proponents of the study, he concluded that
the MTA evidence suggest that: behavioural treatments are effective in the treatment
of attention-deficit hyperactivity disorder, that combined treatments are usually
superior to monotherapies, and that concurrent behavioural treatment allows for
lower medication dosages (Pelham 1999).

Three years following the end of the MTA study, 485 of the original 579 ADHD
subjects (83.8%) now aged 10 to 13 years (mean 11.9 years), participated in the follow-
up study. In contrast to the significant advantage of medication management and
combined treatment over behaviour management and community care for ADHD
symptoms found at 14 and 24 months, the treatment groups did not differ significantly
on any measure at 36 months (Jensen et al. 2007).

Regardless of whether the ADHD participants changed their treatment use, all of the groups showed symptom improvement over baseline at the start of the study. None of the following initial factors moderated the ADHD children's 36-month treatment responses: (a) initial symptom severity, (b) gender (male), (c) existence of co-morbidities, (d) whether they received public assistance, and (e) their parent’s own ADHD psychopathology. However, these initial factors predicted worse outcomes over 36 months, regardless of original treatment assignment. The reviewers concluded that by 36 months, the NIH multimodal study revealed that the earlier advantages of having had 14 months of the medication treatment were no longer apparent. They suggested that this may have resulted from age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medications altogether, or other factors not yet evaluated (Jensen et al. 2007).

Swanson and fifteen co-authors conducted a comprehensive examination of 341 reviews of the effects of stimulant medication on children with attention deficit disorders (Swanson et al. 1993a). Their review found that medication was ineffective for 25 to 40 percent of children with ADHD. A large proportion of those responding to Methylphenidate also showed improvements on a placebo. Across quantitative reviews, the average effect size for symptomatic improvement (0.83) was twice that for benefits on I.Q. and achievement measures (0.35). Amongst those that responded to stimulant medication, temporary management of over activity, inattention and impulsivity could be expected, as well as temporary improvement in compliance.
Hyperactivity and aggression may be reduced, and consequently the amount of academic work completed may increase. However, contrary to the hopes of parents and practitioners, there was no evidence of significant long-term improvement in reading, athletic or game skills, proactive social skills, learning and achievement other than improved attending (Swanson et al. 1993a). In other words, hyperactivity and attending may improve amongst the 60 to 75% of children who respond to psycho-stimulant medication, but their concentration, learning ability and cognitive skills may not. In the review it was also suggested that parents should not expect improvements in long-term adjustment, improved academic achievement, nor should they expect a reduction in antisocial behaviours or misconduct (Swanson et al. 1993a).

Several side effects have been reported during treatment with psycho-stimulants. These include: decreased appetite, insomnia, dysphoria, headaches, weight loss, stomach and leg cramps and the onset or exacerbation of Tics or Tourettes Syndrome (American Psychiatric Association 1994). Schachter and colleagues conducted a meta-analysis of randomized controlled studies of medication treatment for ADD/ADHD (Schachter et al. 2001). They examined 62 randomized trials of stimulant medication, involving 2897 participants with a primary diagnosis of ADHD (with or without hyperactivity). They reported that the studies were of poor quality and had a strong publication bias. Interventions lasted an average of 3 weeks, with no trial lasting longer than 28 weeks. Each primary outcome (hyperactivity index) demonstrated a significant effect of Methylphenidate (effect size reported by teacher 0.78 and by parent 0.54). However, these apparent beneficial effects were tempered
by a strong indication of publication bias, meaning that drug-company-funded studies which failed to support the effectiveness of their product, or reported too many side effects, tended not to be submitted for publication. In addition, there was a lack of robustness in the findings, meaning that the findings varied greatly across studies, especially those involving core features of Attention Deficit Disorder (Schachter et al. 2001). They also concluded that the extension of this placebo-controlled effect beyond 4 weeks of treatment had not been demonstrated, and that the adverse event profile of Methylphenidate required further consideration (Schachter et al. 2001).

A comprehensive review from Oregon State University (The Drug Effectiveness Review Project, 2005) analyzed 2,287 studies involving all stimulant medications prescribed for ADHD. The group rejected 2,107 of the investigations as unreliable and reviewed the remaining 180 to reach their conclusions, published in a 731-page report. Their findings were that: (a) there was no evidence of long-term safety of drugs used to treat ADHD in young children or adolescents, (b) there was a lack of good quality evidence that ADHD drugs improve global academic performance, risky behaviours, social achievements and other measures, (c) there was little evidence of the safety of these drugs, and there were research findings which suggested that some ADHD drugs could stunt growth, (d) evidence that ADHD drugs help adults was not compelling, nor was there evidence that one drug was more tolerable than another, and (e) there was a poor understanding of the pharmacokinetics of these drugs. The review did not suggest that drugs used in the treatment of ADHD are unsafe or not helpful, only that sound scientific evidence is lacking to prove that they are safe and useful in the long
El-Zein and colleagues (2005) concluded that the lack of research on long-term effects of Methylphenidate use in humans warranted grave concerns and further investigation (El-Zein et al. 2005). They discovered that after 3 months, all of the ADHD children on Methylphenidate in their double blind placebo controlled study experienced chromosomal aberrations which could increase cancer risk (El-Zein et al. 2005). They likened the risk to that of the cytotoxic damage that has been found in adult methamphetamine users (Li et al. 2003).

As previously stated, controversy is rising over the possibility of growth suppression while on stimulants, together with estimates that as many as 30% of children with ADHD do not respond to stimulant treatment or cannot tolerate the undesirable side effects (Daley 2004). These concerns and reports of rising adverse cardiovascular events has prompted the FDA to direct manufacturers of all drugs used in the treatment of ADHD to develop patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines (FDA 2006).

According to Daley (2004) children with ADHD are likely better served with multimodal treatment plans, that are individually tailored, including medication, parent/school counseling, and behavioural therapies (Daley 2004). There is also a need for a treatment modality, which would provide permanent results and no side effects. Neurotherapy has no adverse side-effects and has shown promise as an effective
emerging intervention for ADHD (Hirshberg, Chiu & Frazier 2005). It is also the subject of the next chapter, and the focus of this Thesis.

2.10 Neuropsychological Studies of ADHD

This section presents a brief overview of studies, which investigated the neuropsychological aspects of attention in ADHD. Studies that utilised Continuous Performance Tasks (CPTs) are reviewed more extensively as both the CPT-AX task and the Test of Variables of Attention (TOVA) have been used in this research.

Several studies using neuropsychological tasks have found evidence, which has suggested that children with ADHD have deficits in frontal lobe function. These tasks have included: The Stroop tests (Carter et al. 1995b; Gorenstein, Mammato & Sandy 1989; Homack & Riccio 2004; MacLeod & Prior 1996; Savitz & Jansen 2003; Seidman et al. 1997), the Wisconsin Card Sorting Test (Capdevila-Brophy et al. 2005; Gorenstein, Mammato & Sandy 1989; Loge, Staton & Beatty 1990; Pineda et al. 1998; Reitan & Wolfson 1994; Romine et al. 2004), the Tower of Hanoi (Aman, Roberts & Pennington 1998; Klorman et al. 1999a; Klorman et al. 1999b; Murphy 2002), the Hand Movements Test (Breen 1989), the Go/No-Go Task (Shue & Douglas 1992; Van der Meere & Stemerding 1999), and the Task of Covert Orienting of Visuospatial Attention (Posner 1980; Posner, Snyder & Davidson 1980).

Children with ADHD have also exhibited difficulties in the Letter Cancellation task, where they have been found to make significantly more left-sided errors of
omission than non-ADHD children on the same task, implicating deficits of the right parietal lobe function (Fischer et al. 2005; MacLeod & Prior 1996; Malone et al. 1994). Studies of Mental Rotation Tasks have investigated frontal lobe function in various populations. For example, Snow (1990) investigated the construct validity of the Mental Rotation Task and its usefulness in evaluating the performance of children with academic difficulties. He found that children with ADHD had impaired performance suggestive of right parietal lobe deficits (Snow 1990). An fMRI study using the Mental Rotation Tasks revealed widespread frontal, striatal and parietal dysfunction in adolescents with ADHD of the combined subtype (Silk et al. 2005).

Although neuropsychological studies of ADHD have focused on the attentional system, several other factors have been found to affect task performance, leading Barkley to conclude that the deficits in-task performance in ADHD are not due to deficits in the attentional system but may be due to other aspects of information processing (Barkley 1997b). A number of these other aspects of information processing are discussed in the next.

2.10.1 Visuospatial Attention

The first attentional requirement of any mammal is to detect novelty in the environment and identify the location of these changes in space relative to self, a process that relies heavily on vision and hearing and involving overt and covert attention (Pribram & McGuinness 1975; Tucker & Williamson 1984). Overt attention involves directing sense organs towards a stimulus source, while covert attention is the act of mentally focusing on one of several possible sensory stimuli (Wright & Ward
Neuropsychological tests, including Posner's covert orienting of attention paradigm, have been devised to study these systems (Wood et al. 1999). The most consistent findings in these studies have been that children with ADHD experience performance deficits mostly when the cue to target presentation interval is in the range of 350-800 ms, rather than in the range of 100-150 ms (Wood et al. 1999). Furthermore, it is the visual field that receives the cue, rather than the target which is responsible for the greatest cue costs in ADHD (Swanson et al. 1991). Findings from such studies have been largely interpreted as suggesting that covert orienting to cues mediated by the posterior attention system may be normal in children with ADHD, but that overt control of attention, mediated by the anterior attentional system may be deficient in children with ADHD (Carter et al. 1995a; Swanson et al. 1991; Wood et al. 1999).

In contrast, Huang-Pollock and colleagues used a CPT A-X task and a covert orienting paradigm to examine the vigilance, anterior, and posterior attention systems (Huang-Pollock, Nigg & Halperin 2006). Compared to non-ADHD controls, children with the predominantly inattentive and combined subtypes had lower sensitivity to detect targets from non-targets. Performance for both ADHD subtypes decreased over time, consistent with problems in sustained attention. The authors concluded that these results suggested the presence of vigilance system deficits and not anterior or posterior system orienting dysfunctions in either subtype of ADHD (Huang-Pollock, Nigg & Halperin 2006).

Alvarez and colleagues (2004) found that although Posner's covert orienting of
attention paradigm had been used in several studies to study attention deficit in ADHD, findings were inconsistent because of procedural variations. They concluded that despite these limitations, two variables: overall slowing and right hemisphere dysfunction consistently differentiated ADHD from non-ADHD controls (Alvarez & Freides 2004).

2.10.2 **Focused, Selective and Divided Attention**

Studies that have examined focused attention, the ability to ignore or suppress task-irrelevant sensory information in favour of task-relevant information, have generally found no significant difference between children with ADHD and controls (Van der Meere & Sergeant 1988). Selective attention is the ability to focus on task-relevant information while ignoring task-irrelevant information. Results of studies using selective attention tasks in ADHD have been interpreted as suggestive of poor discrimination and poor preferential processing of attended stimuli, which were thought consistent with deficits in selective attention (Jonkman et al. 1997; Satterfield et al. 1988; Satterfield et al. 1990a). However, a review of studies of selective attention, concluded that visual or auditory selective attention deficits are not found consistently in children with ADHD (Van der Meere, Gunning & Stemerdingk 1996). Findings from studies of divided attention, the ability to respond simultaneously to multiple tasks or multiple task demands, have been interpreted as deficits in attentional capacity in children with ADHD (Leung et al. 1994; Leung & Connolly 1994; Van der Meere & Sergeant 1988). Unlike selective attention tasks which showed inconsistent
discrimination of ADHD from normal controls, Continuous Performance Tasks (CPTs) have been found to discriminate ADHD from non-ADHD controls (Conners et al. 2003; Greenberg & Waldman 1993).

2.10.3 **Continuous Performance Task (CPT) and Sustained Attention**

Continuous Performance Tasks have been widely used both as research tools and clinically as an adjunct tool in the diagnosis of ADHD (Forbes 1998; Monastra, Lubar & Linden 2001; Rossiter 1998; Rossiter & La Vaque 1995). CPTs consist of a series of randomly presented stimuli, which can be either targets or non-targets. The targets can be frequent or infrequent, and non-targets can be used to cue targets. The stimuli can be letters, numbers, or symbols depending on the task design. “Errors of omission” are missed targets and are considered a measure of inattention. “Errors of commission” are erroneous responses to non-targets and are considered a measure of impulsivity. The reaction time is the difference in time between the presentation of the stimulus and the response, and is considered a measure of processing speed (Greenberg & Waldman 1993). Variability in the reaction time is also reported in some studies and is considered to be related to distractibility (Forbes 1998; Monastra, Lubar & Linden 2001; Rossiter 1998; Rossiter & La Vaque 1995).

Zalsman and colleagues (2003) attempted to differentiate the attention patterns associated with attention deficit disorder with or without hyperactivity using Continuous Performance Task (CPT). The diagnoses were based on the DSM-III, III-R,
and IV criteria. Of the 39 children who participated in the study, 14 had attention deficit disorder with hyperactivity, and 11 had attention deficit disorder without hyperactivity, while 14 normal children served as a control group. Attention patterns were examined according to the performance of subjects on the CPT and parental scores on the ADHD Rating Scale, the Child Attention Profile, and the Conners Rating Scale. CPT performances were assessed before and after administration of 10 mg of Methylphenidate to the experimental group. They found that the CPT differentiated between the two groups. The ADHD children with hyperactivity made more omission errors than those without hyperactivity, and the performance of both experimental groups improved to an equal degree after the administration of Methylphenidate. Thus, they concluded that firstly, different subtypes of the attention deficit disorders are characterized by different attention profiles and that secondly, Methylphenidate improves scores on Continuous Performance Tasks (Zalsman et al. 2003)

Tinius used the Integrated Visual and Auditory Continuous Performance Test (IVA CPT) to investigate the attentional system of adults diagnosed with mild traumatic brain injury (mTBI), adults diagnosed with ADHD, and controls. On a CPT, the Integrated Visual, and Auditory Continuous Performance Test (IVA), the mTBI and ADHD groups performed significantly lower on the full and secondary scales for attention and response accuracy than controls. For individual scales on the IVA, the mTBI and ADHD groups had lower performance on measures of reaction time, attention, impulsivity, and variability of reaction time. On the Neuropsychological Impairment Scale, the mTBI and ADHD groups reported more neuropsychological
symptoms than the control group, and the mTBI group reported more neuropsychological symptoms than the ADHD group (Tinius 2003).

2.10.4 CPT Task Designs

The cognitive processes purported to be measured by the CPTs and poorer performance of ADHD participants may in turn depend on the nature of the CPT tasks and other “external” variables, which vary considerably between studies (Corkum & Siegel 1993; Losier, McGrath & Klein 1996a). The Test of Variables of Attention (TOVA) is a CPT that was designed as a tool to empirically titrate stimulant medication prescribing and to overcome some of the design shortcomings of other CPTs (Greenberg & Waldman 1993).

The CPT-AX is a more complex cued-target version of the CPT. Tasks that have a higher percentage of targets have been found to discriminate better between children with ADHD and non-ADHD controls (Corkum & Siegel 1993; Losier, McGrath & Klein 1996a). Hence, in this study, both the TOVA and the CPT-AX are used to evaluate attentional performance prior to and post-Neurotherapy.

2.10.5 Performance on the CPTs: Omission and Commission Errors

Several studies have reported that children with ADHD consistently make significantly more omission and commission errors on CPT tasks than normal controls.
Losier and colleagues (1996a) reviewed the CPT errors of omission and commission patterns exhibited by children with ADHD under unmedicated, placebo, Methylphenidate drug, and normal control conditions. They submitted findings from 26 studies to a meta-analysis procedure and found that, in contrast to the contradictory findings of individual reports, children with ADHD made significantly more errors of omission and commission than non-ADHD children (Losier, McGrath & Klein 1996a). Children with ADHD treated with Methylphenidate had significantly reduced rates of both errors of omission and commission errors (Losier, McGrath & Klein 1996a). Using Signal Detection Theory, a means of quantifying the ability to discern between signal and noise (Green & J.A. 1966), Losier and colleagues found that children with ADHD were less sensitive to the difference between targets and non-targets than their normal counterparts, while showing a comparable response bias (the extent to which one response is more probable than another). Similarly, the effects of Methylphenidate were restricted to improving the sensitivity to targets (how
hard or easy it is to detect that a target stimulus is present from background events), while not affecting response bias, in both normal children and those with ADHD (Losier, McGrath & Klein 1996a).

Reviewers have interpreted findings of higher omission errors in ADHD than controls as evidence of inattention and deficits in arousal in ADHD (Corkum & Siegel 1993; Losier, McGrath & Klein 1996a). Additionally, reviewers have interpreted findings of increased commission errors in ADHD compared with controls as evidence of poor behavioural inhibition and impulse control (Barkley 1997b; Halperin 1991; Halperin et al. 1992; Thompson & Thompson 1998a).

In order to demonstrate that ADHD subjects have deficits in sustained attention, there must be evidence that performance in ADHD deteriorates with increased time on task (Hooks, Milich & Lorch 1994). However, such deficits have not been consistently reported in CPT studies, possibly because of the confounding effects of learning difficulties in the ADHD groups in some studies (Van der Meere & Sergeant 1988). Some studies have reported no decrement in error rate with increasing time (Van Leeuwen et al. 1998), while a few have shown an improvement in error rate over time, suggestive of practice effect (Alberts & Van der Meere 1992). Errors of omission and errors of commission are two of the four variables of attention studied in ADHD. Deficits in reaction-time and variability in the reaction-time (VRT) have also consistently been found in children with ADHD and these will be discussed next.
2.10.6 **Performance on the CPTs: reaction time (RT) and Variability in RT**

Several studies have found that children with ADHD have slower reaction-times than normal controls (Greenberg & Waldman 1993; Klorman et al. 1979; Lubar et al. 1995b; Overtoom et al. 1998a; Rossiter 2004a, b; Rossiter 1998; Rossiter & La Vaque 1995; Strandburg et al. 1996a; Thompson & Thompson 1998a; Wood et al. 1999).

Slower reaction-times in ADHD has been interpreted as evidence of inability to process presented information quickly compared to normal controls (Greenberg & Waldman 1993; Rossiter 2004b; Thompson & Thompson 1998a; Wood et al. 1999).

The Conners Continuous Performance Test (CPT) has repeatedly been shown to differentiate ADHD from normal groups (Epstein et al. 2003). The Conners CPT measures variables that include errors of omission and commission, and mean hit reaction-time. Epstein (2003) examined relations between various CPT variables and phenotypic behaviours in a sample of 817 children who were administered the Conners CPT. Children diagnosed with ADHD had more variability in reaction-times (VRT), made more errors of commission and omission, and demonstrated poorer perceptual sensitivity than non-ADHD children. CPT performance measures were highly correlated with symptoms of ADHD but not symptom domain specificity. Increased VRTs over time were related to most ADHD symptoms (Epstein et al. 2003).

By their very nature, Continuous Performance Tasks require sustained attention. However, a number of endogenous and external factors can also affect task performance in CPTs, as discussed next.
2.10.7 **Variables affecting Performance on the CPTs**

Amongst the external variables that can affect task performance in CPTs are: differences in CPT task variables, as previously discussed; selection and matching of comparison groups for age, gender and I.Q.; whether or not feedback or reward is given; whether instructions emphasize speed as opposed to accuracy of response, and the amount of practice given prior to the task (Corkum & Siegel 1993). CPT performance in children with ADHD has also been shown to be influenced by the presence or absence of an examiner (Power 1992).

Many endogenous processes can affect performance on a CPT, including: arousal, motivation, inhibition, momentary concentration problems (Corkum & Siegel 1993; Klorman 1991b; Losier, McGrath & Klein 1996a), impaired effort allocation (Van der Meere & Sergeant 1988), deficits in pre-frontal response control (Fallgatter et al. 2004), decreased cortical arousal (Loo et al. 2004) and age of participants (Aylward, Brager & Harper 2002; Berwid et al. 2005; Lin, Hsiao & Chen 1999).

Performance deficits in CPTs have been found in a number of other disorders, including: anxiety (Epstein et al. 1997; Fischer et al. 2005), Learning Disabilities (Richards et al. 1990), Oppositional Defiant Disorder (Barkley et al. 2001), Conduct Disorder (Fischer et al. 2005), and Reading Disabilities (Aaron, Joshi & Phipps 2004). Although, contrary to the latter study, two studies did not find performance deficits in CPTs in reading disabilities (Hall et al. 1997; McGee et al. 2004).

Swaab and colleagues (2002) used a visual sustained attention task to compare
52 boys with ADHD, 29 boys with Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD), 29 boys with Anxiety or Dysthymia, 43 boys with Pervasive Developmental Disorder, 24 boys with ADHD plus ODD/CD, and 14 boys with ADHD plus anxiety or dysthymia to 55 normal controls. They found that compared with normal controls, children with ADHD were slower, less accurate, more impulsive, less responsive to feedback, and showed less perceptual sensitivity and stability of performance, resulting in a marked decrease in sustained vigilance. However, the only factors that distinguished children with ADHD from those with other diagnoses were reduced responsiveness to feedback and a greater degree of impaired vigilance over time in the visual sustained attention task. They concluded that deficits in sustained attention may be common to all children with psychiatric disorders, while only children with ADHD are characterized *primarily* as having deficits in sustained attention (Swaab Barneveld et al. 2000).

In another study, the discriminant ability of the Test of Variables of Attention (TOVA) to distinguish between children with ADHD and other clinical diagnoses was studied in 146 children, aged 6-12 yrs (Forbes 1998). Results showed that there were large differences between the ADHD group on teacher ratings of activity and inattention. Analysis of the TOVA variables indicated that children in the ADHD group exhibited more omission and commission errors, had longer response time, more variability in response times and more multiple responses than the non-ADHD group (Forbes 1998).

There has been compelling evidence that ADHD is a highly inheritable disorder.
In families where an adult has been diagnosed with ADHD, there is a 57% chance that at least one child will also have ADHD (Biederman et al. 1995). Consequently, the next section provides a brief overview of this aspect of biology that underpins the disorder.

### 2.11 Molecular Biology and Genetics

Genetic studies of ADHD fall into 3 distinct categories: twin, adoption, and family studies, and findings converge to provide strong evidence in support of genetic involvement in this condition (Hechtman 1994). Numerous studies of twins have revealed a robust heritability index of approximately 0.75 to 0.90 for ADHD (Levy et al. 1997; Silberg et al. 1996; Willcutt, Pennington & DeFries 2000). Over 30% of siblings of a child with ADHD also have ADHD (Biederman et al. 1992; Biederman et al. 1990).

Epidemiological studies have demonstrated a significant positive correlation between ADHD and the development of alcoholism or drug abuse in adulthood (Comings 1991). Although there is some evidence that genes that encode noradrenergic receptor or transporter activity may have some action in ADHD (Arnsten 2000; Arnsten, Steere & Hunt 1996; Comings et al. 1999; Comings et al. 2000a; Hechtman 1994; Xu et al. 2001), research into the genetic underpinnings of ADHD has focused on the DA transporter gene and on the gene for the DA D-sub-4 receptor gene (DAD4) receptor. This is probably due to the stimulant modulating response of dopamine and evidence of CSF dopamine anomalies in ADHD leading researchers to investigate dopamine receptors (Thapar et al. 1999). As with most psychiatric disorders
though, examination of pedigrees has not revealed a consistent Mendelian mode of transmission (Cook et al. 1995). Research relating to dopamine-related genetics and its role in ADHD is examined in the following chapter.

2.11.1 Dopamine Receptor and Transporter Genes in ADHD

Efforts to identify the genes associated with the heritability of ADHD have concentrated on dopaminergic alleles. This is because stimulant medications, which have been found to be most successful in the treatment of symptoms of ADHD, produce their clinical effects by inhibiting dopamine reuptake transporters, thereby increasing synaptic availability of dopamine (Ding et al. 1997; Gainetdinov et al. 1999). According to some, ADHD may be associated with dysfunction of the DA D-sub-2 receptor gene (DAD2) which has been identified as a possible genetic variation responsible for alterations in behaviour (Comings 1994). Such alterations in the genetic make-up result in functional deficiency of mesolimbic and frontal lobe dopamine metabolism (Comings 1994). There is evidence to suggest that many childhood and adolescent disruptive behaviours including ADHD, Tourette's Syndrome (TS), Learning Disabilities (LD), substance abuse, Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD), are part of a spectrum of interrelated behaviours that have strong polygenetic components. These components share a number of genes that affect dopamine, serotonin, and other neurotransmitters; and are transmitted from both parents (Comings 1997).
Results from other studies suggest that the DRD4 dopamine receptor gene (Smalley et al. 1998), DRD2 dopamine receptor gene (Comings et al. 1996), and the DAT1 dopamine reuptake transporter gene (Cook et al. 1995) are implicated in ADHD. An attempt to relate the alleles of the D2 (DRD2), D4 (DRD4), and dopamine transporter (DAT1) genes to the behavioural outcomes of Methylphenidate therapy found that only the DAT1 dopamine transporter gene was significant in characterising non-response to Methylphenidate therapy (Winsberg & Comings 1999). Rommelse and colleagues (2008) systematically reviewed studies linking polymorphisms of the DAT1 to neurophysiological and neuropsychological measures. Most studies did not find a relationship between DAT1 and neurophysiological or neuropsychological measures. However, the meta-analysis indicated that the DAT1 dopamine transporter gene was associated with an increased risk for ADHD (Rommelse et al. 2008).

Rommelse and colleagues’ (2008) found that in their own cohort of 350 children and adolescents with ADHD and 195 non-affected siblings, several of the polymorphisms of DAT1 were associated with ADHD. Although ADHD was associated with impaired neuropsychological functioning, they found no convincing association between any of the DAT1 polymorphisms and neuropsychological dysfunction. They concluded that DAT1 did not mediate neuropsychological performance in ADHD. However, they argued that since DAT1 is mainly expressed in the striatum and not in the pre-frontal cortex, DAT1 may modulate striatum-related functions, such as delay aversion, more significantly than pre-frontal-related functions, such as executive functions (Rommelse et al. 2008).
2.11.2 Adrenergic genes and ADHD

Comings examined the effect of 20 genes for dopamine, serotonin, and noradrenergic metabolism on a quantitative score for ADHD in 336 subjects (Comings et al. 2000b). The results indicated that the adrenergic genes played a greater role in ADHD than either the dopaminergic or serotonergic genes combined. Co-morbid phenotypes, Conduct Disorder and Oppositional Defiant Disorder (ODD), were also found to share genes with ADHD (Comings et al. 2000b).

Bellgrove and colleagues (2006) examined the relationship between sustained attention deficits in ADHD and genetic variation in a catecholamine-related gene (Taq I DBH gene polymorphism) (Bellgrove et al. 2006). The DBH gene encodes Dopamine β-hydroxylase, a copper containing enzyme that converts dopamine to noradrenaline. Variation in the Taq I DBH gene polymorphism was related to sustained attention performance. Children possessing two copies of the ADHD-associated risk allele (A2) had significantly poorer sustained attention than those ADHD children who did not possess this allele or a non-genotyped control group. Bellgrove concluded that the DBH gene may contribute to the susceptibility for ADHD (Bellgrove et al. 2006).

Therefore although a clear-cut mode of inheritance and specific genetic abnormalities are still unclear in ADHD, frontostriatal circuits, dopamine and norepinephrine neurotransmitter systems appear to be involved (Hechtman 1994).
2.12 Overview of Neuroimaging Studies of ADHD

Castellanos proposed a model which encompassed a developmental perspective to ADHD, suggesting that ADHD was best characterized behaviourally as a disorder of self-regulation of executive functioning, and that neuroimaging studies indicate that the responsible regulatory circuits include the pre-frontal cortex and the basal ganglia, modulated by dopaminergic innervations from the midbrain (Castellanos 1999). In the following subsections, neuroimaging studies of ADHD are briefly reviewed to provide an overview of these aspects of ADHD research.

2.12.1 Computerized Tomography (CT)

Computerized tomography (CT) is a neuroimaging technique, which exploits the inverse relationship between the absorption rates of X-rays and tissue density. Brain X-ray scans are reconstructed from X-ray intensity measures and resolution is generally considered coarse. The possible dangers of ionizing X-ray radiation on young developing brains has limited the use of CT in studies involving children, and consequently there are few studies in ADHD using CT (Tannock 1998). The few CT studies comparing ADHD to normal controls found few significant differences; possibly resulting from poor resolution of CT. Shaywitz and colleagues (1983) found no group differences in the size of the lateral ventricles or in the size of the frontal lobes (Shaywitz et al. 1983). However, the usual asymmetry of the frontal lobes were not found in ADHD subjects whose frontal lobes tended to be more symmetrical than
controls (Shaywitz et al. 1983). Nasrallah and colleagues (1986) compared the CT scans of young adults with a history of hyperactivity in childhood to CT scans of a group who required evaluation of head trauma, and found no group differences in ventricular or hemispheric areas. However, they found mild to moderate cortical atrophy in 58% of in the hyperactive group, presumed ADHD. It was unclear, however whether these findings could be explained by co-morbid psychiatric conditions or alcohol abuse, or ADHD alone (Nasrallah et al. 1986).

2.12.2 MRI Studies

Magnetic Resonance Imaging (MRI) studies most frequently rely on the relaxation properties of excited hydrogen nuclei in water in the body’s tissues. Parts of the body to be imaged are placed in a powerful, uniform magnetic field. The spins of some of the atomic nuclei within the tissue align in one of two opposite directions parallel to the magnetic field. The magnetic dipole moment of the nuclei then precess around the axial field. The tissue is then briefly exposed to pulses of electromagnetic energy in a plane perpendicular to the magnetic field. As the high-energy nuclei relax and realign, they emit energy, which provides information about their environment, for example white or grey matter, CSF, blood and bone. MRI images are of much higher spatial resolution than CT and are therefore ideally suited for studying structural and morphological differences between normal and patient groups.

Many research groups have examined and compared the corpus callosum of
children with ADHD with normal controls. Baumgardner and colleagues (1996) found no difference in total corpus callosum volume between ADHD subjects and controls, but found a significant decrease in the area of the rostral body (Baumgardner et al. 1996). Other studies found significantly smaller rostrum and rostral body (Giedd et al. 1994) and smaller corpus callosum area in the region of the genu and splenium and in the area just, bones anterior to the splenium (Hynd et al. 1991). Boys with ADHD were found to have significantly smaller left globus pallidus volume and total globus pallidus volume than normal controls (Aylward et al. 1996). The size of the posterior vermis was significantly decreased in ADHD subjects, and the interior posterior, not the superior posterior lobe, accounted for this decrease (Berquin et al. 1998; Mostofsky et al. 1998).

Semrud Clikeman and colleagues (1994) conducted morphological analysis of seven areas of the corpus callosum on the mid-sagittal slice of 15 ADHD children compared to 15 normal controls, and found that the ADHD group had smaller posterior corpus callosum regions, with the splenium accounting for most of the variance (Semrud Clikeman et al. 1994). There were significant group interactions between the smaller isthmus and splenial regions of the posterior corpus callosum and a diagnosis of ADHD, but no main effects for gender or dyslexia (Lyoo et al. 1996). The study, however was criticised because dyslexia has also been associated with differences in posterior corpus callosum (Rumsey et al. 1996).
Castellanos and colleagues (1996a) increased the number of participants in their earlier study (Giedd et al. 1994) with a larger subject group, including those who participated in the 1994 study. They found no significant differences in the total mid-sagittal area of the corpus callosum, nor in any of the seven areas of the corpus callosum examined (Castellanos et al. 1996a). Another MRI study by the same group examined total mid-sagittal area and seven subdivisions of the corpus callosum of 114 healthy children and adolescents, aged 4-18. Significant effects of age and gender on brain morphometry were found, as well as a high degree of between-subject variability. While these findings suggest that ongoing myelination of higher-association areas occur throughout adolescence, they also illustrate the high degree of variability in brain volume and gender-specific changes during the developing years (Giedd et al. 1996). This is likely to make group comparisons difficult, as between-subject-variability and maturation differences may confound findings.

Overmeyer and colleagues (2000) compared the global brain size and the Calossal Areas of 15 boys with ADHD to 15 healthy male siblings, and found no significant differences for corpus callosum size or any of the corpus callosum areas (Overmeyer et al. 2000). They concluded that clinicians should not base their diagnosis of pathophysiology of ADHD on an abnormality of Calossal development (Overmeyer et al. 2000).

Findings of reduced fiber densities in the genu and splenial regions, using light microscopic examination, (Aboitiz 1992) are consistent with the findings of smaller pre-frontal area in MRI studies of ADHD subjects (Casey et al. 1997a; Castellanos et al.
1996a; Filipek et al. 1997; Hynd et al. 1993; Hynd et al. 1990; Rubia et al. 1999) and reduced posterior parietal white matter in ADHD (Filipek et al. 1997).

The above suggest poor myelination in the fibers that link interhemispheric areas and are consistent with Tucker and Williamson’s model of an asymmetrical neural control network. This network links a left anterior ventral dopaminergic tonic activation system to a right posterior dorsal noradrenergic phasic arousal system in attention (Tucker & Williamson 1984). It also gives substance to Voeller’s suggestion that this asymmetrical neural control system is dysregulated in ADHD (Voeller 1991a, b). Dysregulation in the left frontal aspects of this asymmetrical neural control system is expected to affect concentration and sustained mental effort, while dysregulation in the right posterior dorsal part may affect vigilance and orientation (Tucker & Williamson 1984). The findings of smaller corpus callosum mid-body regions linking interhemispheric sensorimotor areas (Aboitiz 1992), may be related to the sensorimotor integration difficulties, poor fine motor control and disinhibition of motor activity observed in ADHD.

Studies have found a significantly smaller area in the right pre-frontal cortex (PFC) of ADHD children compared to non-ADHD controls, suggesting that dysfunction in right pre-frontal cortex may be associated with ADHD (Casey et al. 1997a; Castellanos et al. 1996a; Filipek et al. 1997; Hynd et al. 1993; Hynd et al. 1990; Rubia et al. 1999).

While MRI morphological studies of the corpus callosum have yielded mixed
results, with some consensus, studies of the basal ganglia have been plagued with controversies. The Filipek and Hynd groups have reported L>R asymmetry of the head of the caudate nucleus in normal subjects (Filipek et al. 1997). On the other hand, Castellanos and colleagues have reported the opposite asymmetry (R>L) (Castellanos et al. 1994b; Castellanos et al. 1996a). Filipek and colleagues (1997) reported that despite similar hemispheric volumes, ADHD subjects were found to have: (a) smaller volumes of the head of the caudate (b) smaller left total caudate, with R>L asymmetry; (c) smaller right anterior-superior (frontal) region and white matter; (d) smaller whole bilateral anterior-inferior region; and (e) smaller bilateral retrocallosal (parieto-occipital) region white matter (Filipek et al. 1997). Hynd and colleagues also found ADHD subjects to have smaller volumes of the left caudate with R>L asymmetry (Hynd et al. 1993). These conflicting findings may be due to cohort effects or methodological differences, and do not allow definitive conclusions.

The volume of the caudate nucleus was found to decrease substantially and significantly with age in normal subjects, while no age-related changes were seen in ADHD subjects (Castellanos et al. 1994b; Castellanos et al. 1996b) leading Castellanos and colleagues to conclude that ADHD was associated with the presence of developmental abnormalities of frontal-striatal circuits. One possible explanation is that children with ADHD may initially have similar caudate nucleus volumes to controls, but fail to undergo the cyclic synaptic pruning and myelination associated with normal development (Pueyo et al. 2000; Thatcher 1992), and which leads to the decrease in caudate volume observed in normal adolescents.
Two studies examined other basal ganglia structures including the putamen and the globus pallidus (Aylward et al. 1996; Castellanos et al. 1996a). While neither study reported differences in measures of volume or asymmetry of the putamen, both studies found reduced volume in the globus pallidus in children with ADHD compared to healthy age matched controls. However, Castellanos and colleagues reported a smaller right globus pallidus in ADHD while Aylward’s team reported a smaller left globus pallidus in ADHD (Aylward et al. 1996; Castellanos et al. 1996a).

Casey and colleagues examined the relationship between fronto-striatal structures and response inhibition deficits in children with ADHD and age-matched normal controls using MRI (Casey et al. 1997a). In all three response-inhibition tasks, they observed significant performance differences between children with ADHD and normal controls. Behavioural performance deficits on the tasks correlated with morphological measures of the caudate, and globus pallidus, but not the putamen. Significant correlations also existed between task performance and predominantly right hemisphere pre-frontal cortex and caudate nucleus anatomical measures. The data suggested a role of the right pre-frontal cortex in suppressing responses to salient but otherwise irrelevant events, and the basal ganglia appeared to be involved in executing these behavioural responses. Hence the data supported a possible involvement of right fronto-striatal networks in response inhibition deficits in ADHD (Casey et al. 1997a).

MRI studies have also examined other brain regions, but there were no significant differences between ADHD and normals in the morphology of the
hippocampus, amygdala, temporal lobe, insula and central grey matter (Castellanos et al. 1996b; Filipek et al. 1997). However, this was not the case for the inferior posterior vermis, which is involved in cerebellar-thalamo-pre-frontal circuits as discussed next.

Using retrograde transneuronal transport of herpes simplex virus in primates, Middleton and Strick (1994) identified subcortical neurons in restricted regions of the dentate nucleus of the cerebellum and in the internal segment of the globus pallidus. These neurons were found to project via the thalamus to area 46 of the pre-frontal cortex, an area known to be involved in spatial working memory and higher cognitive functions (Middleton & Strick 1994). Given these findings, the possibility that cerebellar dysfunction is involved in ADHD was investigated in two MRI studies. Berquin and colleagues (1998) quantified the cerebellar and vermal volumes, and the mid sagittal areas of three vermal regions, of 46 right-handed boys with ADHD and 47 matched controls. They found significantly less vermal volume in the ADHD subjects, predominantly in the posterior inferior lobe and not the posterior superior lobe of the vermis, despite adjustment for brain volume and I.Q. (Berquin et al. 1998). Mostofsky and colleagues (1998) found that the size the interior posterior lobe of the posterior vermis was significantly decreased in subjects with ADHD, while the superior posterior lobe was not involved. The finding of abnormal inferior posterior vermal size suggests that dysfunction within cerebellar-thalamo-pre-frontal circuits may at least in part underlie the motor control, inhibition, and executive function deficits reported in individuals with ADHD (Mostofsky et al. 1998).

While findings of morphological brain imaging studies have revealed a general
pattern of structural differences between frontal striatal regions of children with ADHD and controls, these studies have not positively correlated morphological differences to functional difficulties. Hence functional brain imaging studies have attempted to correlate morphological anomalies with functional deficits. Differences in cerebral blood flow, dopamine metabolism and changes in brain activity under cognitive load have also been demonstrated using Positron Emission Tomography (PET) (Zametkin et al. 1993; Zametkin et al. 1990a), Single Photon Emission Computer Tomography (SPECT) (Amen & Carmichael 1997; Amen, Paldi & Thisted 1993; Amen & Waugh 1998; Dougherty et al. 1999; Krause et al. 2000 May 12; Lou et al. 1998; Lou, Henriksen & Bruhn 1984; Lou et al. 1989a), functional Magnetic Resonance Imaging (fMRI) (Bush et al. 1999; Casey et al. 1997b; Rubia et al. 2000; Rubia et al. 1999; Shaywitz, Fletcher & Shaywitz 1997; Vaidya C.J. et al. 1998), and Steady-state Probe Topography (SSPT) (Silberstein et al. 1998b). PET, SPECT, and fMRI studies will be discussed in the next sections, while SSPT will be discussed fully in chapter 4.

2.12.3 PET Studies

Studies of cerebral glucose metabolism, which measure functional brain abnormalities in ADHD using [18F] flurodeoxyglucose, and PET, have yielded inconsistent results. Adults with histories of hyperactivity in childhood who continued to have symptoms and who were parents of children with ADHD, had global reductions in glucose metabolism. The largest reductions were found in the premotor cortex and the superior pre-frontal cortex, areas previously shown to be involved in the control
of attention and motor activity. However, there were also reductions in the striatum, hippocampus, thalamus, and cingulate gyrus (Zametkin et al. 1990a). A gender effect of >12.7% in this study was larger than the effect of ADHD, thus making interpretation of findings more difficult.

Subsequent studies of adolescents with ADHD and matched controls found significantly reduced glucose metabolism in six of 60 brain regions. Additionally, symptom severity was significantly correlated with reduced metabolism in the left anterior frontal lobe (Zametkin et al. 1993). The global cerebral glucose metabolism in ADHD girls was 15% lower than in normal girls, and 19.6% lower than in ADHD boys, with no differences between girls or boys in the control group (Ernst et al. 1994). However, these findings of reduced glucose metabolism only in girls with ADHD were not observed in a larger subsequent replication attempt study of adolescent girls (Ernst et al. 1997).

Matochik (1993) examined the effects of an acute dose of Methylphenidate or Dexamphetamine on cerebral glucose metabolism compared with no medication in adults with ADHD (Matochik et al. 1993). While the drugs did not change global metabolism, there were distinct patterns of both regional increases and decreases (Matochik et al. 1993). However, chronic treatment with either stimulant had no global effect on glucose metabolism, although Methylphenidate was associated with regional effects in 2 of the 60 brain regions sampled (Matochik et al. 1994).
2.12.4 **SPECT Studies**

Several SPECT studies have found striatal hypoperfusion in ADHD. Lou and colleagues conducted a number of studies using SPECT to measure cerebral blood flow in heterogeneous groups of ADHD children with and without learning disabilities and consistently found striatal hypoperfusion in both clinical groups (Lou 1992; Lou, Henriksen & Bruhn 1984; Lou, Henriksen & Bruhn 1990; Lou et al. 1989b). Brain SPECT imaging in 54 ADHD and 18 non-ADHD controls revealed that 65% of ADHD subjects, compared with 5% of controls, had significant pre-frontal cortex deactivation in response to an intellectual challenge (Amen, Paldi & Thisted 1993). Of the ADHD group who did not show decreased perfusion, two-thirds had markedly decreased activity in the pre-frontal cortices at rest (Amen & Carmichael 1997).

On the other hand, posterior cortical regions were hyperperfused in children with ADHD. Methylphenidate reversed the deficits increasing perfusion in the striatum and decreasing perfusion in primary motor and sensory cortices (Lou, Henriksen & Bruhn 1984; Lou et al. 1989b). However these findings were not reproduced in another study which found that ADHD patients showed less activity in both the left frontal and left parietal regions in comparison to control patients (Sieg et al. 1995). Significant differences have been found between children with ADHD and controls in ratios of the right medial temporal cortex to cerebellum, and the right lateral temporal cortex to cerebellum (Kaya et al. 2002). Decreased cerebral blood flow was found in the right lateral pre-frontal cortex, the right middle temporal cortex, both orbital pre-frontal cortices and both cerebellar cortices in children with ADHD, with increased blood flow...
in some parietal and occipital areas (Kim et al. 2002). There was also evidence that left hemisphere dominance in the pre-frontal cortex significantly increased with age in ADHD cases (Oner et al. 2005).

Overall, these findings indicate that hypoperfusion in the PFC and striatum may have functional significance in ADHD. However, findings have been inconsistent, possibly because of small samples, different and wide age range, particularly given the effect of maturation on brain morphology, medication effects, and inclusion of subjects with co-morbidities.

2.12.5 fMRI Studies

Functional Magnetic Resonance Imaging (fMRI) evaluates differences in localized brain activation during performance of a cognitive task, compared to a no-task baseline. FMRI techniques, such as echo-planar imaging, can permit rapid, sensitive, whole-brain measurements of local blood flow-induced MR signal changes seen during cognitive paradigms. It also has finer resolution than PET or SPECT. This section will provide an overview of fMRI studies relating to ADHD. In a later section (3.4.6), further fMRI studies are presented to support a proposed model of neuronal networks that underpins the attentional system, and which may be dysfunctional in ADHD.

Casey and colleagues (1995) used fMRI to examine the pattern of activity of the pre-frontal cortex in normal healthy pre-pubertal children during performance of a
non-spatial working memory task in which the children observed sequences of letters and responded whenever a presented letter was repeated after a non-identical intervening letter. Consistent activation of the inferior and middle frontal gyri was reliably observed within individual subjects during performance of the working memory task relative to the comparison task in which subjects monitored similar sequences of letters for any occurrence of a single, pre-specified target letter. Activation increased and decreased with a time course that was highly consistent with the task manipulations and correlated with behavioural performance (Casey et al. 1995). In a later study (Casey et al. 1997b), Casey and colleagues also examined developmental differences in patterns of activation in the pre-frontal cortex during performance of a Go/No-Go paradigm. Nine children and nine adults were scanned using gradient echo planar imaging during performance of a response inhibition task, and four general findings emerged: (a) the location of activation in the pre-frontal cortex was similar between children and adults, (b) the volume of activation was significantly greater for children relative to adults, observed predominantly in the dorsal and lateral pre-frontal cortices, (c) activation was distributed across both dorsolateral and orbitofrontal cortices, although inhibitory processes were typically associated with more ventral or orbital frontal regions, and (d) activation in the orbital frontal and anterior cingulate cortices correlated with number of false alarms, consistent with animal and human lesion studies (Casey et al. 1997b). These studies set the scene for the use of fMRI in investigating task performance in children with ADHD.

Vaidya and colleagues (1998) used fMRI to compare the performance of
children with ADHD with healthy controls while they performed two Go/No-Go Tasks, a stimulus controlled and a response controlled task, with and without Methylphenidate. Children with ADHD were found to have impaired inhibitory control on both tasks. When off Methylphenidate, children with ADHD had greater frontal activation on one task and reduced striatal activation on the other task. Further, without Methylphenidate, striatal activation was greater in controls than in ADHD subjects. Frontal activation increased with Methylphenidate in both groups. In the stimulus-controlled task, striatal activation showed a group X drug interaction: Methylphenidate produced increased striatal activation in ADHD subjects but decreased striatal activation in control subjects. The drug improved response inhibition in both groups on the stimulus-controlled task, but improved response inhibition in ADHD children only on the response controlled task. Methylphenidate increased frontal activation to an equal extent in both groups. While the drug increased striatal activation in ADHD children, it reduced it in healthy children. The findings suggested that ADHD was associated with a disorder in frontal-striatal function and its modulation during response inhibition (Vaidya et al. 1998).

The suggestion that ADHD may be associated with dysfunction of pre-frontal brain regions was investigated with fMRI by Rubia and colleagues (1999). Brain activation of seven adolescent boys with ADHD was compared to that of nine matched healthy controls while they were performing a stop task, requiring inhibition of a planned motor response, and a motor timing task, requiring timing of a motor response to a sensory cue. The ADHD subjects showed lower power of response in the
right mesial pre-frontal cortex during both tasks and in the right inferior pre-frontal cortex and left caudate during the stop task, supporting findings that ADHD is associated with subnormal modulation of the pre-frontal systems responsible for higher-order motor control (Rubia et al. 1999). Rubia and colleagues (2000) extended their fMRI study to include data from seventeen healthy adolescent and adult controls during performance of the same tasks. A significant age effect was found for pre-frontal activation in both tasks, supporting their hypothesis that delayed neuronal maturation may account for the frontal hypo-activation and subnormal modulation of the pre-frontal systems in ADHD (Rubia et al. 2000). Hypo-activation of frontal circuits may affect executive control of cognition mediated by the anterior cingulate (Carter, Botvinick & Cohen 1999).

Executive control of cognition may be accounted for by three processes in the anterior cingulate: (a) 'motivated attention', associated with limbic circuitry, (b) 'attention allocation', associated with the resolving of incompatible elicited response tendencies, and (c) 'error detection', associated with performance monitoring. While attention allocation suggests a strategic function, motivated attention and error detection suggest controlled evaluative functions (Carter, Botvinick & Cohen 1999). Using event-related fMRI, Carter and colleagues (1999) found support for their proposal that the anterior cingulate shows both error-related activity as well as increased response-related activity during correct responses associated with response competition. This supports the suggestion of an evaluative as well as a monitoring role in the detection of processing conflicts (Carter, Botvinick & Cohen 1999).
Studies of Macaque monkeys have shown that the anterior part of the cingulate cortex is reciprocally connected with the lateral and medial pre-frontal cortices, premotor, and motor cortical regions (Arikuni, Sako & Murata 1994). This connectivity has prompted researchers to investigate the role of the anterior cingulate cortex in attentional processes and impulse control. The anterior cingulate may play a central role in ADHD as it modulates stimulus selection through focused attention and/or mediating response selection. Using microelectrode single neuron recordings in the human anterior cingulate, Davis and colleagues (2000) found evidence of neuronal activity in 19% of thirty-six individual neurons tested during performance of tasks that require attention and effortful thought. (Davis et al. 2000). The Stroop Word-Color Interference Task requires both attention and impulse control for proper performance (Peterson et al. 1999). Studies of the Stroop effect have consistently revealed activation in the frontal lobe; and more specifically in the anterior cingulate cortex and dorsolateral pre-frontal cortex, two structures hypothesized to be responsible for conflict monitoring and resolution (Spreen et al. 2006).

Children with ADHD made more omission errors on a continuous performance test and performed more poorly on the word and interference portions of the Stroop Word-Color Interference Task, suggesting that ADHD may be associated with problems with perceptual-motor speed and processing (Barkley, Grodzinsky & DuPaul 1992). The Stroop Word-Color Interference Task has therefore been used extensively in tasks measuring or seeking to elicit activation of these aspects of the attentional processes. In an fMRI study using a task-switching version of the Stroop Word-Color Interference
Task, the left dorsolateral pre-frontal cortex was found to be more activated during
task preparation, consistent with a role in the implementation of control. In contrast,
the anterior cingulate was more active when responding to incongruent stimuli,
consistent with a role in performance monitoring (MacDonald et al. 2000).

The Counting Stroop was used to examine whether dysfunction in the anterior
cingulate cognitive division (ACCCD) might contribute to producing core features of
ADHD, namely inattention and impulsivity. ACCCD activity was significantly lower in
the ADHD group. ADHD Subjects activated the frontostriatal-insular network,
indicating that anterior cingulate hypoactivity in ADHD was not caused by globally poor
neuronal responsiveness, but by the hypothesized dysfunction of the ACCCD (Bush et
al. 1999). Hence, the anterior cingulate, while mediating purposeful motivated
interactions with the environment, is also involved in monitoring and control of the
performance of behaviours, functions that have been shown to be impaired in children
with ADHD.

One study that investigated alertness induced by warning cues, reported left
superior parietal and right ventral pre-frontal activity (Konrad et al. 2005). Another
study, using event-related fMRI and the Attention Network Test (ANT), examined the
effects of cues and targets within a single reaction-time task as a means of exploring
the efficiency of the alerting, orienting, and executive control networks involved in
attention (Fan et al. 2005). Strong involvement of the thalamus and of anterior and
posterior cortical sites was found in fMRI contrast during performance of the alerting
task. The contrast to the orienting component revealed activation of parietal sites and
frontal fields. The contrast to the executive control network component of the task showed activation of the anterior cingulate along with several other brain areas. Fan and colleagues (2005) reported that with some exceptions, the brain areas involved in activation, orienting and executive control when performing the ANT task were generally consistent with findings from previous fMRI studies that investigated these in separate tasks. Overall, the fMRI results suggested that the functional contrasts within this single task differentially activated three separate anatomical networks, “activation”, “orienting” and “executive control”. These are all essential components of the attentional system (Fan et al. 2005).

Eimer (2001) had proposed that “selective visual attention system” was also necessary and argued that selective attention involved a dynamic interplay between attentional control systems and sensory brain structures, with frontal and parietal brain regions proposed as constituents of a selective attention system (Eimer & Driver 2001). Event-related fMRI was used during a cued spatial-attention task to differentiate the brain activity related to attentional control from that related to selective processing of target stimuli. Results indicated that superior frontal, inferior parietal and superior temporal cortex were selectively activated by cues, indicating that these structures were part of a network for the voluntary control of attention (Hopfinger, Buonocore & Mangun 2000). While the frontal attentional system was concerned with voluntary control of attention, the arousing, alerting and orienting system has been linked to the thalamus and brain stem noradrenergic neurotransmitter system (Berridge & Waterhouse 2003).
Subjects scanned by fMRI while performing a range of attentional orienting tasks primarily activated left-lateralized pre-frontal, premotor and parietal regions. Clonidine, a noradrenergic H-agonist, impaired behavioural measures of the alerting effect, and attenuated left pre-frontal cortex and insula activity during temporal orienting, as well as right superior parietal cortex activity during spatial orienting (Coull, Nobre & Frith 2001). Coull suggested that the anatomical dissociation between the effects of Clonidine during temporal orienting versus spatial orienting revealed the lateralised effect of the noradrenergic modulation of human attentional orienting (Coull, Nobre & Frith 2001).

Attention allocation and directed attention toward a salient stimulus have been shown to be impaired in children with ADHD, as demonstrated with target detection or oddball tasks (Alexander et al. 2008; Frank, Seiden & Napolitano 1994; Johnstone & Barry 1996; Klorman et al. 1990; Ozdag et al. 2004). Tamm and colleagues (2006) investigated the neural correlates of target detection dysfunction in ADHD using event-related fMRI while participants performed a visual oddball task. ADHD subjects made significantly more errors of commission than controls and showed significantly less activation in the bilateral parietal lobes (including the superior parietal gyrus and supramarginal and angular gyri of the inferior parietal lobe), right precuneus, and thalamus. Tamm concluded that the ADHD subjects demonstrated significant impairments in their ability to direct and allocate attentional resources and that these difficulties were associated with significant aberrations in the parietal attentional system, which is known to play a significant role in attention shifting and detecting
specific or salient targets (Tamm, Menon & Reiss 2006).

Konrad and colleagues found that children with ADHD (relative to controls) recruited deviant brain regions for all three attentional networks: less right-sided activation in the anterior cingulate gyrus during alerting, more fronto-striatal-insular activation during reorienting, and less fronto-striatal activation for executive control. Children with ADHD demonstrated altered brain mechanisms associated with all three attentional networks investigated (Konrad et al. 2006).

Children with ADHD performing a Mental Rotation Task under fMRI showed significantly less activation in right parieto-occipital areas, the right inferior parietal lobe and the right caudate nucleus, confirming previous reports of right striatal-parietal dysfunction in adolescents with ADHD (Vance et al. 2007).

2.12.6 Concluding Remarks on Brain Imaging Studies

Overall, the findings of brain imaging studies of ADHD reviewed here confirm the existence of morphological and functional anomalies in several areas of the brain. However, as discussed, there are mixed findings with regard to the normal asymmetry of the caudate nucleus, the size of the exact calossal area and the size of the caudate nucleus and globus pallidus in ADHD. Despite these discrepancies, there is evidence of involvement of the frontal and pre-frontal cortex, the basal ganglia, the anterior cingulate, and the parietal areas in ADHD. The discrepancies reported may result from cohort effects from the small groups studied, methodological differences among
studies, and software differences in algorithms, scanning parameters, equipment resolution and image reproduction methods. In addition, the considerable between-subject differences, differences about age and gender, complications of co-morbidities and the highly heterogeneous nature of ADHD may account for the difficulties in reaching consensus.

2.13 Overview of Event-Related Potential (ERP) Studies of ADHD

ERPs reflect the brain’s electrical response to a stimulus. However, this response is buried in background electrical activity, which may be of no interest to the researcher and therefore considered as electrical “noise”. Hence, the stimulus is presented repetitively and epochs of EEG, time-locked to the stimulus presentation, are averaged over selected “trials”. This technique tends to result in cancellation of the more randomly occurring noise and increases the signal-to-noise ratio, producing an ERP waveform, which is likely to be representative of the subject’s cognitive processes and information processing. Negative and positive excursions of the ERP waveform occur at specific latencies following the onset of the stimulus. Variations in the latencies and amplitudes of the positive and negative components have been associated with various aspects of cognitive processes and information processing. Two components of the ERP have been associated with attentional processes, and these have been studied extensively in ADHD.

The early negative peak components occur at around 100 and 200 milliseconds
following stimulus onset and are often referred to as the N1 and N2 components respectively. These early negative peak components of the ERP have been studied in ADHD mostly during selective attention tasks, frequently with simultaneously presented visual and auditory stimuli. These so-called “oddball paradigms” require subjects to attend to only one of the two signal modalities. The increased negative amplitude of the N1 or N2 peak to rarely presented stimuli as opposed to frequently presented stimuli is called “mismatch negativity” (MMN), while the difference in amplitude of the N1 or N2 peaks between attended and non-attended ERPs is termed “processing negativity” (PN). The later positive peak component occurs at around 300 to 800 milliseconds following stimulus presentation and is referred to as the P3 component or P300 or P3b, and has maximum amplitude over the parietal area (Klorman 1991b).

Although many different visual or auditory stimuli are used in ERP research of ADHD, the Continuous Performance Task (CPT) is probably the most common stimulus task used. Hence, this section will cover some of the key P300 studies and focus mainly on the ERP studies associated with the CPT.

2.13.1 P300 Studies

The amplitude of the P300 component is increased by task relevance [e.g. designation as a target event requiring a particular response] or salient features such as low probability or novelty. It is also thought to reflect capacity allocation. The
latency of the P300 component is influenced by cognitive, perceptual and memory load. Hence, while P300 amplitude reflects allocation of attention, P300 latency, is thought to mark the conclusion of stimulus evaluation processes (Klorman 1991b).


One of the only studies that reported contrary findings is one by Frank and colleagues (1998) who investigated age-related electrophysiological differences between children diagnosed with Learning Disabilities, ADHD, Learning Disabilities without ADHD, and Conduct Disorder. They found no group differences in P300 amplitude or latency when comparing ADHD with normal controls (Frank, Seiden & Napolitano 1998). Another study that compared groups with co-morbidities found no significant group differences in P300 when comparing ADHD alone to ADHD with co-
morbid Tic Disorder and ADHD with co-morbid conduct disorder (Rothenberger et al. 2000). The researchers found that after 4 weeks on Methylphenidate, there were no group differences in P300 amplitude between medicated children, children with ADHD and non-ADHD controls (Taylor et al. 1993). In another study evaluating Methylphenidate in ADHD, P300 amplitude was significantly larger under Methylphenidate than under placebo, and did not differ from controls (Winsberg, Javitt & Silipo 1997).

Visual Continuous Performance Tasks (CPTs) consistently elicited smaller P300 to target stimuli in children with ADHD compared to controls, and this has been interpreted as reflective of attention deficits (Klorman 1991b). Smaller P300 amplitude in ADHD subjects in visual target detection or oddball tasks, were interpreted as reflective of inappropriate allocation of attentional resources (Holcomb, Ackerman & Dykman 1985). Other studies found no significant group differences for P300 amplitude to stimuli in visual and auditory oddball tasks with and without task relevance. Although, children with ADHD showed smaller, though not significant, P300 amplitudes in the visual attention task (Kemner et al. 1996). In another study using an auditory tone discrimination task, children with ADHD were found to lack the right-biased P300 asymmetry of normal controls, suggesting a right hemisphere stimulus processing impairment in children with ADHD (Oades et al. 1996)

Studies by Brandeis’ European group have used ERP microstates, stable topographic ERP segments that are related to specific stages of processing, and LORETA (a reverse source-localization solution using low resolution electromagnetic
tomography) (Pascual-Marqui, Michel & Lehmann 1994), to examine the ERP
topography of children with ADHD and controls (Banaschewski et al. 2003, 2004;
Brandeis et al. 2002; Brandeis et al. 1998; Steger et al. 2000; Van Leeuwen et al. 1998).
Children with ADHD experienced specific problems with response inhibition. For
example, in the STOP task, subjects with ADHD frequently failed to stop responses to a
primary task when a second signal followed. In the GO task, ADHD children had
attenuated P300-type microstates. The “stop” failures of ADHD children were
preceded by a topographically altered N1 microstate, which coincided with the onset
of the “stop” signal. This suggested altered initial orienting of attention to the primary
signal (Brandeis et al. 1998). LORETA analysis indicated mainly posterior activation for
both groups and increased rather than reduced frontal activation in ADHD children.
These results were interpreted as suggesting that information processing in ADHD may
deviate during activation of posterior attention-orienting mechanisms which precedes
and partly determines inhibitory control difficulties in children with ADHD (Brandeis et
al. 1998). These findings were replicated and extended in a larger multi-centre study
(Brandeis et al. 2002) involving 148 children with diagnosis of severe and pervasive
ADHD and control children aged 8 to 14 years. ERPs were recorded during a cued CPT
A-X task. Reliable attention effects were found in the early N1 component, and P3a
and P3b, with larger amplitudes after cues than distractors, and only minor differences
across clinics. Children with ADHD missed more targets, made more false alarms, and
had larger N1 followed by smaller P3b amplitudes after cues than did controls. Cued-
P3b amplitude correlated with subsequent targets being detected. LORETA analysis of
the cued-P3b revealed that some posterior sources were attenuated in children with
ADHD. The researchers concluded that children with ADHD attended to cues with increased initial orienting (larger N1 component) followed by insufficient resource allocation (attenuated P3b component) (Brandeis et al. 2002).

The same group examined ERP microstates in unilateral and bilateral stimulus presentation at visual, central, and pre-motor stages of response conditions (Steger et al. 2000). They found that ADHD boys had reduced GFP of a P300 microstate for bilateral targets, particularly at occipital sites. Findings of deficits in coping with the coordination demands of the bilateral condition were consistent with the group’s previous findings of reduced P300. This led to the suggestion that children with ADHD had resource allocation difficulties to target processing. In addition they also found longer left hand response reaction-time and reduced GFP in the left unilateral condition in ADHD boys compared to controls, which suggested right hemisphere processing deficits in ADHD (Steger et al. 2000).

However, a number of studies have found reduced P300 amplitude in other clinical groups (Klorman, Coons & Borgstedt 1987), including for example: children with autism (Ciesielski et al. 1995), children with learning disabilities (Frank, Seiden & Napolitano 1994, 1998; Harter, Anllo-Vento & Wood 1989; Klorman 1991b) and adults with Schizophrenia (Bernstein et al. 1985; Gruzelier 2002; Javitt et al. 1995). These findings suggest that reduced P300 amplitude may not be specific to attention deficit disorder (Klorman 1991b), but that the main correlates of P300 abnormalities in these patient populations relate to processing difficulties and not “attentional” problems (Frank, Seiden & Napolitano 1998).
Although abnormalities in the amplitude of the P300 component have been the most commonly studied aspect of the ERP in ADHD, studies have also reported increases in the latency of the P300 component. P300 latencies to visual stimuli have been found to be longer in ADHD subjects than in normal controls. As such, it has been suggested that children with ADHD have slower stimulus evaluation and difficulties in attentional processes (Holcomb, Ackerman & Dykman 1985; Strandburg et al. 1996a; Sunohara et al. 1997; Taylor et al. 1993). In another study, P300 latency in ADHD increased across subsequent blocks of a visual target detection task. Researchers concluded that the deterioration of these processes over time was consistent with observations that children with ADHD have difficulties sustaining mental effort (Holcomb, Ackerman & Dykman 1985).

Shorter P300 latencies have been reported in children with ADHD performing an auditory selective attention task (Loiselle et al. 1980) and during a visual categorization task (Robaey et al. 1992). Robaey (1990) found that the overall latency of the parieto-occipital P300 component in the left hemisphere, decreased with age for words but not for pictures in their control group, but not in the ADHD group (Robaye et al. 1990). In a later study, Robaye (1992) suggested that shorter P300 latencies in children with ADHD may be on account of faster processing of the physical attributes of the visual stimuli, resulting in more errors (Robaey et al. 1992). Children with ADHD had shorter P300 latencies, when responding to attended tones compared to non-attended tones, than normal controls, suggesting that ADHD children did not devote adequate time to processing task relevant information (Loiselle et al. 1980).
P300 latency did not differentiate between groups of reading disabled, ADHD and normal controls (Holcomb, Ackerman & Dykman 1986). Contradictory findings for P300 latency may result from the differences in the tasks used to elicit ERPs in these studies. As discussed previously, it appears that when processing visual stimuli, children with ADHD have slower stimulus evaluation as well as attentional difficulties. Their processing and attentional capacity also deteriorates over time when longer mental processes are demanded by the task. On the other hand, shorter P300 latencies in ADHD children may result from faster processing of the physical attributes of the visual stimuli, or to less efficient regulation of processing speed in accordance with task demands (Loiselle et al. 1980; Robaey et al. 1992).

Brown and colleagues (2005) investigated whether ERPs from an inter-modal oddball task could differentiate between two previously identified, predominantly inattentive ADHD subgroups, each with a previously identified EEG profile. The non-target stimulus in the inter-modal oddball task consisted of a counter-phasing checkerboard and the target was a 2000 Hz auditory tone. Stimuli, 20% of which were targets, were presented at a fixed inter-stimulus interval of 1.03 seconds and participants were required to count all targets. The first inattentive ADHD subgroups had cortical hypoarousal (excess slow-wave activity), and the second had maturational lags (EEGs resembled those of younger children, due to a lower dominant frequency). The procedure successfully differentiated between controls and the ADHD children, who had smaller N1, P2, and P300 amplitudes when presented with both the auditory targets and the visual non-targets. Thus, it was concluded that a
generalised stimulus registration, facilitation and processing deficit was occurring in
the inattentive subtype of ADHD. The only difference between the two EEG-defined
subtypes was a relative increase in left-frontal N1 amplitude in the cortically
hypoaroused group (Brown et al. 2005).

ERPs were recorded in children with ADHD and controls during what is known
as, the Stop Signal Task, a two-choice reaction-time paradigm, in which subjects are
required, to withdraw their response upon presentation of a "Stop Signal", in 25% of
the trials (Liotti et al. 2005). Controls demonstrated more successful inhibitions than
failed inhibitions, with greater amplitude of a positive wave peaking around 320 ms
over the anterior medial frontal scalp (P3a). In addition, children with ADHD exhibited
a markedly reduced error-related negativity. Error-related negativity is a sharp
negative wave that is present on error trials in choice reaction-time experiments,
peaking 100 ms after motor onset, and distributed over anterior medial frontal scalp.
The scalp distribution of P3a and the error-related negativity was consistent with a
reduction of activity in the dorsal anterior cingulate cortex and suggestive of a global
deficit in cognitive control operations in ADHD (Liotti et al. 2005). The same group
examined the relationships between the phase of narrow-band EEG activity at stimulus
onset and the resultant ERPs in an auditory oddball task.

Barry and colleagues (2009) used an auditory oddball task, which varied both
stimulus intensity and active versus passive task requirements between groups. At a
number of frequencies, (in 1Hz bands ranging from 1 to 13 Hz), phase-defined brain
states associated with more efficient processing of the stimulus were confirmed. These
were reflected in differences in latency and/or amplitude of all ERP components, and provided evidence of the operation of the three separate phase-influenced mechanisms. The preferred brain states occurred similarly across groups, suggesting that they reflect reflexive aspects of brain function associated with the timing of the stimuli, rather than voluntary attention. It was therefore concluded that markers of cognitive function, such as the P300 are helpful indicators of perceptual and cognitive processing efficiency (Barry et al. 2009c).

2.13.2 ERP Studies Associated with CPTs

Continuous Performance Tasks (CPTs) have been used in conjunction with ERPs to examine attentional processes in ADHD in a number of studies which are reviewed in this section. In two versions of the CPT, P300 amplitude was lower and P300 latency was longer in ADHD compared to normal subjects. Since the early components were normal, these findings were interpreted as indicating reduced involvement in post-decisional processing, (Strandburg et al. 1996a). CPT-X task performance was significantly worse and P300 amplitude to both targets and to non-targets was reduced in hyperactive ADHD children compared with controls (Klorman et al. 1979). The CPT-X is an uncued task, whereby the letter X is presented as a target amongst other non-target letters. In a later study, similar findings were found only for P300s to targets in a CPT-BX, a task similar to the CPT-AX, but using a “B” as a cue instead of an “A”. (Michael et al. 1981). It was therefore suggested that children with ADHD had T deficits in sustained attention resulting from deficits in attentional capacity (Klorman 1991b).
The P300 elicited by the appearance of the letter X preceded by the letter A in the CPT-AX task were recorded at occipital (Oz), parietal (Pz), central (Cz), and frontal (Fz) leads in 16 children with ADHD and 16 normal controls (Overtoom et al. 1998a). Children with ADHD had smaller parietal P300 waves, associated with attention deficits, but did not have smaller N2 waves at Fz or Cz. Since N2 reduction is associated with inhibition, these results did not support the hypothesis of inhibition deficits in that ADHD group. The authors concluded instead that task processing deficiencies in the ADHD group was related to attention rather than to response inhibition (Overtoom et al. 1998a). The next study reviewed used a CPT-AX task in conjunction with erp recording at a larger number of electrode sites.

ERPs were recorded at 30 electrode sites while 11 children with ADHD and 9 normal controls performed the CPT-AX so as to assess preparatory processing, a concept purported to be mediated by the frontal lobes. While no significant group differences were found in the topography of ERP microstates, children with ADHD displayed reduced global field power (GFP), defined as the spatial standard deviation over all voltages in a map. GFP reductions were found in an early P300 microstate to the presentation of the “A” cues but not to the target “X” in the ADHD group. This indicated impaired orienting to cues involving a posterior attention system, rather than impaired executive target processing involving frontal processes. Low resolution electromagnetic tomography (LORETA) indicated that posterior sources may underlie these orienting processes and deficits in ADHD. These findings did not support previous suggestions of frontal lobe involvement in initial processing stages, but
suggested involvement of a posterior attention system instead (Van Leeuwen et al. 1998).

Reduced GFP was also found in a P300 microstate following presentation of the letter A cue in the CPT-AX task in children with ADHD (Brandeis et al. 2002). The P300 amplitude to the cue was correlated with both the speed and the accuracy of response to the target X. This suggested that the cue P300 microstate represents a measure of preparedness in orienting to potential targets in a cognitively critical but behaviourally inactive period of the CPT-AX task. Brandeis and colleagues (2002) suggested that there was insufficient phasic activation of the posterior attention system manifesting as reduced posterior P300 in the ADHD subjects. The reduced P300 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, followed by insufficient resource allocation, suggested by reduced P300 amplitude (Brandeis et al. 2002). However, the findings of increased N1 amplitude are at odds with previous findings of reduced N1 amplitude in ADHD compared to controls (Loiselle et al. 1980; Satterfield, Schell & Nicholas 1994). The differences may be accounted for by the differences in the nature of the tasks. For example, in the CPT-AX task, the N1 component was elicited by a cue. In contrast, in the visual and auditory oddball paradigms there were no cues. These differences highlight the importance of taking the nature of the tasks used in ERP studies into account when interpreting findings.

Banaschewski and colleagues (2003) also recorded ERPs were during a cued
continuous performance test (CPT-A-X), ERP-microstates and Global Field Power (GFP) were analysed. GFP is the moment when maximum scalp electrical activity occurs in a microstate and can be considered as a reference-free characteristic measure of the hilliness (i.e., standard deviation of potential at electrodes with regard to an average reference) of a potential landscape calculated from EEG data (Brandeis et al. 1995).

Children with ICD-10 HD (ADHD) and ODD/CD-only but not co-morbid children displayed reduced P3a amplitudes to cues and certain distractors (distractor-X) linked to attentional orienting (Banaschewski et al. 2003). The researchers concluded that children with ADHD combined type without ODD/CD, suffered from a more general deficit of suboptimal state regulation of energy, including deficits of attentional orienting and response preparation than just a response inhibitory deficit. They concluded that this supported the notion of an involvement of a dysregulation of the central noradrenergic networks. On the other hand, their findings contradict the notion that ADHD+ODD/CD represented an additive co-occurrence of ADHD and ODD/CD. Instead they strongly suggested that their results revealed a separate pathological entity than those identified in ICD-10 as either HD (ADHD) or ODD/CD (Banaschewski et al. 2003). Motor response control during a cued CPT-A-X task was used to investigate task performance and ERP parameters in children with ICD-10 hyperkinetic disorder (ADHD), hyperkinetic conduct disorder (HCD) or oppositional deviant/conduct disorder (ODD/CD) (Banaschewski et al. 2004). Evidence for an inhibition-specific deficit was examined and analysed for possible deviations that may be specific to ADHD/HCD. ERP measures specific for response inhibition were not different between the groups. However, children with HCD committed more errors
and their ERP measures differed most from normal controls. Children with ADHD-only committed more errors and their ERP measures differed most from normal controls during processing of the warning stimulus for motor preparation. Banaschewski suggested that ADHD symptoms could not be fully explained by an inhibition-specific deficit, but that impaired response execution processes were also implicated in the disorder (Banaschewski et al. 2004).

High density electrical mapping was used to index ERPs in subjects performing parametric variations of the CPT-AX task (Dias, Foxe & Javitt 2003). Activation patterns related to overriding a prepotent response (Go to No-Go) differed markedly from those associated with overriding a prepotent non-response (No-Go to Go). Dipole source mapping suggested that withholding a prepotent response (inhibition) is reflected primarily in anterior cingulate/dorsolateral pre-frontal cortex activity during the 350-450 ms latency range following presentation of the No-Go. In contrast, preparing to respond is reflected in activity in the parietal region during the same latency range, followed by a prolonged frontal negativity (contingent negative variation; CNV). Similar patterns of activation were observed whether the changes in preparation were triggered by cue or target stimuli, though target-elicited potentials peaked earlier (Dias, Foxe & Javitt 2003).

Fallgatter and colleagues (2004) investigated mechanisms and structures underlying pre-frontal response control and inhibition in boys suffering from ADHD during performance of a CPT. A post-hoc electrophysiological source localization method was used to analyse the data. Results revealed that boys with ADHD had a
significantly diminished central NO-GO P3 compared to controls. In addition, they lacked the frontal NO-GO-related positive brain electrical field seen in controls. This was associated with a significantly reduced activation of the anterior cingulate cortex in the ADHD boys in the NO-GO condition of the CPT (Fallgatter et al. 2004).

Egner and colleagues (2001) used a Go/NO-GO CPT task as a behavioural measure to evaluate changes in omission and commission errors following Neurotherapy. EEG operant enhancement of the SMR (12-15 Hz) component was associated with reduction in commission errors and improved perceptual sensitivity on a Continuous Performance Task (CPT) in healthy volunteers, while the opposite relation was found for 15-18 Hz enhancement, when controlling for SMR effects. However, both 12-15 Hz and 15-18 Hz enhancement were associated with significant increases in P300 event-related brain potential amplitudes in an auditory oddball task. These relations are interpreted as stemming from band-specific effects on perceptual and motor aspects of attention measures (Egner & Gruzelier 2001). Egner’s (2001) study demonstrated that EEG operant enhancement produced frequency-band-specific changes in healthy volunteers. When used in a patient population, the term Neurotherapy is commonly used. Neurotherapy was used in the present research to treat children with ADHD, and it is discussed in the next chapter.
Chapter 3 - Neurotherapy and the Attentional System

As discussed in chapter 2, there is a need for a more effective, long-term solution with fewer adverse side effects to the treatment of ADHD. In this chapter, studies that indicate that children with ADHD have abnormal conventional and Quantitative EEG are reviewed as part of the rationale for the use of Neurotherapy. The most relevant models of neural control networks that underpin the attentional system are discussed and evidence from fMRI studies that point to dysfunctions in these systems in ADHD are examined. Neurotherapy is then discussed in the context of its attempt to redress the anomalies identified in the neural control networks of attention in ADHD.

Finally, Neurotherapy studies are examined in broad categories, namely: (a) early studies prior to 1985, (b) uncontrolled studies, (c) controlled studies, and (d) studies comparing the effectiveness of Neurotherapy to stimulant medication. Within each category, the studies are presented chronologically to give the reader a grasp on the development of Neurotherapy research and clinical practice over the last four decades.

Much of the criticism aimed at Neurotherapy studies is common to each of these groups. Consequently to avoid repetition, in this review published criticism and replies to these concerns have been grouped together in section 3.13.
## 3.1 Neurotherapy: EEG Biofeedback or Neurotherapy

In this section, Neurotherapy is discussed in broad terms to introduce the
methodology as a concept and as a clinical practice in the treatment of ADHD. To avoid confusion and for the sake of consistency, throughout this thesis, the term Neurotherapy has been used to replace the terms: Electroencephalographic Biofeedback, EEG Biofeedback, and Neurotherapy. Furthermore, EEG discussion will be limited to the electrical activity measured at scalp electrodes.

Electrical activity measured at scalp electrodes originate from cortex, but provide a diffuse picture of the underlying brain electrical activity. Electrical signals are considerably attenuated by the intervening arachnoid membrane, dura mater, skull, scalp muscles and skin (Zappulla 1991). Nevertheless, despite this limitation, scalp recordings can provide valuable information on brain function with high temporal resolution, measured in milliseconds. Hence brain electrical activity indexes the substrate of cognition and behaviours and their analysis can elucidate the functional origins of these domains (Hughes & John 1999).

Although the brain’s electrical activity mediates thoughts and behaviours, people do not have conscious awareness of this neuronal activity (Balkin et al. 2002). However, through Neurotherapy, a representation of the brain’s electrical activity can be displayed on a computer screen, providing an opportunity for individuals to influence this electrical activity in real time through “operant conditioning of the EEG” (Abarbanel 1995). Neurotherapy, is based on the learning theory principles of Applied Behaviour Analysis (ABA) and its practical application, Intensive Behaviour Modification (McEachin, Smith & Lovaas 1993). ABA is based on the principle that rewarding a response associated with a particular behaviour may cause that behaviour
to be shaped and controlled. In Intensive Behaviour Modification, the therapist gives an instruction (the antecedent), the subject produces the correct desirable behaviour (the behaviour), which is then rewarded (the consequence), thereby increasing the likelihood of the behaviour being produced more frequently (Lovaas 1987; McEachin, Smith & Lovaas 1993). During Neurotherapy, the “antecedent” is the effort applied to change an EEG parameter, the change in the EEG parameter is the “behaviour” being modified, and the Consequence is an audio/visual reward provided by the Biofeedback System when the correct EEG parameter is produced (e.g. discrete tone, token counter, game, or video strip playing). The production of the desired behaviour (a change in an EEG parameter) is repeatedly rewarded; resulting in the likelihood of an increase in the production of that particular EEG parameter and associated improvements in the behaviours underpinned by that EEG parameter (Lubar 1991b; Nash 2000a).

Typically, during a Neurotherapy Session, patients view a computer screen, which displays a representation of their brainwave activity obtained via EEG sensors on the scalp. The EEG is processed through digital Neurotherapy software. Features of the processed EEG, namely, amplitude of frequency bands such as Theta, SMR or Beta, are represented on the computer display as bar graphs and used to activate a game in accordance with an algorithm of reward/inhibit criteria.
Visual and auditory feedback reward is provided by the software, contingent on pre-selected criteria being met. In its simplest form, the visual feedback can be presented as bar charts whose levels vary in sympathy with specific brainwave activity. Audio feedback can be provided in the form of a tone which comes on when the desired criteria are reached (Lubar et al. 1995a). Audio/visual feedback can also be in the form of a game, whereby the game only proceeds if the specific brainwave activity meets preset criteria (Lubar et al. 1995a). Initially, as in any learned skill, the EEG changes produced Neurotherapy may be transient, as they are consciously produced during the training session. However, as predicted by learning theory, when the training is repeated often enough, the changes endure, generalise and eventually become crystallized learned skills which carry over to different situations (Lubar et al. 1995a).

3.1.1 Overview of the Generation of EEG Rhythms

Andersen and Andersson (1968) were amongst the first to propose that the
alpha rhythm resulted from the firing pattern of thalamic pacemakers, and that this in turn produced thalamo-cortical oscillations which were picked up as EEG on the surface of the scalp (Andersen, Andersson & Lomo, 1968).

Support for this view was provided by experimental evidence that decorticated cats still produced 12-17 Hz. sleep spindles from thalamic pacemakers independent of the cortex (Morison & Basset, 1945). Sterman demonstrated in his work with cats that signals from somatosensory pathways were conveyed to the cerebral cortex through ventrobasal (VB) relay nuclei in the thalamus (Sterman & Fairchild, 1966). Sterman discovered that when relay cells in these thalamic nuclei become hyperpolarized, they produce a unique burst of discharges, which are relayed to the cortex and, simultaneously to the Nucleus Reticularis Thalami (nRt), which in turn respond with a similar burst of activity. The output of nRt cells are directed back to the VB, releasing the inhibitory gamma amino butyric acid (GABA) neurotransmitter, which again hyperpolarizes the relay cells. This hyperpolarisation initiates another slow depolarization and burst discharge in the relay cells, and the process is repeated causing an oscillation (Sterman, 1996b). Sterman (1996a) described how the feedback between these thalamic cells produces a recurrent oscillatory discharge, which entrains thalamic relay cells.

Furthermore, synchronous volleys of discharge are projected to columns of functionally-related cortical cells, which respond synchronously resulting in rhythmic summations of field potentials, which can be recorded as EEG at the surface of the
cortex, or as scalp potentials. Sterman’s work showed that attenuation of somatosensory input alone can initiate the oscillatory process in thalamic relay cells (Sterman 1996b).

Sterman (1996) reported that transection of spinal somatosensory fibres at a high cervical level, or lesions of brain stem components of this pathway in cats, resulted in a significant increase in both SMR and sleep spindle activity (Bowersox & Sterman 1982; Shouse & Sterman 1979). SMR and sleep spindle activity also increased during physical restraint of cats and primates and in humans with high spinal cord injuries (Sterman et al. 1977). Sterman (1996) concluded that during active behaviour, a number of excitatory sources act on VB thalamic relay neurons to maintain depolarization, suppress bursting in VB and nRt cells and, thus, reduce or eliminate thalamo-cortical SMR EEG rhythms. On the other hand, during inactive behavioural states, attenuation of somatosensory inputs can hyperpolarize VB cells, promoting oscillatory discharges, and initiating SMR rhythms. In his SMR studies with cats (Sterman, Lucas & MacDonald 1972; Sterman, Wyrwicka & Howe 1969; Sterman, Wyrwicka & Roth 1969) and humans (Sterman 1973a, 1981; Sterman, Macdonald & Stone 1974; Sterman & Shouse 1980) Sterman demonstrated that operant conditioning of the production of SMR resulted in the cats and human subjects becoming more proficient at producing behavioural stillness and at increasing SMR.

Another school of thought regarding the generation of EEG rhythms proposed that almost all EEG arises from cortico-cortical loops (Nunez 1995; Thatcher, Krause & Hrybyk 1986). Silberstein (1995) described a model of EEG generation based on
resonant loops between macro-columns of neurons in the cortex with the loop length determining the resonant frequency. For example, given two neuronal regions (R1 and R2), a resonant loop could be formed by forward excitatory projections mainly from layers 2 and 3 of R1 to layer 4 of R2, and inhibitory projections from layer 2 and 3 of R2 to layer 1 of R1. Local resonances are those that occur between adjacent macro-columns and are responsible for producing gamma frequencies (above 30 Hz.) in the EEG. Regional resonances develop between macro-columns that are several centimeters apart and produce the intermediate frequencies such as alpha and lower-beta frequencies. Silberstein (1995) described global resonances as those between the more widely separated frontal-occipital and frontal-parietal regions, and are responsible for the production of delta and theta frequencies. Since the loop-length determines the frequency being generated, there are an almost infinite number of individual frequencies that can be generated. These resonant loops can be driven by thalamo-cortical pacemakers which induce oscillations in cortico-cortical loops (Silberstein 1995).

Silberstein (1995) described the relationship between the brainstem neuromodulators: acetylcholine, norepinephrine, dopamine and serotonin, and the frequencies of resonant loops. Increases in serotonin neuromodulation are associated with hypercoupled states in large resonant loops that produce global resonances. These lead to the slower frequencies, theta, and delta. Increases in neuromodulation by acetylcholine, norepinephrine, and dopamine are associated with hypocoupled states in small regional and local loops leading to the higher frequencies in the EEG,
high-beta and gamma. Thus, each specific brain activity or particular mental state, has an optimal coupling level for optimal performance (Silberstein 1995).

In the next section, EEG and QEEG studies of children with ADHD are examined to establish the framework that links abnormal EEG and QEEG findings, to the rationale for the operant conditioning of abnormal EEG as a treatment for ADHD.

3.2 Relevance of EEG studies of ADHD to Neurotherapy

Early EEG studies found that children with ADHD exhibited EEG abnormalities such as excess slow-wave activity and epileptiform (spike and slow-wave complexes) (Satterfield, Cantwell & Satterfield 1974; Satterfield et al. 1974). These early findings were largely interpreted as indicating the presence of abnormal brain processes in children with ADHD. More specifically Satterfield viewed these as a maturational delay manifesting as cortical underarousal (Satterfield et al. 1972). In the last 30 years or so, Quantitative EEG (QEEG) studies have provided better quantification of the EEG. Fast Fourier Transform and computational techniques have allowed for detailed analysis of absolute and relative power and amplitude values for specific frequency bands of activity. Furthermore, analyses of coherence, phase, brain electrical activity mapping and source localization using LORETA have become more commonplace in clinical practice (Thatcher 1998).
3.2.1 Overview of Conventional EEG Findings in ADHD

Surface electrical activity measured from scalp electrodes consist of complex waves believed to result mostly from the activity of dipoles in columns of underlying neurons (Nunez, 1995). These dipoles generate electricity in thalamo-cortical and cortico-cortical loops generating the scalp’s brain electrical activity (Nunez, 1995). Conventional EEG analysis consists of examining the EEG recording for spike and wave complexes (epileptiform) and for age-inappropriate excesses or deficits of particular frequencies in the individual EEG traces (Hughes & John 1999).

A review of early studies of conventional electrophysiological measures of ADHD children was inconclusive. It was concluded that the resting levels of autonomic functions in hyperactive children were “probably not under- or over aroused”, although some were reported to display resting cortical underarousal (elevated alpha). Findings of studies that examined the impact of stimulation on autonomic functions suggested that some hyperactive children are probably under-reactive to environmental stimulation, or are "underarousable". In evoked-response studies, children with ADHD consistently erred in the direction of "underarousability" (Hastings & Barkley 1978; Rosenthal & Allen 1978).

EEG studies of children with ADHD have generally found more low-frequency cortical electrical activity than in controls particularly in frontal regions (Burnett & Struve 1974; Jus, Andrzejewska & Jus 1968; Kinze 1984; Satterfield et al. 1973; Tresohlava & Vajnorsky 1977). Halperin and colleagues (1986) examined the EEG of 66 mildly sedated hyperactive children and found that 48.5% had abnormal EEGs.
(Halperin et al. 1986). Small (1993) reviewed EEG studies of children with ADHD and concluded that between 30% and 60% of the children in these studies had abnormal EEGs, the incidence of which decreased with age (Small 1993). On the other hand, another conventional EEG examination study (Phillips et al. 1993) revealed that only 1 of 11 ADHD children had an abnormal EEG. As such, the authors concluded that routine EEG examination may be of limited value in ADHD (Phillips et al. 1993). The view that conventional EEG examinations was not particularly useful in ADHD diagnosis and treatment was further supported by findings that abnormalities in conventional EEG examinations did not correlate usefully with medication response (Small 1993).

### 3.2.2 Overview of QEEG Findings in ADHD

While the conventional EEG is mostly concerned with the detection of epileptiform and abnormal waveforms, quantitative EEG (QEEG) is the process of converting artefact-free background EEG signals into their component frequencies and analysing them statistically. This process allows for comparisons to be made between ADHD participants’ brain electrical those of normal controls, or to those in normative databases consisting of hundreds of age-appropriate normal subjects (Hughes & John 1999).

In QEEG analysis, the EEG is recorded from scalp electrodes placed according to the Ten-Twenty International Standard at 19 electrode sites (Thatcher 1998). The EEG signal at each electrode is decomposed into frequency bands using a mathematical
technique known as Fast Fourier Transform. The labeling of these bands is generally as follows: Delta (1-3.5 Hz), Theta (3.5-7.5 Hz), Alpha (7.5-12.5 Hz), and Beta (12.5-40 Hz) (Hughes & John 1999). Although all frequencies are present in all brain states, dominant delta is associated with deep sleep, theta with drowsiness, dreaminess and tuning off, alpha with alert wakefulness, and beta with information processing. Despite their arbitrary labels, excesses or deficits in these “clinical” bands have been associated with psychiatric and behavioural problems (John 1976, 1989).

Normally, theta power levels decrease with age in children, while alpha, and to a lesser extent beta power levels, increase from childhood to adulthood (Gasser et al. 1988; John et al. 1977). Findings of abnormal power spectra compared to normal subjects have been given various interpretations.

Satterfield and colleagues (1984) obtained event-related potentials (ERP) and EEG power spectrum data from 138 hyperactive and 60 normal boys. Hyperactive boys who were younger than 7.5 years of age had decreased power across all frequency bands, whereas older boys had increased alpha and beta power compared to normal boys. These findings may in part reflect activation resulting from visual and auditory processing while watching a cartoon during EEG recording. However, they also highlight the importance of accounting for age in electrophysiological studies of young children. The authors concluded that the data strongly suggested an abnormal brain maturation process in hyperactive children (Satterfield et al. 1984). Mann (1992) found elevated theta power at frontal sites in children with ADHD, and suggested that these findings may reflect a possible maturational delay in children with ADHD (Mann et al.
1992). Matsuura and colleagues (1993) came to the same conclusion when they found more delta and theta waves and fewer alpha wave in a study of 91 children with ADHD, from Japan, China, and Korea (Matsuura et al. 1993). Clarke and colleagues (1998) found increased theta power in children with ADHD in all regions. However, they found that frontal theta was greater in children with the Combined Subtype of ADHD, than in those with the Inattentive Subtype of ADHD, possibly accounting for higher levels of problematic behaviours in the Combined Subtype (Clarke et al. 1998).

Using a much larger number of subjects and measures, Chabot and colleagues (1996) also found increased theta and other EEG power spectra variants in 407 Australian children carefully screened for ADHD compared to the Neurometric Normative Database (John et al. 1977). Theta increases were greatest in frontal regions, but they also found other consistent QEEG patterns, which clustered into five subgroups that accounted for 98% of their subjects. The significant QEEG findings that distinguished each of these clusters from the Neurometric normal population (John et al. 1977) were as follows: (a) **Cluster 1** was characterised by a generalized excess of alpha and a deficit of delta absolute and relative power, frontal theta and alpha hypercoherence and parietal and posterior temporal power asymmetry. Within this cluster, 75.5% of children exhibited a positive response to stimulants, 18.4% had no measurable changes to medication, and 6.1% had adverse responses. (b) **Cluster 2** was characterized by a generalized excess of theta absolute and relative power, decreased alpha mean frequency, and frontal theta hypercoherence. Of the children within this cluster, 50.8% exhibited a positive response to stimulants, 33.9% reported no
measurable changes, and 15.2% had adverse response. (c) **Cluster 3** was characterized by a generalized deficit of theta, alpha, and beta absolute power, a generalized excess of delta, and a deficit of alpha relative power, frontal alpha hypocoherence, and normal power asymmetry values. (d) **Cluster 4** was characterized by excess frontal/central delta and theta and a generalized deficit of alpha absolute power; generalized delta and theta excess, and an alpha deficit of relative power; decreased theta and alpha mean frequency; frontal and central alpha hypocoherence; and atypical frontal, central, and temporal power asymmetry. (e) **Cluster 5** was characterized by essentially normal QEEG findings, although there was a non-significant frontal elevation of delta absolute and relative power.

Chabot and colleagues (1996) used a discriminant function, utilising nine QEEG variables to distinguish between: (a) normally functioning children, (b) children with normal-I.Q. and attention problems. (c) Children with Low-I.Q. and attention problems. The discriminant function resulted in 94.8% correct classification of normal children and 93.1% correct classification of the normal I.Q. children with attention problems. Split-half replication resulted in a specificity of 88% for normal children and a sensitivity of 93.7% for ADHD and children with attentional problems. A total of 95.4% of the low-I.Q. group of children with attention problems were classified as abnormal (Chabot & Serfontein 1996).

Findings of increased slow-wave (delta and theta) brain electrical activity and decreased alpha and fast-wave (beta) activity have been interpreted as suggestive of cortical under-arousal and reduced information processing (Ackerman et al. 1994;
However, not all children with ADHD have increased slow-wave activity. Studies have also found increased beta activity in 13-20% of children with ADHD compared with normal controls, which suggests increased mental activity and/or over-arousal (Chabot & Serfontein 1996; Clarke et al. 2001; Kuperman et al. 1996). Thus the data suggested that ADHD could be characterised by both hypo-arousal and hyper-arousal and that QEEG patterns of children with ADHD suggested deviations from normal development, rather than maturational lag (Chabot & Serfontein 1996).

Similarly, Hermens and colleagues (2005) also argued for deviations from normal development, rather than maturational lag in ADHD. They found that theta power, across both left and right frontal sites, correlated positively and significantly to oddball task errors, with the most robust associations being observed between left frontal theta and oddball task errors in ADHD participants. They speculated that excess frontal theta makes a central contribution to signal detection deficits in ADHD (Hermens et al. 2005b). They suggested that since the oddball task taps the ability to extract task-relevant signals from task-irrelevant background "noise", their findings support the notion that abnormal frontal theta activity in ADHD is related specifically to difficulties with signal detection. They proposed that inattention is a fundamental characteristic of ADHD, with underlying brain disturbances manifested as excess frontal theta leading to signal/noise discrimination deficits (Hermens et al. 2005b).

Elevated resting theta has previously been interpreted as an index of inattention in ADHD (Mann et al. 1992; Monastra, Lubar & Linden 2001).
Consequently, normal levels of resting theta may be necessary for good performance in attention-demanding tasks. Therefore Hermens (2005b) argued that, since the correspondence of increased theta coupled with poorer performance is present across age groups, excess theta reflects a developmental deviation, rather than a maturational lag in ADHD (Hermens et al. 2005b).

However, it cannot be assumed that EEG slowing is characteristic only of ADHD. Children with learning disabilities were evenly distributed in all of the five ADHD clusters identified by Chabot (1996), and EEG slowing has been associated with Learning Disabilities in several studies (Ackerman et al. 1994; Becker et al. 1987; Chabot et al. 1996; Dykman et al. 1982; Hughes & John 1999; Lubar et al. 1985). Both Clarke (2001) and Chabot (1996) concluded that the heterogeneous nature of EEG profiles of children with ADHD and Learning Difficulties needed to be considered when using QEEG as a tool in the diagnosis and differential classification of children with ADHD into neurophysiologic subtypes (Chabot & Serfontein 1996; Clarke et al. 2001).

3.3 **The Rationale for Neurotherapy**

According to Sterman (1996), the theoretical rationale for the use of Neurotherapy arose from Neurophysiological research. This research aimed to clarify the relationship between scalp EEG and thalamocortical and cortico-cortical mechanisms responsible for EEG rhythms and frequency modulations (Monastra et al. 2006; Silberstein 1995; Steriade, Gloor & Llinis 1990; Sterman 1996b). Much of this
research indicated, as reviewed in section 3.1 and 3.2, that Children with ADHD had excessively high power levels of slow-wave (theta and alpha) electrical activity. Consequently, the empirical rationale for Neurotherapy has been that if the abnormal slow-wave power levels found in ADHD can be normalised, then the underlying neurophysiological dysfunctions and the associated behaviours may also normalise (Abarbanel 1995; Lubar 1991b; Nash 2000a).

A number of studies have reported that after around 40 sessions of Neurotherapy Treatment, about 70% of subjects with ADHD were able to reduce their excessively high power levels of slow-waves (theta and alpha) and increase the power levels of their faster brainwaves (SMR and Beta). This was coupled with concurrent improvements in theta/beta ratio and ADHD symptoms, with no adverse side effects reported (Boyd & Campbell 1998; Lubar et al. 1995c; Monastra et al. 2005; Pop-Jordanova, Markovska-Simoska & Zorcec 2005; Sterman 2000b). Sterman suggested that neuropathology, manifested in ADHD as excessive slow-wave activity, and that Neurotherapy directed at normalising these rhythms may yield sustaining clinical benefits (Sterman 1996b; Sterman 2000b).

A further rationale for the use of Neurotherapy has been the need to find a suitable non-pharmacological treatment for ADHD due to reports that the increase in prescription rates of stimulant medication for ADHD had become a major public health concern, as reviewed in section 2.8. A national health survey found that 11% of Australian children and adolescents would meet the diagnostic criteria for ADHD (Birleson, Sawyer & Storm 2000). Psycho-stimulants are the most commonly used
medical treatment for children with ADHD.

There are a number of reasons why stimulant medication has caused public concern. Firstly, the efficacy of stimulant medications wears off after around four hours and in 30 to 40% of patients medication fails to produce the desired improvements (Barkley 1990a). Adverse side effects, such as, loss of appetite, gastrointestinal complaints, aching legs, increase in TICS and Tourettes, exacerbation in disruptive behaviours when the medication wears off are seen in 20-50% of medicated ADHD children (Goldstein & Goldstein 1998). Recent evidence suggests that the overall rate of medication treatment for ADHD has been increasing, to a point that has been causing public concern (Bender 1997; Nash 2000b). An Australian parliamentary study of medication prescription analysis by Federal Electorates stated:

“Medication for ADHD has been controversial, arguably for three main reasons. It is children, often, young children, who are being medicated, the medication being prescribed is amphetamine-based, and the number of prescriptions for such medication has been increasing at a quite dramatic rate. Between 1991 and 1998, prescriptions dispensed for dexamphetamine sulfate has increased by 2400 per cent, while prescriptions for Methylphenidate has increased by 620 per cent over the same period.” (Mackey & Kopras 2001).

Children with ADHD are routinely prescribed stimulant medication with no a-priori tests for assessing medication response, despite evidence that medication response can be predicted by QEEG anomalies (Chabot & Serfontein 1996). The
neurophysiology of children with ADHD has not traditionally been considered when prescribing medication (Hermens et al. 2005a; Hermens et al. 2006). It is now well known that as a group, the EEGs of children with ADHD tend to contain excessive slow-waves (theta, 4-7 Hz and alpha 8-10 Hz) and not enough fast-waves (beta, 15-20 Hz) and their EEG has been described as having a high theta/beta power ratio (Janzen et al. 1995; Lubar & Lubar 1999; Lubar, Swartwood & Timmerman 1995; Monastra, Lubar & Linden 2001; Monastra et al. 1999; Satterfield 1973; Steinhausen, Romahn & Gobel 1984).

Effectiveness studies, comparing stimulant medication to Neurotherapy, have found Neurotherapy to be as effective as stimulant medication in the treatment of ADHD, with no adverse side effects and expectations that the treatment effects are permanent (Fuchs et al. 2003; Monastra, Monastra & George 2002; Rossiter 2004a, b; Rossiter & La Vaque 1995). Consequently, Neurotherapy appears to be an effective treatment for ADHD and one which may not only reduce the rise in prescription rates for stimulant medications, but which may also be effective in treating ADHD symptoms in non-responders to stimulant medication.

3.4 **Neuromodulation of Neural Control Networks Through Neurotherapy**

In this section, studies that describe neural control networks involved in the attentional system are briefly described, followed by a review of papers that outline how Neurotherapy modulates these networks to promote functional optimisation with
resultant improvements in the attentional capacity of children with ADHD. The complexity of the EEG generation and of the attentional systems literature precludes a full coverage of these areas in this thesis. Consequently, the following discussion will be limited to thalamocortical and cortico-cortical involvement.

3.4.1 Posner and Raichle's Model of Attention

Posner and Raichle (1997) proposed a model of attention consisting of three interconnected brain networks:

- **An executive control network**, involves areas of the medial frontal cortex, the anterior cingulate, the supplementary motor area, the basal ganglia and the caudate. This network was described as being responsible for the control of goal-directed behaviour, inhibition of automatic responses and target detection. The executive control network, with connections to the pre-frontal cortex, enables control of working memory, while connections to the posterior parietal cortex enable control of visual orienting and connections to the occipital cortex enable control of processing of visual features.

- **An alerting network**, involves right frontal and right parietal cortex. This network was described as being involved in establishing and maintaining a state of vigilance or alertness conducive to readiness for action. The alerting network is therefore required to sustain attention to perceptual information, and involves noradrenaline activity and connections from the locus coeruleus.
• **An orienting network**, involves the posterior parietal cortex and oculomotor areas. This network is involved in covert orienting to changes in sensory channels, particularly visual channels. The orienting network selects and enhances salient relevant visual input.

According to Posner and Raichle’s model, the regulation of attentional processes are thought to involve dynamic interactions between these networks (Posner & Raichle 1997). The parietal orienting network selects and enhances salient sensory information, which is then transferred to the anterior executive control network. The anterior network processes this information to coordinate the detection of relevant targets and response selection. In this model, the alerting network maintains activation of the orienting and executive networks so as to sustain attention to relevant input information (Posner & Raichle 1997; Posner & Raichle 1998). It has been proposed that deficits in these three systems are directly related to symptoms of ADHD. Symptoms of deficits in sustained attention may be related to dysfunction in the alerting network, symptoms of deficits in selective attention may be related to deficits in the orienting network, and symptoms of deficits in memory organization may be related to dysfunction in the executive network (Swanson et al. 1998).

### 3.4.2 Tucker and Williamson’s Model of Attention

Tucker and Williamson (1984) reviewed the evidence for the underpinnings of the human attentional system, based on the biological mechanism of attention derived
from animal dissections and studies (Pribram & McGuinness 1975). They concluded that there was a self-regulating asymmetrical neural control network, linking a frontal, primarily left, dopaminergic system to a posterior, primarily right, noradrenergic system. The two linked systems were described as a “frontal tonic-activation system” and a “posterior phasic-arousal system” (Tucker & Williamson 1984).

3.4.3 The Tonic ‘Activation’ System:

The tonic activation system, centering on the forebrain basal ganglia, was described as providing a state of tonic motor readiness for action. This implied a state of alertness or vigilance, which Tucker and Williamson (1984) argued was mediated by two related dopaminergic systems:

First, the primary nigrostratal DA pathways, originating in the “substantia nigra” in the brainstem, innervating the caudate nucleus and putamen and handling sensorimotor integration. Increased DA modulation restricts the range of behaviours by increasing informational redundancy. In this context, redundancy refers to the processing of information in related pathways simultaneously while restricting the processing of other information. Thus increased redundancy increases reliability but also restricts alternative information from being processed (Tucker & Williamson 1984).

A related DA pathway, the mesocortical or mesolimbic system with cell bodies in the ventral tegmental bundle and connections to the nucleus accumbens, central amygdaloid nucleus and the lateral septal nuclei supports controlled, motivated
interactions with the environment (Tucker & Williamson 1984). The authors argued that this largely dopamine mediated neural control system does not linearly increase activation but qualitatively facilitates vigilance, tight control of motor output and purposeful behaviours (Tucker & Williamson 1984).

3.4.4 The Phasic ‘Arousal’ System:

The phasic arousal system was described by Tucker and Williamson (1984) as providing responses to changes in sensory information or novelty in sensory channels. They suggested that reiterative loops, that constantly compare new sensory channel patterns to previous ones, enable detection of novelty. The primary noradrenergic pathway, from the dorsal tegmental bundle, originates in the pontine locus coeruleus and projects rostrally to the median forebrain bundle and the limbic system, including the amygdala, hippocampus, thalamus, and neocortex. Tucker and Williamson (1984) proposed that norepinephrine does not linearly increase arousal, but qualitatively facilitates response to perceptual input from environmental novelty. Noradrenergic activity declines with repetitive input (habituation), inhibits neuronal discharge, and reduces spontaneous background activity of neurons. Thus NE may increase signal-to-noise ratio, and augment the cell’s evoked responses to stimuli, thereby increasing sensitivity to change (Tucker & Williamson 1984).

According to Tucker and Williamson (1984), the dopaminergic (DA) system appears to maintain the tonic level of neural activity by increasing the redundancy of
the information (decreasing alternatives) in brain channels. This was demonstrated
elegantly in the behaviour of DAT-KO mice (mice with overstimulated DA pathways
whose dopamine transporter was genetically knocked out) (Gainetdinov et al. 1999). In
novel environments, the behaviours of DAT-KO mice became dominated by
progressively fewer acts (repetitively exploring the same arm of the maze) with
increasing frequency. Hence, tonic activation produces a redundancy bias, which
restricts change and tightly controls or restricts motor output or behaviours. The
qualitative regulatory effect of activation is thus opposite to that of arousal, which
decreases redundancy. Yet for motor functions, a redundancy bias applies a negative
control not unlike the negative feedback on perceptual responsivity provided by
arousal. Behavioural output therefore requires constant change in motor channels.
(Tucker & Williamson 1984).

3.4.5 Sergeant’s Conceptualization of the Cognitive-Energetic Model

Sergeant (2000) advocated the use of a “cognitive-energetic model of
attention” which conceptualised the attentional system at three distinct levels, and
may help guide understanding of the deficits in attention seen in ADHD (Sergeant
2000). At the first level, a lower set of cognitive processes which consisted of
“encoding, central processing and response organisation” was proposed (Sergeant &
Van der Meere 1990b). However, Sergeant (1990) found that in ADHD there were no
deficits of cognitive processes at encoding or central processing, but deficits were
found in motor-response organisation (Sergeant & van der Meere 1990a; Sergeant &
Van der Meere 1990b). A second level of the proposed cognitive-energetic model consisted of the energetic pools: “arousal, activation, and effort”. At this level, it was proposed that the primary deficits of ADHD were associated with the activation pool and, to some extent, effort. The third level of the model contained a management or executive function system. Barkley (1997b) had concluded that executive function deficiencies in ADHD were primarily due to a failure of inhibition, a component of executive function (Barkley 1997b). However, Oosterlaan and colleagues (1998) demonstrated that failure of inhibition was not specific to ADHD, but also applied to children with Oppositional Defiant Disorder and Conduct Disorder (Oosterlaan, Logan & Sergeant 1998). Sergeant (1990b) proposed that the cognitive-energetic model was useful for determining not only ADHD deficiencies and associated disorders, but also for linking human cognitive neuroscience studies with neurobiological models of ADHD (Sergeant & Van der Meere 1990b).

Sergeant’s (2000) conceptualization of the cognitive-energetic model consisting of the energetic pools: “arousal, activation and effort” (Sergeant 2000) is basically an extension of Tucker and Williamson’s model of “tonic activation” and “phasic arousal” (Tucker & Williamson 1984). This in turn was based on a model of “arousal, activation and effort” initially proposed by Pribram and Mc Guiness (1975).

These models were based on anatomical dissections and postulates of the functioning of proposed attentional networks. More recently, researchers have used fMRI in studies in an attempt to localize and demonstrate the function of attentional neural control networks. In the following section, relevant fMRI studies are reviewed.
3.4.6 Support from fMRI Studies for Tucker and Williamson’s Model

Support for Tucker and Williamson’s (1984) model has been provided by a number of studies in latter years. However, findings of studies that have explored the laterality of neural networks underpinning alertness have been inconsistent. A right-sided fronto-parieto-thalamic network was found to be involved in tonic activation (Sturm et al. 1999) and alertness (Sturm & Willmes 2001). The alerting effect was found to primarily activate left-lateralized pre-frontal, premotor and parietal regions, while a temporal orienting task activated the left parietal and frontal cortex (Coull, Nobre & Frith 2001). One study that investigated alertness induced by warning cues reported left superior parietal and right ventral pre-frontal activity (Konrad et al. 2005). Another study, using event-related fMRI and the attention network test (ANT) examined the effects of cues and targets within a single reaction-time task as a means of exploring the efficiency of the alerting, orienting, and executive control networks involved in attention (Fan et al. 2005).

FMRI contrast in an alerting task showed strong involvement of the thalamus and of anterior and posterior cortical sites. The contrast to the orienting component activated parietal sites and frontal fields. The contrast to the executive control network component of the task showed activation of the anterior cingulate along with several other brain areas. Fan and colleagues (2005) reported that with some exceptions, the brain areas involved in activation, orienting, and executive control within the ANT task were generally consistent with findings from previous fMRI
studies that examined these in separate tasks. Overall, the fMRI results suggested that the functional contrasts within this single task differentially activated three separate anatomical networks, “activation”, “orienting” and “executive control”, which are all essential components of the attentional system (Fan et al. 2005).

Selective visual attention has been shown to involve a dynamic interplay between attentional control systems and sensory brain structures, with frontal and parietal brain regions proposed as constituents of a selective attention system (Eimer & Driver 2001). Event-related fMRI was used during a cued spatial-attention task to differentiate the brain activity related to attentional control, from that related to selective processing of target stimuli. Results indicated that superior frontal, inferior parietal and superior temporal cortex were selectively activated by cues, indicating that these structures were part of a network for voluntary control of attention (Hopfinger, Buonocore & Mangun 2000).

The thalamus and brain stem noradrenergic neurotransmitter system have been linked to arousal and alertness (Berridge & Waterhouse 2003). Subjects scanned by fMRI while performing a range of attentional-orienting tasks, primarily activated left-lateralized pre-frontal, premotor and parietal regions when an alerting effect was evoked. Clonidine, a noradrenergic H-agonist, impaired behavioural measures of the alerting effect, attenuated left pre-frontal cortex and insula activity during temporal-orienting, and attenuated right-superior-parietal cortex activity during spatial-orienting (Coull, Nobre & Frith 2001). Coull (2001) suggested that the anatomical dissociation between the effects of Clonidine during temporal orienting versus alerting
demonstrated lateralized neuroanatomical substrates for the noradrenergic modulation of human attentional orienting (Coull, Nobre & Frith 2001).

Attention allocation and directed attention toward a salient stimulus have been shown to be impaired in children with ADHD, as often assessed with target detection or oddball tasks (Alexander et al. 2008; Frank, Seiden & Napolitano 1994; Johnstone & Barry 1996; Klorman et al. 1990; Ozdag et al. 2004). Tamm and colleagues (2006) investigated the neural correlates of target detection dysfunction in ADHD using event-related fMRI while they performed a visual oddball task. ADHD subjects made significantly more errors of commission than controls and showed significantly less activation in the bilateral parietal lobes (including the superior parietal gyrus and supramarginal and angular gyri of the inferior parietal lobe), right precuneus, and thalamus. Tamm (2006) concluded that the ADHD subjects demonstrated significant impairments in their ability to direct and allocate attentional resources and that these difficulties were associated with significant aberrations in the parietal attentional system, which is known to play a significant role in attention shifting and detecting specific or salient targets (Tamm, Menon & Reiss 2006).

While the parietal system is richly enervated by noradrenergic neurons with cell bodies originating from the locus coeruleus, the frontal system is dominated by dopamine neurons with cell bodies originating from the substantia nigra and ventral tegmental bundle (Tucker & Williamson 1984). Evidence for the involvement of dopamine in the attentional system and for dysfunction of dopamine neuromodulation in ADHD is substantial, as evidenced by genetic studies, studies of CSF dopamine
metabolites and the positive response to stimulant medications that block the reuptake of dopamine in ADHD (Arnsten 2006; Barr et al. 2000a; Barr et al. 2000b; Baughman 2000; Blum et al. 2008; Castellanos 1999; Castellanos et al. 1994a; Comings 1994; Cook et al. 1995; Dougherty et al. 1999; Faraone & Biederman 1998; Halperin et al. 1993; Levy 1991; Rowe et al. 1998; Swanson et al. 2000; Viggiano, Vallone & Sadile 2004).

In support of the suggested crucial interplay of the arousal and activation networks, more recent research has suggested that both sustained attention or vigilance (activation), induced by warning cues modulates spatial attention and orienting, requiring phasic arousal at a behavioural and neural level (Bellgrove et al. 2004). An fMRI study found that the cueing effect was larger after an alerting signal, suggesting faster orienting under alertness (Callejas, Lupianez & Tudela 2004). Another study found that on a free-viewing spatial-attention task, participants who performed poorly on a test of sustained attention had significantly attenuated left spatial bias. This provided support for the suggestion that sustained attention exerts a modulatory influence on spatial attention (Bellgrove et al. 2004).

Overall fMRI studies have supported Tucker and Williamson’s (1984) model of an asymmetrical neural control network linking a frontal left dopamine-mediated readiness for action (activation) network to a posterior right noradrenergic-mediated phasic arousal (orienting) network in the human attentional system (Tucker & Williamson 1984).
Models of attention proposed by Tucker and Williamson (1984), Sergeant, Posner and colleagues (2000) relate to an intact attentional system. Evidence is emerging from fMRI studies that ADHD symptomatology is associated with dysfunction in most of these systems. For example, Konrad and colleagues (2006) found that children with ADHD (relative to controls) recruited deviant brain regions for all three attentional networks: less right-sided activation in the anterior cingulate gyrus during alerting, more fronto-striatal-insular activation during reorienting, and less fronto-striatal activation for executive control. Children with ADHD demonstrated altered brain mechanisms associated with all three attentional networks investigated (Konrad et al. 2006).

3.4.7 Proposed Mechanisms of Action for Neurotherapy

Abarbanel (1995) proposed that the mode of action of Neurotherapy Treatment for ADHD could be explained on three levels:

At the simplest level, empirical evidence indicates that elevated theta/beta (or theta/SMR) ratio correlates with the presence of ADHD symptoms. Reducing these ratios through Neurotherapy, has correlated empirically with the resolution of ADHD symptoms (Linden, Habib & Radojevic 1996a; Lubar 1995; Monastra 2005).

On a second level, Abarbanel (1995) suggested that through Neurotherapy,
children may learn to exert neuromodulatory control over the brain circuitry mediating
attentional processes, and that long-term potentiation may consolidate optimisation
of the attentional system processes (Abarbanel 1995). At this level, network theory
suggests that during Neurotherapy, the attentional system may be modulated into a
stable equilibrium (Cohen & Servan-Schreiber 1992; Cohen, Servan-Schreiber &
McClelland 1992). Neurotherapy can be likened to any learned behaviour, such as
walking or riding a bicycle. As the skill is practiced, sensory and proprioceptive input to
the reticular formation initiates feedback regulation and optimisation of the motor
circuits in the sensorimotor cortex and basal ganglia, which, over time, increases long-
term potentiation and automates the skill. Abarbanel (1995) proposed that, during
Neurotherapy Treatment, the forward movement of a spaceship on a computer for
example, might be an index of decreasing theta/beta ratio. Moving the ship forward
requires decreases in theta/beta ratios, which in turn may be interpreted promoting
increased attentional competence and tighter control on movement (Abarbanel 1995).

A third level of explanation addresses how theta/beta ratios, attentional
competence, and control on movement and behaviour are inter-related and mediated.
At this level, Abarbanel (1995) suggested that physiological or anatomical explanations
involve a certain degree of speculation, because of the uncertainties about the
processes that generate field potentials and regulate the attentional processes and
behavioural control (Abarbanel 1995).

In section 3.1.1, Sterman’s (1996) proposal of thalamo-cortical oscillations that
produce rhythmic summations of field potentials, seen as EEG scalp potentials was
discussed. Sterman also proposed that during inactive behavioural states, attenuation of somatosensory inputs could hyperpolarize VB cells, promoting oscillatory discharges, and initiating SMR rhythms. Sterman exploited this mechanism and demonstrated that through operant conditioning of SMR cats (Sterman, Lucas & MacDonald 1972; Sterman, Wyrwicka & Howe 1969; Sterman, Wyrwicka & Roth 1969) and human subjects (Sterman 1973a, 1981; Sterman, Macdonald & Stone 1974; Sterman & Shouse 1980) becoming more proficient at producing behavioural stillness and at increasing SMR.
Certain neurons in the thalamus and the limbic system display intrinsic oscillations in the 6 to 10 Hz range which are affected by inputs from other neurons (Lopes da Silva 1991). Lopes da Silva (1991) described three types of neurons in the thalamic relay system pictured in figure 3.2 above.

As discussed in section 3.1.1., thalamocortical neurons have two separate modes of action: First as relay cells, they depolarize in response to input volleys and...
relay ascending sensory input. Second, as oscillatory cells, they fire in a collective rhythm, thereby blocking input to the associated area of the cortex and inducing cortico-cortical oscillations in that area of the cortex (Lopes da Silva 1991). Brainstem neuromodulation provides either depolarizing or hyperpolarizing influences to thalamic neurons (by affecting resting membrane potentials of reticular thalamic and thalamocortical neurons) and determines which mode of action, relay or oscillatory state is selected (Lopes da Silva 1991).

Sterman (1996) related the generation of SMR, alpha, and theta rhythms to the presence or absence of input to the thalamic oscillatory generators from three specific networks: “vigilance”, “sensorimotor integration”, and “cognitive integration”. He suggested that if input from brainstem neuromodulators associated with vigilance was withdrawn (as in states of inattentive drowsiness) then theta oscillations would appeared. If sensorimotor input from brainstem neuromodulators was withdrawn, then SMR rhythm appeared. If cognitive processing was withdrawn, as in relaxed states without cognitive activity, then alpha rhythm appeared. Thus, according to Sterman’s (1996) scheme, the presence of these rhythms on the EEG indicates the underlying brain states of vigilance, sensorimotor integration, and cognitive processing (Sterman 1996a).

Sterman and colleagues (1994, 1995) investigated behaviours that “suppressed” rhythmic EEG patterns when sensory and cognitive inputs were manipulated, to enable differentiation of EEG responses associated with “simple visual attention”, “purposeful movements”, “visual tracking”, and “visuomotor integration”
(Mann, Sterman & Kaiser 1996; Sterman & Mann 1995; Sterman et al. 1994). EEG spectral analysis, using sequential and overlapping 2 Hz bands, between 5 and 17 Hz were studied. Results indicated that in simple visual attention (eyes open condition) all frequencies between 5 and 15 Hz were significantly suppressed in temporal, parietal, and occipital cortex, with the greatest suppression in the 7-11 Hz range, compared with eyes closed condition (Sterman et al. 1994).

Sterman (1996) suggested that notwithstanding the concept of parieto-occipital "alpha blocking" in earlier EEG literature, this finding supported the view that excitation in specific and nonspecific excitatory pathways alters all sources of rhythmic discharge in the thalamus. Body movements caused sensorimotor rhythm, 11-15 Hz activity to be selectively suppressed in the central cortex. With eye movements from visual tracking, 11-15 Hz activity was selectively suppressed in the temporal-parietal cortex. Sterman (1996) suggested that the underlying neurophysiology predicts that afferent sensory discharge would be increased in appropriate ascending sensory pathways with both body movements and eye movements. The experimentation demonstrated that both body and eye movements did selectively suppress 11-15 Hz activity in appropriate but different thalamocortical pathways. Conversely, a reduction of this excitation would be expected to selectively increase 11-15 Hz activity in these areas (Sterman 1996b).

As previously reviewed in section 3.2, there is evidence of excess theta and alpha and elevated theta/beta ratio in children with ADHD. Hence, the relevance to Sterman's (1996) scheme to Neurotherapy Treatment for ADHD can be drawn:
Promoting lower activity in the theta range and higher power levels in the beta and/or SMR range may promote the associated states of increased stillness, attentiveness, and decreased drowsiness and any other cognitive disturbances associated with elevated theta activity (Abarbanel 1995).

3.5 **The Discovery of EEG Operant Conditioning**

Early studies of operant conditioning of EEG indicated that animals could be trained to influence specific aspects of their EEG (Black, Young & Batenchuk 1970; Delgado et al. 1969, 1970; Hall 1968; Lopes da Silva & Kamp 1969). Sterman (1972) trained cats by EEG operant conditioning, using food reward, to produce 11-15 Hz “alpha spindle” electrical activity over the sensorimotor cortex (Sterman, Lucas & MacDonald 1972). Sterman called this specific EEG activity, associated with behavioural stillness, the “Sensorimotor Rhythm (SMR)” (Sterman & Fairchild 1967; Sterman, Howe & Macdonald 1970; Wyricka & Sterman 1968). In a later study conducted for NASA, Sterman discovered serendipitously that the cats trained to increase SMR brain activity became resistant to chemically induced seizures (Sterman, LoPresti & Fairchild 1975). The conditioned parameter, an increase in the SMR activity being trained, had no intrinsic value for the animals and the associated raising of seizure threshold was an unexpected and unrelated finding. These early experiments resulting in changes in the EEG, increased behavioural stillness, and the raising of the seizure threshold suggested that organic changes may have taken place in the brains of the animals (Sterman, LoPresti & Fairchild 1975).
Sterman (1972) initiated clinical trials using EEG operant conditioning in a 23-year-old female with a 7-year history of intractable tonic-clonic seizures of unknown origins at an average rate of two per month, unrelated to her menses. The patient’s EEG indicated generalised 5-7 Hz excess theta activity, and the protocol used aimed to reduce theta and increase SMR (11-15 Hz) activity. After treatment at the rate of twice a week over 3 months, the seizures stopped and follow-up EEG indicated reduction in the excess theta and increase in SMR activity (Sterman & Friar 1972b). In two subsequent studies, this single-case study was extended to include more subjects, and, using the same protocol Sterman reported that seizure rates and EEG abnormalities significantly reduced in these patients as well (Sterman 1973b; Sterman & Friar 1972a; Sterman, Macdonald & Stone 1974).

Several similar subsequent studies also found that EEG operant conditioning was associated with reduction in theta power, increase in SMR and seizure reduction (Finley, Smith & Etherton 1975; Kaplan 1975; Seifert & Lubar 1975; Upton & Longmire 1975; Wyler, Ward & Fetz 1975). Finley (1976) conducted a blinded Sham feedback study on a male teenager with severe epilepsy, who after one year of SMR biofeedback training had decreased incidence of tonic seizures from eight per hour to less than 1 in 3 hours. SMR increased from 10% to 70%, and epileptiform discharges decreased from 45% to 15%. Blinded non-contingent feedback was introduced for a period of 7 weeks following which SMR decreased significantly (down 8%), and epileptiform discharges increased significantly (up 4%). Rate of seizures increased, but was not statistically significant over the preceding months of contingent feedback. Contingent feedback
was reinstated following the 7-week sham feedback period and recovery of all
variables to their former levels was observed. This blinded ABA design indicates that
the gains were attributable to EEG operant conditioning (Finley 1976).

3.6 Early Clinical use of Neurotherapy: prior to 1985.

Although, up to that time, SMR biofeedback training has been successfully
applied to various forms of epilepsy in humans, its use in decreasing hyperactivity had
been coincidental in cases in which reduction of seizures was the predominant focus of
SMR training. Lubar and Bahler (1976) published a series of case studies, which
demonstrated the effectiveness of Neurotherapy (SMR training) on reducing seizure
activity in University subjects suffering from epilepsy. While doing these studies, Lubar
noted that the subjects reported increased attentiveness, focus and concentration and
reduced fidgetiness (Lubar & Bahler 1976).

Lubar and Shouse (1976b) investigated the effects of Neurotherapy on ADHD in
a single-case blind-crossover (ABA) study with an 8 year 11 months old hyperkinetic
child who was on psycho-stimulant medication for attention deficits and hyperactivity.
Following Neurotherapy Treatment, (SMR enhancement and theta inhibit) two
independent observers reported decreased oppositional and out of seat behaviours
and increased cooperative behaviours. A concurrent increase in attentiveness and
academic output was also reported. Reversed training (inhibit SMR and increase theta)
over a four-week period was then provided, and the original undesirable behaviours
returned. Training was reversed yet again (SMR enhancement and theta inhibit) and the child reportedly regained all previous losses, and school performance and behaviours again improved on all measures. The child was then taken off Methylphenidate, and reportedly continued to do well. Follow-up over several years showed that the gains were maintained (Lubar & Shouse 1976b).

Four hyperkinetic subjects from a cohort of 12 hyperkinetic children and 12 controls were selected for Neurotherapy on the basis that compared to the other subjects; they exhibited the worst classroom misconduct, combined with the lowest levels of SMR and general physiological arousal levels. In addition, their symptoms were reduced by the use of Methylphenidate, but not sufficiently enough to produce normalisation. The same Neurotherapy ABA blind crossover paradigm described in (Lubar & Shouse 1976a; Shouse & Lubar 1978), with SMR enhancement and theta inhibit (Shouse & Lubar 1979), was used on the four subjects.

Three of the four subjects in the study showed contingent increases in SMR which were correlated with reductions in classroom motor activity (Shouse & Lubar 1979). The combination of EEG Neurotherapy Treatment with medication treatment resulted in substantial improvements in tested behaviours that exceeded the effects of medication alone. They reported that a reduction in theta and an increase in SMR correlated with a significant decrease in hyperactivity. Attentiveness also improved, but to a lesser degree. Hyperactivity and attentiveness were significantly improved and/or reversed at every stage of the study design. In every case, when medication was withdrawn, the improvements were maintained with SMR enhancement and
theta inhibit. A decrease in undesirable behaviours such as disruptive motor activities, self-stimulation, out of seat behaviours and oppositional behaviours, were observed. Additionally, an increase in desirable behaviours was observed, as was increased attention span and cooperation. Social behaviours such as self-initiated approaches to peers or teachers, and sustained interactions with them also improved (Shouse & Lubar 1979).

Jackson and Eberley (1982) used Neurotherapy in a pilot study which aimed to decrease the percentage of time that alpha wave activity was being produced while engaged in an arithmetic task. The participants were five mentally retarded adults. Analysis of intra-subject and inter-subject data revealed an overall significant decrease in the total number of alpha bursts, and percentage of time in dominant alpha compared to baseline conditions (Jackson & Eberly 1982). Decreases in Alpha activity have long been acknowledged as evidence of information processing and increased attention. The observed decreases in percentage of time in alpha, correlated with an increase in the percentage of problems completed correctly. This indicated an increase in facilitated attention following Neurotherapy (Jackson & Eberly 1982). In addition, both an automated method of determining head turning and human direct observation confirmed a significant decrease in the number of distractible head-turning responses. This increased attention and reduced distractibility in a developmentally delayed population was observed following successful Neurotherapy down-training of alpha activity (Jackson & Eberly 1982).

Working from a private clinical setting, Tansey and Bruner (1983) used a narrow
band filter centered around 14 Hz for Neurotherapy on a boy aged 10 who had been diagnosed as perceptually impaired with developmental reading disorder, ocular instability and hyperactive behaviours. The boy, who was due to repeat special-education fourth grade, had been on Methylphenidate for a number of years. After three sessions of electromyographic (EMG) biofeedback, but prior to the start of Neurotherapy, the child’s Paediatrician had stopped his medication because of his reduced hyperactivity. The learned reduction of EMG levels was accompanied by a reduction in hyperactivity level below that which had been achieved by past administration of Methylphenidate (Tansey & Bruner 1983b). Following the initial EMG training sessions, contingent amplitude and frequency modulated auditory feedback were used to teach the child to increase 14 Hz activity over the sensorimotor cortex. Following the EMG biofeedback training, the initially observed ADHD was no longer diagnosable. The learned increase in the amplitude of monitored SMR was accompanied by remediation of the developmental reading disorder and the ocular instability. These results remained unchanged, as ascertained by follow-ups conducted over a 24-month period subsequent to the termination of biofeedback training. Furthermore, the child's improvements in reading comprehension and behaviour over the summer period during which Neurotherapy took place, warranted the child being placed in normal fourth-grade (Tansey & Bruner 1983a).

Ten years after treatment had ceased, the boy’s ongoing normal social and academic functioning were noted (Tansey 1993). The boy had completed high school successfully, was attending college, had no attentional problems, and remained
stimulant medication-free. The boy's brainwave patterns were compared with those of 24 previously learning-disabled children, half of whom were classified as perceptually impaired prior to Neurotherapy Treatment (Tansey 1990, 1991), and his EEG measures appeared to have normalised. This confirmed the long-term stability of the outcomes of the 14-Hz Neurotherapy Treatment (Tansey 1993).

Lubar and Lubar (1984) conducted an experiment with six males with ADHD whose ages ranged between 10 and 19 years, to investigate whether Neurotherapy improved school performance. The subjects were described as having varying degrees of learning difficulties, hyperactivity and attentional deficits. Neurotherapy Treatment consisted of either increasing 12-15 Hz sensorimotor rhythm (SMR) or 16-20 Hz beta activity over the sensory motor strip, while suppressing theta activity. In this study, treatment was combined with academic training, including reading, arithmetic, and spatial tasks. Neurotherapy Treatment was conducted twice a week for 10 to 27 weeks (Lubar & Lubar 1984).

At the end of the experiment, all children were reported to have successfully increased their SMR or beta waves, and decreased slow-wave activity and muscle activity in their EEG; as determined by a post-hoc analysis of their brain electrical activity (Lubar & Lubar 1984). All subjects demonstrated considerable improvement in their schoolwork in terms of grades or achievement test scores on the Metropolitan Achievement Test, the Peabody, the Stanford Achievement test, and the California Achievement Test. None of the subjects required medications for hyperactivity after the study. Lubar (1984) concluded that individual results for each subject indicated
that Neurotherapy Treatment, if applied comprehensively, could be highly effective in helping children who experienced attention deficit disorders and difficulties with academic tasks (Lubar & Lubar 1984).

Tansey (1984) used a Neurotherapy Treatment regime, which attempted to redress pathological interhemispheric dysfunction in six learning, disabled boys ranging in age between 10 years 2 months and 11 years 10 months. Neurotherapy Treatment of the sensorimotor rhythm consisted of increasing 14 Hz burst patterns over the Central Rolandic Cortex and was conducted in weekly 30-min training sessions. The results replicated and extended earlier findings by Tansey and Bruder (1983) that operant conditioning of increases in amplitude of the sensorimotor rhythm had a positive effect on learning disability in a ten-year-old boy. In this study, the training appeared to increase bilateral sensorimotor transactions, resulting in substantive reduction and/or remediation in the learning disabilities of the participants (Tansey 1984).

3.7 **Uncontrolled Neurotherapy Studies: 1985 - Present Day**

Tansey (1985) observed discrete brainwave frequencies during Neurotherapy, a procedure that he thought might be reflective of the brain’s functional neurophysiology. Eight boys, ranging in age between 7 years 11 months and 15 years 3 months, were provided with long-term SMR biofeedback training until their learning disabilities were remediation. Concurrently, five narrow frequency bands of brainwave
activity, (5 Hz, 7 Hz, 10 Hz, 12 Hz and 14 Hz), were simultaneously recorded from one active electrode equidistant from reference and ground. These individual frequency recordings were intended to provide a glimpse of the brain’s global response. It was thought that these measures would reflect the dynamic and synergistic processes involved in neural activation of the sensorimotor sub-networks during SMR training. In subjects with a Full Scale I.Q. between 76 and 85 there was a tendency for slow-wave activity to decrease as fast-wave activity increased. For subjects with a Full Scale I.Q. between 102 and 116, there were increased amplitudes over most of the five bands. However, the increased amplitudes were much less at the slower frequencies. In the four subjects who had either a significant Verbal>Performance I.Q, or Performance>Verbal I.Q, there was a 40% greater increase in the lower of the Verbal or Performance I.Q. scores. This also indicated that the SMR training protocol used resulted in changes towards normalisation in functional interhemispheric asymmetry associated with the learning disabilities (Tansey 1985a).

Tansey (1985) administered 33 sessions of SMR training to a 14-year-old girl with a long history of absence seizures that were occurring at the rate of 4-5 per hour, sudden rages, spatial disorientation, attention deficits and academic difficulties. Biofeedback consisted of rewarding increases in 14-Hz neural discharges over the Central Rolandic Cortex. Increases in SMR from operant conditioning resulted in a total cessation of the girl’s absence seizures. In addition, the girl’s sudden rages, spatial disorientation, attending and academic functioning all improved substantially (Tansey 1985b)
Tansey (1990) assessed the effectiveness of an SMR Neurotherapy Treatment protocol in 24 children with learning disabilities, aged between 7 years 4 months and 15 years 6 months. All subjects had high theta/beta power ratios prior to treatment. Following SMR training, slow-wave activity decreased in overall power, 14-Hz SMR power activity increased and theta/beta power ratios decreased significantly. In addition WISC-R profiles normalised along with a significant remediation of the learning disorders (Tansey 1990). In a follow-up paper, Tansey (1991) reported that 22 of the 24 subjects manifested increases in full-scale I.Q. scores on the WISC-R of at least 15 points, with the remaining two obtaining an increase of 13 and 14 points respectively. Tansey (1991) suggested that these results are consistent with an increase in bi-hemispheric skills, and complementary verbal-expressive and visuomotor abilities, which are a prerequisite for successful learning, and necessary for the acquisition of reading and the integration of higher-order learning (Tansey 1990, 1991).

In three separate experiments, Lubar and colleagues (1995b) assessed the effectiveness of Neurotherapy Treatment for 42 ADHD children and adolescents, aged 8-19 years, on both objective and subjective measures. In the first experiment, using 19 subjects, those who successfully decreased theta activity showed significant improvements in the Test of Variables of Attention (TOVA). In the second experiment, using 13 subjects, significant improvements in parent evaluations on the Attention Deficit Disorders Evaluation Scale (ADDES) were obtained following Neurotherapy Treatment. In the last experiment, significant increases in Wechsler Intelligence Scale
for Children-Revised (WISC-R) scores were obtained following Neurotherapy Treatment. Lubar and colleagues (1995b) suggested that the findings of these three studies indicate that Neurotherapy Treatment can be an appropriate and effective treatment for children with ADHD, as it significantly increased their cognitive skills, and decreased their attention deficits (Lubar, Swartwood, Swartwood, & O'Donnell, 1995b).

Thompsons and Thompson (1998a) reviewed the evaluation and treatment charts of 111 consecutive clients diagnosed with ADHD in their clinic. The clients, 98 children, aged between 5 and 17 years, and 13 adults aged between 18 and 63 years, attended 40 Neurotherapy sessions of 50 min duration, combined with the teaching of metacognitive strategies. Reward during Neurotherapy Treatment was contingent mostly on suppressing slow-wave theta (4-7 Hz) activity and occasionally alpha (9-11 Hz) whichever was the most deviantly elevated, as well as increasing fast-wave activity (15-18 Hz) for most clients. However, clients with impulsivity and hyperactivity were initially trained on a protocol that required them to increase SMR (13-15) Hz (Thompson & Thompson 1998a).

Metacognitive strategies relating to academic tasks were taught when feedback criteria were met, indicating that the clients were able to focus and hence were most receptive to learning. The treatment outcomes indicated that although 30% of the children were taking Methylphenidate at intake, only 6% remained on stimulant medications by the end of treatment. Significant improvements were found in ADHD symptoms, on intelligence scales, and in academic performance. The average gain for the Full Scale I.Q. equivalent score was 12 points. A decrease in the theta/beta EEG
ratio was also observed. The positive outcomes of decreased symptoms of ADHD, combined with the academic and intellectual functioning improvements suggest that Neurotherapy combined with teaching of Metacognitive strategies as an adjunct are a useful combination in the treatment of ADHD (Thompson & Thompson 1998a).

Most Neurotherapy Treatment has been carried out in University or clinical settings. However, in a study by Boyd and Campbell (1998), six middle-school students diagnosed with ADHD, aged between 13 and 15 years, underwent SMR biofeedback training in a school setting. Prior to and post-training, they were evaluated with the WISC-III Digit Span subtest and the TOVA, following a 72-hour medication-free period. Five of the subjects received 20 sessions of SMR biofeedback and one received nine sessions. Five out of the six subject improved on their WISC-III Digit Span performance and their TOVA inattention and impulsivity scores. These results supported previously reported findings that Neurotherapy can be effective in the treatment of ADHD, and, in addition, demonstrated that Neurotherapy can be used in a school setting (Boyd & Campbell 1998). Neurotherapy has also been conducted in home setting.

Rossiter (1998) reported on self-administered Neurotherapy for ADHD patients conducted in their own home. The first ten sessions were used to train the adult patients or parents of younger children on how to use the Neurotherapy equipment which consisted of inexpensive, easy to operate, 1 or 2 channel Personal Optimisation Devices (POD) manufactured by Lexicor Medical Corporation. The remaining 50 sessions were conducted at the patients’ homes. Further therapist involvement was to monitor treatment and to make changes in the treatment protocol as necessary.
Results from the initial six patients, aged 7-45 years, were reported. Prior to Neurotherapy Treatment, 13 of 24 standardised TOVA measures (attention, impulsivity, reaction time, and variability in the reaction time) were below average at baseline. After 30 Neurotherapy sessions, only five TOVA variables remained below average. Rossiter (1998) concluded that home based self-administered Neurotherapy may be an effective alternative to therapist-directed treatment for many ADHD patients and can be delivered at a substantially lower cost to clients (Rossiter 1998).

As reported in section 2.13.1, Egner and Gruzelier (2001) recruited healthy volunteers to help assess the relationship between specific Neurotherapy Treatment and electrocortical measures associated with the attentional system. Results indicated that the operant conditioning enhancement of SMR (12-15 Hz) component was associated with a reduction in commission errors and improved perceptual sensitivity on a Continuous Performance Task. However, they found the opposite relation for low beta (15-18 Hz) enhancement, when SMR effects were controlled. Nonetheless, both 12-15 Hz and 15-18 Hz enhancement were associated with significant increases in P300 event-related potential (ERP) amplitudes in an auditory oddball task. They concluded that the results could be interpreted as stemming from band-specific effects of EEG operant conditioning on perceptual and motor aspects of attentional measures (Egner & Gruzelier 2001).

Vernon and colleagues (2003) postulated that given the association between theta activity (4-7 Hz) and working memory performance, and between SMR activity (12-15 Hz) and attentional processing, enhancement of either of these frequencies
might specifically influence particular aspects of cognitive performance. They investigated the possibility by training healthy individuals to either increase SMR or theta activity, and comparing their performances to those of a non-Neurotherapy control-group. The results revealed that after eight sessions of Neurotherapy, participants in the SMR-group were able to enhance their SMR activity selectively, as indexed by increased SMR/theta and SMR/beta ratios. In contrast, those trained to enhance theta activity had no remarkable changes in their EEG. Additionally, the SMR group exhibited a clear and significant improvement in cued recall performance when using a semantic working memory task. The SMR group also exhibited (to a lesser extent) improved accuracy of focused attentional processing when using a 2-sequence Continuous Performance Task. Vernon (2003) concluded that normal healthy individuals could learn to increase specific components of their brain electrical activity. This may be associated with the enhancement of brain connectivity responsible for cued recollection, which might facilitate semantic processing in a working memory task and to a lesser extent focused attention. The control group, who were required to increase theta activity showed no such improvements (Vernon et al. 2003).

One hundred children, aged 6 to 19, with a diagnosis of ADHD of either inattentive or combined subtypes, participated in a one-year, multimodal, outpatient program that included Methylphenidate, parent counseling, and a standardised academic support plan at school. Fifty-one of the participants also received Neurotherapy. Post-treatment assessments were conducted both on and off stimulant medication. When tested on Methylphenidate, participants demonstrated significant
improvements on the TOVA and Attention Deficit Disorder Evaluation Scales (ADDES). When tested while off Methylphenidate, only participants who received Neurotherapy Treatment sustained these gains and had significant reductions in theta/beta power ratios at Cz. Parenting style exerted a significant moderating effect on behavioural symptoms at home but not at school (Monastra, Monastra & George 2002).

Kropotov and colleagues (2005) involved eighty-six children with ADHD, aged 9 to 14, in a study during which event-related potentials (ERPs) were recorded in auditory GO/NO-GO task before and after 15 to 22 sessions of Neurotherapy. Each session consisted of 20 minutes of enhancing the ratio of the EEG power in the 15 to 18 Hz band to the EEG power in the rest of spectrum, and 7–10 min of enhancing of the ratio of the EEG power in 12 to 15 Hz band to the EEG power in the rest of spectrum. Bipolar electrode-placement at C3-Fz was used for enhancing power in the first protocol and C4-Pz in the second protocol. Based on quality of performance during training sessions, the patients were divided into two groups: good performers and bad performers. For GO and NO-GO cues, good performers showed increases in the amplitude of positive ERP components within 180–420 ms. However, no statistically significant differences between pre- and post-training ERPs were observed for bad performers. The ERP differences between post- and pre-treatment conditions for good performers were distributed over fronto-central areas, and appeared to reflect an activation of frontal cortical areas associated with beta training (Kropotov et al. 2005)
3.8 **Controlled Neurotherapy Studies**

Much of the early criticism of Neurotherapy had been that there were no controls to demonstrate that the treatment effects did not result from placebo effects, or the extensive attention received during treatment, the high expectations of parents or merely from attending to the computer task. These concerns were addressed in the following studies.

Eight epileptic patients with mixed seizures, unresponsive to medical treatment, participated in a double-blind crossover study to determine the specificity and effectiveness of operant conditioning of the EEG as an anticonvulsant protocol (Lubar et al. 1981). Baseline levels of seizures were recorded for four months prior to the beginning of treatment. All participants received sham (placebo) feedback for a period of two months, and were then randomly assigned to one of three treatment groups and underwent an ABA-patterned training program lasting a total of ten months. In the first phase, patients trained either to suppress 3 to 8 Hz slow-wave activity, to enhance 12 to 15 Hz activity, or to suppress 3 to 8 Hz while enhancing 11 to 19 Hz activity simultaneously. In the second phase, all patients trained to enhance 3 to 8 Hz slow-wave activity. In the final phase, the initial training contingencies were reinstated (Lubar et al. 1981). Neuropsychological tests were performed before and after Neurotherapy Treatment, and changes in EEG activity were analyzed. Results indicated that five of the eight patients experienced a significant decrease in their mean seizure rates compared with their initial baseline rates, but only following Neurotherapy Treatment (Lubar et al. 1981). This study supports the contention that seizure
reduction is due specifically to Neurotherapy Treatment and not due to a placebo effect.

As previously reviewed, Neurotherapy Training of SMR at Cz had been used to reduce seizures in subjects with epilepsy, to remedy or reduce attention deficits, to reduce hyperactivity and learning difficulties. However, there was a need to establish whether training left or right hemisphere might influence hemisphere-specific functions such as Language skills. As mentioned in chapters 1 and 2, children with ADHD frequently have co-morbidities, including Learning Difficulties. Cunningham and Murphy (1981) implemented Neurotherapy Training with 24 adolescent males with Learning Disabilities (mean age of 15.9 years) who had verbal I.Q. deficiencies generally presumed to result from left hemisphere dysfunction. All subjects were pre-tested on measures of convergent and creative thinking, and were then assigned to eight weekly 21-minute sessions of either one of three conditions (1) Neurotherapy to train the right-hemisphere to increase in mean frequency and the left to decrease. A bipolar montage was used, with active electrodes at T3-P3 and with the reference electrode at FP1. (2) Neurotherapy training to promote a decrease in mean frequency in both hemispheres. A bipolar montage was used, with active electrodes at T4-P4 and with the reference electrode at FP2 and (3) a no-training control condition. The subjects were retested after Neurotherapy on the same measures, 2 months later. Neurotherapy Training produced baseline effects in the presumed dysfunctional left hemisphere and increased arousal while on task, suggesting potential remediation of the left hemisphere arousal deficits associated with language-learning deficits.
A placebo controlled study was used to evaluate whether Neurotherapy would improve concentration and performance in 24 experienced pre-elite archers (Landers et al. 1991). The archers were randomly assigned to one of three groups: correct feedback, sham feedback, and a no feedback control. Results indicated that the correct feedback group significantly enhanced their archery performance, while the sham feedback group showed a significant decrease in performance from pre-test to post-test. The control group showed no significant differences in performance between pre- and post-treatment conditions. EEG analyses at T3-T4 showed changes that were consistent with the training given to the sham, but not the correct feedback group. Results suggested that Neurotherapy could be used to improve concentration and enhance performance even in healthy high-performing subjects. Furthermore, results indicate an effect on the EEG that were specific to the training received (Landers et al. 1991).

Patrick (1996) investigated the impact of 15-sessions of EEG-driven photic stimulation on self-regulation of brain electrical activity. The study used a quasi-experimental waiting-period control group design. Participants were 25 boys with a diagnosis of ADHD aged between 8 and 14 years, 14 of whom were medicated. Repeated measures psychometric tests, consisted of the Raven’s Progressive Matrices, the WISC-R, the Wechsler Individual Achievement Test (WIAT), the Child Behaviour Checklist and Profiles (CBCL-P), the TOVA, and two separate EEG measures. Results indicated that there were no significant changes in any of the tests in the waiting-
period control group. However, in the experimental group, there were significant EEG changes towards normalisation, improvements in the WISC, processing speed and freedom from distractibility scales, WIAT, CBCL-P, and commission test scores in the 4th quarter on the TOVA, indicating improved impulse control. Since 40 sessions of Neurotherapy are considered average in the treatment of ADHD, further work is required to explore the effects of a longer treatment course using EEG-driven Photic stimulation (Patrick 1996).

Linden and colleagues (1996) confirmed the findings of Lubar and colleagues (1995b) in a controlled study, which investigated the effects of Neurotherapy on cognition and behaviour with 18 ADHD children, aged between 5 and 15 years. For the experimental group, training consisted of enhancing beta-activity and suppressing theta-activity. The control group received no Neurotherapy Training. The Neurotherapy group demonstrated increases on the Kaufman Brief Intelligence Test and reduced inattentive behaviours on the Behaviour Rating Scale, compared to the controls (Linden et al., 1996).

Following traumatic brain injury, reports of Attention Deficit Disorder are commonplace (Duff 2004; Hirshberg, Chiu & Frazier 2005; Max et al. 1998). Adults diagnosed with mild traumatic brain injury (mTBI) or ADHD were treated with Neurotherapy and cognitive retraining for their attention deficits (Tinius & Tinius 2001). The waiting-period control group consisted of subjects who did not receive Neurotherapy Training. The choice of protocols was dynamic and based on various parameters as displayed table 3.1. However, the authors did not adequately explain
the reasons for the protocol decisions or the protocol changes during training.

Table 3-1 Treatment Decisions Used by Tinius and Tinius (2001)

Psychological and neuropsychological tests were completed at pre- and post-treatment and compared to the control group who were also tested on two occasions with an interval matching that of the training period (Tinius & Tinius 2001). Using the IVA, a computer administered Continuous Performance Task; significant improvements were found on attention and response accuracy in both the mTBI and ADHD groups
compared to the control group. A self-report showed a significant decline in symptoms in the mTBI and ADHD groups but not in the control group. However, errors on a problem-solving task decreased only in the mTBI group. The combination of Neurotherapy and the cognitive retraining protocol used in this study resulted in significant improvement in the sustained attention of individuals diagnosed with mTBI and ADHD after twenty treatment sessions compared to controls (Tinius & Tinius 2001).

Carmody and colleagues (2001) conducted a Neurotherapy study, on site, in an elementary school with 16 unmedicated schoolchildren with ADHD or attention deficits. Eight children, aged between 8 and 10, were assigned to the experimental group and completed 35 to 47 sessions of Neurotherapy Training over a six-month period. Four participants in the experimental group were diagnosed with ADHD and four were not. The other eight children were assigned to a waiting list control group matched to the experimental group on age, grade, teacher, and diagnosis. Results, as assessed by the TOVA, indicated that the experimental group reduced the number of errors of commission and anticipatory errors made, indicating a reduction in impulsivity. Teacher reports using the McCarney Attention Deficit Disorder Evaluation scales (McCarney 1995) indicated improvements in attention but no changes in impulsivity and hyperactivity. No changes were observed in the waiting-period group control (Carmody et al. 2001).

Fernandez and colleagues (2003) postulated that since children with Learning Disabilities have higher values of theta EEG absolute and relative power than normal children, and that minimal alpha absolute power is necessary for adequate
performance, then training a decrease in the theta/alpha power ratio may reduce learning difficulties. TOVA, WISC-III and EEG were administered to ten children with Learning Difficulties and with higher than normal theta/alpha power ratios. They were then divided into two groups, each with similar socioeconomic status, I.Q. and TOVA values. The five children in the experimental group received Neurotherapy to promote a reduction in theta/alpha ratio, at a rate of two half-hour sessions per week for 10 weeks, at a site with the highest theta/alpha power ratio. Non-contingent (sham) reinforcement was given to the control group. TOVA, WISC-III and EEG measures were obtained at the end of the 20 sessions. WISC-III performance improved and EEG absolute power decreased in all clinical bands only in the experimental group. Children in the waiting-period control group showed only a decrease in relative power in the delta band. Thus, results indicated improvements in cognitive performance and EEG changes towards normalisation in the experimental group only (Fernandez et al. 2003).

Egner and Gruzellier (2004) set out to test a common assumption underlying the clinical use of Neurotherapy. Namely, that the training of specific frequency bands through Neurotherapy is associated with frequency-specific effects. They assessed whether enhancement of SMR (12-15 Hz) and beta1 (15-18 Hz) affected different aspects of attentional processing. Twenty-five subjects were randomly allocated to training for an increase of either SMR or beta1, or to a non-Neurotherapy control group. Subjects were assessed prior and subsequent to the training process on two tests of sustained attention, and on changes in P300 event-related potential (ERP) amplitudes in a traditional auditory oddball paradigm. The results indicated that
frequency-specific training effects were obtained. SMR training was associated with increased perceptual sensitivity (‘d prime’), reduced omission errors, and reduced variability in reaction time. Beta training was associated with faster reaction times and increased target P300 amplitudes. There were no changes evident in the non-Neurotherapy control group. The researchers concluded that Neurotherapy Training of SMR and beta bands elicited significant protocol-specific effects, and that the results indicated a general attention-enhancing effect of SMR training, and an arousal-enhancing effect of beta training (Egner & Gruzelier 2004).

Surface-negative slow cortical potentials (SCPs) originating in the apical dendritic layers of the neocortex may reflect states of behavioural or cognitive preparation; while surface-positive SCPs, may indicate a reduction of the cortical excitation that underpins behavioural inhibition and motivational inertia (Hinterberger et al. 2003). The relationship between negative and positive SCPs and changes in the blood-oxygen-level-dependent (BOLD) signal of fMRI were examined in ten subjects who successfully trained to self-regulate their SCPs through Neurotherapy (Hinterberger et al. 2003). FMRI revealed that the generation of SCP negativity (increased cortical excitation) was accompanied by widespread activation in central, pre-frontal, and parietal brain regions as well as the basal ganglia. The generation of SCP positivity (decreased cortical excitation) was associated with deactivation in supplementary motor areas and motor cortex as well as activation in frontal and parietal structures. These findings suggest that negative and positive electrocortical potential shifts in the EEG are related to distinct differences in cerebral activation.
detectable by fMRI and that these processes can be modulated by Neurotherapy (Hinterberger et al. 2003). It has been shown that P300 amplitude is significantly larger during negative SCP shifts compared to positive ones, suggesting that SCP shifts may be functionally related to arousal and inhibitory activities in the cortex. Furthermore SCPs and local field potentials may share identical neural substrates (Ergenoglu et al. 1998).

Neurotherapy of the SCP was used clinically in a recent study by Gevensleben and colleagues (2009). To overcome some of the methodological shortcomings of previous Neurotherapy Studies, such as non-specific training effects and insufficient statistical power, Gevensleben and colleagues (2009) evaluated the clinical efficacy of Neurotherapy Training in children with ADHD in a multi-site randomised controlled study using a computerised attention skills training (AST) software as the control condition. One hundred and two children with ADHD, aged 8 to 12 years, (diagnosed by a Child and Adolescent Psychiatrist and Psychologist as meeting DSM-IV criteria for ADHD), were randomly assigned to one of two groups with no mean differences in pre-treatment demographic, psychological or clinical variables (Gevensleben et al. 2009). Children with co-morbid disorders, other than Conduct Disorder, Anxiety, Depression, Tic disorder and Dyslexia, were excluded from the study. None of the participants had gross neurological or other organic disorders; all were drug-free and without psychotherapy for at least 6 weeks prior to the start of training and 87 of the participants were drug-naive. Prior to training, several behaviour rating scales, including the German ADHD rating scale (FBB-HKS) the Strength and Difficulties
Questionnaire (SDQ) were completed by parents and teachers, and these were repeated at an intermediate point and post-training. To control for parental expectations and satisfaction with the treatment, placebo evaluation scales were used. Training for each group consisted of two three to four week blocks of 18 sessions each (conducted as nine double sessions of about 50 minutes per session, separated by a short break. Two to three double sessions per week were used, to accommodate for the weekly schedule of the families. Pre-training assessment was conducted during the week prior to training, while intermediate and post-training assessments were done about one week after the last session of the training blocks. Neurotherapy Training consisted of a block of theta/beta training, and of a block of Slow Cortical Potential (SCP) training in a balanced order. On completion of the study, improvements in parent and teacher ratings were superior for those in the Neurotherapy group compared to those in the control group. The effect size was 0.60 for the parent rated scale, and 0.64 for the teacher-rated scale for the FBB-HKS total score of primary outcome measure of hyperactivity, impulsivity and attention. Comparable effects were obtained for theta/beta training and the SCP training protocols. Statistics revealed a trend towards better improvements in the FBB-HKS total score, when theta/beta training preceded SCP training ($F(1,50) = 3.00; p< 0.1$). Parental attitudes towards either treatment groups or controls did not differ (Gevensleben et al. 2009).

Gevensleben and colleagues (2009) argued that since parents of the Neurotherapy groups and the control group did not differ in expectations or in satisfaction with treatment, parental expectation factors should not have influenced
the outcome. Thus, they concluded that non-specific factors did not account for the clinical outcome and that the superiority of the combined NF training indicates clinical efficacy of NF in children with ADHD. They recommended that future studies should investigate how to optimise the benefits of Neurotherapy as a treatment for ADHD, and study the specificity of effects, resulting from SCP training or theta/beta training (Gevensleben et al. 2009).

3.9 Neurotherapy Protocols.

As previously discussed in section 3.2, most patients with ADHD have been shown to have excessive slow-wave activity in QEEG, a finding that has been interpreted as cortical “hypoarousal”, consistent with reduced glucose metabolism under PET or SPECT examinations. However, a smaller percentage of around 10% exhibit cortical "hyperarousal" (Barry, Johnstone & Clarke 2003; Chabot et al. 2001; Chabot & Serfontein 1996; Monastra, Lubar & Linden 2001; Monastra et al. 1999).

Since the early 1970s, specific Neurotherapy protocols have been developed and evaluated in controlled single-case and in group-studies to attempt to remedy the hypoarousal manifesting as excessive slow-wave activity. In all of these studies, children with ADHD have participated in Neurotherapy training during which they were reinforced for producing a reduction in the amplitude of slow-wave theta or alpha activity, while increasing the amplitude of the faster beta or SMR frequencies. Typically, the training required the patient to maintain the reward criteria for a period
of at least 500ms in order to receive contingent audio/visual rewards (Monastra et al. 2005).

Although several protocols have been used in published studies and in clinical practice, few protocols that target cortical regions responsible for attention and behavioural inhibition have been systematically examined in controlled group studies. One such protocol, which has been studied, involved suppression of theta (4-8 Hz) with enhancement of SMR (12-15 Hz) or Beta (16-20Hz) at C3, Cz or C4 scalp location. To control for muscle activity, reward is inhibited when Hi-Beta (24-60 Hz) is above preset threshold. This protocol has been investigated in several uncontrolled studies it was initially used by Lubar with children and adolescents with ADHD through to the age of fourteen (Lubar & Lubar 1984). Although, in Lubar’s (1984) study, EMG and movement were detected by level detectors based on Schmidt triggers.

Rossiter and Lavaque (1995) used this protocol in the first controlled group study of Neurotherapy for ADHD. Results of Neurotherapy Training were compared to those of Methylphenidate treatment (Rossiter & La Vaque 1995). In an attempt to improve attention deficits, hyperactivity and impulsivity, patients with ADHD were encouraged to suppress the production of theta activity while simultaneously increasing their production of SMR or Beta over the Rolandic Cortex. Typically, training was done at C3, C4 or Cz referenced to one ear (other ear grounded), or to linked ears (mastoid grounded) at a sampling rate of at least 128 Hz. Auditory and visual feedback was contingent on the patient’s success in controlling the amplitudes of theta, SMR, Beta or Hi-Beta or on the percentage of time that theta was below or SMR was above
preset thresholds (Lubar & Lubar 1984; Rossiter & La Vaque 1995).

Several controlled group studies published to date have used the protocol some with minor variations in bandwidth (Carmody et al. 2001; Fuchs et al. 2003; Levesque, Beauregard & Mensour 2005; Linden, Habib & Radojevic 1996a; Monastra, Monastra & George 2002; Rossiter 2004a; Rossiter & La Vaque 1995). Fuchs and colleagues (2003) used this protocol in a controlled group study, whereby patients with ADHD of the primarily hyperactive/impulsive subtype received theta/SMR training at C4 and those who were of the primarily inattentive subtypes received Theta/Beta (15-18Hz) training at C3. The patients with combined subtypes received both protocols, one in each half of the training session (Fuchs et al. 2003).

Carmody and colleagues (2001) used a slight variation of this protocol in a controlled-group study in a school setting. In this procedure, students were encouraged to increase production of a restricted range of beta activity (16-18 Hz) while suppressing activity at 2-7 Hz (Carmody et al. 2001). Recordings were obtained at C3 or Cz with linked ear reference. Students who displayed increased aggression or agitation within the first 13-35 sessions of this type of training were considered to be "over stimulated". Such patients were then treated with an SMR training protocol, in which they were reinforced for increasing 13-15 Hz activity and suppressing 2-7 Hz activity at C4 (Carmody et al. 2001).

### 3.10 Studies of the Specificity of Neurotherapy Protocols
Carter and Russell (1981) conducted a pilot investigation to demonstrate the hemisphere-specific training effect of Neurotherapy. Four elementary-school-age boys, with verbal I.Q. 15 or more points below their performance I.Q. on the WISC-R, participated in the study. Neurotherapy Training consisted of promoting a shift in the mean frequency from 8-13 Hz to 13-28 Hz activity in the left hemisphere and back. Results showed increases in verbal abilities and decreases in the difference between Verbal I.Q. and non-Verbal I.Q., indicating that specific effects may be elicited by hemisphere-specific training (Carter & Russell 1981).

Mulholland and colleagues (1983) tested the hypothesis that diverting attention from a Neurotherapy display would be associated with increased variability of the physiological processes that are regulated by Neurotherapy. Conversely, that attending to the Neurotherapy display would decrease variability in the EEG measures. They compared the effects of three conditions (a) attending a biofeedback display, (b) not attending to it and (c) receiving sham biofeedback. The study consisted of two repeated-measures experiments with 16 normal adults of both sexes. The dependent variables were the duration and the mean power of two mutually exclusive, alpha and non-alpha segments of parietal-occipital EEG. The independent variables were a combination of counting tasks including looking at and counting visual flashes and listening to and counting auditory clicks. The durations of alpha and non-alpha segments were modulated by means of an alpha-contingent visual biofeedback stimulus derived from the subject’s own EEG in Conditions (a) and (b) and from sham EEG in Condition (c). In Condition (b), attention to the feedback stimulus was
challenged by instructions to count other, non-contingent auditory clicks. The results indicated that control of alpha and non-alpha segments were least for conditions of the "sham" feedback, and feedback with instructions to count non-contingent auditory clicks, in that order. Control of alpha and non-alpha segments, evidenced by reduced variability in the EEG segments was only seen in Condition (a), suggesting that contingent feedback was associated with control of the EEG measures being attended to (Mulholland, Goodman & Boudrot 1983).

Egner and colleagues (2004) investigated the effect of Neurotherapy Treatment on Spectral EEG Topography, which may underpin cognitive-behavioural outcomes. In order to assess the effect of commonly applied Neurotherapy protocols on spectral EEG composition, two studies involving healthy participants were carried out. In the first experiment, spectral resting EEG was assessed before and after the subjects were trained using three different protocols: SMR (12-15 Hz), beta (15-18 Hz), and alpha/theta (8-11 Hz/5-8 Hz). The specific associations between learning indices and changes in absolute and relative Spectral EEG Topography were assessed by means of partial correlation analyses for each individual training protocol (Egner, Zech & Gruzelier 2004).

The results of this first experiment were used to generate hypotheses for a second experiment, where subjects were randomly allocated to independent groups of SMR, beta, and alpha/theta training (Egner, Zech & Gruzelier 2004). Spectral resting EEG measures prior to and subsequent to training were compared for each individual group. Results across the two studies found only a few consistent associations
between particular protocols and spectral EEG changes. Additionally, these associations did not support the hypotheses with reference to the operant contingencies trained. Overall, SMR training was found to be associated with reduced post-training SMR activity. Alpha/theta training was more consistently associated with reduced relative frontal beta band activity. Egner (2004) concluded that training of specific frequencies affected spectral EEG topography in healthy subjects, but that the effects did not necessarily correspond to either the frequencies or the scalp locations being trained. The consistent association between alpha/theta training and reductions in frontal beta activity support the proposed role of alpha/theta training in reducing over-arousal, agitation, anxiety and stress. Egner remarked that the results highlighted the complexity of the neuronal dynamics involved in self-regulation, and emphasise the need for empirical validation of the relationship between Neurotherapy protocols and neurophysiological outcomes (Egner, Zech & Gruzelier 2004).

The fact that the subjects in the study by Egner and colleagues (2004) were normal subjects, with presumably more normal EEG topography than clinical groups, may be responsible for the lack of correspondence between frequency specific training and changes in the EEG. One would expect that training would result in regression to the mean in clinical groups, and that excursion away from the mean would be less likely in normal subjects whose EEG parameters are already close to the mean. The consistent findings that alpha/theta training reduce frontal beta and produce a calming effect, may reflect the fact that in our modern lifestyles, most people are under some degree of stress/arousal and therefore may benefit from alpha/theta training (Egner,
This study by Kropotov and colleagues (2005) was mentioned in section 3.7 (Uncontrolled Neurotherapy Studies). It is repeated in the context of the specificity of Neurotherapy Training. Event-related potentials (ERPs) were recorded in an auditory GO/NO-GO task before and after 15 to 22 sessions of Neurotherapy in 86 children with ADHD (Kropotov et al. 2005). ERPs of good performers showed increased positive components to GO and NO-GO cues within 180-420 ms over fronto-central areas. These ERP component increases were interpreted as reflecting an activation of fronto cortical areas associated with beta training (Kropotov et al. 2005).

A number of functional neuroimaging studies, including SPECT and PET studies have found dysfunction in areas of the brain that subserved attentional processes in children, adolescents, or adults with ADHD (Amen & Carmichael 1997; Kim et al. 2002; Lou 1991; Lou et al. 1989b; Sieg et al. 1995; Zametkin et al. 1993; Zametkin et al. 1990b). These studies have shown decreased metabolism in the striatum and prefrontal regions during resting state (Amen & Carmichael 1997; Kim et al. 2002; Lou 1991; Lou et al. 1989b; Sieg et al. 1995; Zametkin et al. 1993; Zametkin et al. 1990b). Furthermore an fMRI study found no activation of the anterior cingulate cortex (ACC) in adults with ADHD during performance of the Counting Stroop Task (Bush et al. 1999). Findings from PET and fMRI studies have provided converging evidence, which indicate that the dorsal division of the ACC, the cognitive division of the ACC (ACCcd), plays a key role in the cognitive processes involved in the Counting Stroop Task. This includes: mediating interference, allocation of attentional resources and response.

These findings prompted Beauregard and colleagues (2006) to use fMRI during a Counting Stroop Task and a Go/No-Go task, to measure the effect of Neurotherapy on the brain activity associated with selective attention and response inhibition in children with ADHD. Of the twenty un-medicated children with ADHD who participated in the study, 15 were randomly assigned to the Neurotherapy group and five to a no-treatment waiting-list control group. The training was divided into two phases of 20 sessions each. In the first phase, the children in the experimental group were required to enhance the amplitude of the SMR (12–15 Hz) and decrease the amplitude of theta activity (4–7 Hz) at the Cz location. In the second phase, they were required to inhibit the amplitude of their theta waves (4–7 Hz) and increase the amplitude of their beta waves (15–18 Hz) also at the Cz location (Beauregard & Levesque 2006).

The children from both groups underwent fMRI scanning, while they performed a Counting Stroop Task and a Go/No-Go task, one week before the beginning of Neurotherapy (time 1) and one week after Neurotherapy (time 2). They were also administered an ADHD Symptom Checklist from the DSM-IV, The Digit Span Subtest of the Wechsler Intelligence Scale for Children-Revised, the Integrated Visual and Auditory Continuous Performance Test (IVA), and the Conners Parent Rating Scale-Revised (CPRS-R), one week before the beginning of Neurotherapy and one week after Neurotherapy (Beauregard & Levesque 2006).

Results indicated that prior to and after Neurotherapy, the Counting Stroop
Task was associated with significant activation in the left superior parietal lobule in both groups, while no significant activity was detected for the Go/No-Go task in either the experimental or the control group (Beauregard & Levesque 2006). However, after Neurotherapy, the Counting Stroop Task was associated with significant loci of activation in the right ACCcd (Brodmann area (BA) 32), left caudate nucleus, and left substantia nigra, only in the Neurotherapy group (Beauregard & Levesque 2006).

As previously mentioned, functional brain imaging studies have revealed that the cognitive division of the anterior cingulate cortex (ACCcd) plays a crucial role in the cognitive processes involved in the Counting Stroop Task (Bush, Luu & Posner 2000; Bush et al. 1998; Whalen et al. 1998). The ACCcd has also been found to be implicated in selective attention, selection of appropriate responses, and suppression of inappropriate behavioural responses (Carter et al. 1998; Corbetta et al. 1991a; Corbetta et al. 1991b; Pardo et al. 1990; Paus et al. 1993; Peterson et al. 1999). Consequently, Beauregard and Levesque (2006) claimed that the observed ACCcd activity and improved behavioural performance in the experimental group following Neurotherapy was related to the normalisation of neuronal activity in the ACCcd. For the Go/No-Go task contrast, significant loci of activation were noted, only in the experimental group, in the right ventrolateral pre-frontal cortex, right ACCcd, left thalamus, left caudate nucleus, and left substantia nigra, with no significant activation of these brain regions measured in subjects in the waiting list control group (Beauregard & Levesque 2006).

The pre- to post-treatment comparisons of the average scores on the Digit Span, the IVA, and the CPRS-R, revealed that the Neurotherapy group had significantly
decreased primary symptoms of ADHD (Beauregard & Levesque 2006). Following
Neurotherapy, scores on the inattention and hyperactivity components of the CPRS-R
decreased significantly for the experimental group, and marked improvements in
attention and behavioural inhibition were evident. These behavioural improvements
were associated with enhanced performance on both neutral and interference trials on
the Counting Stroop Task, and for both Go and No-Go trials in the Go/No-Go Task,
while no such changes were noted in the control group. Beauregard and colleagues
(2006) concluded that Neurotherapy had the capacity to functionally normalise the
brain systems mediating selective attention and response inhibition in children with
ADHD (Beauregard & Levesque 2006).

Furthermore in the study by Beauregard and Levesque (2006), prior to
Neurotherapy, No-Go minus Go comparison did not reveal any significant locus of
activation in either group, consistent with the results of previous fMRI studies which
found underactivation of the striatum and pre-frontal areas in children and
adolescents with ADHD during Go/No-Go Tasks (Booth et al. 2005; Durston et al. 2004;
Durston et al. 2003; Schulz et al. 2004; Suskauer et al. 2008b; Teicher et al. 2000).
However, after Neurotherapy Treatment, significant loci of activation were observed in
the right ACCcd (BA 24/32), right ventrolateral pre-frontal cortex (BA 47), left
thalamus, left caudate nucleus, and left substantia nigra. Beauregard and colleagues
(2006) noted that these results were consistent with the results of fMRI studies which
identified the cognitive processes underpinning behavioural inhibition including the
ACCcd (Liddle, Kiehl & Smith 2001), the ventrolateral pre-frontal cortex (Liddle, Kiehl &
Smith 2001; Schulz et al. 2004; Schulz et al. 2005a), and the caudate nucleus (Booth et al. 2005). Furthermore, it has been previously suggested that dopamine, from substantia nigra neurons, has a neuromodulatory effect on frontostriatal attentional circuits related to ADHD (Arnsten 2006; Seamans & Yang 2004; Viggiano, Vallone & Sadile 2004). Hence, Beauregard and Levesque (2006) argued that the activation of the substantia nigra and left caudate nucleus for both the Counting Stroop Task and the Go/No-Go Task following Neurotherapy, suggest that Neurotherapy is able to improve dopamine neuromodulation (Beauregard & Levesque 2006).

3.11 Effectiveness Studies: Comparison of Neurotherapy to Stimulants.

Lubar and colleagues (1995a) measured the QEEG of 23 individuals with ADHD. They examined theta/beta ratios of the ADHD participants, both with and without medication, and found no significant effect of stimulant medication on the theta/beta ratios in the QEEG at all 19 sites evaluated. They concluded that Methylphenidate had very little effect on theta/beta ratios (Lubar et al., 1995a). Methylphenidate and other stimulant medications used to enhance attention produce state-dependent effects. This means that the medication works while it is in the system but that there is virtually no long-term carry-over to the non-dependent state. On the other hand, Neurotherapy works not only while doing training, but has a carry-over effect that lasts for a very long time, perhaps even a whole lifetime (Lubar, 1997).

Rossiter and La Vague (1995) compared the effects of Neurotherapy to
stimulant medication in reducing ADHD symptoms. The study compared the effects of a medical treatment program, to 20 sessions of Neurotherapy. Each group had 23 participants who were matched by age, I.Q, gender and diagnosis. The Test of Variables of Attention (TOVA) was administered pre- and post-treatment. Both groups improved significantly on TOVA measures of inattention, impulsivity, information processing, and variability in the reaction time, and did not differ from each other on TOVA change scores. Rossiter (1995) suggested that Neurotherapy was an effective alternative to stimulants and may be the treatment of choice when medication is ineffective, or produces unacceptable side effects, or when compliance to medication is a problem (Rossiter & La Vaque, 1995). In acknowledgement of criticisms that the statistical analysis used in their study (Rossiter and Lavaque, 1995) was flawed, Rossiter (2004a) re-analyzed the data using the Holm procedure (Stevens, 1999) to control the experiment-wise alpha level for multiple comparisons. All planned comparisons for which significant differences were predicted met their adjusted alpha levels for significance with the experiment-wise $\alpha = .05$. Equivalence/non-inferiority testing indicated that the proportion of the Neurotherapy group significantly improved, was non-inferior, but not-equivalent to that of the medication group (Rossiter 2004a).

Fuchs (1998) compared the effectiveness of Neurotherapy to stimulant medication in 22 children, 8 to 12 years of age, from a Social-Pediatric Hospital, with a primary diagnosis of ADHD. Half of the participants were assigned to a Neurotherapy experimental group and the other 11 were assigned to a control group matched in age and sex. The Neurotherapy group received thirty 45-minutes sessions of Neurotherapy
to enhance SMR and/or beta activity and suppress theta activity, over a period of 10 weeks. The control group of children with ADHD was optimally medicated with Methylphenidate. No other psychological treatment or medication was administered to either group. Both groups were administered a test battery consisting of: an I.Q. test (HAWIK-R), a TOVA, a paper-pencil-test (d2) and the IOWA Conners Behaviour Rating Scales (parent and teacher version), pre- and post-treatment. Results indicated that the children in both the Methylphenidate and Neurotherapy conditions showed comparable and significant improvements in attention and concentration abilities in the objective (d2 and TOVA), and subjective (Conners Behaviour Rating Scales) measurements. Performance I.Q. scores also improved significantly in both groups. Fuchs (1998) reported that while Methylphenidate and Neurotherapy had comparable treatment effectiveness, the gains from Neurotherapy were expected to be permanent, while the gains from medication were expected to be dependent on the continuation of medication treatment (Fuchs 1998).

One hundred children diagnosed with ADHD, either inattentive or combined subtype, aged 6-19 years, participated in a one-year, multimodal, outpatient program that included Methylphenidate, parent counseling and academic support at school (Monastra, Monastra & George 2002). In addition, 51 of the children also received Neurotherapy. Pre- and post-treatment assessments were conducted both while on and off stimulant therapy. Significant improvements were noted on the TOVA and the Attention Deficit Disorders Evaluation Scale (ADDES) (Adesman 1991), while participants were on Methylphenidate. However, only those who had received
Neurotherapy sustained these gains when tested while off Methylphenidate. Only children who had received Neurotherapy had reductions in theta/beta power ratio at Cz, and these changes were statistically significant. ADDES behavioural measures indicated that parenting style exerted a significant moderating effect on the expression of behavioural symptoms only at home and not at school (Monastra, Monastra & George 2002). Arns and colleagues (2009) cautioned that the results from the Monastra and colleagues (2002) Study needed to be interpreted with care, as the study only included subjects with an elevated theta/beta ratio, thereby potentially selecting for those subjects with ADHD who would benefit most from Neurotherapy Treatment. The subjects in that study might therefore not have been representative of the general ADHD population (Arns et al. 2009).

Fuchs and colleagues (2003) selected 34 children, aged 8-12 years with a diagnosis of ADHD to participate in a study comparing the effects of a 3-month Neurotherapy treatment program to Methylphenidate (Fuchs et al. 2003). The children were from families of heterogeneous socioeconomic backgrounds and their diagnoses were made by two independent clinicians: either a Child Neurologist or a Pediatrician together with a Child and Adolescent Clinical Psychologist. None of the children had received any kind of treatment for their ADHD prior to selection for participation in the study. Twenty-two of the participants were assigned to the Neurotherapy group and 12 to the Methylphenidate group according to their parents' preferences. Neurotherapy training consisted of rewarding SMR (12-15 Hz) and beta activity (15-18 Hz). Behavioural measures were assessed using the German version of the IOWA-
Conners Behaviour Rating Scale, and were completed by each child’s teacher and both parents prior to, and after Neurotherapy. Teachers were blinded to the choice of treatment group while parents were not (Fuchs et al. 2003). Both Neurotherapy and Methylphenidate were associated with improvements on all subscales of the TOVA, and on the speed and accuracy measures of the “d2” Attention Endurance Test (Fuchs et al. 2003). Furthermore, ADHD behaviours were significantly reduced in both groups as rated by both teachers and parents on the IOWA-Conners Behaviour Rating Scale. The authors concluded that Neurotherapy was as effective in improving the behavioural problems of children with ADHD as stimulant medication (Fuchs et al. 2003). Further evidence of the effectiveness of Neurotherapy, when compared with Methylphenidate came from Rossiter (2004), who replicated an earlier study (Rossiter & La Vaque 1995).

The replication used a larger sample of children with ADHD, with a wider age range, improved statistical analysis and more comprehensive behavioural data. Thirty-one patients who chose Methylphenidate treatment were matched with 31 patients who chose Neurotherapy Treatment. Of the Neurotherapy patients, 14 received training in the clinic while the remaining 17 received training in their own home. This study design is one described by Kazdin (2003) as an “effectiveness research design” whereby patients choose assignment to either the Neurotherapy, experimental group, or the Methylphenidate, active treatment control group (Kazdin & Nock 2003). The Methylphenidate dose was titrated for optimum effect using the TOVA. Both groups showed statistically and clinically significant improvements on TOVA measures of
attention, impulse control, processing speed, and variability in reaction time. Clinically significant gains were made by the Neurotherapy and Methylphenidate groups based on the percentage of patients showing significant improvement over baseline (84% in each). There were large effect sizes for Neurotherapy (1.01-1.71) and Medication (0.80-1.80), and the percentage of individual TOVA scores showing significant improvement (Neurotherapy: 55%, Methylphenidate: 56%). Post-treatment mean scores for both the Neurotherapy and the Methylphenidate groups fell within the average range of functioning. Both groups had clinically significant improvement in behaviours based on their large effect size. The Neurotherapy group had effect size (1.15–1.75) on the Behaviour Assessment System for Children (BASC) and (1.59) for the Brown ADD Scale. There were no statistically significant differences in the TOVA gain scores between the Neurotherapy and Methylphenidate groups, and the proportion of patients in the Neurotherapy group that significantly improved behaviourally was equivalent to that of the medication group. Confidence interval and non-equivalence null-hypothesis testing confirmed that the Neurotherapy program produced patient outcomes equivalent to those obtained with Methylphenidate (Rossiter 2004b).

### 3.12 Adverse Results and Criticism of Neurotherapy Studies

Although most studies found that Neurotherapy produced beneficial outcomes, Heywood and Beale (2003) found no difference between active Neurotherapy conditions and placebo feedback in their pilot study that used single-case repeated-measures with seven children diagnosed with ADHD. Five of the children had co-
morbid aggressive and/or delinquent behaviours, and three had Learning Difficulties. Only two of the seven received provisional diagnoses of ADHD alone, two of the seven children received medication for their ADHD for the duration of the study, and two of the children did not complete the training. The design was described as A1 A2 B1 A2 B1 (where A1=baseline, A2=placebo, B1=active, and A2=Placebo), with replications consisting of a non-concurrent multiple baseline across participants with embedded ABAB reversal. A total of ten placebo and ten active Neurotherapy sessions were provided. A composite score from seven attention and “activity” measures were used for repeated measures variables (Heywood & Beale 2003).

The active condition in Heywood and Beale’s (2003) study was claimed to be a standard Neurotherapy treatment protocol designed to alter SMR/theta ratios and reduce ADHD behavioural symptomatology. During alternate periods, participants were also trained using a sham placebo protocol that seemed identical to the treatment protocol. Two participants failed to complete all training sessions. However, the training effects on the composite behaviour scores were analyzed both including and excluding these two non-completers (Heywood & Beale 2003). It was thought that this experimental design would reveal the existence of any placebo component underlying the overall treatment effect, and the relative effect size of the placebo and unique treatment components. However, there appeared to be serious methodological flaws in Heywood and Beale’s (2003) study.

First, the only reference in the paper to the active Neurotherapy methodology was this sentence:
“Active sessions used a standard protocol for the treatment of ADHD, reinforcement of 13-15 Hz sensorimotor rhythm (SMR) in the absence of 4-8 Hz theta and with 20-30 Hz high beta above set thresholds (Lubar & Lubar, 1984; Othmer & Othmer, 1991)” (Heywood & Beale 2003) p44.

It is unclear whether Heywood and Beale (2003) understood that Lubar (1984) protocol called for inhibiting theta, as opposed to rewarding SMR in the “absence” of theta, which given that theta is never absent would have resulted in very low reward rates. Also “reinforcement of 13-15Hz SMR ... with 20-30 Hz high beta above set threshold” is not the protocol used by Lubar (1984) or Othmer (1991) who defined beta as 16-20Hz. Rewarding 20-30 Hz may tend to reward components associated with anxiety and muscle tension.

Second, the study made no mention of site preparation, electrode impedances, placement of electrodes for active, ground and reference electrodes, and whether muscle artefact was properly controlled. There was also no mention of the reward rate (the percentage of time that the participants received reward).

Third, the measures used contained indices that are not limited to core deficits of ADHD (attention, impulsivity and hyperactivity), making the composite index used to measure change less sensitive to core behaviours seen in ADHD. Three of these variables were not specifically related to ADHD core behaviours. E.g. Controlled Oral Word Fluency FAS Test, Child Behaviour Checklist, and the Paired Associate Learning Task. Therefore, it is unclear which of these behavioural measures contributed to the
composite score used as an outcome measure. In addition, the CPT used is unspecified and refers to an earlier study by the authors where its nature was again unclear.

Fourth, and probably the most serious, is the study design itself and its relevance to learning theory. The single-case design used a variable sequence of 6-8 (non-active) baseline and placebo sessions, followed by to 4-6 active sessions, and then 1-4 placebo sessions and finally 3-7 active sessions. This sequence is not supported by the basic premises of Applied Behaviour Analysis principles (Sarafino 1996) on which Neurotherapy is founded. The first 6-8 non-active sessions would have taught the participants that they had no control over their brainwaves and primed them for failure or reduced success, the next 4-6 sessions of active feedback would not have allowed participants enough time to master the task before being exposed again to another 1-4 sham-feedback sessions. The 10 active Neurotherapy sessions interspersed with sham would reduce learning rate and not be conducive to acquiring the skills being trained. Despite these flaws, there was a significant trend towards improvement and the effect size amongst subjects was moderate to high. However, Heywood and Beale (2003) concluded based on the five cases analysed, that there was no evidence for a specific effect from Neurotherapy in ADHD.

Early Neurotherapy studies consisted mostly of single-case, series of single-cases or very small uncontrolled groups. The small sample size of the studies and the lack of larger placebo controlled groups have attracted much criticism (Lohr et al. 2001; Loo & Barkley 2005). Critics have suggested that the results cannot be generalised to the ADHD population at large and conclusions cannot be drawn with regards to the
specificity of the treatment effects, because other associated confounding factors, may account for the treatment effects (Lohr et al. 2001; Loo & Barkley 2005). Barkley (1992) concluded that there was not enough evidence from well-controlled scientific studies at that time to support the effectiveness of Neurotherapy for ADHD children. He criticised studies for having small numbers of subjects, for lacking appropriate control groups, for using diagnostic criteria that were unspecified or ambiguous, for using multiple interventions that confounded treatment effects, and for using outcome measures susceptible to practice and/or placebo effects. Barkley's (1992) criticisms were valid, as acknowledged by Lubar (1993) and were subsequently addressed by controlled studies using larger number of subjects and better controls (Beauregard & Levesque 2006; Fuchs et al. 2003; Gevensleben et al. 2009; Monastra 2005; Monastra, Monastra & George 2002; Rossiter 2004b).

In a paper criticising methodological issues relating to Neurotherapy studies as a whole, Lohr and colleagues (Lohr et al. 2001) examined several uncontrolled Neurotherapy studies (Alhambra, Fowler & Alhambra 1995; Fenger 1998; Lubar et al. 1995c; Nall 1973; Tansey 1991; Thompson & Thompson 1998b), and two controlled studies (Linden, Habib & Radojevic 1996b; Rossiter & La Vaque 1995). Lohr and colleagues (2001) examined a number of “efficacy studies” of Neurotherapy, claiming that there was an insufficient number of ADHD cases of time-series experimental designs in (Lubar & Lubar 1984), (Lubar & Shouse 1976b) and (Lubar & Shouse 1977) to meet the criteria for specific and efficacious (well-established) treatment according to the criteria set out by Chambless and Hollon (Chambless & Hollon 1998). However,
none of the studies examined by Lohr and Colleagues (2001) were “efficacy studies”. All were “effectiveness” studies, and as will be argued below, the criteria used for evaluating efficacy studies does not apply.

In addressing the criticisms of Lohr and Colleagues (2001), Rossiter (2004) suggested that first there was a need to distinguish “efficacy” versus “effectiveness” research and differentiate between their goals and methodologies. Kazdin (2003) placed “efficacy” and “effectiveness” studies at the different ends of a continuum with reference to clinical research methodologies for the assessment of treatment outcomes. According to Kazdin (2003), efficacy studies are conducted under strict laboratory and quasi-laboratory conditions, with an emphasis on controlling experimental variables to ensure internal validity. This is to determine whether treatment outcomes are due to the treatment itself or due to confounding factors or chance. Efficacy studies therefore require clinical trials in which patients are randomly-assigned to treatment or control groups and employ highly-structured treatment protocols closely monitored for therapist compliance (Kazdin 2003; Kazdin & Nock 2003). Participants are screened for co-morbidities to produce homogeneous patient groups and confounding factors are controlled for. Efficacy studies generally only provide the intervention being evaluated to the experimental group. In stark contrast to clinical practice, other treatments, ordinarily available to patients with the disorder being studied, are not provided (Kazdin 2003; Kazdin & Nock 2003).

Weisz and colleagues (Weisz et al. 1995a; Weisz et al. 1995b; Weisz & Jensen 2001; Weisz & Jensen 1999; Weisz, Weiss & Donenberg 1992) have argued that
interventions with demonstrated efficacy are not necessarily effective when applied to clinical settings. They related that meta-analyses of laboratory outcome studies revealed consistent beneficial effects with children and adolescents. However, the therapy in most of the efficacy studies differed from everyday clinic therapy in several ways, and the clinic-based therapy showed markedly poorer outcomes than research-based therapy studies, suggesting that efficacy studies lacked external validity. I.e. the findings could not be generalised to real-world clinical environments (Weisz et al. 1995a; Weisz et al. 1995b; Weisz & Jensen 2001; Weisz & Jensen 1999; Weisz, Weiss & Donenberg 1992).

The failure of “efficacious” treatments to successfully transfer to clinical settings may result, in part, from the very experimental controls that define the efficacy studies and ensure their internal validity (Weisz & Weiss 1989; Zimmerman, Mattia & Posternak 2002). Zetin and colleagues (2007) replicated Zimmerman’s (2002) study and found that 91% of their 803 outpatient clinical sample would not have qualified for inclusion in a randomised clinical trial of SSRIs based on the exclusion criteria outlined in Zimmerman (2002). They concluded that clinical trials only evaluated a small subset of patients, and that the efficacy of the treatment evaluated had little external validity because of the very restrictions that proved their efficacy (Zetin & Hoepner 2007).

Zimmerman (2002) and Zetin (2007) aimed their criticism at the “gold standard” of pharmacological research: “randomized placebo controlled trials”. However, efficacy studies of psychotherapy or biofeedback outcomes are subject to
the same limitations regarding external validity. Weisz and colleagues (2001) examined over 500 child and adolescent psychotherapy studies, focusing on effectiveness and efficacy research. They found numerous efficacy studies with substantial evidence of benefit, while very few studies demonstrated the effectiveness of the same treatment in everyday practice. They argued that there was a need for: greater use of treatment models used in clinical practice settings, tests of outcome mediators and moderators, tests employing a broader range of treatment delivery models, and research bridging the gap between lab-tested treatments and the conditions of real-world practice (Weisz & Jensen 2001).

Weiss and colleagues (2006) pointed out that in contrast, “effectiveness” research is typically conducted in a clinical setting with fewer exclusion criteria and control procedures that characterise “efficacy” research (Weiss, Gadow & Wasdell 2006). The subjects of effectiveness studies come to a clinic, often with severe symptoms and co-morbidities, seeking treatment and expecting improvement, thereby excluding the possibility of a placebo control. The patient chooses the treatment and randomization is not possible. Heterogeneity of the patient groups increases the ability of the study to assess the real-world effectiveness of the treatment and has high external validity, but low internal validity. An effectiveness study therefore evaluates a treatment as it is actually administered in everyday clinical practice. While an effectiveness study can demonstrate that a treatment is clinically effective, it cannot categorically demonstrate that the treatment only and not extraneous factors contributed to the positive outcomes (Clarke 1995). Where efficacy studies
demonstrate whether a treatment can work, effectiveness studies tell us whether they actually do work (Weiss, Gadow & Wasdell 2006).

Weiss (2006) argued that “efficacy” clinical trials usually include those patients that are seen the least by clinicians while excluding those that they see the most. Consequently, in efficacy clinical trials involving children with ADHD, small differences in effect size in a few key studies have become crucial indicators for rating treatments as first line or second line (Weiss, Gadow & Wasdell 2006). Such studies give no consideration to those variables which would otherwise confound efficacy trials, such as: patient preferences, co-morbidities, difficulties with sleep or appetite, compliance, timing of functional impairment, and substance use. These “effectiveness variables” although less well studied, are critical to day-to-day clinical decisions. Weiss (2006) further argued that since it has been estimated that fewer than 10% of the patients seen in clinical practice comply with and persist with treatment, there is a need to learn more about why patients discontinue treatment and to explore measures of effectiveness empirically. Hence, he argues, effectiveness studies are important if regulatory bodies are to have the data needed to balance the “risk of treatment” against the “risk of failing to treat”. Consequently, effectiveness clinical trials and naturalistic follow-up studies are needed to allow for the evaluation of the true clinical impact of short-term efficacy trials (Weiss, Gadow & Wasdell 2006).

Lohr and colleagues (2001) criticised Rossiter and La Vaque (1995) on the following counts: (1) for using an active treatment control; (2) for non-random assignment of patients; (3) for allowing the provision of collateral treatments; (4) for
using non-standardised and invalid assessment instruments; (5) for providing artefact-contaminated EEG feedback; and (6) for conducting multiple non-alpha-protected t-tests (Lohr et al. 2001). Rossiter argued that, except for those related to the statistical analyses; the criticisms are invalid or are not supported. They were based on the “unsubstantiated opinions” of the critics, who erroneously used criteria applicable to “efficacy studies”, to critique Rossiter and La Vaque (1995) “effectiveness study”, and their comments reflected a lack of familiarity with the Neurotherapy research literature (Rossiter 2004a).

Lohr (2001) criticised Rossiter and La Vaque (1995) for not randomly assigning children with ADHD to the Neurotherapy Treatment or the stimulant medication group, and commented that some children in the Neurotherapy Treatment group had received stimulant medication prior to starting Neurotherapy Treatment. In addition, they made further criticisms that children receiving either treatment were permitted o also receive other treatment modalities including behaviour modification and supplemental educational tutoring. They noted that assessment of treatment effects included the Test of Variables of Attention (TOVA) and the Behaviour Assessment System for Children (BASC), and that multiple one-tailed t-tests were not alpha-protected. The analyses showed improvements with no statistical differences between the groups. Lohr’s (2001) criticism was that while the statistical analyses suggested improvements resulting from Neurotherapy, the analyses conducted increased the likelihood of false positive effects (Type 1 errors). However, it could be argued that since the same measures and analyses were also applied to the Medication group,
Type 1 errors may have occurred in the medication group as well. Since both treatment groups responded equally well and there were no statistical differences in the outcome measures between the groups, the criticism of the statistics although valid does not affect the effectiveness of either treatment.

Lohr (2001) also criticised Rossiter and La Vaque (1995) for using non-standardised measures of minimal ecological validity. They stated, as an example, that the dependent variables included an “unspecified questionnaire completed by parents assessing symptoms and functioning”. However, it is difficult to understand this criticism since the Behaviour Assessment System for Children (BASC), which is a standardised test, was used. Doyle and colleagues (1997) assessed the Convergent validity of the BASC by correlating BASC scale scores with scale scores on the Child Behaviour Assessment System for Children (CBCL/4-18). Results showed the validity of the BASC was comparable to that of the CBCL/4-18 and that given its conceptually derived scales, the BASC may prove to be a useful tool for assessing childhood disruptive behaviour (Doyle et al. 1997). The ecological validity of the BASC was later examined independently and found to be a comprehensive and psychometrically sound assessment tool which had much to offer Psychologists working with children and adolescents (Gladman & Lancaster 2003).

Lohr and colleagues (2001) also criticised the use of the TOVA because of it having “questionable ecological validity as a measure of treatment efficacy”. Shadish
and Cook (2009) argued that for a research study to possess ecological validity, the methods, materials and setting of the study must approximate the real-life situation that is under investigation. However, unlike internal and external validity, ecological validity is not necessary to the overall validity of a study (Shadish & Cook 2009). Criterion validity, on the other hand, is more relevant as it is a measure of how well variables predict behavioural outcomes based on information from other variables (Shadish & Cook 2009). Hence, criterion validity is achieved if the TOVA variables relate to behavioural criteria that Psychologists agree upon (Messick 1995; Shadish & Cook 2009). A number of studies have found that scores on the TOVA correlate with behavioural symptoms of ADHD and other behavioural measures of attention (Braverman et al. 2006; Chae, Jung & Noh 2001; Forbes 1998; Huang et al. 2007; Llorente et al. 2007; Manor, Sever & Weizman 1999; Preston, Fennell & Bussing 2005; Rossiter 2004b; Thompson & Thompson 1998b; Wada et al. 2000; Wu et al. 2007). In addition, the TOVA has been designed and used as an index of attentional measures (Greenberg & Waldman 1993).

Lohr and colleagues (2001) conceded that the TOVA is a continuous performance test (CPT) that is intended to be an index of attention. While they cite Barkley (1991b) as evidence that CPT measures consistently discriminate between children with ADHD from normal, children they also cite Halperin and colleagues (1992) as having found that the CPT inconsistently discriminates between ADHD children and psychiatric control children. However, Halperin’s (1992) paper reported that children with ADHD demonstrated major improvements on the CPT after treatment with
stimulant medication and concluded that inattention may be a nonspecific symptom of childhood psychiatric disorders (Halperin et al. 1992). In other words, children with psychiatric disorders also suffered from attention deficits, which were identified by the CPT, supporting the view that the TOVA is an index of attention. Rossiter (1995) did not use the TOVA to discriminate between ADHD, non-ADHD or other psychiatric disorders, but used the TOVA as an index of attention, and measured changes in variables in the attentional system before and after treatment in each group. Hence, the evidence presented by Lohr and colleagues (2001) in support of the criticism was not relevant and did not support their premise. In any case, the CPT studies cited by Lohr and colleagues (2001) did not use the TOVA, but rather a variety of other CPTs. Hence, their conclusions would not necessarily apply to the TOVA, which was specifically designed to overcome some of the deficits of other CPTs, as a test of attention not restricted to ADHD subjects (Greenberg & Waldman 1993).

Guidelines for the evaluation of Clinical Efficacy of Psychophysiological Interventions were established by a working party of the International Society for Neurotherapy Research (ISNR) and the Association for Applied Psychophysiology and Biofeedback (AAPB). These guidelines are similar to those from the American Psychological Association (APA), and specify five types of classifications ranging from level 1: “Not empirically supported” to level 5: “Efficacious and specific” (Monastra 2005; Moss & Gunkelman 2002).

To meet the criteria for Level 4: “Efficacious,” a treatment must meet the following criteria:
“(a) in a comparison with a no-treatment control group, alternative treatment group, or sham (placebo) control utilising randomized assignment, the investigational treatment is shown to be statistically significantly superior to the control condition or the investigational treatment is equivalent to a treatment of established efficacy in a study with sufficient power to detect moderate differences; (b) the studies have been conducted with a population treated for a specific problem, from whom inclusion criteria are delineated in a reliable, operationally defined manner; (c) the study used valid and clearly specified outcome measures related to the problem being treated; (d) the data are subjected to appropriated data analysis; (e) the diagnostic and treatment variables and procedures are clearly defined in a manner that permits replication of the study by independent researchers, and (f) the superiority or equivalence of the investigational treatment have been shown in at least two independent studies” (Moss & Gunkelman 2002) p15.

In addition, to meet the criteria for Level 5: “Efficacious and Specific”, the treatment needed to be demonstrated to be statistically superior to a credible sham therapy, pill, or bona fide treatment in at least two independent studies (Moss & Gunkelman 2002)

Monastra and colleagues (2005) critically reviewed the Neurotherapy literature using the joint working party’s criteria, as it applied to ADHD, and assigned a “Level 3: Probably Efficacious” ranking. Loo and Barkley (2005) published a review article (discussed in section 3.12) calling for more scientifically rigorous studies before Neurotherapy could be considered efficacious (Loo & Barkley 2005). Holtmann and
Stadler (2006) concluded that although Neurotherapy had gained promising empirical support in recent years, there was still a strong need for more empirically and methodologically sound evaluation studies (Holtmann & Stadler 2006). Overall, the main concerns raised were the lack of well-controlled, randomized studies, small group sizes and possibility of confounds such as the additional time spent with a therapist or cognitive training (Arns et al. 2009).

### 3.13 Meta-analysis of Neurotherapy Studies

To address these issues, Arns and colleagues (2009) used a meta-analysis approach to examine the evidence-based level of Neurotherapy in the treatment of ADHD (Arns et al. 2009). In statistics, a meta-analysis is a technique that combines the results of several studies that are concerned with shared research hypotheses. This is usually done by identification of a common measure of effect size, which is then modeled using a form of meta-regression (Egger & Davey Smith 1997). After controlling for study characteristics, the resulting overall averages can be considered meta-effect sizes, more powerful estimates of the true effect size than those derived from each individual study (Egger & Davey Smith 1997).

Arns and colleagues (2009) included more recent Neurotherapy studies in a meta-analysis that addressed some of the concerns previously raised (Holtmann & Stadler 2006; Lohr et al. 2001; Loo & Barkley 2005). Meta-analysis provided an opportunity to integrate the results of many studies and aggregated the lower number
of subjects from smaller studies into a larger subject pool. This allowed for more powerful investigation of the overall effect size across studies, and examination of the clinical relevance of these methods in a quantitative manner (Arns et al. 2009). Since ADHD is characterized by persistent symptoms of inattention, impulsivity and/or hyperactivity, the investigators focused on the effects of Neurotherapy and stimulant medication on the core symptoms of ADHD (Arns et al. 2009):

The inclusion criteria for studies were as follows: (a) subjects had to have a primary diagnosis of ADHD; (b) a controlled between-subject design, with either randomised or non-randomised passive (waiting list) or active (stimulant medication, biofeedback, or cognitive training) control groups; (c) prospective within-subject design studies or; (d) retrospective within-subject design studies with a large enough sample (N>500) to provide a reliable representation of daily practice; (e) Neurotherapy Treatment had to be provided in a standardised manner, and no more than two treatment protocols could be used; and (f) standardised pre- and post-assessment means and standard deviations for at least 1 of the following domains had to be available: hyperactivity, inattentiveness, or Continuous Performance Task (CPT) commission errors. When the means and standard deviations from a given study were not available, they were requested from the authors. Not all authors responded or were still able to retrieve this information, and if there was insufficient information available, the study was excluded from the meta-analysis (Arns et al. 2009).

Fifteen studies were found to fulfill the inclusion criteria providing 1194 subjects. Of these, six studies used randomized allocation of subjects, and three
compared Neurotherapy with stimulant medication, the current “gold standard” in the
treatment of ADHD (Arns et al. 2009). Many of the controlled studies used semi-active
control groups such as cognitive training, EMG Biofeedback, or group therapy. Since
cognitive training can improve inattention and hyperactivity/impulsivity, within-subject
effect size was also calculated (Arns et al. 2009).

Post-hoc analyses did not reveal any differences between either: theta/beta,
theta/SMR and slow cortical potential (SCP) Neurotherapy Treatment effects (Arns et
al. 2009). Arns (2009) expected higher effect size for hyperactivity, given the original
rationale by Lubar and colleagues for using SMR training in hyperkinetic syndrome
(Lubar & Shouse 1977; Lubar & Lubar 1984). However, this expectation was not met by
the meta-analysis, lending support to the view that these protocols may modulate the
same underlying networks. Twelve percent of all subjects in the meta-analysis were on
medication, and there were no differences in outcome measures found between
medicated and unmedicated subjects, suggesting that being medicated does not alter
the effects of Neurotherapy Treatment (Arns et al. 2009)

3.14 Future Directions for Neurotherapy Research

ABA reversal design is an accepted scientific method of investigation in
behaviour therapy and has been used extensively in the behavioural sciences for
decades. Early studies used ABA reversal design to demonstrate the specificity of the
association between Neurotherapy and ADHD symptom changes (Lubar et al. 1981;
Lubar & Shouse 1976b; Shouse & Lubar 1979). The fifth revision of the Declaration of
Helsinki, adopted in October 2000 by the World medical Association (WMA), and amended in October 2006, reinforces the long-standing prohibition against offering placebo instead of effective therapy, and required of health professionals to make an oath that the health of their patients will be their first consideration” (World Medical Association 2006). The WMA left no doubt that if a beneficial treatment for a condition had already been recognised, it is unethical to offer placebo in place of such treatment to anyone in a study of the same condition. These early studies (Lubar et al. 1981; Lubar & Shouse 1976b; Shouse & Lubar 1979) would have contravened the Declaration of Helsinki, as they reversed the amelioration of symptoms of patients and would not have been approved by ethics committees in more recent times. However, they provided very useful early insights and evidence of the efficacy of Neurotherapy.

Michels and colleagues (2003) have drawn attention to the discrepancy between the spirit of the Declaration and the common practice of using placebo controls in randomised trials even if effective treatments exist. They argue that despite the mandates of the Declaration of Helsinki and concern from ethicists and scientists, the US Food and Drug Administration (FDA) continues to demand and defend placebo-controlled evidence of efficacy and safety for the development of many new pharmaceuticals, even if effective therapy exists. Michels (2003) has argued that the FDA’s arguments defending their practice are insufficient to justify medical research that violates the Declaration of Helsinki (Michels & Rothman 2003).

The statistical reanalysis of the data from Rossiter and La Vaque (1995), the results of the replication study of by Rossiter (2004b) and the results of other studies
comparing Neurotherapy to Medication (Fuchs 1998; Fuchs et al. 2003; Monastra, Monastra & George 2002), support the view that Neurotherapy Treatment in those effectiveness studies produces patient outcomes that are equivalent to those obtained with stimulant medication (Rossiter 2004b). However, effectiveness research design limits the conclusions that can be drawn from these studies. In effectiveness studies, compromises are made in research methodology and experimental controls for practical and ethical reasons. Patients are allowed to choose between treatment groups, the studies use patient groups with co-morbidities, and clinicians tailor individual protocols based on presenting symptoms and/or baseline QEEG (Rossiter 2004b). Such deviations from strict experimental controls, to increase internal validity, are considered serious flaws in an efficacy study. However, in an effectiveness study, they are unacceptable variations, despite representing more environmentally relevant clinical conditions. Hence, despite the less stringent experimental controls, effectiveness studies clearly demonstrate that Neurotherapy is “clinically” effective (Rossiter 2004b).

There is little doubt that since stimulant medication is considered an effective treatment for ADHD, future Neurotherapy studies should continue to use an effectiveness “equivalent treatment design” with a stimulant medication group as the treatment control (La Vaque & Rossiter 2001).
Chapter 4: Steady-State Visually-Evoked Potentials

This chapter explains the use of steady-state visually evoked potentials (SSVEP) in the investigation of brain electrical activity during cognitive processes. The essential features of SSVEP technology are explained, and its advantages over other electrophysiological techniques are discussed. An historical overview of studies using SSVEPs in the investigation of cognitive processes is discussed, along with a description of Steady-State Probe Topography (SSPT). Finally, hypotheses relating to the evaluation of the effectiveness of Neurotherapy in the treatment of ADHD subjects are presented. The chapter is divided into the following sections:

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4.1 Steady-State Evoked-Potentials Compared to ERPs

As discussed in Chapter 2, an evoked response potential (ERP) is a transient
response to a stimulus. In a steady-state evoked potential paradigm, a steady-state sinusoidal signal, presented across the visual field, entrains neurons into following the waveform of the sinusoidal signal. When a stimulus is presented, the brain’s evoked responses modulate the steady-state sinusoidal waveform. Since the steady-state evoked potential is presented continuously, it can be represented in the frequency domain and defined by a number of discrete frequency bands superimposed on the frequency spectrum of the background EEG (Regan 1977b). The amplitude and latency components of the steady-state evoked potential can be extracted for analysis. If the brain worked as a linear system, the information contained in an ERP would be equivalent to that extracted from a steady-state evoked potential. However, since brain electrical activity is chaotic, steady-state evoked potentials are able to provide additional information to that obtainable from transient ERPs (Regan 1977b).

The steady-state evoked potential technique has distinct advantages over transient ERPs (Regan 1976; Regan 1977b): Firstly, since there are no established ERP analysis standards, although there are conventions, experimenters may adopt different methods to set baseline levels and resolve peak overlaps when extracting ERPs. On the other hand, SSVEPs are quantified using a mathematical method which can be repeated in any EEG laboratory with expectations that close agreement will be achieved between labs (Regan 1976; Regan 1977b). Secondly, mains interference may overlap with transient ERPs in the time domain, while it is separated from SSVEPs in the frequency domain (Regan 1976; Regan 1977b). Thirdly, steady-state evoked potentials can be defined by the amplitude and phase components of a few discrete
frequencies (Regan 1976; Regan 1977b). Finally, SSVEP requires significantly shorter recording times than those required for ERPs, and can be a distinct advantage in clinical situations, particularly those involving hyperactive and fidgety children (Regan 1976; Regan 1977b).

4.2 Steady-State Evoked-Potentials and Cognitive Processes

An early study failed to demonstrate the sensitivity of steady-state evoked potentials (SSVEP) to cognitive processes, prompting Regan (1977B) to suggest that ERPs were a better tool than steady-state evoked potentials for studying variables of attention (Regan 1977b). Wilson and O'Donnell (1986) were the first to demonstrate a relationship between SSVEPs and human cognitive processes when they found a significant correlation between scores in the “Sternberg Memory Scanning Task” and the latency of the SSVEP (Wilson & O'Donnell 1986). They found that SSVEPs from signals within the 15-23Hz range were correlated with the rate of change of response speed to apparent latency, while those within the 40-59Hz range were related to the response speed intercept for zero items. These findings prompted Wilson and colleagues (1986) to suggest that SSVEP latency may be associated with speed of cognitive processing. However, a subsequent study by the same authors failed to find a relationship between SSVEP and performance on a mental workload task (Wilson & O'Donnell 1988).

SSVEPs are considered repetitive ERPs with frequency components that remain
stable in amplitude and phase over time. As a result of this stability over time, the amplitude and phase components of SSVEPs have generally been evaluated over relatively long time intervals (Regan 1977b). For example, SSVEP components were evaluated over a period of seven minutes and the latency component found to vary by one percent while the amplitude component varied by seven percent (Regan 1977b). However, when variations in SSVEP components were evaluated over the shorter period of one minute, much higher variability was observed. Regan (1977b) thought that the increased variability over short time periods was due to increased background EEG noise on account of the wider bandwidth used (Regan 1977b). Linden and colleagues (1987) found significant associations between the late components of the ERP and selective attention, but failed to demonstrate a relationship between the steady-state auditory evoked potential and selective attention (Linden et al. 1987). Galambos and colleagues (1988) suggested that the increased variability in steady-state evoked potentials, observed over short time periods, might be related to cognitive processes. However, they could not demonstrate a relationship between the steady-state auditory evoked potential and changes in arousal (Galambos & Makeig 1988).

Silberstein and colleagues (1990) suggested a number of factors that could account for why these earlier studies failed to find a relationship between SSVEPs and cognitive processes, namely that: (a) SSVEP amplitude rather than latency may be related to cognitive processes, (b) the small number of sites used may have excluded possible changes at other sites from being observed, and (c) the use of overly long
time periods in SSVEP calculations may have masked more transient changes. The group used a technique now known as Steady-State Probe Topography (SSPT), and found a relationship between visual vigilance and SSVEP amplitude for the first time (Silberstein et al. 1990).

4.3 **Key Features of the Steady-State Probe Topography**

The SSPT technique had key features, which maximized the chances of observing changes in the SSVEP resulting from cognitive processes. These key features included: (a) the SSPT probe-ERP technique; (b) a high density 64 electrode array to maximise the chances of detecting localised SSVEP topographic changes; (c) an analysis technique which enabled the SSVEP to be calculated in single-second time periods, thereby enabling the continuous monitoring of cognitive processes, and maximizing the chances of detection of transient changes at any interval during the cycle of the task being analysed; and (d) low sensitivity to artefacts and extraneous noise that could contaminate the EEG and reduce signal-to-noise ratio (Silberstein et al. 1990).

Silberstein and colleagues (1990) were the first to use a probe-ERP consisting of a task-irrelevant 13 Hz sinusoidal visual flicker presented continuously in the visual field while subjects undertook a visual vigilance task (Silberstein et al. 1990). According to Silberstein (1990), the technique used in their study was based on the ‘probe paradigm’ described by Galin and Ellis (1975). The latter used task-irrelevant visual stimuli presented at 3-second intervals while subjects were engaged in block design
and writing tasks, and found task-dependent probe-ERP asymmetry, similar to that from task-related EEG alpha power asymmetry distribution. Language-related tasks elicited alpha power reductions in the left hemisphere while block design elicited alpha power reductions in the right hemisphere (Galin & Ellis 1975). Similarly, Shucard and colleagues (1977) had used an auditory probe-ERP while subjects performed various cognitive tasks, and also found that the amplitude of the probe-ERP was related to the hemispheric asymmetry expected of the mode of cognitive processing (Shucard, Shucard & Thomas 1977). Additionally, hemispheric specificity was found in other studies. For example, amplitude reductions of an auditory probe-ERP in the left hemisphere were found during a covert articulation task (Papanicolaou, Eisenberg & Levy 1983). Evidence of right-parietal amplitude reduction of a visual probe-ERP in a visuospatial mental-rotation task was found in dyslexic children, and the amplitude changes of the visual probe ERP were used to differentiate between dyslexic children and controls in a reading task (Johnstone et al. 1984).

The probe-ERP technique is based on the premise that an irrelevant probe stimulus, associated with task-related cognitive processing, evokes lower probe-ERP amplitudes (Papanicolaou & Johnstone 1984; Silberstein et al. 1990). This approach is supported by findings that probe-ERP amplitude attenuation is associated with an increase in regional cerebral blood flow, a measure of increased brain activity (Papanicolaou et al. 1987; Papanicolaou & Johnstone 1984). Several models were proposed to explain the attenuation of the probe-ERP with increased task demand, including a “limited resource” model, which assumed that cortical regions might have a
limited capacity for processing information from multiple sources. This limitation was thought to account for the reduced responsiveness to the probe stimulus when subjects were engaged in concurrent tasks (Papanicolaou & Johnstone 1984). However, the “limited resource” model was challenged by Silberstein’s (1998) group who found that during an increase in attentional state, 13 Hz SSVEP amplitude reductions coincided with increases in the 40Hz SSVEP amplitude (Nield et al. 1998).

4.3.1 SSVEP Amplitude

Silberstein and colleagues (1990) used a continuous 13 Hz sinusoidal visual flicker as their probe stimulus and observed reductions in amplitude of the SSVEP in the central/parietal region during the interval that subjects were anticipating the appearance of a target in a visual vigilance task. The reduction in SSVEP amplitude was attributed to increased regional brain activity (Silberstein et al. 1990). In a SSVEP study using the Wisconsin Card Sort Test, it was found that in the 1-2 second interval after the occurrence of the cue to change sort criterion, the pre-frontal, central and right parieto-temporal regions showed a pronounced attenuation in SSVEP amplitude, which was interpreted as an increase in regional cortical activity (Silberstein, Ciocciari & Pipingas 1995).

Subjects performing a low and high demand version of an object working memory task had reduced SSVEP amplitudes at left and right parieto-occipital sites during the perceptual component of the task (Silberstein et al. 2001). However, during
the hold or memory component of the graded memory task, the SSVEP amplitude exhibited a load-dependent increase at frontal and occipito-parietal sites. Silberstein and colleagues (2001) suggested that perceptual processes may be associated with SSVEP amplitude reductions, whereas holding information in short-term working memory may be associated with SSVEP amplitude increases. Silberstein (2001) speculated that, while being held in working memory, information is reticulated between cortico-cortical and thalamo-cortical loops that utilize cortical layer one, resulting in an increased SSVEP amplitude (Silberstein et al. 2001). Reduced SSVEP amplitudes during the perceptual phase of the graded memory task (Silberstein et al. 2001), are consistent with findings from a previous study which also found SSVEP amplitude reductions at occipito-parietal areas while performing a visual vigilance task (Silberstein et al. 1990).

4.3.2 SSVEP Latency

When the phase change of the SSVEP for any given task leads the phase of a reference or control task, it is referred to as SSVEP latency reduction. When the phase lags behind that of the reference task, it is referred to as SSVEP latency increase. Silberstein et al. (1996) remarked that shorter response times in a Continuous Performance Task (CPT) correlated with larger SSVEP latency reductions at frontal sites. Consequently, they proposed that latency reductions result from transient increases in neuronal information processing speed. In turn, the increased processing speed may
reflect increased coupling strength between neuronal populations which would manifest as reduced phase delay (Silberstein et al. 1996).

### 4.3.3 64 Electrode Recordings

Silberstein and colleagues (1990) recorded brain electrical activity from 64 scalp electrodes at sites that were accommodated within the 74 locations of the International 10-10 System of electrode placement. Measuring ERPs with 64 channels has become quite common, as this number of electrodes seems to achieve an adequate spatial resolution for observing the effects of ERPs over gross brain regions (Silberstein et al. 1990).

### 4.3.4 SSPT Signal Analysis Technique

The original suggestion by Regan (1997) that variations in the SSVEP amplitude were probably due to noise in the background EEG, was dispelled by Silberstein and colleagues (1990) who demonstrated that SSVEP amplitude changes were related to cognitive changes rather than to noise in the background EEG (Silberstein et al. 1990). In that study, using a computerised version of the Wisconsin Card Sort Test, SSVEP was recorded from 64 scalp electrodes and was elicited by a spatially uniform continuous 13 Hz sinusoidal visual flicker (Silberstein et al. 1990). Silberstein’s group (1995) showed that the amplitude and phase latency of the SSVEP could be calculated using
short periods of 1 to 5 seconds of EEG. They also argued that in theory, the SSVEP could be calculated using as little as 1/13 of a second (77ms) of data, using a 13 Hz probe stimulus. However, such short time periods would carry a penalty, as the higher background noise would not allow for clean extraction of the evoked potentials. Hence signal averaging over several trials would be needed to improve signal-to-noise ratio (Silberstein, Ciorciari & Pipingas 1995). Pipingas(2003) obtained reliable results with a temporal resolution of 870ms by averaging data from only 5 stimulus items (Pipingas 2003). While Harris obtained reliable results with a temporal resolution of 180ms (Harris et al. 2001).

Although not possessing the high temporal resolution of ERP techniques, which are measured in milliseconds, SSPT enables the amplitude and latency components of evoked potentials associated with cognitive processes to be investigated over wide periods ranging from seconds to minutes. The evaluation period of the SSVEP can be tailored to allow the experimenter to focus on the specific time points associated with cognitive processes that occur during cognitive tasks. Thus, in contrast to techniques such as PET which have a temporal resolution of around one minute, SSPT possesses not only the fine temporal resolution, but also the temporal continuity to allow monitoring of relatively rapid cognitive processes over time.

4.3.5 SSPT and Recording Artefacts

One of the main advantages of the SSVEP method over transient ERP is the
technique’s insensitivity to background noise in the EEG, mains interference, and non-probe-related signals when a sufficient number of stimulus cycles are averaged.

Averaging effectively reduces bandwidth, thereby increasing signal-to-noise ratio.

While Regan measured the SSVEP over long time periods of several minutes to achieve high signal-to-noise ratio (Regan 1977b), Silberstein’s group studied cognitive changes over a much shorter time scale measured in seconds and with considerably fewer stimulus cycles (Silberstein et al. 1990). Despite the fewer stimulus cycles required to study shorter SSVEP periods, Silberstein’s group described that with an integration period of only a few seconds, the SSVEP was insensitive to muscle artefact, eye-blinks and 50Hz mains interference (Silberstein, Burkitt & Wood 1993). They experimented by adding varying amounts of different types of artefact to the EEG before calculating the SSVEP, and demonstrated that even when the artefact and the EEG signal had equal variances, the resultant SSVEP was not substantially different from the original SSVEP and that only muscle artefact in the EEG seemed to have a small impact on the SSVEP (Gray et al. 2003; Gray et al. 1996; Silberstein, Burkitt & Wood 1993).

4.3.6 **SSVEP Studies at the Brain Sciences Institute**

This section is a list of studies conducted by Silberstein’s group at the Brain Sciences institute, Swinburne University. While they do not relate to Neurotherapy or ADHD, these studies provides an overview of the SSVEP studies conducted to-date and highlight the versatility of the SSVEP technology in elucidating cognitive processes.
The first SSVEP study from Silberstein’s group investigated the correlation between the magnitude of the SSVEP and various aspects of a visual vigilance task (Silberstein et al. 1990). The SSVEP was recorded from 64 scalp electrodes and was elicited by a 13 Hz sinusoidal visual flicker continuously presented while subjects undertook a visual vigilance task. The vigilance task consisted of a sequence of 60 squares, followed by a further 60 circles and then a further 60 squares. Each viewing of the 180 shapes constituted a Trial. Trials 1 and 2 were identical while Trial 3 differed from the first two in that one of the circles was modified and subjects were challenged to identify the modified circle. A comparison of trials 2 and 3 indicated that anticipation of the appearance of the modified circle was associated with SSVEP attenuations in centro-parietal regions, while the appearance of the modified circle was associated with attenuations of the SSVEP in the occipito-parietal regions. These results illustrate the differences between the cortical activation patterns which occur during different phases of a visual vigilance task (Silberstein et al. 1990).

SSVEP topography associated with the performance of a computerised version of the Wisconsin Card Sort Test was investigated (Silberstein, Ciorciari & Pipingas 1995). The sort criterion was automatically changed after subjects had sorted 10 cards correctly and on the 11th card, feedback always constituted a cue for a change in the sort criterion. It was found that in the 1-2 sec interval after the occurrence of the cue to change sort criterion, a pronounced attenuation in SSVEP amplitude and an increase in phase lag occurred in pre-frontal, central, and right parieto-temporal regions. The changes, which were interpreted as an increase in regional cortical activity, were not
apparent when the sort criterion did not need to be changed. The results indicated that pre-frontal and right parieto-temporal activation was modulated during the performance of the Wisconsin Card Sort Test, reaching maximum when a change in sort criterion was required (Silberstein, Ciorciari & Pipingas 1995).

Changes in SSVEP topography associated with the onset of spontaneous auditory hallucinations was studied in eight schizophrenic patients (Line et al. 1998). A large and significant decrease in SSVEP latency in the right temporo/parietal region occurred in the second prior to the report of auditory hallucinations, while a control task produced no significant decrease in SSVEP latency in the same region. Findings suggested that activity in the neural networks in the right temporo-parietal area may be implicated in spontaneous auditory hallucinations, lending support to corresponding neuropsychological theories (Line et al. 1998).

Patterson and colleagues (1998) investigated whether subjects breathing a safe mixture of air and butanol compared with filtered medical air would demonstrate SSVEP topographic changes. Subject were required to detect differences between randomly delivery equal volumes of air or butanol injected into the inspiratory airflow of the apparatus (Patterson et al. 1998). The results from a panel of 10 female subjects, who all identified the butanol correctly, showed that butanol delivery resulted in sequences of changes in SSVEP amplitude and latencies in parietal, frontal and temporal regions. While parietal changes were consistent with other studies, results revealed more dynamic temporal changes involving pre-frontal and parietal regions at different periods around butanol delivery (Patterson et al. 1998).
In a study that examined stimulus evoked changes in the SSVEP phase topography and the putative role of travelling waves, eighteen subjects viewed a central-field checkerboard and full-field flicker stimulus temporally modulated at the peak alpha rhythm frequency (Burkitt et al. 2000). EEG was recorded from 10 midline scalp electrodes and the bipolar SSVEP was obtained from differences between adjacent electrodes. The checkerboard pattern elicited SSVEP phase progressions in 14 subjects consistent with travelling waves, with estimated phase velocities ranging from 7 to 11 ms after correcting for folded cortex. The flicker stimulus elicited SSVEP phase reversals in nine subjects, suggestive of standing waves. Six subjects demonstrated a phase topography specific to the stimulus with travelling wave patterns associated with the checkerboard and standing wave patterns associated with the flicker. The differences in wave patterns demonstrated that travelling and standing waves emerge under different spatial configurations of visual input to the cortex and affect the spatio-temporal dynamics of the SSVEP (Burkitt et al. 2000).

The relationship between posterior frontal SSVEP latency changes and delayed recognition memory was examined (Silberstein et al. 2000a). Thirty-five female subjects viewed an 18 min television documentary program interspersed with 12 unfamiliar television advertisements, while brain electrical activity was recorded from four pre-frontal, two posterior-frontal and two occipital sites. Delayed recognition memory was tested after 7 days for images that coincided with the 20 most prominent frontal SSVEP latency minima and maxima during the viewing of 10 contiguous advertisements (advertisements 2-11). Results indicated that images that coincided
with posterior frontal latency minima had a 58.7% recognition rate, while images coinciding with SSVEP latency maxima had a 45.3% recognition rate. SSVEP latency variations associated with the differences in performance was only significant at the left-posterior-frontal site, suggesting that regions of the frontal-cortex may be used to assess the strength of naturalistic long-term memory encoding (Silberstein et al. 2000a).

The SSVEP of patients diagnosed with Schizophrenia and normal controls were studied while performing the A-X version of the Continuous Performance Task (CPT A-X) described in section 2.10.4 (Silberstein et al. 2000b). Results indicated that following the appearance of the cue A and target X, the control group demonstrated a transient SSVEP latency reduction at parietal and pre-frontal sites, while the group of patients with Schizophrenia showed no such SSVEP latency reduction. The pre-frontal SSVEP latency changes in the 500 ms interval following the appearance of the 'X' were correlated with mean individual reaction time in both populations. This finding led to the suggestion that the SSVEP latency reduction in normal controls may index excitatory processes and that its absence in schizophrenic patients may be a manifestation of reduced pre-frontal activity observed with other neuroimaging modalities (Silberstein et al. 2000b).

SSVEP was recorded while 30 subjects performed a low and high demand version of an object working memory task (Silberstein et al. 2001). During the perceptual component of the task, the SSVEP amplitude was reduced at left- and right-parieto-occipital sites. During the hold or memory component of the task, the SSVEP
amplitude exhibited a load-dependent increase at frontal and occipito-parietal sites, while the SSVEP latency exhibited a load-dependent reduction at central and left frontal sites. It was suggested that SSVEP amplitude changes index cortical information processing modes. As such, perceptual processes were associated with an SSVEP amplitude reduction, while holding information in active short-term or working memory was associated with an SSVEP amplitude increase. SSVEP amplitude and latency were discussed in terms of changes in the behaviour of cortico-cortico and thalamo-cortical loops utilising cortical layer I, which constitute a neurophysiological mechanism for holding information in working memory (Silberstein et al. 2001).

The International Affective Picture System (IAPS) has been used in brain imaging studies to examine emotional processes (Lang, Bradley & Cuthbert 2008). Seventy-five IAPS images, categorized as unpleasant, neutral, or pleasant, were presented to 16 healthy subjects while SSVEP was recorded from 64 scalp sites (Kemp et al. 2002). Analysis subtracted the activity associated with the presentation of neutral images, from the activity associated with the presentation of pleasant as well as unpleasant images. Results demonstrated that both pleasant and unpleasant valence were associated with transient, widespread, and bilateral frontal SSVEP latency reductions, while only unpleasant images were associated with a transient bilateral anterior frontal SSVEP amplitude decrease. These findings suggested that substantial overlaps existed in frontal neural circuitry associated with the processing of pleasant and unpleasant images relative to neutral images (Kemp et al. 2002).

In a later study, Kemp and colleagues (2004a), investigated how 5-HTP acutely
modulated SSVEP, heart rate (HR) and subjective ratings associated with the viewing of 75 IAPS images of different emotional valence. Seventeen healthy subjects were tested in a randomised double-blind, placebo-controlled design, under two acute treatment conditions: placebo or SSRI (20 mg, Citalopram). Results indicated that under the placebo condition, processing of images of unpleasant valence was associated with a decreased SSVEP amplitude (activation) and latency reduction (excitation) in frontal and occipital cortices, while pleasant images were associated with amplitude decreases (activation) and latency increases (reduced excitation) within frontal and left temporo-parietal cortices. On the other hand, Citalopram, relative to placebo, produced SSVEP increase (reduced activation) to unpleasant valence within frontal and occipital cortices, but potentiated SSVEP amplitude decreases (more activation) to pleasant valence within parieto-occipital cortices. Furthermore, Citalopram, relative to placebo, also suppressed differences in heart rate associated with the viewing of pleasant and unpleasant images, but did not alter the subjects’ subjective responses to emotional images. These results suggested that responsiveness to pleasant and unpleasant stimuli following neurochemical modulation may vary across different measures (i.e. self-report, HR and SSVEP). Findings also suggested that Citalopram potentiated SSVEP response to pleasant valence and suppressed SSVEP response to unpleasant valence (Kemp et al. 2004a). The processing of unpleasant images, relative to neutral ones, produced SSVEPs with widespread, predominantly right sided, frontal latency reductions in females but not in males and may have implications for the pathophysiology of mood disorders such as depression (Kemp et al. 2004b).
Anticipatory anxiety was associated with increased SSVEP latency within medial anterior frontal, left dorsolateral pre-frontal and bilateral temporal regions compared to baseline, while increased SSVEP amplitude and decreased SSVEP latency were observed within occipital regions (Gray et al. 2003). The observed SSVEP latency increases within frontal and temporal cortical regions were interpreted as suggestive of increased localised inhibitory processes within regions reciprocally connected to subcortical limbic structures. SSVEP latency decreases in occipital regions were suggestive of increased excitatory activity, while SSVEP amplitude increases were possibly associated with an attentional shift from external environment to internal processes. These SSVEP findings provide support for the involvement of both excitatory and inhibitory processes associated with frontal, anterior temporal, and occipital cortical regions during anticipatory anxiety (Gray et al. 2003). SSVEP research had focused on amplitude and latency differences, in the next study, SSVEP synchronization was investigated instead.

SSVEP event-related partial coherence was used to examine the SSVEP synchronization between brain regions while 22 males undertook a sequential version of the Shepard and Metzler Mental Rotation Task (Silberstein, Danieli & Nunez 2003). The 180-degree rotation was associated with increased synchronization between: bilateral pre-frontal and parieto-occipital sites, left frontal and right parietal sites, and bilateral parietal and occipital sites, compared to the 60-degree rotation. Silberstein (2003) suggested that the working memory components of the task may be associated with increased synchronization between pre-frontal and parieto-occipital regions,
while the visuo-motor components may reflect increased synchronization between the left frontal to right parietal regions (Silberstein, Danieli & Nunez 2003). Silberstein (2006) described the changes in long-range synchronization as a key mechanism for the integration and segregation of cortical regions mediating cognitive processes. As such, cognitive proficiency in the Mental Rotation Task is associated with functional connectivity, which is reflected in SSVEP event-related partial coherence. This correlation was found to be both positive and negative for various regions at different points in time. Silberstein suggested that cognitive aptitude as demonstrated by the Mental Rotation Task is related to the brain's capacity to enhance relevant functional connectivity between cortical regions associated with cognitive demands, while simultaneously attenuating irrelevant connections or shutting down unnecessary communications. Thus, cognitive aptitude is dependent on functional connectivity sculpting, an important component of the neural substrate of learning and aptitude (Silberstein 2006).

Silberstein and Song (2004) used SSVEP to investigate the relationship between cortical coupling, reflected in event-related partial coherence and cognitive processing speed, while 55 participants performed a computerized version of the Ravens Progressive Matrices. Subjects were required to identify the probe, a shape that was consistent with a matrix of displayed shapes, by pressing a micro-switch with either the right or left hand to indicate a match or non-match. The SSVEP event-related partial coherence was calculated for all 2016 unique electrode pairs. The linear correlation between SSVEP event-related partial coherence and processing speed were
calculated for all electrode pairs, for all time points during the 3-sec interval that the probes were on the screen. Electrode pairs where SSVEP event-related partial coherence (neural synchronization) was significantly correlated with processing speed were identified, using correlation coefficient thresholds corresponding to \( p=0.001 \).

Results indicated that 800ms before the appearance of the probe, the synchronization between specific pre-frontal, frontal and central sites was correlated with processing speed, suggesting that this relationship may reflect the efficiency of working memory processes and speed of information processing (Silberstein et al. 2004).

Ellis and Colleagues (2006) investigated the temporal dynamics associated with spatial working memory within its neural networks using SSVEP. The findings identified three different time periods of significance during the Spatial n-Back Task: (1) an early perceptual/encoding period (approximately 0-500 ms), (2) an early delay period just following the stimulus disappearing from view (approximately 850-1400 ms), and (3) a late period lasting for the length of the final second of the delay and anticipation of the new stimulus (approximately 2500-3500 ms). The delay period was associated with increases in frontal and occipital region amplitude, consistent with previous findings in more basic working memory tasks. The two different SSVEP components during the delay may reflect the additional "executive" demands associated with the n-back task, and suggest variable roles for the pre-frontal cortex during different stages of the delay. Findings supported the hypothesis that memory load modulates activity within the networks identified, consistent with previous neuroimaging studies (Ellis, Silberstein & Nathan 2006).
To investigate age-related changes in SSVEP amplitude and latency associated with memory performance, 15 older (59-67 years) and 14 younger (20-30 years) adults performed an object working memory task and a contextual recognition memory task, whilst the SSVEP was recorded (Macpherson, Pipingas & Silberstein 2009). Retention of a single object in the low demand object working memory task was characterised by smaller frontal SSVEP amplitude and less latency decreases in older adults than in younger adults, indicative of an age-associated reduction in neural processes. Recognition of visual images in the more difficult contextual recognition memory task was accompanied by larger, more sustained SSVEP amplitude and latency decreases over temporal-parietal regions in older adults, while younger adults demonstrated a transient, frontally mediated pattern of activity. Findings provided support for compensatory processes in the ageing brain; where there were lower task demands, older adults demonstrated reduced neural activation, whereas when task demands were greater, neural activity increased (Macpherson, Pipingas & Silberstein 2009).

4.3.7 SSVEP Studies of ADHD

While performing the A-X version of the Continuous Performance Task (CPT-AX), children diagnosed with ADHD, failed to show the expected sustained parietal SSVEP amplitude attenuation in the interval between the presentation of the ‘A’ and the ‘X’ (Farrow et al. 1996). During the CPT-AX, children with ADHD and controls were
required to press a micro-switch when the letter X appeared, only if an A had preceded it. In the interval between the appearance of the A and of the X in the correctly executed trials, controls showed transient reductions in SSVEP latency, whereas subjects with ADHD showed either no change or an increase in pre-frontal SSVEP latency at right pre-frontal sites (Silberstein et al. 1998a).

In a later study, Silberstein and colleagues (1998) used the same SSVEP technique to investigate the rapid and continuous changes during the CPT-X and CPT-AX tasks (Silberstein et al. 1998a). In the CPT-X task, subjects pressed a microswitch whenever the letter X appeared during presentation of a series of letters. Subjects were 17 boys diagnosed with ADHD and 17 healthy controls free from ADHD symptoms. All subjects were required to perform a low-demand visual vigilance task (pressing a button on the appearance of number 5, in a sequentially presented series of numbers 1 to 5), followed by the reference task (CPT-X) and the cognitive task (CPT-AX). The stimulus used to evoke the SSVEP was a 13 Hz sinusoidal flicker presented across the subjects’ visual fields through specially built glasses which enabled the subject to view the task computer and the sinusoidal flicker simultaneously (Silberstein et al. 1998a). Recording, artefact rejection, and signal processing procedures were described by Silberstein and colleagues (Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).

During the period that the A was presented, control subjects had generally lower SSVEP amplitude than the mean value for the reference task at Fz (a central pre-frontal site) (Silberstein et al. 1998a). This suggests increased frontal activity compared
with the reference task. In contrast, ADHD subjects displayed increased SSVEP amplitudes during the same period, suggestive of reduced activation during the period that the A was presented (Silberstein et al. 1998a).

Control subjects had SSVEP latency reductions associated with the appearance of the A and X and even more prominent reductions on the disappearance of the A. Boys with ADHD did not have these latency reductions, leading the authors to conclude that the ADHD subjects may have had inadequate excitation of pre-frontal networks (Silberstein et al. 1998a).

4.4 Formulation of Hypotheses for the Present Research

A number of tools were used in this study to evaluate the effect of Neurotherapy on changes in behaviours, attentional parameters and the brain electrical activity that may underpin these changes in children with ADHD. The Australian Twin Behaviour Rating Scale (ATBRS) has been found useful in measuring DSM-IV symptoms in children with ADHD (Levy & Hay 1991). The Test of Variables of Attention (TOVA) is a computer-administered Continuous Performance Task CPT that has been widely used to measure variables of attention and which is sensitive to attentional dysfunctions in ADHD (Greenberg & Waldman 1993). The A-X version of the Continuous Performance Task (CPT-AX) and Steady State Visually Evoked Potentials (SSVEP) has also been found to be sensitive to attention deficits in ADHD (Silberstein et al. 1998a).
If Neurotherapy is to be an effective treatment for ADHD, there should be changes towards normalisation of the SSVEP amplitude and latency of ADHD children following Neurotherapy, associated with significant improvements in behavioural measures. The SSVEP changes could be expected to approximate the SSVEP findings of non-ADHD controls as found by Silberstein (Silberstein et al. 1998a) and (Farrow 2003).

The aims of this study were to investigate whether Neurotherapy is an effective treatment for the core behavioural deficits in children with ADHD, and whether there are changes towards normalisation in indexes of brain function associated with changes in behaviours following Neurotherapy. To achieve these aims, changes in the following measures post-Neurotherapy were examined: (a) behavioural measures on the ATBRS, (b) attentional measures for key-presses during the CPT-AX task, (c) TOVA scores and (d) amplitude and latency of the SSVEP during the performance of the CPT-AX task. This leads to the testable hypotheses that following Neurotherapy:

1. Behavioural measures as assessed with the updated version of the Australian Twin Behaviour Rating Scale (ATBRS) will significantly improve towards normalisation;

2. There will be significant improvements in attentional measures of reaction-time, omission errors and commission errors, as assessed by key-presses during the CPT-AX task and as assessed by TOVA scores of omission, commission, reaction-time and variability in the reaction-time;

3. Subjects will demonstrate diffuse group SSVEP amplitude reductions, referenced to the mean of the baseline task, throughout the A-X task interval, and amplitude
reductions at frontal sites in preparation for the presentation of the X, not seen prior to Neurotherapy,

4. Subjects will demonstrate group SSVEP latency reductions, not seen prior to Neurotherapy, at right pre-frontal sites throughout the A-X interval and on appearance of the X and

5. Subjects will demonstrate group SSVEP latency reductions, not seen prior to Neurotherapy, in the right parietal region during the period between the presentation of the A and of the X.
Chapter 5: Participants and Methodology

5.1 Introduction

As discussed in chapter 2, inattention, poor impulse control and inhibition are core deficits in Attention Deficit/Hyperactivity Disorder (ADHD). The Test of Variables of Attention (TOVA) was designed as an instrument to index attentional parameters (Greenberg & Waldman 1993) as discussed in section 3.12. It has good criterion validity, as it is a measure whose variables predict behaviours based on information from other variables (Messick 1995; Shadish & Cook 2009) that Psychologists agree upon (Braverman et al. 2006; Chae, Jung & Noh 2001; Forbes 1998; Huang et al. 2007; Llorente et al. 2007; Manor, Sever & Weizman 1999; Preston, Fennell & Bussing 2005; Rossiter 2004b; Thompson & Thompson 1998b; Wada et al. 2000; Wu et al. 2007). The CPT-AX task when used in conjunction with Steady State Visually Evoked Potentials (SSVEP) has been shown to be sensitive to deficits in attention in ADHD (Silberstein et al. 1998a). The TOVA is therefore an appropriate measure of changes in attention. The A-X version of the Continuous Performance Task (CPT-AX) is also appropriate to use as a Steady State Probe Topography (SSPT) task, to investigate changes in brain function in children with ADHD, before and after Neurotherapy. As discussed in chapter 4, SSPT using 64 electrodes provides the high temporal and spatial resolution required to examine dynamic changes in patterns of brain activity during the CPT-AX task.
This chapter describes the participants, experimental methodology, and instruments used to test the effectiveness of Neurotherapy in the treatment of ADHD in accordance with the experimental hypotheses presented in chapter 4. The tasks used, EEG method, and SSVEP signal processing are identical to those used in previous studies at the Brain Sciences Institute, Swinburne University (Farrow 2003; Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995).

In the current study, behavioural measures and changes in TOVA scores following Neurotherapy are used to assess the effectiveness of Neurotherapy as a treatment for ADHD. In addition, changes in amplitude and phase latency in the SSPT while children perform the CPT-AX task are used to assess changes in brain function resulting from Neurotherapy. The chapter is divided as follows:

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5.2 Ethics Approval and Participants

The thesis was approved by the Human Research Ethics Committee of Swinburne University of Technology. The parents of all participant children received an Ethics Committee-Approved information pack that outlined the purpose of the study in a common language statement. In addition, the pack also contained a brief overview of the research regarding Neurotherapy in the treatment of ADHD (Appendix A).

Participants who initially enrolled into the study and underwent the initial assessment battery were 42 boys who attended the Behavioural Neurotherapy Clinic in Doncaster (Australia) for treatment for their ADHD between June 1999 and March 2002. Prior to coming to the clinic, all but five of the 42 boys had been diagnosed by their Paediatrician as having ADHD. Parents brought the children to the clinic for of a number of reasons: (a) the prescribed stimulant medication had adverse unacceptable side effects such as poor appetite, poor sleep, mood disturbance, emergence or exacerbation of TICS, increased hyperactivity, and increased behavioural disturbance when medication had worn off; (b) the prescribed stimulant medication produced no clear benefits; or (c) the parents objected to long-term use of medication and wanted to try Neurotherapy as an complementary treatment, in the hope that their child might not need to take medication after Neurotherapy. Parents were expected to pay the normal fees for treatment as any other client of the clinic.

Parents filled out a behavioural screening questionnaire, the Australian Twin
Behaviour Rating Scale (Appendix B), discussed in section 5.4.1, and were re-assessed by Psychologists at the Behavioural Neurotherapy Clinic for ADHD criteria. In addition to ADHD, the children had the typical mix of co-morbidities usually encountered in clinical practice. This included Learning Difficulties and Oppositional Defiant Disorder and mood disorder.

Although gathered for assessment, the teacher questionnaires were considered generally less reliable for a number of reasons: (a) teachers only knew the “medicated children” while they were on medication and therefore on their best behaviour, which would introduce a confounding factor for initial assessments of medicated children compared to non-medicated ones; (b) since assessment was done at various times of the year, many of the teachers had different length of exposure to the children, which may have affected the reliability of their assessment; and (c) some of the children had different teachers pre- and post-Neurotherapy assessment and inter-rater differences between teacher reports may have introduced further confounding factors.

Of the 42 participants who initially enrolled in the research, the data for only 17 participants were able to be included in the study. In summary, 11 had original assessments but never started treatment, or stopped treatment before 20 sessions of Neurotherapy. The most common reason given was that their Paediatrician or medical practitioner had told them that there was no research to justify the expense of Neurotherapy Treatment and that they would be wise to continue on stimulant medication, as it was a proven and safe method of treatment. The next most common reason given was lack of financial resources to complete a course of treatment. The
pre-Neurotherapy EEG data for four of the participants were unusable, as it was
discovered well after they started treatment that a fault in the EEG recording
equipment had caused a loss of synchronization the between task-presentation
computer and the 13 Hz steady-state stimulus. Two participants left Melbourne to live
interstate or overseas close to the end of Neurotherapy Treatment before follow-up
SSVEP could be arranged. In five other cases the parents refused to subject their
children to the follow-up SSVEP recording, as they felt that they had achieved their
desired improvements, and further testing procedures would not benefit their child.
Three of the children, according to the parents, refused to participate in follow-up
SSVEP.

Final participants included in the study, were 17 boys aged 7-15 years (mean
10.35; Std.Dev. 2.34) for whom data was available. All had been on stimulant
medication (Methylphenidate or Dexamphetamine) at time of initial assessment for a
period ranging from three to78 months (Mean 19.4, Std. Dev. 20.3). They were
administered the initial TOVA and EEG measures after a drug washout period of 48
hours.

Those children who were medicated remained on stimulant medication until
the parents felt that they no longer needed it. Most parents stopped medication of
their own accord, or on the advice of their medical practitioner. All children except one
had stopped medication by the end of the study. The one child who remained on
medication had a normal TOVA at intake (TOVA-ADHD score 2.44) although he met the
DSM-IV criteria for ADHD and Conduct Disorder. After 55 sessions, his TOVA-ADHD
score had improved to 3.2. Throughout the treatment period, his parents had gone through an acrimonious separation, and his behaviours at home with his mother only improved after his father left to work abroad. His behaviours at school also improved, but he was under-achieving academically.

5.3 Procedures: TOVA and EEG Administration

A Test of Variables of Attention (TOVA) was administered to all participants at the Behavioural Neurotherapy Clinic as part of their initial assessment, and after every 20 sessions of Neurotherapy until the TOVA scores and behavioural measures had normalised.

EEG recordings for SSVEP analysis were recorded at Swinburne University of Technology in the EEG Laboratory of the Brain Sciences Institute, located at 400 Burwood Road, Hawthorn. On the day of the recording, each participant and the accompanying parent/s were showed the EEG laboratory at Swinburne University Brain Sciences Institute, and introduced to the EEG recording equipment. The procedures to be used in the study were explained to the child and to the parent/s. The parent and the child then signed the Informed Consent Form. Each participant was required to sit at a distance of 1.3 meters in front of the monitor of the CPT-AX task computer. The baseline and CPT-AX task instructions were given and both tasks were rehearsed. When each participant was fully competent with the tasks, the electrode sites were prepared for the recording. Strict safety instructions were observed to
minimize possible cross-contamination between experimenter and participants and vice versa, in accordance with the Safety Protocols set out by the Brain Sciences Institute. The nose and ear reference leads and a 64-electrode Electro cap of suitable size were fitted. The electrodes were gelled with Electro cap electrode gel and the EEG signals were checked for integrity by examination of the spectrum and waveform of the EEG acquired from each electrode.

Glasses specially designed to produce the steady-state 13 Hz sinusoidal stimulus were then fitted and held in place with micropore tape. Their operation was then checked. The baseline task was explained to participants, namely that they were to press both buttons only after seeing the number 5 in a series of sequentially presented numbers 1 to 5 and the task was then rehearsed. The baseline task commenced and brain electrical activity was recorded. The CPT-AX task was then explained and rehearsed. However, for the CPT-AX, participants were asked to respond as fast as possible following the appearance of the X if the letter preceded it was an A, without making mistakes, thereby emphasizing an equal need for speed and accuracy (Farrow 2003; Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).

Participants received between 40 and 67 sessions of Neurotherapy (Mean number of sessions 46) as described in section 5.7, after which the ATBRS behavioural assessment questionnaire was completed again, another TOVA was administered, and the complete SSVEP EEG recording was repeated while performing the baseline and the CPT-AX task. The data was group-analysed and results examined, reported, and
5.4 **Procedures: Behavioural Assessments**

In order to assess whether participants initially met the criteria for ADHD, and to measure behavioural changes resulting from treatment, an updated version of the Australian Twin Behaviour Rating Scale (ATBRS) (Levy & Hay 1991) was administered to all children pre- and post-Neurotherapy. A copy of the questionnaire is presented in Appendix A. In a previous study examining differences in parental reports of ADHD, speech, reading and behaviour problems, this questionnaire was found to have a high reliability yielding more conservative ratings than diagnostic interviews (Levy et al. 1996).

Despite the fact that most participants had previously been assessed by independent Paediatrician and had been prescribed stimulant medication, they were reassessed by two Board Registered Psychologists at the Behavioural Neurotherapy Clinic using the ATBRS questionnaire and a clinical interview. All of the participants met the DSM-IV criteria for ADHD. The questionnaire was also used in previous SSPT studies of the effects of stimulant medication on ADHD children at Swinburne University (Farrow 2003; Farrow et al. 1996), and was chosen because it promoted consistency, in case it was later decided to compare results with the Farrow studies (1996, 2003). In addition, a Test of Variables of Attention (TOVA) (Greenberg & Waldman 1993) was administered pre- and post-Neurotherapy. The CPT-AX task also
included measures of attention, as assessed by an analysis of key-presses.

5.4.1 DSM-IV Behavioural Criteria

The mother or father of each subject completed an updated version of the ATBRS (Levy & Hay 1991; Levy et al. 1996). The updated questionnaire contained items from the DSM-IV diagnostic criteria for ADHD (American Psychiatric Association 1987). The instructions to parents were to circle a number (0, 1, 2, or 3) as the item applied to their child, according to the following code:

0=not at all, 1=just a little/sometimes, 2=pretty much/often, 3=very much/very often.

To match the response criteria of Farrow (2003) to the current study, the following criteria were applied to all symptoms of ADHD. A response of 2 or 3 was considered symptomatic. A response of 0 or 1 was deemed not symptomatic. A parent of each participant was also given a questionnaire, containing only the ADHD items of the ATBRS (Levy & Hay 1991), to be completed and returned by mail by the child’s teacher to preserve confidentiality of responses. The number of symptoms endorsed was then summed up to obtain a “summed symptom score” for each disorder, which were used to establish diagnostic criteria. All Subjects had summed symptom scores in excess of eight.

It is noteworthy that all subjects had already been diagnosed independently by their Paediatrician as having ADHD and were presumably on an optimal medication
regime. The purpose of the ATBRS (Levy & Hay 1991) scoring was to obtain a baseline behavioural measure of ADHD symptoms, based on the DSM-IV criteria pre- and post-Neurotherapy.

5.4.2 **Test of Variables of Attention (TOVA)**

The TOVA (Test of Variables of Attention) CPT (Greenberg & Waldman 1993) was designed as a tool to titrate the effects of medication and to overcome some of the potential design deficits of other CPT tasks. The TOVA uses the following figures as target and non-target respectively (Greenberg & Waldman 1993).

![Figure 5.1 TOVA target and Non-Target Screens](image)

The TOVA uses rectangular figures as target and non target instead of letters or numbers to avoid the possible confounding effects of lexical and/or numerical processing (Greenberg & Waldman 1993). They are positioned in the centre of the computer screen, and target and non-target differentiation does not rely on left or right differentiation to avoid confounding effects of left or right visual field neglect (Greenberg & Waldman 1993). The task is presented in monochrome to avoid the
possible confounding effects of varying colour sensitivities in participants. The TOVA has two normative databases: one of normal participants aged 6 to 66 and another of children with ADHD (Greenberg & Waldman 1993). The 24-min task is divided into four 6-min quarters. In the first two quarters, targets are presented once in every five presentations, while in the third and last quarters targets are presented four times out of every five presentations. TOVA Z-scores for each quarter and for each of the parameters: omission, commission, reaction time, and variability in the reaction time are calculated. The Z-scores are compared to a database of normal participants of the same age and I.Q. and are normalised for I.Q. and age. The TOVA also has a database of scores from children with ADHD. An ADHD score of less than -1.80 is considered suggestive of ADHD, while scores which are above -1.80 are considered inconclusive (Greenberg & Waldman 1993). The TOVA was administered before and after Neurotherapy Treatment to provide an empirical measure of changes in variables of attention.

5.4.3 The CPT-AX Cognitive Task.

All participants performed a baseline task and the CPT-AX task while their brain electrical activity was being recorded. For both tasks, the stimulus presentation lasted for 2 seconds and appeared every 3.5 sec. A blank screen was presented during the 1.5 sec inter-stimulus interval. Altogether, 80 stimuli were presented for each task, amounting to a total task time of 280 seconds. In each task, the target was presented 11 times.
Participants were required to sit 1.3 metres away from the stimulus computer screen. The stimuli appeared in the centre of the screen subtending a horizontal and vertical angle of about 1° as viewed from the participant’s position. The stimuli were presented as white characters on a dark monochrome monitor screen. Using a Tektronix J16 narrow angle digital photometer, the average luminance of the stimuli was 13.0 Cd/m², and that of the monochrome monitor background of 1.2 Cd/m², as measured by a Tektronix J16 narrow angle photometer (Farrow 2003; Farrow et al. 1996).

The presentation sequences of the baseline and the A-X task are summarised in figure 5.2 below.

**Figure 5.2 Timing sequences for the baseline and CPT-AX tasks**

The yellow band indicates the 10-sec epoch of SSVEP data centered on the appearance of the targets, which were used for event and group averaging as, discussed in section 5.4.3

For both tasks, participants responded to targets by pressing buttons on a small
rectangular hand-held button box with two 1.5 cm square buttons mounted on the surface. The thumbs rested on the buttons, while the box was held in the hands resting on the participant’s lap. Participants were instructed to press the two buttons simultaneously using both thumbs only when they saw a valid target. A two button press was used, one in each hand, so that any motor-component effects on the SSVEP would be bilateral. Electronic circuitry ensured that button-bounce was eliminated, so as not to appear as multiple presses. Participants were instructed on the nature and requirements of both the baseline and the CPT-AX task, and practiced both tasks to the satisfaction of the experimenter to ensure that they were competent before proceeding (Farrow 2003; Farrow et al. 1996).

Following practice runs, the tasks were presented in the following order for all participants. First, participants performed the “baseline task” which was a low-demand vigilance task, during which participants were shown the numbers 1, 2, 3, 4, 5 and 6 in that order, and were required to press both buttons on the appearance of the “6”. The sequence was repeated sixteen times. Participants then performed the CPT-AX cognitive task, during which they were sequentially shown letters and they were required to press both buttons on the appearance of the letter “X”, but only when preceded by the letter “A”. The letter “A” was sometimes followed by a letter other than an “X”, and the letter “X” was sometimes preceded by a letter other than “A”. There were also non-target sequences of two letter combinations consisting of the non-cue and non-target letters: “D, E, G, J, K, L, O, P, S, V, W, Y, and Z”. For each of the two series of the CPT-AX tasks presented, fifteen A-X target sequences were presented.
These two tasks were then repeated in the same order to provide the following sequence of EEG recordings: Baseline 1, CPT-AX 1, Baseline 2, and CPT-AX 2. Both the baseline and CPT-AX task responses involved identical sensory and motor components (Farrow 2003; Farrow et al. 1996).

The baseline task provided a measure of baseline SSVEP activity. Activity during CPT-AX was referenced to this baseline level and the amplitude and latency components evoked by the CPT-AX task were extracted by subtracting the baseline SSVEP from the CPT-AX recording. The intervals between the presentation of stimuli and participant responses (reaction times) were recorded automatically by the recording software with an accuracy of 1 ms, and enabled the calculation of the following parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPT-AX</th>
<th>TOVA</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors of Omission</td>
<td>✓</td>
<td>✓</td>
<td>Missing a target</td>
</tr>
<tr>
<td>Errors of Commission</td>
<td>✓</td>
<td>✓</td>
<td>Reacting to a non-target</td>
</tr>
<tr>
<td>Errors of Responses to blanks</td>
<td>✓</td>
<td></td>
<td>Reacting to a blank screen</td>
</tr>
<tr>
<td>reaction-time</td>
<td>✓</td>
<td>✓</td>
<td>Interval between stimulus presentation and response</td>
</tr>
<tr>
<td>Variability in the reaction-time</td>
<td></td>
<td>✓</td>
<td>Statistical variability in reaction-time</td>
</tr>
</tbody>
</table>

Table 5-1 Variables measured in TOVA and CPT-AX task key-presses

Response times of less than 100 ms were considered anticipatory errors and were excluded. Responses greater than 1500 ms were also excluded and counted as “responses to blank errors”. Group differences in these response time measures were
calculated using one-way analyses of variance (Farrow 2003; Farrow et al. 1996).

5.5 **EEG Recording**

A 64 electrode cap, manufactured by Electrocap Inc. with electrodes accommodated within the International Ten-Ten system, was used to record brain electrical activity while participants performed the baseline and CPT-AX cognitive tasks.

*Figure 5.3 64 electrode sites, accommodated within the Ten-Ten System*
The recording was made with linked ears as reference, and ground was provided by a nose electrode. A 12 bits analog/digital (A/D) converter card, from Data Translation Corporation, plugged into an IBM PC compatible computer, was used to sample and digitize the 64 channels of EEG at a rate of 208Hz per channel. Data signals were fed to a pre-amplifier, band pass filtered (3 dB down at 0.1 Hz and 30 Hz) and saved to the data acquisition computer. All instrumentation, with the exception of the A/D converter card were designed and constructed at the Brain Sciences Institute (Farrow 2003; Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990; Simpson 1997).

5.6 Steady-State Probe Stimulus

A steady-state 13 Hz sinusoidal flicker was used as the stimulus to evoke the SSVEP. This 13 Hz stimulus was superimposed over the visual field using a set of purpose-designed glasses held securely to the recording cap with micropore tape. From the participant’s viewpoint, the field of view covered by the flicker was 160° horizontally and 90° vertically. The luminance of the 13 Hz sinusoidal waveform was 3.2 Cd/m2 at its peak, and 1.2 Cd/m2 at its minimum when viewing the blank screen of the task monitor. The purpose-built glasses had two sets of red, light-emitting diode (LED) arrays whose intensity varied in accordance with the amplitude of a 13 Hz sinusoidal signal. The flicker was projected onto a translucent screen to produce a uniform visual field onto a pair of half-silvered mirrors, which allowed the visual flicker to be superimposed over the participants viewing field, while they viewed the
cognitive task computer screen. To prevent the stimulus signal from
 electromagnetically contaminating the EEG leads, the LED arrays were enclosed in a
small Faraday Cage. There was a non-linearity of less than 0.5% between stimulus
voltage and light intensity of the LEDs (Farrow 2003; Pipingas 2003; Simpson 1997).

For each steady-state stimulus cycle, the same 16 EEG data points were
repeatedly sampled, and were time-locked to the task presentation at a positive going
zero-crossing point of the 13 Hz waveform. This time lock was necessary to ensure that
correct SSVEP amplitude and latency data associated with any aspect of the cognitive
tasks could be accurately extracted from the EEG recording (Farrow 2003; Silberstein,
Ciorciari & Pipingas 1995; Silberstein et al. 1990). The experimental setup is
represented in figure 5.4 below.
5.6.1 SSVEP Calculation

The 16 EEG data points were multiplied by the corresponding 16 points in the reference waveform and then integrated to give the Sine Fourier Coefficient. The reference waveform was then shifted by 90 degrees relative to the EEG data points prior to multiplication to give the Cosine Fourier Coefficient. All EEG data points for every one of the 64 electrodes and the task were analysed in a similar way and stored in a file on hard disk as a series of sine/cosine pairs. An overlapping window of 10
stimulus cycles, shifted repeatedly by one stimulus cycle between calculations, was used to average the 13 Hz Sine and Cosine Fourier Coefficients.

Long integration periods improve signal-to-noise ratio, while short integration periods enable tracking of rapid changes in SSVEP amplitude and phase (Silberstein et al. 1990). Hence, a 10-stimulus-cycle averaging was a compromise that provided Fourier Coefficients, with acceptable signal-to-noise ratio and temporal resolution.

This averaging process was repeated for each task and for each of the 64 electrodes over the whole 280 seconds of data. The following equations were used to calculate the Fourier amplitude and phase of the SSVEP coefficients at each time point yielding 64 amplitude and phase time-series for each task and for each participant, one set of data pre-Neurotherapy and one post-Neurotherapy:

\[ \text{SSVEP amplitude} = \sqrt{a_n^2 + b_n^2} \]
\[ \text{SSVEP phase} = \arctan\left(\frac{b_n}{a_n}\right) \]
where \(a_n\) = Cosine Fourier Coefficient, \(b_n\) = Sine Fourier Coefficient.

(Farrow 2003; Farrow et al. 1996; Pipingas 2003; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990)

5.6.2 Artefact Detection and Compensation

The SSVEP is relatively insensitive to artefacts such as EMG and EOG because these artefacts either have a broad power spectrum, or, in the case of mains interference, is limited to 50Hz, while the SSVEP power is focused at 13 Hz (Silberstein et al. 1990). This relative insensitivity to artefacts allows for a relaxation of artefact rejection criteria, not possible in studies of EEG power spectra. Nonetheless, the raw
EEG and SSVEP data at individual electrodes were be examined, using two different test criteria, to determine whether recordings from individual electrodes were contaminated by artefact above allowable threshold levels (Farrow 2003; Pipingas 2003; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).

Firstly, in this study, a statistical comparison technique was used to detect data whose voltages exceeded the maximum input voltage limit of the analogue to digital converter, as might occur during electrode pops (periodic disconnection between an electrode and the scalp) or intermittently faulty electrodes. Since the amplitude of the EEG has a Gaussian distribution, the amplitude distribution of the data recorded at each electrode and for each task was correlated with a Gaussian function to find out which recording failed to meet the Gaussian distribution. Electrodes with a signal whose correlation coefficient with the Gaussian function were less than 0.75, were classified as unacceptably noisy (Farrow 2003; Farrow et al. 1996; Pipingas 2003; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).

Second, the SSVEP time-series at each electrode was compared to the mean time-series of the four nearest electrodes for correlational disparity. In a 64-channel system, the data from adjacent electrodes are expected to be highly correlated, since electrical signals from the brain’s surface are spatially ‘smeared’ after they pass through the layers of dura mater, skull and scalp (Nunez 1981a, 1981b). If the correlation coefficient of the data between each electrode and its nearest neighbours was less than 0.6 the electrode was considered suspect and the data tagged as unacceptable. This second test is particularly useful for detecting electrodes
contaminated by EMG and 50Hz mains, whose artefacts display a Gaussian-like amplitude distribution, and may therefore slip past the first stage of detection. Data at suspect electrodes were replaced with the weighted average data from the four nearest electrodes, which passed both test criteria. If more than seven electrodes were deemed suspect for any one participant, that participant was excluded from the study (Farrow 2003; Farrow et al. 1996; Pipingas 2003; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990). However, there were only a few suspect electrodes across all the recordings, and therefore no subjects were excluded because of suspect electrodes.

5.6.3 Event Averaging

As discussed in section 5.7.1, signal averaging improves signal-to-noise ratio. Therefore, in order to determine changes in the SSVEP associated with the various components of the cognitive tasks for correct behavioural response, 10 second epochs of SSVEP data centered on the appearance of a letter “X” preceded by a letter “A” were averaged for correct responses. For each participant, this was done for each of the 64 electrodes, pre- and post-Neurotherapy. For the baseline task, 10 sec epochs of SSVEP data centered on the presentation of the target “5” were similarly processed (Farrow 2003; Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).
5.6.4 Group Averaging

Since there is considerable between-subject variability in the magnitude of the SSVEP, the data for each individual were normalised prior to examining group effects. For each subject, a normalisation factor was calculated by averaging the mean SSVEP amplitude for the 10 sec epoch centered on presentation of the number 5 in the baseline task. For every participant, each of the 64 amplitude time-series data was divided by that individual’s normalisation factor prior to inclusion in the cross-participant average (Farrow 2003; Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990).

Cross-participant averaging resulted in two set of group data from the 17 ADHD participants pre- and post-Neurotherapy Treatment. Each data set included the SSVEP amplitude and phase time-series for the baseline and CPT-AX target condition for all 64 electrodes.

SSVEP differences between baseline and cognitive states were obtained by subtracting the baseline mean values of the time-series at each point in the 10 second epoch, from the corresponding CPT-AX time-series values at relevant points during the CPT-AX task. These differences could then be interpreted as SSVEPs associated with the task demands of the CPT-AX in ADHD, either pre- or post-Neurotherapy.

In chapter 7, SSVEP amplitude differences from baseline are reported in normalised units, and phase differences are expressed as latency changes, with a phase difference of 1 radian being equivalent to a latency change of 12.24 ms (Farrow

5.6.5 **Topographic Mapping and Statistical Comparisons**

The differences between the amplitude time-series associated with the CPT-AX task and the baseline mean were calculated. The results were represented as two-dimensional colour topographic maps. Inter-electrode colour graduations were calculated using a spherical “spline interpolation procedure” (Cadusch, Breckon & Silberstein 1992). This process was then repeated for the latency time-series (Cadusch, Breckon & Silberstein 1992). In this procedure, pre-Neurotherapy baseline task values were set at zero, and changes in the amplitude and phase latency of the pre- and post-Neurotherapy related CPT-AX tasks were expressed as deviations from this “zero” level. Equating the baseline activity of the pre- and post-Neurotherapy groups in this way takes into account two factors: First, any group differences associated with sensory-motor processing would be controlled, enabling direct comparison of the CPT-AX activity with attentional processing. Second, since Neurotherapy Treatment may influence the post-Neurotherapy baseline task levels, referencing CPT-AX values to the pre-Neurotherapy baseline task level eliminates this confounding variable.

The topographic maps were made from a 256-colour scale. Increases in activation, corresponding to amplitude and latency reductions, were displayed as warmer (yellow to red) colours. Decreases in activation, corresponding to amplitude and latency increases, were displayed as cooler (green to blue) colours. The following
account of the Significance Probability Mapping (SPM) is one commonly used at the Brain Sciences Institute to describe the methodology and is quoted from Farrow (2003).

“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 pre- and post-Neurotherapy conditions (Silberstein, Ciorciari & Pipingas 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 CPT-AX. 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” (Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995) in (Farrow 2003) p. 120

“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 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 0.05, 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 1981a, 1981b; Silberstein, Ciorciari & Pipingas 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” (Farrow et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1990) in Farrow (2003) p. 121

5.7 Neurotherapy Treatment Protocols

The majority of Neurotherapy studies reviewed in chapter 3, relating to the treatment of ADHD, reported positive outcomes using two protocols: (1) inhibiting theta and promoting SMR over the sensory-motor cortex, and (2) inhibiting theta and promoting beta, while in both cases inhibiting feedback when muscle tension was above threshold set by the clinician. Both of these were used in this study. The decision to use more or less of a specific protocol during training was based on a clinical judgement whether behavioural and motor-inhibition, or focus and
concentration were primary needs for the participant. Generally, the following guidelines were followed and varied as deemed clinically necessary:

- Theta/SMR training was used to promote behavioural stillness and better motor control and inhibition, as discussed in chapter 3. The protocol was as follows: Suppress theta (4-7Hz) and reward SMR (11-14Hz) at Cz while suppressing muscle activity (>30Hz) in the EEG for 20 sessions.

- Theta/Beta training was used to promote increased attentiveness and improvements in sustained attention as discussed in chapter 3. The protocol was as follows: Suppress theta (4-7Hz) and reward beta (15-20Hz) at Cz while suppressing muscle activity (>30Hz) in the EEG.
# Chapter 6: Results

## 6.1 Introduction

This chapter reports on the changes following Neurotherapy Treatment using the following measures: (a) amplitude and phase latency in the SSVEP while children performed the CPT-AX task, (b) changes in the ATBRS (Levy & Hay 1991) behavioural scores, (c) changes in key-presses during the CPT-AX task and (d) changes in TOVA scores. The chapter is divided as follows:

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<td>SSVEP Time-Series Latency Graphs</td>
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<tr>
<td>6.5</td>
<td>Summary of SSVEP Findings</td>
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## 6.2 ATBRS (Levy & Hay 1991) : ADHD Behavioural Questionnaire

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The Australian Twin Behaviour Rating Scale (ATBRS (Levy & Hay 1991)) parent questionnaires were completed by parents and teachers for each participant pre- and post-Neurotherapy. The total number of symptoms, and the group means of the number of DSM-IV symptoms of ADHD reported by both parents and teachers are presented in table 6.1.

<table>
<thead>
<tr>
<th>ATBRS Number of ADHD symptoms reported</th>
<th>Mean number of symptoms reported</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parents</td>
<td>Teachers</td>
</tr>
<tr>
<td>Pre-Neurotherapy</td>
<td>11.2 (2.2)</td>
<td>7.7 (2.87)</td>
</tr>
<tr>
<td></td>
<td>Range: 8-14</td>
<td>Range: 4-13</td>
</tr>
<tr>
<td>Post-Neurotherapy</td>
<td>5.3 (2.11)</td>
<td>4.7 (1.80)</td>
</tr>
<tr>
<td></td>
<td>Range: 2-9</td>
<td>Range: 2-9</td>
</tr>
<tr>
<td>Paired Differences</td>
<td>5.9 (2.1)</td>
<td>3.0 (2.2)</td>
</tr>
<tr>
<td>Paired sample t-test</td>
<td>$t(16)= -11.6, p \leq 0.000$</td>
<td>$t(16)= -5.6, p \leq 0.000$</td>
</tr>
</tbody>
</table>

Table 6-1 Mean number of symptoms of ADHD from the ATBRS Analysis of parent and teacher reports of symptoms which occurred “often or very often” (std. dev. in parentheses) from the 18 behaviours listed in the DSM-IV, pre- and post-Neurotherapy (n=17).

As presented in table 6.1, there is a significant difference between post- and pre-Neurotherapy measures in the mean number of ADHD symptoms identified by parents and teachers of the students.

### 6.3 Measures of Key-Press Task Responses during EEG Recording

The mean reaction times, number of: correct responses, omission errors, commission errors, and responses during the blank interval, were calculated from the
baseline and CPT-AX task responses. These are presented in table 6.2, both for pre- and post-Neurotherapy.

SSVEP EEG was recorded pre- and post-Neurotherapy while the subjects performed the baseline task and the CPT-AX task in the following order:

Baseline Task 1 - REST - CPT-AX Task 1 - REST - Baseline Task 2 - REST - CPT-AX Task 2

For each of the 17 subjects, the two pre-Neurotherapy baseline tasks were added together to provide 34 baseline key-press data sets. Similarly, the data for the two pre-Neurotherapy CPT-AX tasks were added together to provide 34 CPT-AX key-press data sets. The process was repeated for the post-Neurotherapy key-press data.

Paired Samples t-Test for post- to pre-Neurotherapy

<table>
<thead>
<tr>
<th>Key-press measures</th>
<th>Mean Values</th>
<th>Paired Differences: post- minus pre-Neurotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CPT-AX Task1+Task2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean reaction-time</td>
<td>784</td>
<td>555</td>
</tr>
<tr>
<td>Num: Correct responses</td>
<td>213</td>
<td>354</td>
</tr>
<tr>
<td>Num: Omission errors</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Num: Commission errors</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Num: Responses in Blanks</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Baseline Task1+Task2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean reaction-time</td>
<td>692</td>
<td>418</td>
</tr>
<tr>
<td>Num: Correct responses</td>
<td>225</td>
<td>357</td>
</tr>
<tr>
<td>Num: Omission errors</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Num: Commission errors</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Num: Responses in Blanks</td>
<td>24</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 6-2 Mean reaction-times and number of errors pre- and post-Neurotherapy in subjects performing the baselines and CPT-AX tasks (n=17).
As reported in table 6.2, prior to Neurotherapy Treatment, the subjects had significantly slower reaction times and made significantly fewer correct key-presses during the baseline and CTP-AX task. Following Neurotherapy, they made significantly fewer omission and commission errors than before Neurotherapy, while performing both the baseline and the CPT-AX tasks. They also made fewer responses during the blank periods, consistent with a significant decrease in their response time. In scoring the data, reaction times of less than 100 ms were considered invalid anticipatory responses, and were excluded from group averages.

6.3.1 Changes in Mean TOVA Scores

The results of the TOVA, which was conducted pre-, and post-Neurotherapy, are presented in figure 6.1 and table 6.3. TOVA scores are standardised such that a person with an average I.Q. of 100 is expected to score close to 100 on all TOVA measures (Greenberg & Waldman 1993).

![Comparison of Standardised TOVA](image)
The results indicate that the TOVA scores improved significantly on all measures following Neurotherapy, with the group mean scores considered normal and not indicative of ADHD. The TOVA also provides an ADHD score. A score of -1.80 or less is suggestive of ADHD while scores above -1.80 are considered inconclusive. The mean TOVA-ADHD score for the research group was -3.7 prior to Neurotherapy and improved to +1.0 after Neurotherapy. Paired-samples t-tests were conducted to compare the TOVA Scores from pre- to post-Neurotherapy and the results are presented in Table 6.3.

<table>
<thead>
<tr>
<th>Standardised mean scores</th>
<th>Paired Differences (Post-Pre) Neurotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOVA scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRE</td>
</tr>
<tr>
<td>Omission errors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83.41 (26.80)</td>
</tr>
<tr>
<td>Commission errors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92.76 (22.71)</td>
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<tr>
<td>reaction-time (RT)</td>
<td></td>
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<tr>
<td></td>
<td>81.35 (20.29)</td>
</tr>
<tr>
<td>Variability in RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.88 (24.41)</td>
</tr>
<tr>
<td>ADHD score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-3.71 (3.55)</td>
</tr>
</tbody>
</table>

*Table 6-3 Paired sample t-tests and significance levels of changes in TOVA Scores. Std.Dev. in brackets (n=17)*

Paired-samples t-tests were conducted to compare the TOVA scores between the pre- and post-Neurotherapy conditions. The mean and standard deviations and
paired differences statistics are presented in table 6.3. Following Neurotherapy Treatment, group scores indicate that the subjects performed significantly better on all measures of the TOVA. Standardised mean scores indicate that TOVA scores normalised, and were not indicative of ADHD. It is important to remember that in this study all subjects were trained until they normalised their TOVA scores, as is common practice in clinical treatment using Neurotherapy, rather than training to a set number of sessions (usually 40).

6.4 **Changes in SSVEP Electrophysiology**

This section describes the findings of SSVEP amplitude and latency responses related to cognitive and attentional processing during the execution of the CPT-AX task, prior to and following Neurotherapy Treatment. Topographic maps, presented in sections 6.4.1 and 6.4.5, highlight the degree of brain activation at key points during the performance of the CPT-AX task pre- and post-Neurotherapy. In addition, the topographic maps contrast treatment changes and their significance levels. SSVEP amplitude time-series illustrations for selected electrode sites are presented in section 6.4.4, while SSVEP latency time-series illustrations are presented in section 6.4.5. The sites selected for presentation are representative of sites where SSVEP changes in activity referenced to baseline were thought to be the most functionally significant in the topographic maps.

Both the topographic maps and the time-series graphs have their unique usefulness. The maps provide a view of activation at all sites at specific time points,
providing an opportunity to investigate the spatial relationships in SSVEP responses. In contrast, the time-series illustrations provide a display of SSVEP responses at one specific electrode for all time points, providing an opportunity to investigate the temporal nature of the SSVEP responses in these regions of interest. Topographic distribution of the SSVEP amplitude and latency differences pre- and post-Neurotherapy, and side-by-side are presented in Figure 6.2, Figure 6.3, and Figure 6.4 respectively.

Silberstein and colleagues (1996) suggested that SSVEP latency changes may index variations in the speed of neural information processing, and may be a reflection of excitatory and inhibitory processes. They argued that this interpretation is supported by findings that faster response times in a visual vigilance task were associated with larger pre-frontal SSVEP latency reductions (Silberstein et al. 1996). More recently this interpretation was reinforced by findings in a study of SSVEP latency changes in ADHD, where a lack of pre-frontal SSVEP reductions in ADHD was associated with increased reaction-times. Normal controls demonstrated transient pre-frontal SSVEP latency reductions following the appearance of the target X while subjects diagnosed with ADHD showed no such latency reduction. Silberstein (1998) suggested that the failure to exhibit transient SSVEP latency reductions in ADHD might be associated with inadequate excitation of pre-frontal networks (Silberstein et al. 1998a). Thus a reduction in latency could be interpreted as increased neuronal excitation associated with faster processing speed, while an increase in latency could be interpreted as less neuronal excitation (or an inhibitory effect) and slower
processing speed.

As described in section 5.6.5 above, Bonferroni corrections for multiple comparisons need to be applied to the significance thresholds presented in figures 6.2 and 6.3 to correct for multiple recording sites. Thus, the usual p-value of 0.05 needs to be divided by 5. As such, a p-value of 0.01 on the Hotelling’s T maps was used as the threshold for statistical significance. Similarly, when multiple time points are considered this should be further divided by 4 (p = 0.0025). Consequently, in the Hotelling’s T maps, areas inside the iso-T contour representing an uncorrected p-value of 0.001 are regions of significant SSVEP differences, while areas inside the iso-T contour representing a p-value of 0.005 are regions of SSVEP differences approaching significance. Six time points were selected in the maps to examine the SSVEP dynamics:

1. At 230 ms prior to the appearance of the cue letter A,
2. On appearance of the cue letter A,
3. At 615 ms prior to the appearance of the X, around which time, participants may be expected to be preparing for the possible appearance of a target X, after being cued by the A,
4. On appearance of the target letter X,
5. At 500 ms after the appearance of the X, just prior to the key-press responses. These occurred on average at 784 ms pre-Neurotherapy, and 555 ms post-Neurotherapy.
6. At 1134 ms after the appearance of the target X, a point at which the target is still displayed on the screen.
Important Notice:

The colour convention used in the following maps is reversed to that which has been traditionally used in previous SSVEP studies and publications from the Brain Sciences Institute at Swinburne University of Technology. This was due to an oversight in the setting of convention parameters in the software and does not affect the results.
Figure 6.2 Topography of CPT-AX - Baseline Differences Pre-Neurotherapy

Cooler colours indicate reduced SSVEP normalised amplitude, and reduced latency in milliseconds between CPT-AX and Baseline tasks means. Hotter colours indicate increased SSVEP normalised amplitude and increased latency in milliseconds between CPT-AX and Baseline tasks means. Hotter colours in Hotelling’s T indicate the strength of these differences, with Iso-T contours representing uncorrected p values of 0.05, 0.01, 0.005, and 0.001.
Figure 6.3 Topography of CPT-AX - Baseline Differences Post-Neurotherapy

Cooler colours indicate reduced SSVEP normalised amplitude, and reduced latency in milliseconds between CPT-AX and baseline tasks means. Hotter colours indicate increased SSVEP normalised amplitude and increased latency in milliseconds between CPT-AX and baseline task means. Hotter colours in Hotelling’s T indicate the strength of these differences, with Iso-T contours representing uncorrected p-values of 0.05, 0.01, 0.005 and 0.001.
Figure 6.4 Topography of SSVEP Amplitude and Latency Differences

Topographic differences for SSVEP amplitude in normalised units and latency in milliseconds between baseline mean and CPT-AX time-series, pre- and post-Neurotherapy. The rows indicate time points in the CPT-AX task. The left two columns are maps of the normalised amplitude pre- and post-Neurotherapy. The right two columns are maps of the normalised latency differences in milliseconds relative to the baseline. Cooler colours indicate reduced SSVEP normalised amplitude and reduced latency in milliseconds referenced to the baseline. Warmer colours indicate increased SSVEP normalised amplitude and increased latency in milliseconds relative to the baseline.
6.4.1 Topography of SSVEP Amplitude Changes in CPT-AX Task

As previously discussed, a reduction in SSVEP amplitude can be interpreted as increased activation, while an increase in amplitude can be interpreted as a reduction in activation. The topographic maps in Figure 6.2 indicate that prior to Neurotherapy children with ADHD exhibited diffuse increases in SSVEP amplitude suggestive of reduced cortical activation during the CPT-AX task interval. Reduced amplitude changes only occurred around 1 second after appearance of the letter X.

Following Neurotherapy, as presented in Figure 6.3, there were strong amplitude reductions in the left temporo-parietal regions, which started prior to the appearance of the letter A and were sustained to varying degrees throughout the task and beyond the presentation of the letter X. There were also strong amplitude reductions at frontal sites prior to the appearance of the X.

6.4.2 Topography of Latency Changes in CPT-AX Task

Prior to Neurotherapy, the children with ADHD showed increases in SSVEP latency compared to baseline at most sites. There was a small reduction in SSVEP latency in the left pre-frontal area at FP1 and a mild reduction in latency in the midline central and parietal areas around 600 ms prior to the appearance of the target X. However, these mild reductions in SSVEP amplitude compared to baseline were no longer present on presentation of the target X.
In contrast, after Neurotherapy there were SSVEP latency reductions compared to baseline in right parietal areas. This occurred prior to appearance of the cue letter A which maintained until the appearance of the target X. On the appearance of the target X, there were very strong latency reductions compared to baseline in the right pre-frontal and frontal areas at FP2 and F8. This suggests more excitatory (or less inhibitory) effects at these sites during processing of the appearance of the target X.

The appearance of the target X was associated with strong right pre-frontal and right parietal latency reductions compared to baseline following Neurotherapy which were absent in children with ADHD prior to Neurotherapy. These findings suggest that post-Neurotherapy there was increased processing speed during the A-X interval.

### 6.4.3 Topography of Hotelling’s T Significance

The post-Neurotherapy Hotelling’s T maps in Figure 6.3 show that the most significant differences in the SSVEP occurred in right parietal regions at 230 ms prior to the appearance of the cue letter A. The effect was increased on the appearance of the A, and then peaked at the appearance of the X. This suggests a consistent and significant SSVEP effect in the right parietal area post-Neurotherapy in preparation for the appearance of the cue letter A, on presentation of the A, and on the appearance of the target X.

In addition, the Hotelling’s T maps post-Neurotherapy in Figure 6.3 show a significant SSVEP effect at the appearance of the target X, suggesting a significant
increase in processing speed in the right frontal and pre-frontal area when recognition of the target and its processing are crucial for successful task execution.

6.4.4 SSVEP Time-series Amplitude Graphs

A reduction in amplitude of the SSVEP has been interpreted as an increase in activation in previous studies using SSVEP (Silberstein et al. 1996; Silberstein et al. 1998a), in a similar way that a reduction in alpha is widely interpreted as an increase in activation (Farrow 2003; Silberstein et al. 2001; Silberstein et al. 1990).

The following time-series amplitude graphs have been selected to illustrate the findings discussed in section 6.4.2. They illustrate that there was minimal activation or decreased activation at most sites during the A-X interval in children with ADHD while they performed the CPT-AX task, prior to Neurotherapy. In contrast, post-Neurotherapy there were decreases in SSVEP amplitude compared to baseline, suggesting increases in activation that were contingent with task-demands, associated with presentation of the cue letter A, disappearance of the A, and presentation of the target letter X.
Figure 6.5 SSVEP Amplitude Time-Series at Electrode 0, (Left pre-Frontal site)

Steady state visually evoked potential (SSVEP) amplitude during the target sequence in the CPT-AX task as a function of time in subjects with ADHD pre- and post-Neurotherapy. The dashed horizontal line represents the mean normalised amplitude for the baseline task, which was set to zero for both conditions. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X). A reduction in normalised amplitude can be interpreted as increased activation, while an increase in amplitude can be interpreted as a reduction in activation.

Figure 6.5 illustrates that prior to Neurotherapy, SSVEP amplitude changes, compared to baseline mean, were minimal at all time points throughout the CPT-AX task, whereas following Neurotherapy there were large amplitude reductions contingent with task demand. This finding is relevant to the neuromodulatory model of Tucker and Williamson (1984) and will be explored in the discussion section.
Figure 6.6 Amplitude Time-Series at Electrode 4, (Right pre-Frontal site)

Steady state visually evoked potential (SSVEP) amplitude during the target sequence in the CPT-AX task as a function of time in subjects with ADHD pre- and post-Neurotherapy. The dashed horizontal line represents the mean normalised amplitude for the baseline task, which was set to zero for both conditions. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (☐) and the letter X appears (X). A reduction in normalised amplitude can be interpreted as increased activation, while an increase in amplitude can be interpreted as a reduction in activation.

Similarly, figure 6.6 above and figure 6.7, on the next page, also illustrate that prior to Neurotherapy, compared to baseline, SSVEP amplitude reduction were minimal or even increased, at some time points, during the CPT-AX task. In contrast, following Neurotherapy there were large amplitude reductions in anticipation of changes in task presentation. These findings are relevant to the neuromodulatory...
model of Tucker and Williamson (1984) which will be explored in the discussion section.

*Figure 6.7 Amplitude differences at electrode 20, (F8 fronto-temporal right)*

Steady state visually evoked potential (SSVEP) amplitude during the target sequence in the CPT-AX task as a function of time in subjects with (ADHD pre- and post-Neurotherapy). The dashed horizontal line represents the mean normalised amplitude for the baseline task, which was set to zero for both conditions. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X). A reduction in normalised amplitude can be interpreted as increased activation, while an increase in amplitude can be interpreted as a reduction in activation.
Figure 6.8 Amplitude differences at electrode 50, (P4 Parietal right)

Steady state visually evoked potential (SSVEP) amplitude during the target sequence in the CPT-AX task as a function of time in subjects with ADHD pre- and post-Neurotherapy. The dashed horizontal line represents the mean normalised amplitude for the baseline task, which was set to zero for both conditions. CPT-AX related amplitude changes are therefore expressed as differences from the baseline. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (☐) and the letter X appears (X). A reduction in normalised amplitude can be interpreted as increased activation, while an increase in amplitude can be interpreted as a reduction in activation.

Figure 6.8 illustrates that prior to Neurotherapy SSVEP amplitude changes referenced to baseline were minimal. In contrast, post-Neurotherapy there were SSVEP amplitude reductions throughout the task. More importantly, on appearance of the A and of the X, there were large amplitude increases. These have implications in Tucker and Williamson’s (1984) model, which will be explored in the discussion.
6.4.5 **SSVEP Time-series Latency Graphs**

A decrease in latency has been interpreted as an increase in excitation and increased processing speed in previous studies using SSVEP discussed in section 4.3.6. The SSVEP latency dynamics were graphed from 500 ms prior to the appearance of the cue letter A, until 2 seconds after the appearance of the target X, a point at which the target is still displayed on the screen. The following time-series diagrams, illustrate that prior to Neurotherapy there were minimal reductions in latency in ADHD children while they performed the CPT-AX task, whereas post-Neurotherapy there were task-specific reductions in latency particularly at right pre-frontal, frontal, central and right temporal sites associated with processing of the target X.
Figure 6.9 Latency Differences at electrode 4 (Pre-frontal right)

SSVEP latency time-series for pre- and post-Neurotherapy conditions in the CPT-AX task. The dashed horizontal line represents the mean latency for the baseline task and is set to zero for both conditions. CPT-AX task-related latency changes are expressed as differences from the baseline in milliseconds. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X). A reduction in latency is interpreted as increased excitation, while an increase in latency can be interpreted as less excitation or increased inhibition.

The time-series in figure 6.9 shows that before Neurotherapy there was minimal reduction in latency compared to baseline throughout the CPT-AX task at this right pre-frontal site, whereas following Neurotherapy, there was a large transient reduction in latency on the appearance of the X, suggesting increased excitation, presumably necessary for rapidly recognising and processing of the target X. This has implications for the functional connectivity-sculpting model proposed by Silberstein (2006) and will be explored in the discussion section.
Figure 6.10 Latency differences at Electrode 20, (F8, Frontal right)

SSVEP latency time-series for pre- and post-Neurotherapy conditions in the CPT-AX task. The dashed horizontal line represents the mean latency for the baseline task and is set to zero for both conditions. CPT-AX task-related latency changes are expressed as differences from the baseline in milliseconds. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X). A reduction in latency is interpreted as increased excitation, while an increase in latency can be interpreted as less excitation or increased inhibition.

Figure 6.10 indicates that prior to Neurotherapy, this site had minimal SSVEP responses compared to baseline, and remained close to baseline level throughout the task, suggesting no changes in excitation during the A-X interval. However, following Neurotherapy, there was a small but sustained reduction in latency throughout the A-X interval, and that there was a very strong reduction in latency just prior to and on presentation of the letter X, suggesting strongly increased excitatory processes and
faster processing speed on the presentation of the target X.

**Figure 6.11 Latency differences at Electrode 50, (P4, Parietal right)**

SSVEP latency time-series for pre- and post-Neurotherapy conditions in the CPT-AX task. The dashed horizontal line represents the mean latency for the baseline task and is set to zero for both conditions. CPT-AX task-related latency changes are expressed as differences from the baseline in milliseconds. The vertical lines represent the time points at which: the letter A is presented (A), the letter A disappears and the blanking interval commences (□) and the letter X appears (X). A reduction in latency is interpreted as increased excitation, while an increase in latency can be interpreted as less excitation or increased inhibition.

Figure 6.11 indicates that prior to Neurotherapy, this parietal site had very few SSVEP responses compared to baseline, and responses remained close to baseline throughout the task, suggesting minimal changes in excitation throughout the A-X interval during the task. However, following Neurotherapy, there was a strong and sustained reduction in latency compared to baseline throughout the A-X interval. Just prior to and on presentation of the letter X, this latency reduction decreased considerably, suggesting decreased excitatory processes and a slowing of processing speed just prior to and on the presentation of the target X. This finding will be
appraised in the discussion section in the context of anticipatory processes, habituation, and the noradrenergic system, as proposed in Tucker and Williamson’s (1984) model of the attentional system.

6.4.6 **Summary of SSVEP Findings**

Prior to Neurotherapy, children with ADHD showed diffuse amplitude increases, compared to baseline, throughout the CPT-AX task. However, post-Neurotherapy, they demonstrated diffuse amplitude reductions throughout the CPT-AX task. In particular, SSVEP amplitude reductions compared to baseline were the strongest at frontal, central and temporal sites prior to presentation of the target X.

Following Neurotherapy, in the time interval between presentation of the A and of the X, there were widespread and sustained decreases in SSVEP amplitude compared to baseline, particularly in the left temporo-parietal region and in the right fronto-temporal region, suggesting increased levels of cortical activation in those regions (Farrow 2003; Silberstein et al. 2001; Silberstein et al. 1990). The topography depicted in Figure 6.3 and the time-series amplitude graphs illustrate the decreases in SSVEP amplitude following Neurotherapy, suggesting that Neurotherapy is associated with widespread and sustained increases in activation during performance of the CPT-AX task.

In previous SSVEP studies, transient reductions in SSVEP latency compared to baseline, have been interpreted as suggestive of increased processing speed (Farrow et
al. 1996; Silberstein et al. 1996; Silberstein, Ciorciari & Pipingas 1995; Silberstein et al. 1998a). Consequently, in this study, transient reductions in SSVEP latency have been interpreted as suggesting increased excitation associated with increased processing speed.

Prior to Neurotherapy, the ADHD subjects showed minimal to no changes in SSVEP latency compared to baseline throughout the A-X interval, and following the appearance of the X. However, following Neurotherapy, there was evidence of sustained latency reductions compared to baseline throughout the A-X interval in right parietal areas. In addition, there was a strong transient latency reduction compared to baseline at right pre-frontal sites compared to baseline just prior to and on the appearance of the target X which was sustained for around 500ms.

6.5 **Summary of Results**

As a group, the children with ADHD performed significantly better on the ATBRS (Levy & Hay 1991), TOVA and CTP-AX key-presses following Neurotherapy. Prior to Neurotherapy, they made significantly more errors of commission and errors of omission, and had slower reaction-times on both CPTs as well as more variability in their reaction-time on the TOVA. Their TOVA-ADHD group score was suggestive of a diagnosis of ADHD prior to Neurotherapy, which was no longer the case after Neurotherapy.

In addition to group differences in behavioural measures, the SSVEP data
demonstrated group differences in SSVEP amplitude and latency changes from pre- to post-Neurotherapy during the performance of the CPT-AX task. Following Neurotherapy, presentation of the cue letter A and the target X was associated with diffuse amplitude reductions, suggesting increased cortical activation. More specifically, frontal lobe amplitude reductions associated with cue and target processing were greater and parieto-occipital amplitude reductions were seen compared to the pre-Neurotherapy condition. Following Neurotherapy, processing during the A-X interval of the CPT-AX task was associated with frontal, central and parietal reductions in SSVEP latency differences from baseline, which were not observed prior to Neurotherapy. Overall, following Neurotherapy, SSVEP responses to both cue and target stimuli suggest essential increases in regional activation and excitation not seen prior to Neurotherapy.
Chapter 7: Discussion

7.1 Introduction

This chapter presents a discussion of the results reported in chapter 6, relating them to the Neuropsychological, Electrophysiological and Neurotherapy literature and their relationship to the hypotheses presented in section 4.4. It is argued in the following discussion, that the results of this study suggest that in children with ADHD, attentional networks are modulated towards higher efficiency by Neurotherapy. This is evidenced by changes in SSVEP measures and associated behavioural improvements.

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7.2 ATBRS Behavioural Findings

The hypothesis stating that DSM-IV ADHD behavioural measures as assessed by the updated version of the Australian Twin Behaviour Rating Scale (ATBRS) (Levy & Hay 1991) will significantly improve towards normalisation, was supported. As presented in table 6.1, there was a significant difference between post- and pre-Neurotherapy measures in the mean number of ADHD symptoms endorsed by parents and teachers. Overall, the ATBRS (Levy & Hay 1991) scores were no longer indicative of ADHD, with the exception of one of the 17 boys who continued to meet the criteria at a reduced level (from 14 behaviours to 9 endorsed).

As discussed in sections 3.5 to 3.8, many studies have reported similar results (Fuchs et al. 2003; Lubar 1985, 1995; Monastra 2005; Monastra, Monastra & George 2002; Rossiter 2004b; Rossiter & La Vaque 1995; Tansey 1991). The behavioural improvements following Neurotherapy are also consistent with a recently published meta-analysis of ADHD studies that investigated the effect of Neurotherapy in children with ADHD in a series of controlled studies (n=476) as well as pre/post-design studies (n=718) (Arns et al. 2009). The mean effect size for inattention following Neurotherapy was 1.0238 (95% CI 0.84-1.21; Total N=324), for impulsivity 0.9394 (95% CI 0.76-1.12; Total N=338) and for hyperactivity 0.7082 (95% CI 0.54-0.87; Total N=375) (Arns et al. 2009).

The most likely reason for the lower rates of symptoms reported by teachers
prior to Neurotherapy compared with parents is that all of the children in the study were on medication during school hours for over half of the study’s duration. Therefore teachers did not observe the full extent of their problem behaviours. Nonetheless, post-Neurotherapy, when the children had been off medication for around 2 months, the teachers endorsed less ADHD symptoms than they did prior to the study. Some parents stopped Neurotherapy Treatment for their child at 40 sessions against advice because they felt that their child no longer met criteria for ADHD, or that they could not afford to continue treatment. Those children who continued for 10 sessions more than the number of sessions required for TOVA-ADHD score normalisation (ADHD score > -1.80), increased their scores even further. Most of the children came off stimulant medication permanently after around 20-30 sessions of Neurotherapy, and there were no notable exacerbation of symptoms reported by parents and teachers. Unfortunately, some parents did not report exactly when the children stopped medication, so a mean figure could not be calculated.

7.3 Discussion of Result of CPT-AX Key-Presses and TOVA Findings

The hypothesis, which stated that following Neurotherapy there would be significant improvements in empirical attentional measures, as assessed by changes in reaction time, omission errors and commission errors in key-presses during CPT-AX task and TOVA scores of omission, commission, reaction time, variability in the reaction time and TOVA-ADHD scores, was supported.

As reported in table 6.2, following Neurotherapy the subjects had significantly slower reaction times in key-presses in the CTP-AX task. They also made
significantly fewer omission and commission errors than prior to Neurotherapy, while performing both the baseline and the CPT-AX tasks. They also made significant fewer responses during the blank periods following the presentation of the target X in the CPT-AX task, consistent with a decrease in their response time. Prior to Neurotherapy, some children tended to play with the keys and randomly press the keys, displaying reduced behavioural inhibition. These behaviours were not observed following Neurotherapy, which might also account for the fewer errors in the blank intervals following presentation of the target X.

Following Neurotherapy, ADHD children performed significantly better than they had done prior to Neurotherapy. They responded to targets in the TOVA and CPT-AX task with shorter reaction times, fewer omission and commission errors and less variability in the reaction time. Furthermore, all of the post-pre difference scores were significant. These results are in accordance with previous studies of Neurotherapy, which have consistently reported significant improvements or normalisation of TOVA scores of children with ADHD following Neurotherapy Treatment (Alhambra, Fowler & Alhambra 1995; Boyd & Campbell 1998; Cho et al. 2004; Fernandez et al. 2003; Lubar et al. 1995a; Monastra, Monastra & George 2002; Rossiter 2004b; Rossiter 1998; Rossiter & La Vaque 1995; Thompson & Thompson 1998b; Xiong, Shi & Xu 2005).
7.3.1 Reaction times

Children with ADHD have been found to have slower reaction-times in CPT tasks than normal controls (Barkley & Grodzinsky 1994; Barry et al. 2009b; Bush et al. 2008; Fassbender et al. 2009; Greenberg & Waldman 1993; Johnstone et al. 2007; Klorman et al. 1979; Overtoom et al. 1998b; Schulz et al. 2005b; Simmonds et al. 2007; Wood et al. 1999). They also had longer P300 latencies to CPT targets, suggesting that they have slower stimulus-evaluation processes (Holcomb, Ackerman & Dykman 1985; Strandburg et al. 1996b; Taylor et al. 1993). Their slower reaction-times have been shown to be associated with deficits in the pre-frontal cortex (Bush et al. 2008; Rubia et al. 2008; Schulz et al. 2004; Sheridan, Hinshaw & D’Esposito 2007; Simmonds et al. 2007; Suskauer et al. 2008a; Zang et al. 2005). Children with ADHD were also found to have processing speed deficits in non-CPT tasks (Shanahan et al. 2006) and slower reaction-time in a computer paced task (Van der Meere, Marzocchi & De Meo 2005) compared with controls.

Silberstein and colleagues (1998) demonstrated that children with ADHD lacked the SSVEP latency reductions, with respect to the mean latency during A-X interval of the CPT-X reference task at right pre-frontal sites. On the other hand, non-ADHD controls demonstrated a strong SSVEP latency reduction at right pre-frontal sites coinciding with the appearances of the A and X and the disappearance of the A, significant only at electrode 20 (F8). Compared with the prominent frontal SSVEP latency reductions observed in controls, subjects with ADHD showed only a slight right frontal latency reduction at the appearance of the A and latency increases at other
frontal and temporal sites throughout the A-X interval. These deficits were also associated with significant reductions in reaction-time (Silberstein et al. 1998a).

Silberstein’s group (1996) had previously suggested that such latency reductions may reflect increased efficiency of coupling between pre-frontal neural networks, consistent with the group’s previous findings that faster responses in the CPT-AX were associated with larger pre-frontal SSVEP latency reductions (Silberstein et al. 1996). A possible relationship between SSVEP latency reductions in the A-X interval and dopaminergic processes was suggested on account of the correspondence between the frontal location of SSVEP latency reduction and the dopaminergic distribution in the primate neocortex (Silberstein et al. 1996). The possibility of such a relationship is further strengthened by findings of: reduced or non-existent frontal SSVEP latency reduction in subjects with ADHD (Silberstein et al. 1996; Silberstein et al. 1998a); long-standing evidence pointing to dopaminergic deficits underlying the symptoms of ADHD (Levy & Swanson 2001); and the positive response of children with ADHD to Methylphenidate a dopamine-reuptake-inhibitor (Levy 1991; Levy & Swanson 2001; Rohde et al. 2003; Viggiano, Vallone & Sadile 2004). These findings were consistent with PET neuroimaging studies which found reductions in glucose metabolism in the premotor cortex and the superior pre-frontal cortex in ADHD (Zametkin & Cohen 1991) and findings of pre-frontal dopaminergic dysfunction in ADHD (Ernst et al. 1998). Event-related fMRI confirmed that children with ADHD did not activate frontostriatal regions in the same manner as normally developing children, but rather relied on a more diffuse network of regions (Durston et al. 2003).
In this study, following Neurotherapy, subjects responded with significantly faster reaction-times; they responded 229 ms faster in the CPT-AX and 274 ms faster in the baseline task, than before Neurotherapy. They also normalised their initially slow reaction times in the TOVA, with reference to the TOVA database of ADHD and of normal subjects. This improvement in reaction-time is consistent with prior findings of improved reaction-time in ADHD children following Neurotherapy (Alhambra, Fowler & Alhambra 1995; Arns et al. 2009; Boyd & Campbell 1998; Fernandez et al. 2003; Fuchs 1998; Fuchs et al. 2003; Gevensleben et al. 2009; Lubar et al. 1995b; Rossiter 2004b; Rossiter 1998; Rossiter & La Vaque 1995; Thompson & Thompson 1998a).

Klorman and colleagues (1991) used the latency of the P300 component as a measure of the contribution of stimulus evaluation (prior to motor processes) to reaction time by measuring responses to targets and non-targets. Their findings suggest that children with ADHD had difficulties allocating attentional capacity to stimuli in order to speed up stimulus evaluation processes (Klorman 1991b). In this study, post-Neurotherapy, at 500 ms prior to the presentation of the X, there was a strong latency reduction compared to baseline in right pre-frontal areas (figures 6.9 and 6.10) which was associated with significant reductions in reaction time. Hence, this could be interpreted as evidence that following Neurotherapy, latency reductions at right frontal sites are associated with increased excitation, and following Klorman’s (1991), and Silberstein’s (1996,1998) argument, a speeding up of stimulus evaluation processes leading to faster response times seen in the CPT-AX and TOVA tasks.
7.3.2 Variability in the Reaction-Time (VRT)

A major component of the ADHD score in the TOVA is the variability in the reaction-time (VRT) (Greenberg & Waldman 1993). This measure arose from the studies used to establish the normative database for the TOVA which found that children with ADHD had consistently higher VRT than normal controls (Greenberg & Waldman 1993). The empirical data linking ADHD to increased VRT is consistent with findings from a study which used event-related fMRI to examine cognitive and neural processes in two independent samples of children and adolescents with ADHD and matched controls (Durston et al. 2007). Children and adolescents with ADHD had increased VRTs compared to non-ADHD controls. Functional imaging results from both samples showed that individuals with ADHD had diminished cerebellar activity to violations of stimulus timing, and diminished ventral pre-frontal and anterior cingulate activity under task. Findings were deemed consistent with the view that ADHD may be related to impaired fronto-cerebellar, as well as fronto-striatal circuitry (Durston et al. 2007).

Further support for the involvement of frontal circuits in VRT were provided by a study using fMRI to examine the neural correlates of VRT during tasks requiring response inhibition (Simmonds et al. 2007). Intra-individual VRT (described as a measure of motor response preparation) was found to correlate with errors of commission, such that individuals with higher VRT also had increased commission errors. Simmonds (2007) found that children with less VRT and fewer commission errors were able to rely on premotor circuits involving the pre-supplementary motor
area important for response selection, while those with less consistent performance recruited pre-frontal circuits that are usually involved in more complex aspects of behavioural control (Simmonds et al. 2007).

It has been suggested that children with ADHD may have difficulties allocating attentional resources (Holcomb, Ackerman & Dykman 1985), and may inefficiently tie up pre-frontal circuitry, needed for behaviour control, instead of using pre-supplementary motor areas (Simmonds et al. 2007). This suggestion is supported by findings from a study of suppression of BOLD response in fMRI while performing a reaction-time task, which found that increased VRT in Children with ADHD was associated with an inability to deactivate ventromedial pre-frontal cortex under increased reaction time task demands (Fassbender et al. 2009). Increased VRT in ADHD has also been interpreted as suggestive of reduced perceptual sensitivity and response consistency and was related to most ADHD symptoms (Epstein et al. 2003).

The suggestions of inefficient allocation of attentional resources in ADHD, tying up pre-frontal circuits instead of using pre-supplementary motor areas, leading to reduced perceptual sensitivity and response consistency, are consistent with Silberstein’s (2006) claims that cognitive proficiency is associated with functional connectivity which is reflected in SSVEP event-related partial coherence. Silberstein (2006) suggested that cognitive aptitude, as demonstrated in the Mental Rotation Task, is related to the brain’s capacity to enhance relevant functional connectivity between cortical regions associated with cognitive demands, while simultaneously attenuating irrelevant connections or shutting down unnecessary communications.
Thus, cognitive aptitude is dependent on functional connectivity sculpting, an important component of the neural substrate of learning and aptitude (Silberstein 2006).

Several studies have reported improvements or normalisation in VRT following Neurotherapy (Alhambra, Fowler & Alhambra 1995; Arns et al. 2009; Boyd & Campbell 1998; Fernandez et al. 2003; Lubar et al. 1995b; Rossiter 2004b; Rossiter 1998; Rossiter & La Vaque 1995; Thompson & Thompson 1998a). The normalisation of the VRT following Neurotherapy in this study suggests that Neurotherapy may be effective in improving, if not normalising, attentional resource allocation, perceptual sensitivity, and response consistency in boys with ADHD, as well as improving cognitive proficiency associated with functional connectivity sculpting.

7.3.3 **Omission Errors**

Several studies have reported that children with ADHD make significantly more omission errors on CPT tasks than normal controls (Aylward, Gordon & Verhulst 1997; Banaschewski et al. 2004; Barkley et al. 2006; Berwid et al. 2005; Cho et al. 2002; Corkum, Schachar & Siegel 1996; Corkum & Siegel 1993; DuPaul et al. 1992; Epstein et al. 1998; Hall et al. 1997; Halperin et al. 1990; Levy & Hobbes 1997; Losier, McGrath & Klein 1996b; Lubar et al. 1995b; Matier Sharma et al. 1995; Nigg, Hinshaw & Halperin 1996; Oades 2000; Oyler, Rosenhagen & Michal 1998; Riccio & Reynolds 2001; Rossiter 2004a, b; Rossiter 1998; Rossiter & La Vaque 1995; Strandburg et al. 1996c; Teicher et al. 2004; Thompson & Thompson 1998a; Van den Bergh et al. 2006; Van Leeuwen et al.
Consistent with these findings, Table 6-2 illustrates that following Neurotherapy, ADHD subjects in this study made significantly fewer errors of omission in the SSVEP baseline task, the CPT-AX task and in the TOVA. Losier and colleagues (1996) reviewed the CPT patterns of errors of omission exhibited by children with ADHD under unmedicated, placebo, Methylphenidate, and normal control conditions. Their meta-analysis found that children with ADHD made significantly more errors of omission than non-ADHD children, and that Methylphenidate resulted in statistically significant reductions in omission errors. Signal Detection Theory parameters revealed that children with ADHD were less sensitive to the difference between targets and non-targets and that Methylphenidate improved this sensitivity, while not affecting response bias, in both normal children and those with ADHD (Losier, McGrath & Klein 1996a).

The time-series illustrations in section 6.4.5 revealed that following Neurotherapy, there was a large transient reduction in SSVEP latency, compared to baseline, on the appearance of the X, suggesting increased excitatory processes and a speeding up of stimulus processing (Silberstein et al. 1996). In addition, as discussed in section 7.4.3, increased parietal activation and excitation just prior to presentation of the target X can be interpreted as increased signal-to-noise ratio, enabling improved sensitivity to the difference between targets and non-targets, and consequently reduced omission and commission errors.
Reviewers have interpreted findings of more omission errors by children with ADHD than controls, as evidence of inattention and deficits in arousal in ADHD (Corkum & Siegel 1993; Losier, McGrath & Klein 1996a). In this study, following Neurotherapy, the consistent decreases in SSVEP amplitude in the A-X interval relative to the mean of the baseline task (section 6.4.4) are consistent with the notion of increased activation or arousal (Silberstein et al. 1996). Hence, the reduction in SSVEP amplitude and significant reduction in omission errors following Neurotherapy can also be interpreted as being associated with increases in arousal.

Findings of more commission errors by children with ADHD, than controls, suggest poor behavioural inhibition and poor impulse control (Barkley 1997b; Halperin 1991; Halperin et al. 1992; Thompson & Thompson 1998a). Similarly van der Meere and Sergeant (1988) suggested that increased omission errors in ADHD may be due to deficits in arousal, effort or motivation, rather than inattention (Van der Meere & Sergeant 1988). Consequently, the improvements in omission and commission scores in the present study during the baseline task, the CPT-AX tasks, and during the TOVA can be interpreted as improvements in arousal, effort, motivation, behavioural inhibition, and impulse control. Furthermore, since the TOVA is a normative database of thousands of normal controls (Greenberg & Waldman 1993), normalisation of TOVA scores following Neurotherapy suggests the normalisation of the dopamine-mediated frontal-lobe tonic activation system and of the noradrenalin-mediated parietal phasic arousal system described by Tucker and Williamson (1984); and thought to be dysfunctional in ADHD by Sergeant (Sergeant 2000). In this study, following
Neurotherapy, there was evidence of SSVEP latency reductions during crucial periods of the CPT-AX task. This suggests improvements in excitatory processes associated with a speeding up of stimulus identification and processing, while widespread SSVEP amplitude reductions during the A-X interval suggested an increase in cortical arousal or dopamine mediated tonic activation.

Halperin and colleagues (1990) found a relationship between inattention scores and slower reaction-times, as well as a greater number of omission and commission errors to Xs not preceded by an A in the CPT-AX task (Halperin et al. 1990). This combination of parameters was subsequently used together with the reduction in amplitude of the parietal P300 to the target X, as an inattention index in an ERP study of the CPT-AX to assess inattention in ADHD (Overtoom et al. 1998b). However, since the impulsivity score and frontal N2 to letters other than X preceded by an A did not differ from those of controls, Overtoom and colleagues (1998b) concluded that in the CPT-AX task, ADHD children exhibited attentional rather than inhibitory deficits (Overtoom et al. 1998b). Prior to Neurotherapy, children with ADHD in the present study, had deviant TOVA scores for response time, omission, commission and variability in response times, compared to the TOVA database of normal controls. Omission errors have been interpreted as evidence of attentional difficulties (Overtoom et al. 1998b) and commission errors as inhibitory control difficulties (Barkley 1997b; Halperin 1991; Halperin et al. 1992; Thompson & Thompson 1998a). Consequently, following Neurotherapy, significantly fewer omission errors suggest improvements in attention, while the normalisation of response times suggests
normalisation of attentional and inhibitory deficits.

7.3.4 Commission Errors

Greater numbers of commission errors by children with ADHD than by controls, have been interpreted as suggestive of evidence of poor inhibition and poor impulse control (Barkley 1997b; Halperin 1991; Halperin et al. 1992; Thompson & Thompson 1998a). Errors of commission in ADHD have been used as a measure of impulsivity (Riccio et al. 2002). In this study, following Neurotherapy, subjects made significantly fewer errors of commission in the baseline task, the CPT-AX and in the TOVA. When compared to other neuropsychological tasks, CPT commission errors have been found to distinguish ADHD subjects from normal controls better than any other measure (Levy & Hobbs 1997). Levy and Hobbs (1997) also found that CPTs that used normalised commission errors and age-normalised mean reaction-time (such as the TOVA) can discriminate between ADHD and non-ADHD subjects better than non-normalised CPTs (Levy & Hobbes 1997)

Van der Meere (1996) argued that fast-inaccurate performance as a measure of impulsivity in ADHD, does not explain other aspects of deficient task performance. Instead he suggested that poor task performance in ADHD might be on account of a combination of hasty scanning, overly-rapid decision making, poor planning and response inhibition problems; related to low tonic activation (Van der Meere 1996). Sergeant (2000) also suggested that tonic activation is necessary for response
inhibition, and that inhibition deficits in ADHD may result from an inability to dynamically modulate activation in response to task demands (Sergeant 2000). In this study, following Neurotherapy, children with ADHD made significantly fewer errors of commission in the baseline task, the CPT-AX task and in the TOVA. This significant decrease in commission errors indicates that the children responded significantly less impulsively following Neurotherapy. This finding is also reflected in the participants’ behavioural scores on the ATBRS (Levy & Hay 1991). Furthermore, following Neurotherapy, there were consistent decreases in SSVEP amplitude responses at most sites, suggestive of increases in tonic activation throughout the task, and in particular, during the A-X interval. Consistent with Van der Meere and Sergeant’s (2000) arguments, these findings may have resulted from any combination of: improved inhibition, increased tonic activation, faster motor processing, or other information processing improvements (Sergeant 2000; Van der Meere 1996).

Using event-related fMRI, Suskauer and colleagues (2008b) examined differences in activation between children with ADHD and normal controls. Their findings suggested that abnormalities in medial frontal regions important for the control of voluntary actions and motor response selection, contribute to deficits in response inhibition in children with ADHD (Suskauer et al. 2008b). The TOVA was designed to test response inhibition (Greenberg & Waldman 1993); and is divided into four quarters each of about six minutes duration. In the first two quarters, the target is presented once in every five presentations, while in the third and fourth quarters the target is presented four times out of five presentations. Children with ADHD have been
shown to make far more errors of omission in the second half of the test, which is a measure of response inhibition or impulse control, while the first half is a measure of vigilance and sustained attention (Forbes 1998; Greenberg & Waldman 1993; Wada et al. 2000). Consequently, since total commission errors in CPT-AX key-presses and on the TOVA reduced significantly following Neurotherapy, these improvements can be interpreted as consistent with improvements in response inhibition.

7.3.5 Conclusions on Improvements in TOVA and CPT-AX

After Neurotherapy, ADHD children has significantly shorter reaction-times, significantly less variability in their reaction-times, made significantly fewer errors of omission and commission in the baseline task, the CPT-AX task, and in the TOVA. Overall, there were more errors made during the CPT-AX task than the baseline task, pre- and post-treatment, consistent with the greater task demands and memory load of the CPT-AX task. Several studies have reported that children with ADHD consistently make significantly more omission and commission errors on CPT tasks than normal controls (Aylward, Gordon & Verhulst 1997; Banaschewski et al. 2004; Barkley et al. 2006; Berwid et al. 2005; Cho et al. 2002; Corkum, Schachar & Siegel 1996; Corkum & Siegel 1993; DuPaul et al. 1992; Epstein et al. 1998; Hall et al. 1997; Halperin et al. 1990; Levy & Hobbies 1997; Losier, McGrath & Klein 1996b; Lubar et al. 1995b; Matier Sharma et al. 1995; Nigg, Hinshaw & Halperin 1996; Oades 2000; Oyler, Rosenhagen & Michal 1998; Riccio & Reynolds 2001; Rossiter 2004a, b; Rossiter 1998; Rossiter & La Vaque 1995; Strandburg et al. 1996c; Teicher et al. 2004; Thompson & Thompson
1998a; Van den Bergh et al. 2006; Van Leeuwen et al. 1998; Wood et al. 1999; Zalsman et al. 2003). Losier and colleagues (1996a) reviewed the CPT patterns of errors of omission and commission exhibited by children with ADHD under: unmedicated, placebo, and methylphenidate drug condition as well as normal controls. They found that children with ADHD were less sensitive to the difference between targets and non-targets than their normal counterparts, while showing a comparable response bias. The effects of Methylphenidate were restricted to improving the sensitivity, while not affecting response bias, in both normal children and those with ADHD (Losier, McGrath & Klein 1996a). In contrast, the TOVA results in this study indicated that Neurotherapy improved both response bias and sensitivity to the difference between targets and non-targets.

Swanson (1998) related Posner and Raichle’s (1997) model to performance in CPTs. They associated symptoms of deficits in sustained attention to the alerting network; deficits in symptoms of selective attention to the orienting network; and symptoms of impulsivity to the executive network (Swanson et al. 1998). The improvements in TOVA scores of omission and commission errors following Neurotherapy are consistent with improvements in the functioning of both the anterior executive network and the posterior orienting network. More evidence in support of this is provided in the following section, which examines SSVEP findings in the current study.
7.4 **SSVEP Electrophysiological Findings**

In order to evaluate the effectiveness of Neurotherapy as a treatment modality, differences in cortical activity using SSVEP in children with ADHD before and after treatment with Neurotherapy, were examined in this study.

Topographic evidence (figure 6.2) indicates that prior to Neurotherapy, there were large SSVEP amplitude increases, referenced to the mean of the baseline task, throughout the A-X interval of the CTP-AX task. There were also minimal SSVEP latency reductions, referenced to the mean of the baseline condition, throughout the A-X interval of the CTP-AX task. In contrast, following Neurotherapy (figure 6.3), there were diffuse SSVEP amplitude reductions throughout the task and, in particular, on presentation of the target X, suggestive of increased cortical arousal. There were also strong SSVEP latency reductions on presentation of the X in right pre-frontal, frontal and parietal areas. Hotelling’s T iso-T contours (figure 6.3) indicates that changes in parietal areas on the appearance of the A and X and changes in right frontal and pre-frontal areas are significant. In this section, the SSVEP findings of the study and their relevance to other research findings are discussed.

7.4.1 **SSVEP Amplitude Changes in Frontal Regions**

As discussed in section 7.3.2, children with ADHD have difficulties allocating attentional resources (Holcomb, Ackerman & Dykman 1985), and may inefficiently tie up pre-frontal circuitry (needed for behaviour control) instead of using pre-
supplementary motor areas (Simmonds et al. 2007). Furthermore, they may have an inability to deactivate ventromedial pre-frontal cortex under increased reaction-time task demands (Fassbender et al. 2009). Findings, that children with ADHD have difficulties allocating resources efficiently are consistent with Silberstein’s (2006) suggestions, which stated that cognitive aptitude is related to the brain’s capacity to enhance relevant functional connectivity according to task demands. When needed, relevant functional connectivity between regions associated with cognitive demands are increased, while irrelevant connections are simultaneously attenuated or shut down (Silberstein 2006). Tucker and Williamson postulated that dynamic increases in arousal would result in increased redundancy modulation, primarily dopaminergic and frontal, which would restrict the rate of change in information processing by suppressing the processing of unnecessary information (Tucker & Williamson 1984).

Prior to Neurotherapy, low arousal in the frontal lobes of children with ADHD manifested as minimal to no reduction in SSVEP amplitude under task demands. It is argued that this would result in less redundancy in the frontal dopamine-mediated neural control system, causing inefficient allocation of neural resources and poor motor and behaviour control. Behaviourally there would be low vigilance and loose control of motor output. This model therefore explains why children with ADHD have increased RT, VRT, commission and omission errors in TOVA and CPT-AX task as well as an increase in inappropriate behaviours.

Posner and Raichle (1997) proposed that medial frontal activation underpins processes of an executive network, believed to be involved in the detection and
recognition of stimuli; their task relevance; and motor preparation. Evidence post-
Neurotherapy in this study, of frontal SSVEP amplitude reductions, referenced to the
mean of the baseline task, (figures 6.3, 6.5-6.7), is suggestive of increased frontal
activation throughout the task, and in particular in the A-X interval. Furthermore, pre-
frontal amplitude reductions were seen peaking around 700-800 ms prior to any
change on the screen (figures 6.5 and 6.6). This suggests that dynamic increases in pre-
frontal activation occurred in anticipation of changes in visual information and are
related to increased efficiency of cognitive processing. This is consistent with increased
activation in the medial frontal executive network proposed by Posner and Raichle
(1997), facilitating the detection and recognition of stimuli; their task relevance; and
motor preparation.

Suggestions of dynamically increased frontal hemisphere activation following
Neurotherapy is also consistent with Tucker and Williamson’s (1984) model that
proposes dopamine-mediated frontal lobe “tonic activation” necessary for “readiness
for action” in the human attentional system (Sergeant 2000; Tucker & Williamson
1984). The tonic activation system was described as dynamically providing a state of
tonic motor readiness for action, or a state of alertness or vigilance. Tucker and
Williamson (1984) argued that vigilance was mediated by two related dopaminergic
systems, which together provided the readiness for action circuits centering on the
forebrain basal ganglia. These systems support controlled, motivated interactions with
the environment. Tucker and Williamson (1984) argued that this largely dopamine-
mediated neural control system did not “linearly increase activation” but responded
“dynamically to environmental demands”. Under increased activation, this neural control system would manifest increased redundancy, or restriction of unnecessary information processing, to qualitatively facilitate vigilance, tight control of motor output and purposeful behaviours (Tucker & Williamson 1984).

7.4.1.1 Conclusion for SSVEP Amplitude Changes in the Frontal lobe

Tucker and Williamson’s (1984) model predicts that in preparing for action, as in anticipation of a need for action, there would be a dynamic and qualitative changes in tonic activation, that would dynamically modulate frontal lobe dopaminergic activity according to task demand. This dynamic sculpting of frontal lobe activity would result in efficient resource allocation in frontal and prefrontal systems. Such dynamic sculpting was not seen in children with ADHD. However, following Neurotherapy, there was clear evidence of task relevant changes in SSVEP amplitude. This is consistent with dynamic optimisation of the dopaminergic system following Neurotherapy, brought about by self-regulation, and resulting in more efficient resource allocation.

This is the first time that optimisation of frontal lobe function from Neurotherapy has been demonstrated on a millisecond basis, providing in the process, support for Tucker and Williamson’s (1984) model of the attentional system.

7.4.2 SSVEP Amplitude Changes in the Right Parietal Region
Tucker and Williamson (1984) also proposed that while activation and redundancy modulation is primarily dopaminergic, and promotes efficient allocation of frontal lobe resources for sequential information processing and tight control over motor action and behaviour, it is complemented by a parietal arousal network. Arousal was described as a phasic and transient response that enhances the salience of relevant information in sensory channels, by increasing signal-to-noise ratio in the parietal noradrenergic system (Tucker & Williamson 1984). Hence noradrenergic function may be important for short-term fluctuations in arousal, particularly those caused by environmental stimuli (Aston-Jones & Bloom 1981). The noradrenergic system appears responsive only to novel environmental stimuli, and its activity declines with repetitive presentation of the stimulus, a phenomena called habituation (Aston-Jones & Bloom 1981). Reviewing evidence from animal studies and in-vitro experiments, Tucker and Williamson (1984) elaborated that norepinephrine inhibited the spontaneous, background activity of parietal cells, but also augmented the cells' evoked response to sensory stimulation. Hence the model proposed that while noradrenaline augments brain activity at a behavioural level, it paradoxically inhibits neuronal activity (Tucker & Williamson 1984). They argued that since noradrenergic modulation does not increase neural activity directly, but rather enables responsivity to environmental stimulation, the noradrenergic control system is inherently linked to external inputs, which specifically elicit locus coeruleus activity. Pribram & McGuinness (1975) had proposed that in order for the brain to orientate to changes, “neuronal models” from repetitive sensory inputs must exist. Tucker and Williamson (1984) reiterated that an orienting response could only be generated when new stimuli differ
from the neuronal models, and that an essential component of this noradrenergic model is the need for habituation following repetitive inputs, so that novelty could be detected (Tucker & Williamson 1984).

Prior to Neurotherapy in this study, the presentation of the cue letter “A” evoked only a weak “increase” in SSVEP amplitude referenced to the baseline mean (figure 6.8). However, post-Neurotherapy, the letter “A” evoked a large increase in SSVEP amplitude, referenced to the baseline mean. A smaller increase in SSVEP amplitude was also observed post-Neurotherapy on presentation of the “X”. For participants in the CPT-AX task, the objective and therefore the focus of cognitive processes, is the identification of the target, namely, appearance of an “X” preceded by an “A”. The detection of the cue “A” is all-important as it initiates the most cognitively active part of the whole CPT-AX exercise.

Dynamic increases in SSVEP amplitude in the right parietal cortex on presentation of the A and X are consistent with an involvement of the posterior noradrenergic phasic arousal response and “habituation” as suggested by Tucker and Williamson’s (1984) model and discussed in section 3.4.4. The latter indicated that in response to a change in a sensory channel, there would be a phasic reduction in background firing of noradrenergic neurons in the parietal cortex, enhancing signal-to-noise ratio in that sensory channel and thereby enhancing perceptual sensitivity (Tucker & Williamson 1984). This reduction in background firing would be expected to manifest as an increase in SSVEP amplitude. Hence the cue- and target-contingent increases in SSVEP amplitude, referred to baseline mean, in the right parietal cortex,
Following Neurotherapy support an interpretation of an enhanced functioning of the parietal cortex noradrenergic system in the CPT-AX task. The strong reduction in the variability of the reaction times following Neurotherapy suggests increased perceptual sensitivity, supporting the above interpretation.

7.4.2.1 Conclusion for SSVEP Changes in Right Parietal Areas.

Following Neurotherapy, activation increased diffusely throughout cortical areas, reaching significance in central and parietal areas during the A-X interval of the CPT-AX task, and in right pre-frontal and frontal areas on the appearance of the X, as evidenced by the higher Hotelling’s T values in (figure 6.3). The increased SSVEP amplitude on presentation of the cue letter A, and on presentation of the target letter X, provides strong support for Tucker and Williamson’s (1984) model of an asymmetrical neural control network in the attentional system.

ADHD has been associated with increased variability in reaction-times, reduced perceptual sensitivity, and reduced response consistency (Epstein et al. 2003). This study, for the first time, provides evidence that Neurotherapy dynamically increases noradrenaline neuromodulation, and facilitates the reduction in the background firing of noradrenergic neurons, thereby increasing perceptual sensitivity, reducing variability in reaction-times and distractibility.
7.4.3 SSVEP Latency Changes in Right Frontal and Pre-frontal Regions

A recent controlled study using fMRI pre- and post-Neurotherapy (Beauregard & Levesque 2006), revealed significant loci of activation in the right anterior cingulate, the left caudate nucleus, and the left substantia nigra in the Neurotherapy group performing the Counting Stroop Task, compared to ADHD controls. In addition, while performing the Go/No-Go Task, significant loci of activation were noted post-Neurotherapy in the right ventrolateral pre-frontal cortex, right cognitive division of the anterior cingulate cortex (ACCcd), left thalamus, left caudate nucleus, and left substantia nigra. Since no significant activation of these brain regions was found in ADHD control subjects, Beauregard and colleagues (2006) concluded that Neurotherapy has the capacity to functionally normalise the brain systems that mediate selective attention and response inhibition in children with ADHD (Beauregard & Levesque 2006). Although different tasks and measures were used in the current study, results are consistent with changes seen in the study by Beauregard and Levesque (2006). The frontal-lobe SSVEP latency reductions following Neurotherapy are suggestive of improved selective attention and response inhibition, as evidenced by TOVA and CPT-AX reductions in omission and commission errors.

Silberstein and colleagues (1998) found that in the interval between the appearances of the A and the X of the correct trials of the CPT-AX, normal control subjects had transient reductions in SSVEP latency relative to the reference task at right pre-frontal sites, while ADHD subjects displayed no change or an increase in pre-frontal SSVEP latency. They proposed that normal controls exhibited more activation in
pre-frontal areas, and a higher speed of pre-frontal neural processing, than children with ADHD (Farrow 2003; Farrow et al. 1996; Silberstein et al. 1998a). In this study, prior to Neurotherapy, ADHD subjects showed widespread increases or minimal decreases in SSVEP latency, relative to the mean of the baseline task, at most sites throughout the CPT-AX task. However, following Neurotherapy, there were sustained decreases in SSVEP latency differences at right pre-frontal and frontal sites, the largest changes being seen on the appearance of the target X (figures 6.9 and 6.10).

Consequently, findings of frontal SSVEP latency reductions from the current study could be interpreted as being associated with faster processing speed, consistent with findings of shorter reaction-times in other studies (Silberstein et al. 1996; Silberstein et al. 1998a). This interpretation is also consistent with findings that up training beta frequencies improved processing speed Egner and Gruzellier’s (2004).

Tucker and Williamson (1984) suggested that tonic activation was a state of readiness for action which is “dynamically” mediated by dopamine in the frontal lobe in response to task demands (Tucker & Williamson 1984). Following Neurotherapy, there were strong, task-contingent, latency reductions in pre-frontal and frontal regions in response to the target X (figure 6.9 and 6.10). This finding suggests that Neurotherapy Treatment increases task-contingent neuromodulation of dopaminergic activity in the right pre-frontal and frontal cortex in the CPT-AX-task, promoting a speeding up of processing and facilitating efficient and faster task performance. This is consistent with the significant improvements found in reaction time in the CPT-AX task (table 6.2) and in the TOVA (figure 6.1) following Neurotherapy.
Silberstein (2004) found in the progressive Ravens Matrices Task, that synchronization between specific pre-frontal, frontal and central sites was correlated with processing speed, efficiency of working memory processes, and speed of information processing (Silberstein et al. 2004). Furthermore, Silberstein (2006) also suggested that cognitive aptitude is related to the brain's capacity to enhance relevant functional connectivity between cortical regions associated with cognitive demands, while simultaneously attenuating irrelevant connections or shutting down unnecessary communications (Silberstein 2006). In the present study, following Neurotherapy, the dynamic task-related amplitude reductions and the sharp frontal SSVEP latency reductions associated with processing of the target (figures 6.9 and 6.10) suggest that Neurotherapy resulted in increased activation, faster processing speed and enhanced functional connectivity in right pre-frontal and frontal regions.

7.4.3.1 Conclusion for SSVEP latency Changes in the frontal lobe

Although different tasks and measures were used in the current study, results are consistent with changes seen in the study by Beauregard and Levesque (2006). The frontal-lobe latency reductions following Neurotherapy are suggestive of improved selective attention and response inhibition, as evidenced by TOVA and CPT-AX reductions in omission and commission errors respectively. Furthermore, SSVEP latency reductions following Neurotherapy, suggest that these behavioural improvements are the result of increases in activation, and of a speeding up of pre-frontal lobe processes, and improvements in executive functions in ADHD.
This study provides evidence of how Neurotherapy promotes self-regulation of frontal lobe processes, improving functional processes towards normal, if not normalising them. Furthermore, for the first time, support for Tucker and Williamson’s (1984) model of dynamic dopaminergic activation is evidenced by task-contingent neuromodulation of SSVEP latency and amplitude.

7.4.4 SSVEP Latency Changes in the Right Parietal Region

The ability to allocate and direct attention toward a salient stimulus is impaired in children with ADHD, as assessed by target detection or oddball tasks (section 2.13). Adolescents with ADHD made significantly more errors of commission consistent with significant impairments in directing and allocating attentional resources (Tamm, Menon & Reiss 2006). These difficulties are associated with significant aberrations in the parietal attentional system, which is known to play a significant role in attention shifting and detecting specific or salient targets (Tamm, Menon & Reiss 2006).

Van Leeuwen and colleagues (1998) found that impaired orienting to cues, involving a posterior attention system rather than frontal processes, determined the initial processing stages in ADHD. Low resolution electromagnetic tomography (LORETA) indicated that posterior sources may underlie these orienting processes and deficits in ADHD (Van Leeuwen et al. 1998). Findings did not support previous suggestions of frontal lobe involvement in initial processing stages and suggested involvement of a posterior attention system instead (Van Leeuwen et al. 1998).
Parietal involvement in initial stages of target processing was found in children with ADHD performing a Mental Rotation Task under fMRI, revealing significantly less activation in right parieto-occipital areas, the right inferior parietal lobe and the right caudate nucleus. This confirms previous reports of right striatal-parietal dysfunction in adolescents with ADHD (Vance et al. 2007).

As discussed in section 7.4.2 of this study, the strong increase in SSVEP amplitude in the right parietal area on presentation of the A and X (figure 6.8) is suggestive of decreased activation. This is consistent with Tucker and Williamson’s (1984) model, which predicts that noradrenergic neurons from the locus coeruleus in the brainstem, projecting to the cortex, rapidly respond to habituation by suppressing the background firing of neurons in the right parietal cortex, thereby decreasing activation, but increasing perceptual sensitivity. Furthermore, the SSVEP latency reductions provide a more complete picture of the involvement of the parietal area in the CTP-AX task, as discussed next.

In the current study, prior to Neurotherapy, there were minimal SSVEP latency changes in the right parietal region in response to the CPT-AX task (figure 6.11). However, Following Neurotherapy, large SSVEP latency reductions were maintained in the right parietal area until the disappearance of the A, after which further SSVEP latency reduced even further, until just prior to the appearance of the X, suggesting heightened excitation, and a speeding up of parietal processing in anticipation of the appearance of the X. On the appearance of the X, habituation caused the high state of excitation, which had been maintained until then, to be relaxed, and a large latency
increase occurred which lasted until the key-press had been executed.

The right parietal region is thought to be involved in a vigilance network responsible for maintaining alertness (Posner & Raichle 1997). Thus, the high excitatory state throughout the A-X task is consistent with sustained vigilance to allow for fast recognition of the target. The objective of the CPT-AX task is to catch the X preceded by an A, and this requires a heightened state of vigilance. The SSVEP latency changes seen following Neurotherapy can therefore be interpreted as a change towards optimisation of the noradrenergic system, which facilitates vigilance and perceptual sensitivity to stimuli.

7.4.4.1 Conclusion for Latency Changes in the Right Parietal Region

Tucker and Williamson (1984) suggested that the noradrenergic system which responds to novel external stimuli modulates its own activity through habituation which relaxes phasic excitation in the right parietal cortex, once novelty or change in a sensory channel is detected. The behavioural outcomes from the TOVA and CTP-AX key-presses, lend support to the proposal that Neurotherapy modulates the noradrenergic system towards normal functioning.

7.5 Criticism and Limitations of the study

Statistics in this study examined differences between pre- and post-
Neurotherapy, referenced to the pre-Neurotherapy baseline task, and may be
criticised for lacking a direct statistical comparison of pre- to post-Neurotherapy effects. It was decided to use the pre-Neurotherapy baseline as a common reference for both pre- and post-Neurotherapy SSVEP to avoid the possible confounding factor of differences in baseline. The statistical comparison to a common baseline, rather than a direct statistical comparison of pre- to post-Neurotherapy may not be an issue. Farrow (2003) also used a common reference baseline task for SSVEP comparison. However, in a separate analysis of Farrow’s (2003) data SSVEP effects in the CPT-AX were referenced to the mean SSVEP amplitude and latency in the CPT-X rather than the baseline task mean (Silberstein et al., 1998). This analysis demonstrated that the group differences in SSVEP amplitude and latency during the A-X interval were maintained, despite the use of a different reference task.

Farrow (2003) raised the issue of the high degree of co-morbidity associated with children with ADHD as a group. A high incidence of Oppositional Defiant Disorder, Conduct Disorder, and Learning Difficulties are commonplace among clinical samples of children with ADHD. Farrow (2003) also reported a high degree of variability in SSVEP responses between subjects with ADHD, not seen in normal controls. Despite the uncertainties of the effect of co-morbidities on the electrophysiological and behavioural indices of children with ADHD, all subjects in this study responded to Neurotherapy by normalising their SSVEP responses, TOVA scores and ATBRS behavioural measures. This indicates that Neurotherapy may improve common mechanisms that underpin these childhood disorders.

This study did not have a control group. A placebo control group would have
gone a long way towards proving that Neurotherapy is an efficacious and specific treatment for ADHD. However, the subjects in this study were paying clients in a clinic and their parents were not prepared to participate in a placebo group of any form. Although second best, it was decided to investigate changes in SSVEP brain electrical activity following Neurotherapy in a group of medicated children with ADHD. The fact that these children were of a wide age-range, and that treatment took place over a period of 4-6 months, would have reduced any confounding effects of maturation. The MTA study found no net benefits for optimally medicated children over a three year period (Arnold et al. 2004; Pelham et al. 2000; Pelham 1999), indicating that children with ADHD did not improve their core deficits over that period, and needed continuing medication to maintain gains. Hence, it could be argued that is highly unlikely that the beneficial outcomes of this study can be explained by maturational improvements over a six months period. In particular, the fact that all but one child was able to stop medication around halfway through the Neurotherapy Treatment program and were able to normalise their TOVA and ATBRS behavioural measures post-Neurotherapy indicate in all likeliness Neurotherapy is responsible for the improvements.

Since as discussed in section 3.12, double blind controlled studies with sham feedback are considered unethical, then effectiveness studies with stimulant medication group as control, and with random assignment, may be the best option for indicating effectiveness. Since several such studies have already been carried out, and a meta analysis of controlled studies has already found Neurotherapy to be efficacious and specific (Arns et al. 2009), further studies should continue to elucidate the
mechanisms of Neurotherapy and add to the acceptance of Neurotherapy as the mainstream treatment for ADHD.

Chapter 8. Summary.

This research used SSPT to investigate changes in cortical activity following Neurotherapy Treatment of 17 boys diagnosed with ADHD. SSVEP amplitude and latency changes associated with attentional processing, referenced to the mean of a baseline task, were examined at times of heightened attention during the A-X interval of the CPT-AX task. This ADHD group was heterogenous, with co-morbidities usually seen in this population, and participants were nominated by their parents to participate. All were on stimulant medication at the start of the study, and initial testing was carried out off-medication after a medication washout period of 48 hours. All but one boy were able to stop medication well before the end of the study.

The hypothesis that following Neurotherapy, behavioural measures, as assessed by the updated version of the Australian Twin Behaviour Rating Scale (ATBRS), will significantly improve towards normalisation was supported. As presented in table 6.1, there is a significant difference between post- and pre-Neurotherapy scores in the mean number of ADHD symptoms endorsed by parents and teachers of the students.

The hypothesis that there would be significant improvements in attentional measures of reaction-time, omission and commission errors, as assessed by key-presses during the CPT-AX task and by TOVA scores was supported and all changes
were significant. As discussed in sections 3.5 to 3.8, many studies have reported similar results in ADHD e.g. (Fuchs et al. 2003; Gevensleben et al. 2009; Lubar 1985, 1995; Monastra 2005; Monastra, Monastra & George 2002; Rossiter 2004b; Rossiter & La Vaque 1995; Tansey 1991). The results of behavioural improvements following Neurotherapy in the current study are also consistent with those of a recently published meta-analysis of ADHD in which the effect of Neurotherapy on children in controlled studies were investigated (Arns et al. 2009).

The hypothesis that following Neurotherapy, subjects would demonstrate diffuse SSVEP amplitude reductions referenced to the mean of the baseline task throughout the A-X task interval not seen prior to Neurotherapy was supported. Topographic evidence (figure 6.2) indicates that prior to Neurotherapy there were large SSVEP amplitude increases, referenced to the mean of the baseline condition, throughout the A-X interval of the CTP-AX task. Prior to Neurotherapy, lack of arousal in the frontal lobes of children with ADHD, associated with reduced dopamine neuromodulation, manifested as minimal to no reduction in SSVEP amplitude, compared to baseline, under task demands. This in turn would result in less redundancy in the frontal dopamine-mediated neural control system, causing inefficient allocation of neural resources and poor motor and behaviour control, evident in increased reaction time, variability in the reaction time, commission, and omission errors in TOVA and CPT-AX tasks as well as an increase in inappropriate behaviours.

In contrast, following Neurotherapy (figure 6.3), there were diffuse SSVEP
amplitude reductions throughout the task and, in particular, on presentation of the target X, suggestive of increased cortical arousal. Evidence of frontal SSVEP amplitude reductions post-Neurotherapy (figures 6.3, 6.5 and 6.7) suggest increased frontal activation when processing of the cue A and target X. This finding is consistent with increased activation in the medial frontal executive network proposed by Posner and Raichle (1997).

The hypothesis that subjects would demonstrate group SSVEP latency reductions, not seen prior to Neurotherapy, at right pre-frontal sites throughout the A-X interval and on appearance of the X, was supported. In this study, prior to Neurotherapy, ADHD subjects showed widespread increases or minimal decreases in SSVEP latency, referenced to the mean of the baseline task, at most sites (except pre-frontal left) throughout the CPT-AX task. However, following Neurotherapy, there were sustained reductions in SSVEP latency at right pre-frontal and frontal sites, referenced to the mean of the baseline task. The largest changes were seen on the appearance of the target X, as demonstrated in figures 6.9 and 6.10. Consequently, findings of frontal SSVEP latency reductions from the current study suggest faster processing speed, consistent with findings of shorter reaction times in behavioural measures. The proposal that Neurotherapy Training of beta frequencies results in strong frontal SSVEP latency reductions associated with faster processing speed, reduced hyperactivity, better impulse control and increased concentration, is also consistent with Egner and Gruzellier’s (2004) findings.
reductions, not seen prior to Neurotherapy, in the right parietal region during the period between the presentation of the A and of the X, was also supported. In the current study, prior to Neurotherapy, there were minimal SSVEP latency changes in the right parietal region in response to the CPT-AX task (figure 6.11). However, following Neurotherapy, large SSVEP latency reductions were maintained in the right parietal area until the disappearance of the A, after which SSVEP latency reduced even further until just prior to the appearance of the X. At which point the high state of excitation, which had been maintained until then, was relaxed and a large latency increase occurred.

At this point, an explanation of how Neurotherapy may modulate these various aspects of the attentional system is timely. As discussed in section 3.1.1., thalamocortical neurons have two separate modes of action: First as relay cells, they depolarize in response to input volleys and relay ascending sensory input. Second, as oscillatory cells, they fire in a collective rhythm, thereby blocking input to the associated area of the cortex and inducing cortico-cortical oscillations in that area of the cortex (Lopes da Silva 1991). Brainstem neuromodulation provides either depolarizing or hyperpolarizing influences on thalamic neurons, by affecting the resting membrane potentials of reticular thalamic and thalamocortical neurons, and determines which mode of action, relay or oscillatory state, is selected (Lopes da Silva 1991). Sterman (1996) related the generation of SMR, alpha, and theta rhythms to the presence or absence of input into the thalamic oscillatory generators from three specific networks: vigilance, sensorimotor integration’ and cognitive integration.
Sterman (1996) suggested that:

- If input from brainstem neuromodulators associated with vigilance was withdrawn, as in states of inattentive drowsiness, then theta oscillations appeared.
- If sensorimotor input from brainstem neuromodulators was withdrawn, then SMR rhythm appeared.
- If cognitive processing was withdrawn, as in relaxed states without cognitive activity, then alpha rhythm appeared.

Thus, according to Sterman’s scheme, the presence of Theta, alpha or SMR in the EEG indicates the underlying brain states of vigilance, sensorimotor integration and cognitive processing (Sterman 1996a). Sterman and colleagues (1994) investigated behaviours that “suppress” rhythmic EEG patterns when sensory and cognitive inputs are manipulated to enable differentiation of associated EEG responses:

- In simple visual attention, when eyes-open condition was compared with eyes-closed condition, all frequencies between 5 and 15 Hz were significantly suppressed in temporal, parietal, and occipital cortex, with the greatest suppression in the 7-11 Hz range.
- Body movements caused SMR, 11-15 Hz activity to be selectively suppressed in central cortex.
- With eye movements from visual tracking, 11-15 Hz activity was selectively suppressed in the temporal-parietal cortex (Mann, Sterman & Kaiser 1996; Sterman & Mann 1995; Sterman et al. 1994).
As previously reviewed in section 3.2, there is evidence of excess theta and alpha and elevated theta/beta ratio in children with ADHD. Hence, the relevance of Sterman’s (1996) model to Neurotherapy Treatment for ADHD can be drawn: If there is excess theta in the EEG, suppressing theta and promoting beta and/or SMR range may promote the associated states of increased stillness, attentiveness, and decreased drowsiness and any other cognitive disturbances associated with elevated theta activity (Abarbanel 1995).

It follows from Sterman’s (1996) model that if abnormally elevated frequencies in the theta and/or alpha range are suppressed, and SMR and/or beta frequencies are promoted over the central cortex, then thalamocortical circuits that resonate at these frequencies will be modulated towards optimisation, resulting in associated improvements in those aspects of the attentional system subserved by these oscillations. In turn, each thalamo-cortical circuit connects to many adjacent and remote cortical areas through a multitude of cortico-cortical connections. Operant conditioning of a thalamocortical oscillation over the central cortex may therefore generate a multitude of “optimised” cortico-cortical resonances over the whole cortex, reminiscent of the rich resonances generated from acoustic couplings when a single string of a guitar is plucked.

Studies such as the current one, which set out to investigate the brain/behaviour correlates, are needed to elucidate mechanisms of action of Neurotherapy. A suggestion for future studies would involve using the SSVEP event-related partial coherence technique (SSVEP-ERPC) described in (Silberstein et al. 2004)
SSVEP event-related coherence could be calculated for all unique electrode pairs for all time points during the A-X interval. Using correlation coefficient thresholds corresponding to \( p=0.001 \) those electrode pairs where SSVEP-ERPC or neural synchronization are significantly correlated with processing speed or other selected parameters could be identified providing further useful information that may elucidate the processes associated with the attentional models proposed.

For the first time, the use of SSVEP in this study enabled frontal lobe and right parietal lobe processes in the attentional system to be investigated on a millisecond basis. The study demonstrated the dynamic modulation of Dopamine and Norepinephrine in the attentional system and supported Tucker and Williamson’s (1984) model of attentional processes. The SSVEP and behavioural findings reported in this study are in accord with those of previous studies (reviewed in chapter 3); showing that Neurotherapy can significantly improve attention, response inhibition, stimulus selectivity, and behaviours in children with ADHD and provide further support to the view that Neurotherapy can be considered an effective treatment for children with ADHD.
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APPENDIX A

Subject Code

Information on research project

PROJECT TITLE: Investigation of the Effectiveness of Neurotherapy in the treatment of Attention Deficit Hyperactivity Disorder (ADHD), using Steady State Probe Topography (SSPT)

INVESTIGATOR: Jacques Duff, (PhD candidate) Brain Sciences Institute

SUPERVISORS: Prof. Richard B. Silberstein, (Director) Brain Sciences Institute.
Dr Frederick C. Jarman, (Paediatrician) Centre for Community Child Health and Ambulatory Paediatrics, Royal Children’s Hospital, Melbourne.

Background
Using Quantitative electroencephalography (EEG), a technique which statistically analyses the frequency content of the EEG at various sites on the scalp, patterns have been found in the EEG of ADHD children that are consistent with findings revealed by other neuro-imaging studies carried out over the last decade. ADHD children tend to have too many slow (tuned off) brainwaves and not enough fast (thinking) brainwaves.

Neurotherapy has shown promise in the treatment of ADHD. During Neurotherapy, the child’s real-time Quantitative EEG (QEEG) is displayed on a computer in the form of a game, and audio-visual rewards are given when the child produces a specific brainwave pattern. There is significant evidence in the literature that suggest that if a corrective brainwave pattern is specifically rewarded, patients may learn, to generate the more adaptive pattern permanently.

Findings of numerous studies suggest that, as a result of training of subjects to produce the more “normal” brainwave pattern, the behaviours and cognitive deficits associated with ADHD tend to shift towards normalisation-. This change towards normalisation of the EEG is associated with a reduction in hyperactivity and impulsivity, and an increase in attention and cognitive skills. Results of several studies and extensive clinical use indicate that Neurotherapy treatment is effective in about 85% of cases, and is permanent.

A recent book by William Sears, a Paediatrician and former Assistant Professor at the University of Southern California School of Medicine, outlines the clinical use of Neurotherapy, and suggests that the state of the research and clinical practice no longer makes this an unproven treatment. Neurotherapy is currently used in over 800 clinics worldwide, including around 30 in Australia. Some of the practitioners are paediatricians and psychiatrists, but most are psychologists trained in applied psychophysiology.
APPENDIX A

Project outline:
This study breaks new ground in neurotherapy research in that it utilises the high temporal and spatial resolution of Steady State Probe Topography (SSPT) to examine changes in the brain electrical activity of ADHD children, while they perform a continuous performance task (CPT), before and after neurotherapy. The study has the potential to demonstrate whether there have been changes at a synaptic level.

The BSI component of the study will involve filling out a behavioural questionnaire, and three one hour Topographic EEG recording sessions at the BSI EEG Lab, over an eight month period.

A 64-sensor cap will be placed on your child’s head. The sensors contained in the cap are designed to sit gently on the scalp and record the electrical activity naturally emitted by the brain. A small quantity of recording gel, which is water soluble, will be squirted into each electrode helping to make good contact between the electrode and the scalp. In addition, your child will wear a set of half-mirrored glasses. Your child will be able to see through these glasses and at the same time will see a dim flickering red light.

If your child presently suffers or has ever suffered from SEIZURES, we ask that he/she withdraws from the BSI part of the study due to a small risk associated with flashing lights.

There is no risk associated with Neurotherapy, which is highly effective in reducing seizures

Your child will be asked to perform a series of tasks, which he will be able to practice first. He will watch a computer screen and press a response button when particular images are presented on the screen. These simple attention tasks are designed to activate different areas of the brain at different times. In this way we can measure the activity occurring in different regions of the brain at different times throughout the tasks your child performs.

Participation is voluntary and your initial agreement does not stop you or your child from discontinuing the study at any time. This research is independent of your child’s medical treatment under the guidance of your Paediatrician or of Neurotherapy treatment at the Behavioural Neurotherapy Clinic.

Your child’s treatment at the Behavioural Neurotherapy Clinic will not be affected in any way should you or your child choose to withdraw from the study at any stage.

Should you have any further questions regarding this study, please do not hesitate to ask the investigator conducting the recordings. Alternatively, any questions may be directed to:

Jacques Duff (telephone 9842 0370) or to the research supervisor,
Professor Richard Silberstein (telephone 9214 8273).

Should you have a query that neither the investigator conducting the experiment nor the senior investigator were able to satisfy, or any complaint about the way you or your child have been treated during this study, please write to:

The Chair
Human Experimentation Ethics Committee
Swinburne University of Technology
PO Box 218
Hawthorn, Vic., 3122.

Thank you very much for your participation.
AGREEMENT TO PARTICIPATE IN RESEARCH PROJECT

PROJECT TITLE: Effectiveness of Neurotherapy in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) using SSPT.

INVESTIGATOR: Jacques Duff, (Ph.D. candidate) Brain Sciences Institute

SUPERVISORS: Prof. Richard B. Silberstein, (Director) Brain Sciences Institute. Dr Frederick C. Jarman, (Paediatrician) Centre for Community Child Health and Ambulatory Paediatrics, Royal Children’s Hospital, Melbourne.

(The Parent/Guardian of the participant) have read, or have had read to me, the information relating to this research study. I understand the information provided in both the letter inviting our participation and the attached project description. Any questions I have asked have been answered to my satisfaction.

I give permission for my child ____________________________

to participate in the research study entitled: Effectiveness of Neurotherapy in the treatment of Attention-Deficit/Hyperactivity Disorder using SSPT. I realise that I or my child may withdraw from the study at any time without explanation and that this would not in any way affect my child’s treatment and care at the Behavioural Neurotherapy Clinic.

I agree that research data collected for the study may be published or shared with other researchers on the condition that my child’s name is not used and that there is no other way in which my child could be individually identified.

Signature of Parent/Guardian ____________________________
Date ____________________________

Relationship to the Participant ____________________________

Signature of Participant ____________________________
Date ____________________________

Name of Investigator ____________________________

Signature of Investigator ____________________________
Date ____________________________
<table>
<thead>
<tr>
<th>BSI PROTOCOL SHEET</th>
<th>SUBJECT PARTICULARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECT CODE</td>
<td>ADNT</td>
</tr>
</tbody>
</table>

**NOTE:**
1. Your child's personal details will remain confidential.
2. For questions requiring a YES/NO response, please CIRCLE the correct response.

- **Surname**
- **Given Names**
- **Date of birth**
- **Age**
- **Sex**
- **Handedness (right or left)**
- **Today's Date**
- **Current Time**
- **Name of your child’s Paediatrician**
  (who referred you for this testing)
- **Does your child presently suffer or has he ever suffered from epilepsy?** YES/NO
- **If yes, specify**
- **Does your child have a colour deficiency (e.g. colour blindness)?** YES/NO
- **If yes, specify**
- **Does your child have any other visual problems (e.g. short sightedness, lazy eye, etc)?** YES/NO
- **If yes, specify**
- **Has your child ever sustained a serious head injury?** YES/NO
- **If yes, specify**
- **Does your child presently suffer or has he ever suffered from any neurological or psychiatric disorders (other than ADHD)?** YES/NO
- **If yes, specify**
- **Does your child presently suffer or has he ever suffered from any other serious medical conditions or disabilities?** YES/NO
- **If yes, specify**
- **Has your child had any recent illness?** YES/NO
- **If yes, specify**
- **Does your child currently take any prescription drugs?** YES/NO
- **If yes, specify**

This form was completed by

**Relationship to child**
<table>
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<th>Answer</th>
</tr>
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<tbody>
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<td>Child's name</td>
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</tr>
<tr>
<td>Nickname</td>
<td></td>
</tr>
<tr>
<td>Grade/year at school</td>
<td></td>
</tr>
<tr>
<td>Contact address</td>
<td></td>
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<tr>
<td>Telephone number</td>
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<tr>
<td>Mother's name</td>
<td></td>
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<tr>
<td>Father's name</td>
<td></td>
</tr>
<tr>
<td>Name of person completing forms</td>
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<tr>
<td>Relationship to child</td>
<td></td>
</tr>
<tr>
<td>Date forms completed</td>
<td></td>
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</tbody>
</table>
APPENDIX A

BSI PROTOCOL SHEET  HANDEDNESS INVENTORY

Please indicate your child’s preference in the use of hands in the following activities by placing a tick (✓) in the appropriate column.

Where the preference is so strong that your child would never try to use the other hand unless absolutely forced to, put 2 ticks (✓✓).

If your child would equally use either hand, tick (✓) both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which the hand preference is wanted, is indicated in brackets.

Please try to answer all the questions, and only leave blank if your child has no experience at all of the object or task.

<table>
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<th>LEFT</th>
<th>RIGHT</th>
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<td>3</td>
<td>Throwing</td>
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<tr>
<td>4</td>
<td>Scissors</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Toothbrush</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Knife (without fork)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Spoon</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Broom (upper hand)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Striking a match</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Opening box (lid)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Which foot do you prefer to kick with?</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Which eye do you use when using only one?</td>
<td></td>
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LO =  

(Leave these spaces blank)

DECILE =

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APPENDIX A

BSI PROTOCOL SHEET

EXPERIMENT: Effectiveness of Neurotherapy in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) using SSPT.

SUBJECT IS IN: First Treatment Group / Waiting Group Control (delayed treatment)

NAME OF SUBJECT: ___________________________ DATE: ___________________________

EXAMINERS' NAMES: ___________________________ TIME: ___________________________

MEDICATION STATUS

HEAD CIRCUMFERENCE cm: CAP USED: Blue / Red
STIMULUS FREQUENCY 13 Hz: STIMULUS GAIN: 0.16
NOSE-L EAR IMPEDANCE KΩ: NOSE-R EAR IMPEDANCE KΩ
DUDS PRE-RECORDING: GOGGLES ON @ am/pm
RECORDING BITS: 12 GOGGLES OFF @ am/pm

<table>
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<th>DATA FILE NAMES</th>
<th>TASK</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
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<td>ADNT#**1.RWA</td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>A**BSTK1.FIL,ASC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADNT#**2.RWA</td>
<td>AX task 1</td>
<td></td>
</tr>
<tr>
<td>A**AXTK1.FIL,ASC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADNT#**3 RWA</td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>A**BSTK2.FIL,ASC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADNT#**4 RWA</td>
<td>AX task 2</td>
<td></td>
</tr>
<tr>
<td>A**AXTK2.FIL,ASC</td>
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<td></td>
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</table>

ADNT: Study code (Effectiveness of Neurotherapy for ADHD);
**: Subject code: 01-50 First Treatment Group; 51-99 Waiting Group Control
#: Recordings: A- 1st recording no-med @ T = 0 (Treatment group)
B- 2nd recording no med @ T = 4 months
P- Practice recording

COMMENTS:

__________________________________________________________________________

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**CHILD BEHAVIOUR QUESTIONNAIRE**

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

**Compared to other children of the same age, how applicable are the following items (1 to 18) for this child now or within the past 6 months?**

0 = not at all; 1 = just a little / sometimes; 2 = pretty much / often; 3 = very much / very often

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Is easily distracted by external stimuli (e.g. noise or conversation)</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>Has trouble following through on instructions and fails to finish school work, chores or duties</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>Has difficulty keeping attention on work or games</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>Does not seem to listen when spoken to directly</td>
<td>0</td>
</tr>
<tr>
<td>5.</td>
<td>Loses things necessary for tasks or activities at home or school (e.g. books, pencils, toys, tools)</td>
<td>0</td>
</tr>
<tr>
<td>6.</td>
<td>Has difficulty organising tasks and activities</td>
<td>0</td>
</tr>
<tr>
<td>7.</td>
<td>Fails to give close attention to details or makes careless mistakes in school work or other activities</td>
<td>0</td>
</tr>
<tr>
<td>8.</td>
<td>Is forgetful in daily activities</td>
<td>0</td>
</tr>
<tr>
<td>9.</td>
<td>Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (e.g. school work or homework)</td>
<td>0</td>
</tr>
<tr>
<td>10.</td>
<td>Is “on the go” or acts as if “driven by a motor”</td>
<td>0</td>
</tr>
<tr>
<td>11.</td>
<td>Leaves seat in classroom or other situations in which remaining seated is expected</td>
<td>0</td>
</tr>
<tr>
<td>12.</td>
<td>Has difficulty playing or engaging in leisure activities quietly</td>
<td>0</td>
</tr>
<tr>
<td>13.</td>
<td>Runs about or climbs excessively in situations where it is inappropriate</td>
<td>0</td>
</tr>
<tr>
<td>14.</td>
<td>Fidgets with hands or feet or squirms in seat</td>
<td>0</td>
</tr>
<tr>
<td>15.</td>
<td>Talks excessively</td>
<td>0</td>
</tr>
<tr>
<td>16.</td>
<td>Has difficulty awaiting his/her turn</td>
<td>0</td>
</tr>
<tr>
<td>17.</td>
<td>Blurs out answers to questions before they have been completed</td>
<td>0</td>
</tr>
<tr>
<td>18.</td>
<td>Interrupts or intrudes on others (e.g. butts into conversations or games)</td>
<td>0</td>
</tr>
<tr>
<td>19.</td>
<td>For the above questions (1 - 18) circled “2” or “3”, how old was the child when you first noticed any of these behaviours?</td>
<td>[ ] years</td>
</tr>
<tr>
<td>20.</td>
<td>To what extent is this child’s behaviour, as described by items 1 - 18, distressing or disruptive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) at home</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>b) at school</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>c) elsewhere</td>
<td>0</td>
</tr>
</tbody>
</table>
APPENDIX B

Compared to other children of the same age, how applicable are the following items (21 to 28) for this child now or within the past 6 months?

0 = not at all; 1 = just a little / sometimes; 2 = pretty much / often; 3 = very much / very often

21. Argues with you, his/her teacher or other adults 0
22. Loses his/her temper or throws tantrums 0
23. Actively defies or refuses to comply with adults’ requests or rules 0
24. Deliberately annoys people 0
25. Blames others for his/her own mistakes or misbehaviour 0
26. Is touchy or easily annoyed by others 0
27. Is angry and resentful 0
28. Is spiteful or vindictive 0
29. To what extent is this child’s behaviour, as described by items 21 - 28, distressing or disruptive?
   a) at home 0
   b) at school 0
   c) elsewhere 0

Compared to other children of the same age, how applicable are the following items (30 to 44) for this child now or within the past 12 months?

0 = not at all; 1 = just a little / sometimes; 2 = pretty much / often; 3 = very much / very often

30. Lies or breaks promises to obtain goods or favours, or to avoid obligations (i.e. ‘cons’ others) 0
31. Has stolen items of nontrivial value without confronting a victim (e.g. shoplifting) 0
32. Has stolen with confrontation of a victim (e.g. mugging, purse-snatching, extortion) 0
33. Has been physically cruel to animals 0
34. Has deliberately lit fires with the intention of causing serious damage 0
35. Has been absent from school without permission, beginning before 13 years of age 0
36. Initiates physical fights 0
37. Has run away from the parental home overnight at least twice (or once without returning for a lengthy period) 0
38. Has broken into someone else’s house, building or car 0
39. Has deliberately destroyed other people’s property (other than by lighting fires) 0
40. Has forced someone into sexual activity 0
41. Has used a weapon that can cause serious physical harm to others (e.g. bat, brick, broken bottle, knife or gun) 0
42. Has been physically cruel to people 0
43. Stays out at night against parental instruction, beginning before 13 years of age 0
44. Bullies, threatens or intimidates others 0
45. For the above questions (30 - 44) circled “1”, how old was the child when you first noticed any of these behaviours? [ ] years
46. For the above questions (30 - 44) circled “2” or “3”, how old was the child when you first noticed any of these behaviours? [ ] years
47. To what extent is this child’s behaviour, as described by items 30 - 44, distressing or disruptive...
### APPENDIX B

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>a)</td>
<td>at home</td>
<td>0</td>
</tr>
<tr>
<td>b)</td>
<td>at school</td>
<td>0</td>
</tr>
<tr>
<td>c)</td>
<td>elsewhere</td>
<td>0</td>
</tr>
</tbody>
</table>

**Compared to other children of the same age, how applicable are the following items (48 to 55) for this child now or within the past 4 weeks?**

0 = not at all; 1 = just a little / sometimes; 2 = pretty much / often; 3 = very much / very often

- **48.** Shows excessive distress when away from or anticipating being away from home or family members
  - 0

- **49.** Refuses or is reluctant to go to school or elsewhere because of fear of separation
  - 0

- **50.** Refuses or is reluctant to fall asleep without a parent or other close person nearby
  - 0

- **51.** Shows excessive worry about something bad happening to his/her parents or other family members
  - 0

- **52.** Shows excessive worry that something bad will separate him/her from his/her parents (e.g. getting lost or being kidnapped)
  - 0

- **53.** Is excessively scared or reluctant to be alone at home or elsewhere without significant adults
  - 0

- **54.** Complains of headaches, stomach aches, nausea or vomiting when separated or anticipating separation from parents or family members
  - 0

- **55.** Has recurrent bad dreams or nightmares about separation from the family
  - 0

- **56.** For the above questions (48 - 55) circled “2” or “3”, how old was the child when you first noticed any of these behaviours?
  - [0] years

- **57.** To what extent is this child’s behaviour, as described by items 48 - 55, distressing or disruptive
  - a) at home
    - 0
  - b) at school
    - 0
  - c) elsewhere
    - 0

- **58.** Has anything happened recently to this child which may account for the behaviours described by items 48 - 55? (please describe)

- **59.** Is there anything you would like to add about this child’s behaviour or about events in his/her life that may have affected him/her?

- **60.** Have you previously sought professional help for this child for any behaviour problems? YES / NO
  - If yes, please state the person's profession (e.g. school counselor, psychologist), what they said about your child’s problems, and how old the child was at the time.
    - a) Profession:
    - b) What they said:
    - c) Child’s age:

- **61.** Have you previously sought help for this child for any learning problems? (Yes/No)
  - If yes, please state the person’s profession, what help was given (e.g. remedial reading, tutoring), and how old the child was at the time.
    - a) Profession:
    - b) What help was given:
    - c) Child’s age: