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An investigation of attentional deficits and their treatment in adult ADHD: evidence from behavioural and neurophysiological findings

by

Simona Salomone

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

2013

To the men of my life:

to my dad because he worked very hard all his life for my well-being and education;

to my husband for his love and support;

to my son to teach him that is life you must love everything you do.

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Summary

Attention-Deficits/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that affects both children and adults and is associated with a range of cognitive and behavioural difficulties. Particularly, a sustained attention deficit seems to be one of the hallmark symptoms of ADHD. The aim of this thesis is to advance our understanding of the sustained attention deficits in adult ADHD. In the first chapters of this thesis the neural underpinnings underlying sustained attention deficits in adults with ADHD are explored by combining neurophysiological measures with cognitive and neuropsychological testing. The second part of this thesis focuses on the treatment of sustained attention deficits in adult ADHD by exploring the effects of an attention program which focuses on addressing the real life problems associated with ADHD. Chapter 1 begins by providing a broad overview of ADHD across the lifespan and outlines the theoretical basis for the experiments conducted in this thesis. Chapter 2 describes electroencephalography (EEG) and it discusses the contribution of the EEG literature to our knowledge of the neuophysiological biomarkers of ADHD in children and adults.

Chapter 3 begins with a review of studies that have documented prominent sustained attention deficits in children and adults with ADHD. It is explained that the aim of the experiment described in chapter 3 is to investigate the neurophysiological underpinnings of sustained attention deficits in adults with ADHD using classic EEG measures and pupillometry. Additionally, this study explores the hypothesis that an impairment in noradrenergic function may underlie this deficit. Importantly, it is argued that no studies have previously investigated pupil measures and their link with sustained attention deficits in ADHD. A review of pupillometry studies is then provided and the relationship between pupil measures and noradrenergic function found in animal and human studies is also described. The behavioural results of the study indeed show a pattern of sustained attention deficits in adults with ADHD compared to adult

controls in an auditory oddball task. Furthermore, some differences emerge in event-related potentials (ERPs) and pupil measures underlying behavioural deficits. These results provide evidence of sustained attention deficits in adults with ADHD. Furthermore, the finding that adults with ADHD have decreased pupil diameter might suggest that a potential noradrenergic dysfunction might be involved in the pathophysiology of sustained attention deficits in adult ADHD.

Chapter 4 focuses on exploring the electrophysiological correlates that precede sustained attention failures in adult ADHD. Adults with ADHD and adult controls undergo an EEG assessment while performing the Continuous Temporal Expectancy Task (CTET). Behavioural, EEG and ERP measures are compared between the two groups. The results indicate that there are two main neurophysiological correlates of attentional failures that can distinguish adults with ADHD from controls, suggesting the lack of a necessary mechanism to facilitate processing of task-relevant information and impaired task engagement in adult ADHD.

Chapter 5 describes the main study of this thesis that is a single-blind randomized controlled trail (RCT) aimed to test the efficacy of Self-Alert Training (SAT) on several primary outcome measures, such as ADHD symptoms and cognitive, social and psychiatric measures in adult ADHD. It is stressed that the final aim of the training is to teach participants to self-alert in key real life settings to improve everyday life function. Detailed descriptions of the study methodology, participants' training schedule and training programmes are provided. The results of the study show interesting long-term improvements in ADHD symptoms and in social and psychiatric function in adults with ADHD. Additionally, improved everyday-life function also emerge from qualitative outcomes of the study, suggesting that SAT was successful in ameliorating everyday-life function in adult ADHD.

Finally, chapter 6 consists of a discussion of the issue raised in this thesis and offers suggestions for future research.

List of Publications

Published articles

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

- **Salomone, S.**, Shanahan, J.M., O'Connell, R.G., Bramham, J., Robertson, I.H. A biofeedback-based programme to improve attention and impulsivity in adults with ADHD. (2012). *The Irish Journal of Psychology*, vol 33, issue 2-3

- **Salomone, S.**, Kelly S.M., Robertson, I.H., O'Connell. RG. An investigation of the electrophysiological underpinnings of attentional failures in adult ADHD using the Contingent Temporal Expectancy Task (CTET). Paper in preparation

- **Salomone, S.**, Shanahan, J.M., Fleming, G.R., O'Connell, R.G., Bramham, J., Robertson, I.H. Self-Alert Training (SAT) to improve attention and impulsivity in adult ADHD. Paper in preparation

The following is a list of published peer-reviewed journal articles that have not been included in this thesis but that resulted from work that has been conducted during my PhD:

- **Salomone, S.**, Robertson, I.H., Lynch, T., Pender, N., Fearon, C., Marnane, M., Balsters, J.H., Dockree, P.M. Autoimmune Brainstem Encephalopathy causing a partially reversible Minimally Conscious State and Selective Cognitive Impairments: a unique case report (2013). *Neurocase.* In print

- McAvinue, L.P., Golemme, M., Castorina, M., Pigni, F., Tatti, E., **Salomone, S.**, Brennan, S., Robertson, I.H. An evaluation of a working memory training scheme in older adults. (2013). *Frontiers in Aging Neuroscience*. In print

Published Abstracts

- **Salomone, S.**, Shanahan, J.M., O'Connell, R.G., Bramham, J., Robertson, I.H. A biofeedback-based programme to improve attention and impulsivity in adults with ADHD. Eunethydis - Second International ADHD Conference, Barcelona, May 2012.

- **Salomone, S.**, Kelly, S.M., Robertson, I.H., O'Connell. R.G. Using the Continuous Temporal Expectancy Task (CTET) to investigate neurophysiological underpinnings of lapses in attention in adult ADHD. Eunethydis - Second International ADHD Conference, Barcelona, May 2012.

- **Salomone, S.**, Robertson, I.H., Lynch, T., Pender, Dockree, P.M. ERP and cognitive abnormalities in a rare neurological autoimmune syndrome: a case study. International Conference on Cognitive Neuroscience (ICON), Mallorca, September 2011

- **Salomone, S.**, Robertson, I.H., Lynch, T., Pender, N., Dockree, P.M. A unique case of autoimmune coma: neuropyschological evidence. 8th Annual Psychology, Health and Medicine Conference, Galway, April 2011.

List of abbreviations

ACC	Anterior Cingulate Cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-C	ADHD Combine subtype
ADHD-H	ADHD Predominantly Hyperactive Subtype
ADHD-I	ADHD Predominantly Inattentive Subtype
ARCEQ	Attention-Related Cognitive Errors Questionnaire
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AT	Attention Training
BESA	Brain Electric Source Analysis
BDI	Beck Depression Inventory
BAI	Beck Anxiety Inventory
CAARS -S: L	Conners' Adult ADHD Rating Scale – Self Report
CAARS-O: L	Conners' Adult ADHD Rating Scale – Observer Form
CNV	Contingent Negative Variation
CTET	Continuous Temporal Expectancy Task
CV	Coefficient of Variation
DA	Dopamine
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual for Mental Disorders
EDA	Electrodermal Activity
EEG	Electroencephalography
EMFQ	Everyday life Memory Failures Questionnaire
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
GHQ	General Health Questionnaire
IQ	Intelligence Quotient
LC	Locus Coeruleus
MPH	Methylphenidate
MTA	Multimodal Treatment Study of ADHD

NA	Noradrenaline
PFC	Prefrontal Cortex
RT	Reaction Time
SAT	Self-Alert Training
SART	Sustained Attention to Response Task
SCR	Skin Conductance Response
SD	Standard Deviation
SES	Self Efficacy Scale
SSVEP	Steady-State Visual-Evoked Potential
TEA	Test of Everyday Attention
VLPFC	Ventrolateral Prefrontal Cortex
WURS	Wender Utah Rating Scale

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Chapter 1 ADHD: An overview

Attention Deficit/Hyperactivity Disorder (ADHD) is a neuropsychiatric developmental disorder characterized by distractibility, hyperactivity and impulsive behaviours and the inability to remain focused on tasks or activities (A.P.A. 2000). ADHD is one of the most common psychiatric disorders that presents in childhood, affecting an estimated 3% to 7% of school-aged children (The American Psychological Association – A.P.A., 2000). The prevalence of ADHD in adults is estimated from epidemiological studies in the range of 2-5% (Kessler et al., 2005, Murphy and Barkley, 1996). Until recently, the disorder was considered by many to resolve during adolescence and young adulthood with little or no continued impact in adult life (Hill and Schoener, 1996), although descriptions of the adult condition appeared in the psychiatric literature from 1976 (Wood et al., 1976).

1.1 Diagnosis in childhood

The diagnostic assessment of ADHD in children involves the use of both diagnostic interview methods as well as child behavioural rating scales (Pelham et al., 2005; Root & Resnick, 2003).

The general definition of ADHD is provided by the DSM IV which states that its onset occurs prior to age seven, predominantly before the age five. The DSM IV divided ADHD symptoms in two axes: hyperactivity/impulsivity and inattention with each axis being composed of 9 symptoms (A.P.A, 2000). Inattention is described as a failure to pay attention to details or distractibility and an inability to sustain attention over extended periods of time. Hyperactivity manifests as excessive movement, restlessness, fidgeting and talking too much. Impulsivity is described as the inability to inhibit one's action and the tendency to interrupt or intrude others. Extensive psychometric studies have provided empirical support for the symptoms thresholds used to diagnose ADHD in children (Lahey et al.,

1994) and there is general agreement that ADHD can be reliably diagnosed in children through the use of the formal diagnostic criteria outlined in the fourth edition of the Diagnostic and Statistical Manual for Mental Disorder, revised version (DSM-IV-TR; A.P.A., 2000).

The new edition of the DSM-IV, the DSM V has been recently published (A.P.A., 2013) and the diagnostic criteria for ADHD are similar to those in the DSM-IV. In this thesis diagnostic criteria of the DSM-IV are described, as all participants with ADHD in this thesis were diagnosed using the DSM-IV version.

The DSM-IV manual specifies three ADHD-subtypes depending on the number of symptoms that are manifest. ADHD Combined (ADHD-C) subtype applies to children that exhibit six or more inattentive symptoms and six or more hyperactive/impulsive symptoms. ADHD Predominantly Hyperactive/Impulsive (ADHD-HI) subtype applies to children who present with of six or more hyperactive/impulsive symptoms and fewer than six symptoms of inattention. Finally, ADHD Predominantly Inattentive (ADHD-I) subtype applies to the inverse situation in which children are above threshold on the inattention axis but below threshold on the hyperactive/impulsive axis. DSM IV also includes the category of "ADHD in partial remission" for individuals who no longer meet the full criteria. Each DSM IV subtype has different prevalence rates in boys versus girls as well as distinctive patterns of comorbidity and cognitive functioning (McBurnett & Pfiffner, 2009; Marks et al., 2005). The C and HI subtypes are more often diagnosed in boys (9.1% vs 2.6%) and the I subtype is more often observed in girls (Wolraich et al., 1996). I and C subtypes are equally prevalent among school-aged children and more common than the HI subtype (Faraone et al., 1998) which is thought to decrease with age and may actually be a developmental precursor of the C subtype (Cantwell, 1972). The C subtype tends to be associated with younger age of symptom onset and to be associated with a high rate of comorbid oppositional defiant disorder (ODD) and conduct disorder (CD) than I subtype (Carlson et al., 2000, Lahey et al., 2002).

The assessment is conducted with parents but clinicians must also use other sources of information such as teachers - report cards or informal behavioural observations to develop an accurate clinical formulation. The aim of the assessment is to establish whether or not the child has significant, developmentally inappropriate level of at least six out of nine symptoms, as explained above, on one or more axes. The clinician must also establish that symptoms were present before the age of seven, that they have persisted for at least six months and that they are not better accounted for by other psychiatric conditions or transient events such as head injury or trauma. Specifically, the symptoms must cause functional impairments and be evident in at least two everyday-life settings. A number of rating scales and psychological instruments have been developed for the assessment of suspected ADHD. One of the most used ADHD rating scales is the Conners' Rating Scale Revised (CRS-R, Conners, 1999). Three different versions of the CRS-R are available, for parents (Conners' Parent Rating Scales Revised), teachers (Conners' Teacher Rating Scales Revised) and adolescents (Conners-Wells Adolescent Self-Report Scale), all of which are available in both short and long versions. Another diffuse instrument is the Swanson, Nolan, and Pelham—IV (SNAP-IV, Swanson et al., 1983) which is a rating scale developed for both parents and teachers (SNAP-IV Teacher and Parents Rating Scale). Rating scales are often used during the diagnostic assessment; however they are more helpful in assessing and monitoring response to treatment than making the diagnosis itself.

A key clinical feature observed in patients with ADHD is comorbidity. In children, psychiatric disorders comorbid with ADHD include oppositional defiant disorder, conduct disorder, mood disorder (both unipolar and bipolar), anxiety disorders and learning disorders (Kessler, 2005; Pliszka, 1998). Although comorbidity can be attributed to issues related to referral and the screening artefacts (Caron and Rutter, 1991), recent reviews of the literature show that these artefacts cannot explain the high levels of psychiatric comorbidity observed for

ADHD (Angold et al., 1999). Figure 1.1 illustrates the prevalence rates of common comorbid diagnoses of childhood ADHD and how these diagnoses are affected with respect to gender (Biederman et al., 1996; Pliszka, 1998). Comorbidity rates are shown to be different among boys and girls. Most of the scientific literature cites evidence of poorer cognitive functioning in ADHD girls and more severe behavioural problems in boys with ADHD (Biederman et al., 1999, 2002; Gaub and Carlson, 1997; Pliszka, 1998). A meta-analysis of 17 clinic-based studies on ADHD gender differences by Gaub and Carlson (1997) suggested that girls with ADHD tend to be more intellectually impaired and have higher rates of mood and anxiety disorders. By contrast, boys were shown to have higher comorbidity with conduct disorder. In a systematic evaluation of the impact of gender on the clinical features of ADHD, Biederman et al. (2005) reported that girls with ADHD were less at risk for comorbid disruptive behaviour disorders than boys with ADHD. In another study, Biederman et al. (1999) found lower rates of conduct disorder and higher rates of internalising disorders among girls with ADHD, according to Gaub and Carlson (1997). Conduct disorder is commonly associated with social impairment, family disruption and severe behaviour disturbance and this may be the reason why boys tend to present more frequently to the psychiatric services (Safer & Krager, 1998; Wilens et al., 2004). These finding might explain the substantial discrepancy in the male/female ratio between clinic-referred (10:1) and community (3:1) samples of children with ADHD (Biederman et al., 2002). Furthermore, this gender discrepancy suggests that girls with ADHD might be under-identified and under-treated. (Biederman, 2005).

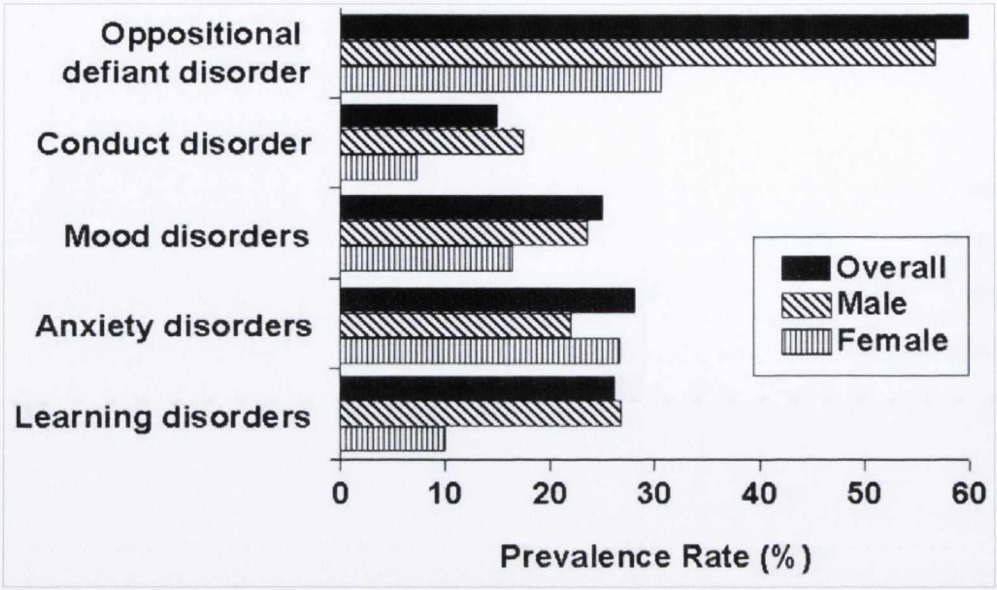


Figure 1.1. Approximate prevalence of comorbid diagnoses in children with ADHD (Biederman, 2005)

1.2 Diagnosis in adulthood

Diagnosis of ADHD in adulthood is problematic due to the fact that ADHD has historically been considered to be a disorder of childhood (Ross & Ross, 1976). Psychometric studies have provided empirical support for symptom thresholds used to diagnose ADHD in children (Lahey et al., 1994) and there is a general agreement that ADHD can be reliably diagnosed in children through the use of formal diagnostic criteria. However the diagnosis of ADHD in adults is much less clear (Riccio et al., 2005) and continues to be an area of controversy within the literature (Faraone et al., 2000).

In diagnosing ADHD in adults, clinicians and researchers in North America most often use the criteria outlined in the DSM IV-TR. As for children, three subtypes are recognised among adults with ADHD, with the ADHD-Inattentive subtype being the most common diagnosis (Erk, 2000). However, the use of DMS-IV criteria for ADHD in adults has been criticised.

Barkley (1998) suggests that applying current ADHD criteria to adults is not developmentally sensitive. The DSM-IV criteria for ADHD were designed for and selected based on studies with children and validation studies of ADHD criteria in adults have not been conducted (Belendiuk et al., 2007). For this reason, it has been suggested that the symptom list in DSM-IV may be inappropriately worded for adults and that diagnostic criteria may be too stringent or restricted when applied to adults (Heiligenstein et al., 1998). Moreover, some symptoms, such as procrastination, overeating to frustration, poor motivation, insomnia and time-management difficulties are common complains for adults with ADHD, but are not included in DSM-IV. Finally, the level of impairment caused by ADHD symptoms may be different between adults and children, and symptoms will affect more domains in adult life, including marital, familial and occupational.

Indeed, longitudinal studies demonstrate, in general, that ADHD symptoms appear to decrease as age increases. Data from clinical and epidemiological samples of children, adolescents and young adults demonstrate an overall reduction of ADHD symptoms over time (Hart et al., 1995; Heiligenstein et al., 1998; Levy et al., 1997; Millstein et al., 1997). Specifically, it appears that hyperactive-impulsive symptoms decline more with increasing age, whereas inattentive symptoms of ADHD tend to persist (Achenbach et al., 1995; Hart et al., 1995). In fact, Millstein et al. (1997) found that symptoms of hyperactivity and impulsivity ameliorate as persons reach adulthood, but inattention remains a prominent clinical feature in more than 90% of adults.

The decrease in ADHD symptoms over time may indicate true remission of symptoms, but it may also indicate a measurement problem, specifically a reduced sensitivity of ADHD symptom criteria with age. If this is true, then using the same symptom threshold to define deviance at each age will reduce the number of diagnosable cases among older individuals (Faraone et al., 2000). Heiligenstein et al (1998) addressed this issue by determining ADHD symptom thresholds specific to college students. First the authors determined the number of DSM-IV diagnoses

of ADHD, finding that 4% met the DSM-IV criteria. ADHD was then defined as deviation from the norm: students were identifying as having ADHD if their total symptom score exceeded the 93rd percentile (+1.5 SD) of the sample. This redefinition increases the prevalence to 11% and students who met this criterion still demonstrated clinically significant symptoms. A prospective study by Barkley et al. (2002) defined adult ADHD by using both DMS-III criteria and a developmentally referenced criterion (DRC; 98th percentile, +2 SD). Using the DSM-IV parental interview resulted in an ADHD rate of 42%. However this rate increased to 66% when the DCR was employed. Clearly, the results of both studies suggest that DSM-IV criteria threshold may be too stringent for adult diagnosis.

Therefore, as cited before, the recently published DSM V contains some changes in the diagnostic criteria and symptoms definition in relation to adult ADHD. For example, a symptom threshold change has been made for adults, to reflect their substantial evidence of clinically significant ADHD impairment, with the cut off for ADHD of five symptoms, instead of six required for younger persons both for inattention and for hyperactivity/impulsivity (A.P.A., 2013)

The diagnosis of ADHD in adults also requires a careful consideration of differential diagnoses as it can be difficult to differentiate ADHD from a number of psychiatric conditions (Pary et al., 2002). Conditions such as major depression, bipolar disorder, generalized anxiety, obsessive-compulsive disorder (OCD), substance abuse or dependence, personality disorders (borderline and antisocial personality disorders) and learning disabilities can be difficult to distinguish from ADHD symptoms. For example, the differential diagnosis of ADHD from mood and conduct disorders may be difficult because of common features such as mood changes, inability to concentrate, memory impairments, restlessness and irritability (Adler, 2004). Differential diagnosis of learning disabilities can also be problematic because of the interrelated functional aspects of the disorders that have the common outcome of poor academic functioning.

Adults with ADHD show substantial lifetime prevalence rates of comorbid disorders (Biederman et al 1993, 1994; Shekim et al 1990). Lifetime prevalence of comorbid anxiety disorders in adults with ADHD is approaching 50%, while mood disorders, antisocial disorders, and alcohol/drug dependency also show substantial prevalence rates (Figure 1.2) (Biederman et al 1993, 1994; Shekim et al 1990). Outcome studies have demonstrated that individuals diagnosed with ADHD in childhood are at risk for developing comorbid conditions (Barkley, 2006; Weiss & Hechtman, 1993). Biederman and colleagues (1993) found a relatively high incidence of lifetime diagnoses of anxiety disorders (43% to 52%), major depressive disorder (31%), ODD (29%), CD (20%), antisocial personality disorder (12%) and alcohol and drug dependencies (27% and 18% respectively) in their sample of adults with ADHD.

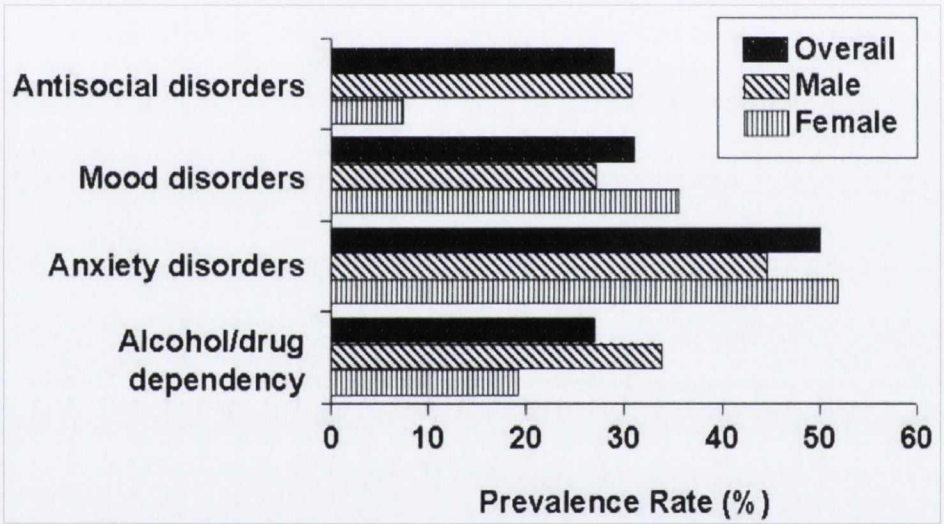


Figure 1.2. Approximate prevalence of comorbid diagnoses in adults with ADHD (Biederman, 2005)

Moreover, studies have been conducted to investigate relationships between ADHD subtypes and comorbid disorders in adults with ADHD. Millstein et al. (1997) found higher rates of ODD, bipolar disorders and substance use disorders in patients with ADHD-C than those with other subtypes and higher rates of ODD, OC and PTSD in patients with ADHD-H than in the ones with ADHD-I. In their study, Sprafki et al., (2007) found that all three subtypes reported more

severe comorbid symptoms than did a control group, with the ADHD-C group obtaining the highest ratings of comorbid symptom severity.

In addition to comorbid psychiatric disorders, adults with ADHD often complain of psychosocial difficulties. Indeed, Biederman et al. (1993) found a much higher rate of separation and divorce among adults with ADHD than among controls and their samples of adults with ADHD had lower socioeconomic status, poorer past and current global functioning estimates as well as higher occurrence of prior academic problems relative to the control group. Likewise, Murphy and Barkley (1996) documented higher rates of educational, employment and marital problems in adults with ADHD. Multiple marriages were more common in the adult ADHD group and significantly more adults with ADHD had performed poorly, quit or had been fired from a job compared with healthy adults. Also, significantly more adults with ADHD had a history of poorer educational performance and more disciplinary actions against them than did adults without ADHD. Low self-concept and low self-esteem are common secondary characteristics of adults with ADHD, often resulting from problematic educational experiences and interpersonal difficulties (Jackson et al., 1997). Adults with ADHD often have strong feelings of incompetence, insecurity and ineffectiveness and live with a chronic sense of underachievement and frustration (Murphy et al., 1995).

1.2.1 Assessment of adults with ADHD

The diagnosis of adult with ADHD is a clinical decision-making process (Faraone & Biederman, 1998). A diagnosis is established through the use of a comprehensive examination assessing psychopathology, functional impairments, pervasiveness of the disorder, age of onset and absence of other disorders that could better explain the symptoms (Rosler et al., 2006). Given the difficulties with the formal diagnostic criteria for ADHD, determining the diagnosis of ADHD in adults presents different challenges than childhood diagnoses (Riccio et al., 2005). There is no a single neurobiological or neuropsychological test that can determine

a diagnosis of ADHD on an individual basis (Rosler et al., 2006). Instead, a combination of clinical interviews, behavioural rating scales, family history and neuropsychological evaluation are commonly used to determine a diagnosis of ADHD in adults. The use of reports from multiple informants is considered best practice, as evidence from multiple studies suggest that adults with ADHD tend to overestimate their symptoms and the severity of those symptoms (Barkley et al., 2002; Fisher, 1990; Wender, 1995). A comprehensive clinical interview is one of the most effective methods to identify ADHD in adults (Adler, 2004; Murphy & Adler, 2004, Wilens et al., 2004). Open questions about childhood and adult behaviours can be used to elicit information necessary to diagnose the disorder. Interviews also include questions regarding developmental and medical history, school and work history, psychiatric history and family history of ADHD and other psychiatric disorders (Barkley, 2006). Although many clinicians use unstructured interviews to assess adult ADHD, semi-structured interviews are also available. For example, the Conners' Adult ADHD Diagnostic Interview for DSM IV (CAADID, Epstein, Johnson & Conners, 2000) is a semi-structured interview that assesses for the presence of DSM IV ADHD symptoms and collects information related to history, developmental course, ADHD risk factors and comorbid psychopathology. The Structured Clinical Interview for DSM IV Criteria for Axis I (SCID-I, First, Spitzer, Gibbon & Williams, 2002) can be used to diagnose ADHD and also to assess comorbidity in adults. That scale is also useful to rule out other disorders as being the cause of ADHD symptomatology. Finally, the Diagnostic Interview for ADHD in adults (DIVA, Kooij & Francken, 2010) has recently been published. The DIVA is based on the DSM-IV criteria to diagnose ADHD and it assesses symptoms in both childhood and adulthood. It also contains specific questions about the age of onset and impairments in different life domains.

Self-report behavioural checklists are commonly used in the assessment of ADHD. In addition to self-report scales, rating scales should be completed by an individual's spouse or other significant relatives to provide useful information in

determining the individual's overall life functioning. Parents can also complete such rating scales to provide information regarding current and childhood functioning (Barkley, 2006). One of the most used ADHD rating scales is the Conners' Adult ADHD Rating Scale (CAARS, Conners, Erhart & Sparrow, 2003). The CAARS assesses ADHD symptoms in adults and it comprises short, long and screening self-report and observer rating scale forms. The CAARS produces eight scales, including scales based on DSM IV criteria and an overall ADHD index. It has been demonstrated that the ADHD index produces an overall correct classification rate of 85% and the sensitivity of the ADHD index has been estimated at 71% (Conners et al., 1999). Another commonly used ADHD rating scale is the Wender Utah Rating Scale (WURS, Ward, Wender & Reimherr, 1993). The WURS is an assessment tool used to retrospectively diagnose ADHD. Other self-report rating scales that are regularly employed in the diagnosis of adult ADHD include: the Brown Attention-Deficit Disorder Rating Scale for Adults (Brown ADD-RS, Brown, 1996), the Current Symptoms Scale (Barkley & Murphy, 1998), that is an 18 items scale with both a patient version and an informant version, and the Adult ADHD Self-Report Scale-version (ASR-v1.1, Adler, Kessler & Spencer, 2003), all of which can be used to assess current and retrospective symptoms and functioning. However, they may be subject to reported biases and errors in memory (Wadsworth & Harper, 2007). Nevertheless, research has been demonstrated that rating scales can accurately reflect the frequency and intensity of symptoms (Wadsworth & Harper, 2007) and, when used retrospectively, are valid indicators of symptomatology (Murphy et al., 2005). Research also suggests that semi-structured clinical interviews can reliably and accurately diagnose ADHD in adults (Epstein & Kollins, 2006). However, this literature is in its infancy and more research is needed to corroborate these findings.

1.2.2 Neuropsychological testing in adults with ADHD

Neuropsychological testing plays a meaningful role in the assessment of ADHD. However, Barkley (2006) stresses that caution is needed in interpreting such data, as there is no significant test or battery of tests that has adequate predictive validity or specificity to make a reliable diagnosis of ADHD. In adult ADHD, neuropsychological testing is most beneficial when the results are used to support conclusions based on history, rating scales and analysis of current functioning.

Woods and his colleagues (2002) reviewed the role of neuropsychological evaluation in the diagnosis of adults with ADHD. In their review of 35 studies, the authors found that the majority of the studies demonstrated significant discrepancies between adults with ADHD and normal control participants on a least one measure of executive function or attention. The most prominent and reliable executive function and attention measures found to differentiate adults with ADHD were the Stroop tasks (Stroop, 1935) and continuous performance tests (CPTs). Stroop tasks are complex word- and colour-naming procedures that require visual attention and inhibition, while CPTs are computer-based tasks that assess attentional lapses, vigilance and impulsivity (Spreen & Strauss, 1998). In addition, Wood et al. (2002) found that verbal letter fluency tasks (i.e. generating words beginning with a specific letter or words belonging to a specific category) and auditory verbal list learning tasks (e.g. California Verbal Learning Test, Delis et al., 1987) were also able to discriminate between adults with ADHD and controls. However, the authors stressed that the validity of these tests is limited by methodological and sample variability, differences in the techniques used and uncertainty regarding the validity of the neuropsychological assessment used to distinguish ADHD from other psychiatric or neurological conditions in the studies reviewed. Schoechlin and Engel (2005) also attempted to determine neuropsychological performance differences in adults with ADHD. The authors performed a meta-analysis of 24 empirical studies reporting results of at least 1 of 50 neuropsychological tests comparing adults with ADHD to controls. The authors categorised each test into 1 of 10 functional domains: verbal intelligence, visual-figural problem solving, abstract verbal problem solving with working memory, executive function, fluency, simple attention, sustained attention,

focused attention, verbal memory and figural memory. For each of these 10 domains a full effect size was calculated (d). Adults with ADHD exhibited a significant performance deficit in 8 of the 10 domains. The highest effect sizes (d between.50 and.60) were found in verbal memory, focused attention, sustained attention, fluency and abstract verbal problem solving with working memory. The findings of Schoechin and Engel (2005) are somewhat inconsistent with those of Woods et al. (2002). Although both studies noted differences between adults with ADHD and controls on tasks of verbal memory and fluency, Schoechin and Engel did not find that performance on executive function tasks was a strong predictor of the distinction between adults with ADHD and controls. This non-significant finding may have occurred for a number of reasons. Firstly, as authors noted, there is no a common definition of executive functions. Secondly, Schoechin and Engel's decision to limit their assessment of executive functions to tasks considered to assess 'executive' processes may have lead to a decreased effect size, especially if ADHD affects some executive functions more than others. Woods et al. (2002) concluded that although a general profile of attentional and executive function impairment is evident in ADHD, expansive impairments in these domains (i.e., impairments on all attention and executive function tasks) is not common.

In line with this, researchers agree that a neuropsychological assessment is most sensitive to the detection and diagnosis of ADHD when the assessment incorporates multiple tests that assess a broad range of attention and executive function aspects (Alexander et al., 2000; Woods et al., 2002). Finally, cognitive assessments can be useful to improve the validity of an ADHD assessment and in assessing the efficacy of pharmacological and/or psychological interventions (Epstein et al., 2003).

1.3 Neurobiological bases of ADHD

1.3.1 The Fronto-Striatal deficit in ADHD

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

Accumulated evidence from functional neuroimaging and lesion studies with humans, animals and primates has provided evidence that the fronto-striatal circuitry involves several brain regions, such as the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), the basal ganglia (BG), and the anterior cingulated cortex (ACC) (Bradshaw et al., 1999 & 2000). Regions of the frontal cortex are responsible for sending information to the striatum which in turn constitutes the input circuit of the BG. Information is output from the BG, via the globus pallidus and thalamus, back to the frontal regions. Thus the system acts as a closed feedback loop, though it receives information from other cortical regions and is subject to a range of modulatory neurotransmitters, such as dopamine and noradreline. The brain areas which constitute the fronto-striatal circuitry can be at least partially dissociated according to the executive function they mediate (Bradshaw, et al., 1999; Chow and Cummings, 1999). Executive functions are a group of high-order cognitive processes that provide one with the ability to behave in a flexible and goal-oriented manner by attending to current relevant events, switching between cognitive strategies or response modes, inhibiting inappropriate behaviours and thoughts, focusing one's attention and monitoring one's actions (Bradshaw & Sheppard, 2000).

The DLPFC appears to play a role in several executive functions, but has been most closely linked to working memory, self-monitoring, goal-direction and goal flexibility (Fuster, 1999; Hester & Garavan, 2004). Damage to the OFC results in dysfunctions of the inhibitory system in both social and cognitive domains (Pennigton & Ozonoff, 1996). The ACC has a well establish role in monitoring conflicting responses, emotions and thoughts and is also involved in motivational processes and the regulation of arousal (see Bush, 2010 for a review). The BG and striatum are involved in a range of important functions such as motor learning and movement control but they are also known to mediate working memory and attentional allocation and filtering. BG and the striatum have also been linked to several reward processes because of their connections with dopaminergic pathways (Ring & Serra-Metres, 2002). These areas do not operate in isolation but have reciprocal connections with other structures including the medial temporal lobes and the cerebellum (Sowell et al., 2003). Changes within these structures have been implicated in the neurobiology of several neurodevelopmental disorders including Tourette's syndrome, autism, obsessive compulsive disorder and schizophrenia as well as ADHD which may account for many common aspects seen in the cognitive, motor and emotional characteristics of these disorders (Bradshaw & Sheppard, 2000).

The hypothesised link between ADHD and the fronto-striatal dysfunction has its origins in two observations. First, lesions of the frontal lobes produce symptoms of hyperactivity, impulsivity and distractibility in both animals and humans (Fuster, 1989). Lesions of the striatum in animals also produce many of the typical ADHD symptoms, such as hyperactivity, poor response inhibition and poor working memory (Max, Fox et al., 2002). Second, the symptoms of ADHD can be successfully treated by psychostimulants that are known to enhance the activity of dopamine and noradrenaline (Madras, Miller, & Fischman 2005).The integrity of the fronto-striatal system is dependent on ascending modulatory projections from the dopaminergic and noradrenergic neurotrasmittiter systems, and research with

humans and animals indicates that decreased activity within these systems influences the ability to control behaviour and produces symptoms which are associated with ADHD (Arnsten et al., 1998; Diamond et al., 2004). In recent years, ADHD has been investigated in far more direct manner using neuropsychological tests, structural and functional neuroimaging techniques and modern molecular genetic tools.

1.3.2 Neuropsychological dysfunctions in ADHD

Neuropsychological deficits have been studied in children, teenagers and adults with ADHD (Barkley et al., 1997; Seidman et al., 2006; Sergeant et al., 2003; Sonuga-Burke et al., 2002; Valera et al., 2006; Willcut et al., 2005). As ADHD has increasingly been understood as a developmental brain disorder affecting regions projecting to the prefrontal cortex (PFC), neuropsychological theories have tended to emphasise putative dysfunctions of PFC, especially executive dysfunctions (Barkley, 1997; Tannock, 1998). While there are a number of other theories that seek to explain the cognitive and behavioural problems associated with ADHD, as reviewed by Sergeant et al. (2003), executive function (EF) deficits are well documented in the literature (Barkley et al., 1997; Byrne et al., 1998; Miyake et al., 2000; Seidman, 2006; Sergeant et al., 2003; Sonuga-Burke et al., 2002; Valera et al., 2006; Willcut et al., 2005).

There are some problematic issues that must be considered in evaluating deficits in EFs in ADHD. First of all, executive functions (EFs) are not tied to a unitary process. EFs typically involve inhibition and impulse control, working memory, cognitive flexibility and planning and organisation (Denckla, 1989). In addition to the issue of heterogeneity there is also an issue regarding the precise definition of EFs. For example, Sergeant et al (2002) note that there are "33 definitions of EF". However, factorial analyses have suggested at least four EF factors: response inhibition and execution, working memory, set shifting and interference control

(Miyake et al., 2000; Willcut et al., 2005). Inhibition in particular has been suggested to be a potential locus of core deficit in ADHD (Barkley, 1997).

Although there are more than a hundred studies that have examined neuropsychological functioning in ADHD in childhood, there are few studies examining such functioning in ADHD preschoolers (ages 3-5) or children just entering school (age 5-7) (Seidman, 2006). Overall, this small body of work is consistent with that observed in older children with ADHD (Valera et al., 2006). Compared to healthy preschoolers, preschooler with ADHD have been shown to display more inhibitory deficits and to be more delay aversive (Dalen et al., 2004; Sonuga-Burke er al., 2002), performing poorly on visual search and cancellation tasks (Barkley et al., 1997), visual and/or auditory vigilance tasks (Byrne et al., 1998), motor control, working memory (Mariani et al., 1997) and tasks of pre-academic skills including tests of memory, reasoning and conceptual development (DuPaul et al., 2001). Some studies have also demonstrated that these cognitive dysfunctions are related to levels of hyperactivity and inattention (Berlin et al., 2002; Harper et al., 1992). The neuropsychological functioning of elementary school-age ADHD children has been studied extensively since the early 1970s (Seidman, 2006). Numerous studies have compared groups of ADHD children, typically aged 6-12, to controls and have generally shown group differences (Frazier et al., 2004). While the hypothesis of EF impairment has received substantial support, several studies have not found EF deficits in children with ADHD and additional studies have found that children with ADHD performed poorly on some EF tasks but not others (Barkley et al., 1992; Seidman et al., 2004; Sergeant et al., 2002). The body of studies that found significant differences between controls and ADHD children saw that ADHD children as a group exhibited weak performance on various tasks of vigilance, verbal learning, working memory, set-shifting, planning and organisation, complex problem solving and response inhibition (Barkley et al., 1998; Seidman et al., 1997, 2000). Deficits on the Stroop color-word test appear to be among the most significant neuropsychological impairment (Barkley et al., 1997). Few studies have been

conducted to investigate neuropsychological deficits in teenagers with ADHD. Seidman et al. (2005) conducted studies on people with ADHD aged from 12 to 20 years old finding that executive dysfunctions that characterise the disorder in childhood are also found in teenagers. These data demonstrated that both samples of healthy control children and children with ADHD improve their performance as they get older, but the deficit between groups remains significant. In the only published longitudinal study of neuropsychological functions, Fisher et al. (1990) demonstrated consistent stable impairments from childhood to older teenage years. This study supports the notion that these abnormalities will be present in adults with ADHD.

Over the past decade, research in neuropsychological dysfunctions in adult ADHD has intensified. A meta-analysis was conducted on neuropsychological deficits in adults with ADHD (Hervey et al., 2004). The authors included only samples with persons 18 years old and older and with a control group. They reviewed 33 published studies and found that neuropsychological deficits are largely consistent with those described in children. Impairments were relatively consistently observed in attention, behavioural inhibition and memory. Similar results were derived from a qualitative review (Woods et al., 2002). Seidman (2006) reviewed the literature on neuropsychological deficits in adults with ADHD and they point out that neuropsychologists have literally hundreds of tests to choose from in composing an assessment battery for ADHD. In their review more than 70 tests were used to compare ADHD adults and controls. However, many of these tests were used in only one or two studies and their sensitivity cannot be determined. The authors found that the five tests that most consistently differentiated adults with ADHD from controls and were used in at least seven studies were: versions of the CPT, the Stroop, Train Making, Verbal Fluency ("FAS") and sub-tests on the Wechsler Intelligent Scale (WAIS), as the Digit Symbol that is a measure of perceptual motor speed and the Arithmetic sub-test, which taps into working memory.

In summary, the neuropsychological difficulties found in adults with ADHD appear to be qualitatively similar to those seen in children with the disorder. Nevertheless, additional research is needed because not all studies demonstrate impairment of the same tasks or functions, nor do all the studies control for the various confounds (e.g., psychiatric comorbidities) associated with the disorder (Seidman et al., 2006). Moreover, there is a lack of longitudinal neuropsychological research from childhood to adulthood and this type of design is necessary to determine the continuity of neuropsychological deficits.

In chapter 3 and 4 of this thesis neuropsychological deficits in adult ADHD are investigated focusing on the investigation of sustained attention impairments. In the experiment reported in chapters 3 and 4, neuropsychological tests were combined with direct investigation of brain function through the use of neurophysiological measures, such as EEG power spectral measures and Event-Related Potentials (ERP), to allow a more sophisticated understanding of neuropsychological dysfunctions and their neural underpinnings in adult ADHD.

1.3.3 Neuroimaging evidence

Structural and functional neuroimaging studies can provide more direct evidence for ADHD brain dysfunctions.

Structural imaging, particularly morphometric and volumetric MRI, have generally helped to establish that in ADHD there are widespread abnormalities in the volumes of brain circuits relevant to attention and motor control (Bush, 2010). In addition to relatively consistent findings of decreased total cerebral volume of approximately 3 to 5% (Castellanos et al., 2001, Seidman et al., 2005, Valera et al., 2007), volumetric studies have also found more specific abnormalities within defined regions of the lateral prefrontal cortex, cingulate cortex, striatum, cerebellum and corpus callosum (Castellanos et al., 1996, Kates et al., 2002). Smaller cingulate cortical volumes have been reported in adults (Seidman et al.,

2006) and children (Semrud-Clikeman et al., 2006) with ADHD. A number of studies have shown basal ganglia and cerebellar volumetric abnormalities. The globus pallidus has been shown to be smaller (Castellanos et al. 1996). Caudate studies have also suggested smaller caudate volumes in ADHD but have been inconsistent. Some have reported decreased volume of caudate in ADHD patients relative to controls (Semrud-Clikeman et al., 2006, Castellanos et al., 2002), whereas others found no volume differences (Hill et al., 2003) or larger caudate in ADHD patients (Mataro et al., 1997). Multiple studies have reported structural abnormalities of the cerebellum in ADHD patients (Berquin et al., 1998, Valera et al., 2007, Castellanos et al., 2002) and abnormalities of corpus callosum volume and morphometry have also been reported many times in ADHD (Hynd et al., 1991, Hill et al, 2003, Valera et al., 2007). Finally, cortical thickness quantification through high-resolution MRI structural scans has been recently applied to the study of ADHD showing that children with ADHD had significant global thinning of the cortex, most prominently in the medial and superior prefrontal regions (Shaw et al., 2007). These data in children are generally consistent with the findings of Makris et al. (2007) that show selective cortical thinning of fronto-parietal areas as well as the cingulate cortex in adults with ADHD. Overall, although some discrepancies exist, the weight of evidence indicates that both global and regional volumetric abnormalities occur in ADHD.

Functional studies support fronto-striatal dysfunctions in ADHD. The most consistent finding is a dysfunction of the dorsal anterior cingulate cortex (dACC) (Bush, 2010). Numerous fMRI, PET and event-related potential (ERP) studies have reported dACC hypofunction in ADHD, using various tasks and techniques (Bush et al., 1999, Durston et al., 2007, Tamm et al., 2004, Zang et al., 2005). Moreover, a meta-analysis by Dickstein et al. (2006) found the dACC among the short list of brain regions that were hypoactive in ADHD patients relative to healthy controls. Recently, Bush et al (2008) used fMRI to show that six weeks of methalphenidate (MHP) significantly increased dACC activation, as compared to placebo, in adults with ADHD. Similarly an ERP study reported that stimulant

treatment increased dACC activity (Pliszka et al., 2007). These findings provide the evidence that dACC dysfunction contributes to ADHD. Evidence indicating wider fronto-parietal and dACC dysfunction was provided by a voxel based meta-analysis of 16 ADHD imaging studies by Dickstein et al (2006). ADHD was found to be associated with significant hypoactivity of the dACC, dorso-lateral prefrontal cortex (DLPFC), ventro-lateral prefrontal cortex (VLPFC), superior parietal cortex, caudate and thalamus. Moreover, limiting the focus to studies on response inhibition tasks, a more limited set of regions were identified including VLPFC, dACC, parietal cortex, caudate nucleus and precentral gyrus but not the DLPFC. It appears that the DLPFC and the VLPFC have important and separable roles in ADHD (Bush, 2010). Caudate functional abnormalities were found in the above meta-analysis especially using response inhibition tasks, as go/no-go tasks or stop signal tasks (Durston et al., 2003; Epstein et al., 2007; Rubia et al., 1999). The parietal cortex has only recently been the focus of ADHD imaging studies. Tamm et al. (2006) reported that ADHD subjects performing a visual oddball task showed less activation of parietal cortical areas, including the superior parietal gyrus and multiple areas of the inferior parietal lobe, along with lower precuneus and thalamus activation. Parietal hypofunction has also been observed in ADHD in tasks of mental rotation/spatial processing (Silk et al., 2005), task switching (Smith et al., 2006) and sequential finger tapping (Mostofsky et al., 2006). The cerebellum has also been recognised as part of the disordered circuitry that underlies ADHD. A number of fMRI studies have identified functional abnormalities of the cerebellum in ADHD. The majority of the studies have reported decreased cerebellar activation in ADHD during task performance (Durston et al., 2007, Valera et al., 2005, Zang et al., 2005) or at rest (Anderson et al., 2002, Kim et al., 2002), however other studies have found increased cerebellar activation in ADHD (Rubia et al., 2009, Schulz et al., 2004). It is clear that more focused studies on the cerebellum's potential role in ADHD are needed.

Although abnormalities of the striatum, dACC, fronto-parietal areas and cerebellum have been reported to be central in functional imaging studies of

ADHD, other brain regions have been found to be impaired in fMRI studies. Thalamic abnormalities have been reported during active tasks (Dickestein et al., 2006, Tamm et al., 2006) and at rest (Zhu et al., 2008) and occipital cortex abnormalities have been identified (Dickstein et al., 2006, Valera et al., 2005). Differences in the temporal cortex between groups with ADHD and controls have been noted during active tasks (Rubia et al., 2009) and controlateral motor cortex hypoactivity during motor sequencing has been reported (Mostofsky et al., 2006).

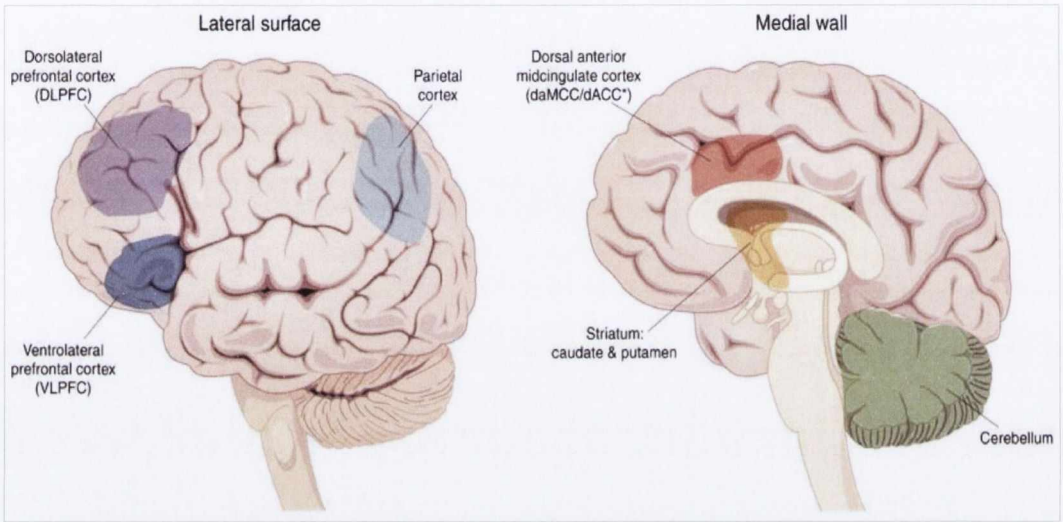


Figure 1.3. Brain structures implicated in ADHD.

Note: Different neural regions have been implicated in ADHD. In particular, the dorsal anterior cingulate cortex (dACC), dorso-lateral prefrontal cortex (DLPFC), ventro-lateral prefrontal cortex (VLPFC), parietal cortex, striatum and cerebellum (Bush, 2010).

Both structural and functional imaging studies of ADHD have indicated that brain abnormalities are predominantly right lateralised (Carter al., 1995; Castellanos et al., 1996; Vance et al., 2007). For example, Castellanos et al. (1996) used anatomic magnetic resonance to compare twelve cortical and subcortical regions in 57 children with ADHD and 55 matched controls. They found smaller right caudate compared to left caudate, smaller right globus pallidus, smaller anterior frontal regions and smaller cerebellum in the ADHD group. Vance et al. (2007) used functional MRI to compare 12 ADHD children with 12 controls in a mental rotation task which requires spatial working memory. The ADHD group showed significantly less activation in right-occipital areas, the right inferior parietal lobe

and the right caudate nucleus. These findings are consistent with the hypothesis of a predominantly right-sided dysfunction in ADHD.

Functional connectivity fMRI studies demonstrate that the functional abnormalities not only affect isolated brain regions but also the functional inter-regional interconnectivity between these regions. Thus during resting state, children and adults with ADHD showed reduced functional connectivity relative to healthy controls in fronto-striatal, cingulate, fronto-parietal, temporo-parietal and fronto-cerebellar networks (Zhu et al., 2008; Castellanos er al., 2008; Zang et al., 2005). Reduced functional connectivity has been observed in the context of cognitive tasks in children with ADHD relative to controls between the inferior frontal cortex (IFC) and the basal ganglia, parietal lobes and cerebellum, and between cerebellum, parietal and striatal regions during sustained attention tasks (Rubia et al., 2009). In adults with ADHD, deficits in functional inter-regional connectivity relative to healthy subjects were observed between the right and left IFC and other areas such as basal ganglia, cingulate, parieto-temporal and cerebellar regions during motor response inhibition and working memory (Wolf et al., 2009). In adults, however, there is also additional evidence for compensatory increased connectivity between ACC, superior frontal lobe and cerebellum (Wolf et al., 2009).

Functional pharmaco-imaging studies are also greatly informative. By showing the ways in which drugs act on different brain regions, these studies can help our understanding the mechanisms of drug effects and may also indirectly help to identify abnormalities in the neural circuitry that may underlie ADHD (Bush, 2010). For example, Vaidya et al. (1998) in an fMRI study on the effects of methylphenidate (MHP) on children performing a go/no-go task, showed not only that fronto-striatal activity differed between ADHD children and controls, but also that the groups' response to MHP differed. MHP increased prefrontal activation to an equal extent in both groups on one task, but on the other go/no-go task MPH increased striatal activation in the ADHD group while reducing striatal activation

in the control group. An acute fMRI study (Epstein et al., 2007) showed that MPH produced increased activation of the caudate and cerebellum along with inconsistent changes in other brain regions in both children and adults with ADHD. Pliszka et al. (2007) using ERPs found that stimulant treatment increases ACC activity in ADHD. Finally, subsets of children from a long-term (one year) fMRI study of ADHD found data which suggest MPH induced changes in the insula, putamen and cingulate cortex (Konrad et al., 2007).

1.3.4 Genetic influences

Family, twin and adoption studies show that ADHD is a familial disorder with high heritability, indicating that significant genetic component influences risk for the disorder (Faraone et al., 2001; Levy et al., 1997).

Several studies have reported an elevated prevalence of ADHD among family members of individuals with ADHD (Faraone et al., 2001; Faraone et al., 1997). Most family studies have identified a two to eightfold increase in the risk of ADHD in parents and siblings of children with ADHD (Biederman et al., 1990; Faraone et al., 1992). A study of siblings of adults with ADHD (Manshadi et al., 1983) and a study of children of adults with ADHD both documented very high rates of ADHD in the families of adults with ADHD (Biederman et al., 1995). These data suggest that persistent ADHD might be a useful phenotype for molecular genetic studies (Faraone et al., 2000b). Because other environmental differences could account for elevated risk, two double blind, single case studies specifically examined the risk to siblings of ADHD children when environmental factors are considered as well (Biederman et al., 1990, 1992; Faraone et al., 1992, 2000). After controlling for gender, intactness of family and socio-economic status, these studies confirmed the familiarity of ADHD.

Studies on twins have been used to establish ADHD heritability and to assess the degree to which this disorder is influenced by genetic factors (Coolidge et al.,

2002; Gills et al., 1992; Martin et al., 2002). Studies on twins are a very direct method of examining the heritability of ADHD. Monozygotic ("identical") twins share essentially 100% of their genes, whereas dizygotic ("fraternal") twins, like other siblings, share 50% of their genes. The extent to which identical twins are more concordant for ADHD than fraternal twins can be used to compute heritability, which is the degree to which variability in ADHD in the population can be accounted for by genes. In his overview Biederman (2005) reported estimates of heritability from 20 twin studies from the United States, Australia, Scandinavia and Europe (Figure 1.4). The mean heritability estimate of 76% shows that ADHD is among the most heritable of psychiatric disorders.

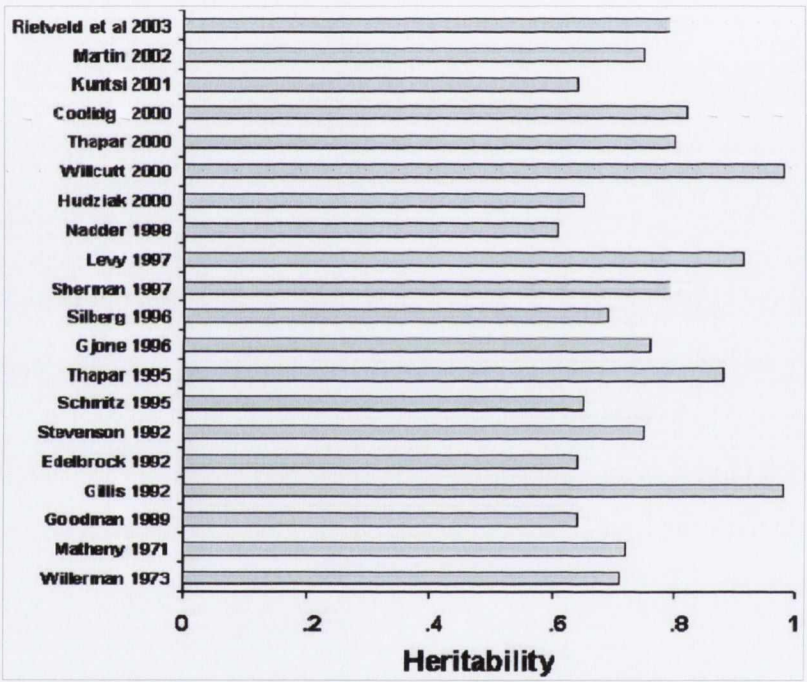


Figure 1.4. Estimates of heritability of ADHD from 20 twin studies (Biederman, 2005)

Adoption studies of ADHD also implicate a genetic etiology. Early studies showed that the adoptive relatives of hyperactive children are less likely to have hyperactivity or associated disorders than the biologic relatives of hyperactive children. (Cantwell, 1972; Morrison & Steward, 1973). In their study, Sprich e al. (2000) reported that adoptive relatives of adopted children with ADHD had rates of ADHD and other associated disorders that were lower than those observed in

the biological relatives of nonadopted ADHD children and similar to those found in relatives of control probands. Biological relatives of children with ADHD also perform more poorly on standardised measures of attention than do adoptive relatives of children with ADHD (Alberts et al., 1986).

Molecular genetic studies of children with ADHD provide direct support for the association of specific genes with ADHD. Genetic studies have focused on the analysis of monoamine system genes, due to the marked and rapid response of ADHD symptoms to stimulants that block the reuptake of dopamine and norepinephrine. Genetic variants within or near to the D4 (DRD4) and D5 (DRD5) dopamine receptor genes provide the most consistent findings supported by meta analysis (Li et al., 2006). Numerous other studies find evidence of association with the dopamine transporter gene (DAT1), the dopamine beta-hydroxylase gene (DBH), the serotonergic transporter (5-HTT), the serotonergic receptor (HTR1B) and the synaptosomal associated protein, 25 kDa (SNAP-25) (Faraone et al., 2005). Taken together these candidate gene findings are thought to explain around the 3.2% of the variance in ADHD symptoms in children (Kuntsi J. et al., 2006). More recently whole genome association studies have identified novel genes such as CDH13 as potential risk factor (Franke et al., 2009). Although most studies have focused on children with ADHD, it is interesting to note that the only two studies to investigate DRD4 association in adults with ADHD were both positive (Muglia et al., 2000; Lynn et al., 2005).

1.4 Causal Models of ADHD

1.4.1 Simple causal models

Several explanatory models of ADHD have been proposed since the first clinical description of the disorder. Researchers have tried to answer the central question of where, within the brain/mind of the ADHD child, the site of dysfunction that causes ADHD is located (Sonuga-Barke, 1994). Traditionally, explanations of

ADHD have been based around simple causal models of simple, common core dysfunctions. Two classes of models have been more influential than the others. The first group of models focuses on executive dysfunction due to deficient inhibitory control (Morton & Frith, 1995; Barkley, 1997) and the second group focuses on impaired signalling of delayed rewards arising from disturbances in motivational processes (Sagvolden, 1991; Sonuga-Barke et al. 1998). Another more recent model is the cognitive energetic model developed by Sergeant (2000). The first class of models can be labelled as cognitive dysfunction models (Sonuga-Barke, 2004) and until recently have been considered the dominant class of explanations of ADHD psychopathology.

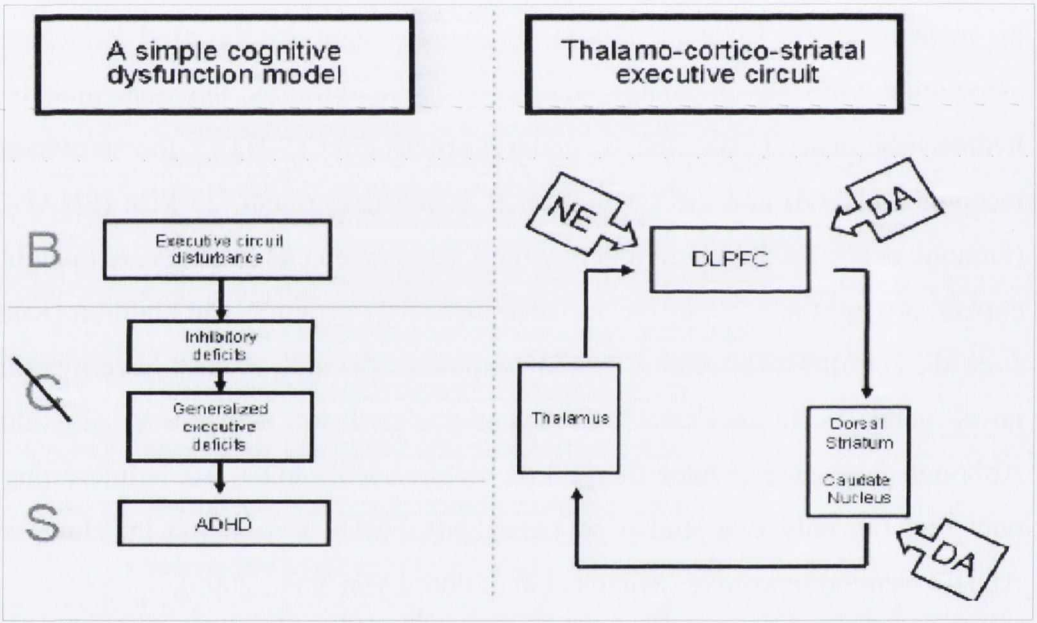


Fig.1.5. Schematic representation of a simple cognitive deficit model of ADHD (adapted from Barkley, 1997) and simplified frontostriatal circuitry.

Note: B, C and S represent biology, cognition and symptoms respectively (Morton and Frith, 1995).

The particular cognitive model presented in figure 1.5 represents Barkley's unified theory of ADHD, known as the behavioural inhibition model (Barkley, 1997). Executive dysfunctions are central in Barkley's model of ADHD and ADHD symptoms are thought to be caused by deficits in inhibitory-based executive deficits. Inhibition represents a super-ordinate executive function,

which permits the proficient performance of four executive abilities: working memory, internalisation of the speech, self-regulation of affect-motivation arousal and reconstruction. Barkley's model is supported by the fact that deficits on tasks thought to measure executive functions are a frequently observed characteristic of people with ADHD (Barkley. 1997; Seidman et al., 2006; Sergeant et al., 2003; Sonuga-Burke et al., 2002; Willcut et al., 2005) with a substantial amount of evidence implicating response inhibition deficits (Nigg, 2001). Response inhibition refers to the ability to inhibit an inappropriate proponent or ongoing response in favour of a more appropriate alternative. At a neurobiological level, there is growing evidence that inhibitory control and other executive functions are underpinned by one of a number of functionally segregated but anatomically proximate basal ganglia-thalamocortical circuits (Alexander et al., 1990). As shown in figure 1.5, these executive circuits link the prefrontal cortex to the dorsal striatum and caudate nucleus via glutaminergic cells. Inhibitory connections link dorsal striatum and caudate to the thalamus with excitatory noradrenergic cells connecting back to the prefrontal cortex (Heyder et al., 2004). Data from structural and functional neuroimaging studies support the hypothesis that deficits in inhibitory-based executive functions in ADHD are associated with disturbances in this circuit (Bush et al., 1999; Castellanos et al., 2002; Rubia et al., 1999). Finally, dopamine, which is implicated in ADHD on the basis of pharmacological and genetic studies (Levy & Swanson, 2001) is a key modulator of this circuit.

A number of motivation-based dysfunction models have been proposed as alternatives to cognitive theories of ADHD. These models shift the focus from deficits in inhibitory control to impaired reward processes (Sagvolden, 1991, Sagvolden et al. 1998). Figure 1.6 represents one such model which builds on the general idea of Sagvolden and colleagues (1998). In this, ADHD is the outcome of a neurobiological impairment in the power and efficiency with which the contingency between present actions and future rewards is signalled. This leads to a reduction in the control exerted by future rewards on current behaviour, a diminution in their "value", and an increase in the extent to which they are

discounted. This account is supported by the consistent finding that children with ADHD often display hypersensitivity to delay and consequent difficulties in waiting for salient outcomes, as well as working efficiently over an extended period of time (Neef et al., 2001, Sonuga-Barke et al., 1996, Trip & Alsop, 2001). This difficulty of waiting seems to be independent of inhibitory deficits associated with executive dysfunction (Solanto et al., 2001; Sonuga-Barke et al., 1994). A double dissociation between inhibitory deficits and waiting for valued outcomes is suggested by the fact that children with ADHD can wait even when waiting involves inhibition, but they often choose not to wait even when waiting does not involve inhibition (Sonuga-Barke et al., 1994).

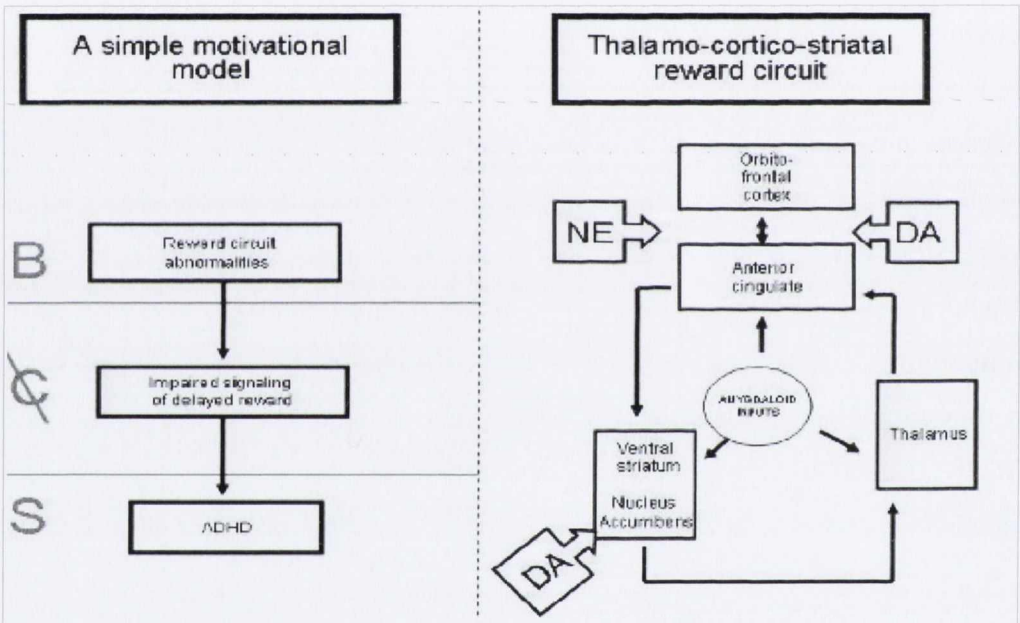


Fig.1.6 Schematic representation of a simple motivational model of ADHD (adapted from Sagvolden et al, 1998) and simplified frontostriatal circuitry

Note: B, C and S represent biology, cognition and symptoms respectively (Morton and Frith, 1995).

Interestingly, the neurobiology of impaired signalling of delayed rewards and inhibitory-based executive deficits seem to share some common elements. The ability to wait for delayed rewards seems to be related to alterations in another of the dopamine-modulated thalamocortical-basal ganglia circuits mentioned previously (Alexander et al., 1990), although in this context the motivational or

affective circuit likely plays a dominant role (McClure et al., 2004). This circuit links the ventral striatum (in particular the nucleus accumbens) to frontal regions (especially the anterior cingulate) and orbitofrontal cortex (Zink et al., 2004; Rogers, 2004). The amygdala also seems to be implicated in this system, possibly playing a role in defining the motivational significance of incentives (Winstanley et al., 2004). Once again, dopamine is a key neuromodulator of the reward-signalling function of this circuit (Wightman & Robinson, 2002). Studies have demonstrated a specific role for this circuit in signalling rewards, coding incentive value and regulating other behavioural processes involved in the maintenance of responding under conditions of delayed rewards (Burk & Mair, 2001; Wade et al., 2000).

An alternative motivational approach is provided by the delay aversion hypothesis: this can be seen as an extension of the simple motivational model (Sonuga-Barke et al., 1994). According to this hypothesis, delay aversion is a negative emotional reaction to the imposition of delay and it is a developmental consequence of the failure of an impulsive child to engage effectively with delay-rich environments. This negative emotional response is manifested behaviourally as attempts to avoid or escape delays, compounding the exiting tendency of the child to choose impulsively in settings in which choices between immediate and delayed rewards are available. In other settings in which delay cannot actually be reduced by behaving in this way, attempts are made to "systematically" reduce the perception of time spent during delay by attending to interesting aspects of the child's environment or by acting on that environment to make it more interesting and absorbing. According to the model, such aspects of delay aversion would be characterised as inattention and overactivity. In this way, aversion delay is hypothesised to cause impulsiveness, inattentiveness and overactivity.

An alternative model has been proposed by Sergeant (2000), which is known as the cognitive energetic model of ADHD. This model suggests that there may be

certain aspects of inhibition which are impaired in ADHD children; however those deficits also depend on the energetic state of the child.

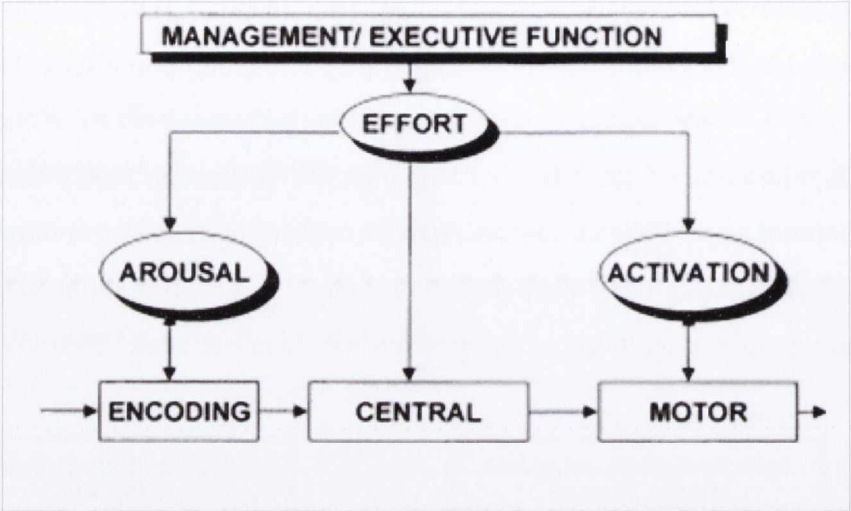


Fig. 1.7. The cognitive energetic model (Sergeant, 2000)

The cognitive energetic model includes three levels (figure 1.7). The first level is composed by computational mechanisms of attention and includes four stages: encoding, search, decision and motor organisation. These stages of information processing are associated with task variables. The second level encompasses three energetic pools. These pools include effort, which is conceived as the necessary energy to meet task demands. Effort is said to be required when the current state of the organism did not meet the state required to perform a task. The second pool is arousal and it is defined as a phasic responding which is time locked to stimulus processing. Tonic changes of physiological activity are thought to represent the operation of the third pool, which is activation. The cognitive energetic model includes a third level: management or evaluation mechanisms. This level is associated with planning, monitoring, detection of errors and their correction and it currently represents the concept of executive functions (response inhibition, strategic planning, mental representation of a task). Evidence that supports the cognitive energetic model comes from studies in which the event rate (the speed with which stimuli are presented) is modified during the task. In general, children with ADHD have been found to perform more poorly in conditions of relatively

slow event rates as compared with fast and moderate event rates (Chee et al., 1989; Meere et al., 1992). In a study by Meere et al. (1995) children with ADHD children were compared on their performance of a go/no-go task. Stimuli were presented at three rates: a fast (1 s), medium (4 s) or slow (8 s) presentation rate. ADHD children made more commission errors in the fast and slow conditions, but not in the medium condition, suggesting that ADHD children's lack of inhibition is modulated by their inability to adjust their state. The cognitive energetic model claims that response inhibition deficit in ADHD is dependent among the state of the subject and the allocation of energy to the tasks. Particularly, it suggests that activation pool is perhaps necessary for inhibition of a motor response (Sergeant, 2000).

Due to the conception of ADHD as discrete disease resulting from a single core dysfunction, cognitive and motivational models have traditionally been regarded as competitive rather that complementary. The two models clearly have a number of distinctive elements. For example, inattentiveness and overactivity are fundamental features in the executive model, while in the motivational model one might expect inattentiveness to be displayed only in delay-rich environment. At the most fundamental level, however, the two models are most distinctive in terms of the presence of inhibitory deficits (the cognitive model) and impaired response to delay (the motivational model). Studies have been conducted to directly test those two models to establish which one is most likely able to explain ADHD deficits. A head-to-head study (Solanto et al., 2001) compared the two models in a sample of school-age children with a diagnosis of combined ADHD. Children performed the stop signal task, in which a dominant response already initiated is inhibited after a stop signal, and a choice reaction time task, in which children had to choose between a small immediate and a large delayed rewards. The results indicated no association between choices of the small immediate reward (delay aversion) and stop signal reaction time (inhibitory failures), suggesting that inhibitory deficits and delay aversion were independent characteristics. Furthermore, performance on both tasks was found to be strongly and

independently associated with ADHD. Together the two measures allowed nearly 90% of children with ADHD to be correctly classified. This study confirmed that delay aversion and poor inhibitory control are central but unrelated characteristics of ADHD. Moreover, the independence of these measures combined with their high diagnostic value encourages the view of ADHD as a product of two distinct processes, one underpinned by poor inhibitory control and the other mediated by delay aversion.

1.4.2 From single models to multiple pathways models

Results from the head-to-head study presented above (Solanto et al., 2001) suggest that ADHD is not likely to be a discrete disorder, characterised by neuropsychological homogeneity, as proposed by the single models paradigms. The results show, in fact, that two uncorrelated processes (inhibitory failures and delay aversion) make a distinctive contribution to predicting disorder. This data thus indicates therefore that multiple pathways models might be needed to fully explain the ADHD phenomenon. On the basis of data from such head-to-head studies, a dual pathway hypothesis of ADHD has been proposed by Sonuga-Barke (2002).

In his dual pathway model Sonuga-Barke (2002) describes ADHD as a developmental outcome of two distinct psyshological/developmental processes. As shown in figure 1.7, one process describes ADHD as a predominantly motivational disorder mediated by the emergence of delay aversion during childhood (ADHD as a motivational style with acquired cognitive characteristics). The second process sees ADHD as a disorder of the regulation of thought and action resulting from inhibitory dysfunction (ADHD as a disorder of the regulation of thought and action). Each process has a number of different components and different conceptual levels.

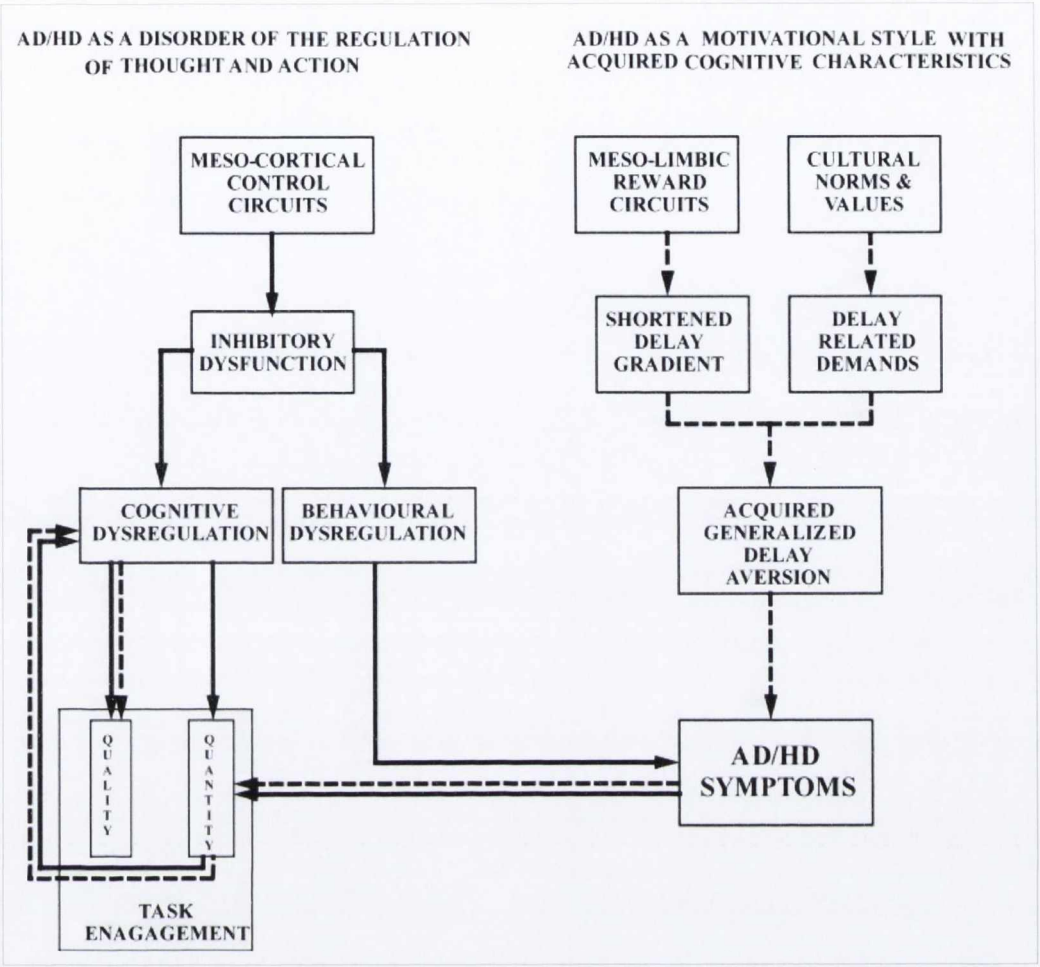


Fig 1.8. A schematic representation of the dual pathway model (Sonuga-Barke, 2002)

The first component is the developmental outcome. In the model this is separated into ADHD behavioural symptoms (impulsiveness, inattention and hyperactivity) and task engagement, the quantity and quality of task. Then there are the psychological processes that underpin these developmental outcomes. These can be subdivided into primary characteristic (deficient inhibitory control) and secondary process characteristics (cognitive and behavioural dysregulation).

The dysregulation of thought and action pathway (DTAP) originates from frontal and pre-frontal high order control circuits, with projections to the basal ganglia and into the striatum. Functions of this circuit are regulated by the meso-cortical branch of the dopamine circuit. The DTAP pathway is characterised by a core

dysfunction in inhibitory control. This causes two different developmental outcomes: ADHD behavioural symptoms and poor quality task engagement. ADHD symptoms are mediated by behavioural dysregulation while the effects on task engagement are mediated by cognitive dysregulation. Furthermore, cognitive dysregulation also mediates the quantitative aspect of task engagement, causing a feedback loop from task-engagement-quantity back to executive function. The motivational style pathway (MSP) is associated with alterations in brain reward circuits, especially the ventral-striatal network, associated with meso-limbic branch of dopamine system. This alteration causes a shortened "delay of reward gradient", which means that children with ADHD discount the value of future events at a higher rate than other children. This leads to a preference for immediacy (i.e. behavioural impulsiveness). Cultural norms and practices, on the other hand, play a crucial role in creating altered reward mechanisms. For example, parents who are unforgiving to failures to wait are more likely to create the context of delay aversion in ADHD in impulsive children. Both the above mentioned mechanisms contribute to create the acquired generalised delay aversion deficit which leads to ADHD symptoms. The impact of ADHD symptoms on the quantity and quality of task engagement will be similar to that proposed for the DTAP.

Although initial results are suggesting the existence of multiple pathways in ADHD, further study of the relationship between these processes is obviously required to properly test this hypothesis. Research should use multivariate approaches with measures from different cognitive and motivational domains (e.g., inhibitory-based executive processes and delay-related motivational processes) with large sample of children of different ages. This would allow for the study of continuities and discontinuities between motivational and cognitive components of ADHD. Research should also explore the interactions between motivational and cognitive features of the disorder during development (Sonuga-Barke, 2005). Finally, as Nigg et al. (2004) suggest, a dual pathway account might not be exhaustive and other pathways might be hypothesised. For instance, other

neuropsychological mechanisms, such as deficits in state regulation (Sergeant, 2005) and alerting and orienting processes (Banaschewski et al., 2003), with distinct neurobiological origins, have been implicated in ADHD.

1.5 Treatments

Both pharmacological and behavioural-psychosocial treatments have been developed for children and adults with ADHD. Stimulants are the first line pharmacological treatment, however new alternative drugs are available (Barkley, 1988; Spencer, 2001; Wolraich et al., 2005). Behavioural psychosocial therapy is the only psychological intervention whose efficacy has been demonstrated (MTA Cooperative Group, 2004; NIH, 2000, Pelham et al., 1999). Few studies have used multimodal approaches for ADHD (Root & Resnick, 2003; Rostain et al., 2006; Safren et al., 2005), which should be preferential treatments for ADHD (Murphy, 2005). For example, Murphy (2005) in his review recommends that, as for most other psychiatric conditions, treatment of ADHD should take a multimodal approach, including pharmacological therapy, psychoeducation and therapeutic interventions, such as Cognitive Behavioural Therapy (CBT).

1.5.1 Pharmacological treatments

The pharmacological treatment of ADHD relies on agents that affect dopaminergic and noradrenergic neurotransmission, namely, the stimulants, antidepressants, and antihypertensives. A new agent, a noradrenergic reuptake inhibitor, has also become available.

The most commonly used stimulants are dopamine agonists, such as methylaphenidate (MPH, i.e. Ritalin, Concerta, Focalin, Aquasym) and amphetamine compounds (i.e. Adderall, Dexedrine). The precise neurobiological mechanism by which they have their effect on symptoms is not known, but drugs

such as MPH increase extracellular levels of dopamine by inhibiting dopamine transporters and stimulating the release of dopamine from presynaptic sites (Madras et al., 2005). Stimulants have been shown to be affective for 70% of adolescents and seem to operate in a dose-dependent manner in improving cognition and behaviour (Wolraich et al., 2005). The beneficial effects of stimulants are of similar quality and magnitude for adolescents of both genders and for younger and older children. Moreover, controlled studies in adults with ADHD have demonstrated response rates ranging from 25% to 78% for methylphenidate (Biederman et al., 2006; Spencer et al., 2005) and response ranging from 54% to 70% for amphetamine (Horrigan & Barnhill, 2000; Paterson et al., 1999). Response rates with placebo for adults with ADHD were reported to be 10%. Although stimulants are effective in adult ADHD, it is estimated that at least 30% of individuals do not adequately respond to, or are not able to tolerate, stimulants (Barkley, 2006; Spencer, 1996). In addiction stimulants are associated with a number of shortcomings. First, they are controlled substances, which may increase both the potential for abuse and the barriers to treatment. In addition, mood disorders that are often comorbid with ADHD may have an adverse impact on responsivity to stimulant drugs (Barkley, 2006). In particular stimulants have demonstrated poor response rates with comorbid manic symptomatology and may in fact cause worsening of mood instability (Biederman et al., 1999). Thus, in many cases, it must be necessary turn to other drug classes (i.e. antidepressant) as well as alternative treatments (e.g., behavioural treatments) in treating the disorder.

Atomoxetine (Strattera) is a recently approved non-stimulant agent that has been approved for adolescents with ADHD. Atomoxetine is a highly specific, noradrenergic reuptake inhibitor with efficacy for ADHD. Initial trials suggest that Atomoxetine is effective for ADHD plus co-occuring disorders such as anxiety, tics and depression and it demonstrates no abuse liability (Wolraich et al., 2005), although there is yet far less evidence in the use of this medication.

The tricyclic antidepressants, e.g. imipramine (Tofranil) and desipamine (Norpramine) block the reuptake of neurotransmitters including noradrenaline. Tricyclic antidepressants are effective in controlling behavioural problems and improving cognitive impairments associated with ADHD but are less effective than the majority of stimulants, particularly for cognitive impairments. The tricyclic antidepressants, however, should be considered only when adequate trials with both stimulant medications (amphetamine compounds and methylphenidate) have failed, atomoxetine is ineffective and behavioural interventions have been tried (Wolraich et al., 2005).

Antidepressants have generally been demonstrated to be an effective therapy for adults with ADHD. Most of the studies have examined the efficacy of the noradrenergic compounds bupropion, venlafaxine, desipramine and atomoxetine. Bupropion is an atypical antidepressant and it is thought to have both indirect dopamine agonist and noradrenergic effects. Maidment (2003) reviewed the literature examining the efficacy of antidepressants in the treatment of adult ADHD. Of those agents that have undergone controlled trials, he concluded that there is the most evidence supporting the use of desipramine, followed by atomoxetine. Results on bupropion are unclear and there are no definitive data on the effects of venlafaxine.

Antihypertensive agents such as clonidine and guanfacine have been investigated in the treatment of children with ADHD. There drugs are thought to inhibit the release of norepinephrine, increasing dopamine turnover and reducing blood serotonin levels (Barkley, 2004). The antihypertensive agent clonidine has been used increasingly as a second-line medication for treatment of ADHD, particularly among adolescents with hyperactivity and aggressiveness. Although the effect of clonidine is not as robust as that of stimulants, a meta-analysis suggested a moderate effect size (0.58) for this agent on symptoms of ADHD co-occurring with tics, aggression or conduct disorder (Connor et al., 2000). There is little research examining the efficacy of antihypertensive agents on adults with ADHD.

One controlled study examined the effect of guanfacine on ADHD in adults finding that drugs significantly reduced ADHD symptoms relative to placebo (Taylor & Russo, 2001). However, more research is necessary before any firm conclusions can be drawn.

As explained above, pharmacological treatments have several limitations and are not always effective. Particularly, it has been shown that stimulants, that are the most commonly used pharmacological intervention, do not produce long-term changes. For example, Swanson et al. (2003) shows that, despite clear beneficial effects on daily classroom performance (e.g., academic productivity), stimulants have no long-term effects in academic achievement in children and adolescence with ADHD. Similarly, although stimulants clearly improve disruptive behaviour and peer interactions, there is no evidence of long term changes in the interpersonal relationships that are disturbed in adolescents and adults with ADHD (Hinshaw, 1991). Thus, despite the overwhelming evidence for their safety and efficacy in short-term studies, the shortcomings of stimulant medications highlight the need for psychological treatments for ADHD, primarily behavioural interventions.

1.5.2 Behavioural and psychosocial interventions

Behavioural psychosocial therapy is the only empirically validated non-medical treatment for ADHD in childhood (MTA Cooperative Group, 2004; NIH, 2000, Pelham et al., 1998, see Redm). Reviews by Pelham and Hinshaw (1992) and Wells (2000), suggest that empirically validated behavioural psychosocial treatments for ADHD are of two broad types.

The first is clinical behavioural psychotherapy. These studies involve parent and teacher training and consultation in outpatient settings and have found significant improvements in child behaviour across a wide range of domains in both home and school settings on behaviour checklists and through observation. Aggressive

classroom behaviour has been found to be normalized with clinical behavioural psychotherapeutic treatment alone. There is evidence from these studies that combined clinical behavioural psychotherapeutic treatment and medication treatment are superior over either alone. The second type is direct contingency management. These studies have been completed in institutions where close control of contingencies is possible and generally show more significant results than clinical behavioural psychotherapy. An example of a direct contingency management program is Pelham's summer treatment program (Pelham, 2000). In this study, improvements found are typically at the same levels as low dose medication alone; when low dose medications and direct contingency management are combined, the effects are similar to those produced with high dose medication.

Psychosocial interventions and cognitive behavioural therapy (CBT) play an important role in fully treating ADHD in adulthood (Safren, 2006) and there is clear evidence that CBT and psychosocial interventions are an effective alternative treatment for adults ADHD (Stevenson et al., 2002, 2003; Safren et al., 2005). Stevenson et al. (2002, 2003) examined both therapist-delivered and self-directed psychosocial treatments for adults with ADHD. In the therapist-delivered study (Stevenson et al., 2002), 22 adults with ADHD were randomly assigned to the treatment group, and 21 were assigned to the waiting list control group. At the post-treatment assessment, individuals assigned to the treatment condition reported reduced ADHD symptoms, better organizational skills and reduced anger problems. Many of the improvements were maintained at one year follow-up.

In the self-directed study (Stevenson et al., 2003), 17 individuals were assigned to the treatment group, and 18 were assigned to the control group. Statistically significant differences emerged between the two groups, where the treatment ADHD group reported reduced ADHD symptom severity, improvement in organizational skills and self-esteem and reduction in anger. These improvements were maintained at the two month follow-up. The efficacy of CBT has also been

demonstrated (Safren et al., 2005, 2006). Safren et al. (2005) conducted a randomized controlled trial of CBT for adults with ADHD. They found that adults with ADHD that received CBT (n=31) had less severe ADHD symptoms and lower global severity index than those randomly assigned to continued psychopharmacology alone.

Despite the clear evidence of their efficacy, behavioural interventions have several shortcomings, as for pharmacological treatments (Pelham, 1999). Although behavioural interventions improve children greatly, they are less likely than medication to normalize children on parent and teacher rating scales (Pelham, 1993). Moreover, however direct contingency management interventions for children with ADHD show in many cases dramatic improvements, some parents and teachers are unable or are unwilling to implement a complicated behavioural intervention. Even when parents and teachers are willing to initiate elaborate interventions, they typically do not continue them without ongoing consultation (Miller & Prinz, 1990). A final possible limitation of behaviour therapy for children and adults with ADHD is the lack of evidence of long term effects. Demonstration of the continuation and/or maintenance of treatment effects over time are one of the major concerns of those using behavioural interventions (Pelham, 1999).

1.5.3 Multimodal approaches

Both pharmacological and behavioural treatments have recognised limitations, as explained before. These limitations have led to the growing practice of combining behavioural treatments with pharmacological interventions for ADHD.

The Multimodal Treatment Study of ADHD (MTA) sponsored by the National Institute of Mental Health and Department of Education in the U.S.A is the largest randomised treatment study of childhood psychiatric disorder (Root & Resnick, 2003). In this study, 579 children with combined type ADHD, aged between 7 and 9. Nine were randomised to four treatment groups: community care, medical

management, behavioural therapy and combined medical and behavioural therapy. In the initial report the authors found that the combined therapy group and the medical management group had significantly greater improvements than the behavioural therapy or the community care groups on core ADHD symptoms, although the first two groups didn't differ statistically in their level of improvement (MTA Cooperative Group, 1999). However, Conners et al. (2001) subsequently used a single outcome "composite score" analytic approach obtained from combining parent and teacher report score. This outcome measure allowed for measurement using a single composite outcome measure. They found the combined treatment to be superior statistically to all other treatments. The combined treatment approach produced about 12% more successes than the medical management treatment approach alone. Also, the combined approach outcomes were achieved with significantly lower medication doses than were used in the medical management treatment (MTA Cooperative Group, 1999). Those improvements were maintained after 14 months and also 24 months, however a more recent follow-up study by Jensen et al. (2007) showed that the earlier advantage of the combined treatment group was no longer apparent after 36 months, possibly due to age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medications altogether or other factors not yet evaluated. These results stress the efficacy of a multimodal approach for children with ADHD. They especially demonstrate that non-medical treatments can have stronger effects than those of medication (Swanson et al., 2002) and also that those effects were maintained over a 24-month period. Improvements were absent after 36 months, indicating that the issue of treatment's long term efficacy remains open.

Studies using combined CBT and pharmacological treatment have been conducted in adults with ADHD (Rostain et al., 2006; Safren et al., 2005). For example, Rostain et al. (2006) examined the effects of 6 months of combined medication and CBT in a group of 46 adults with ADHD. At post-treatment, ADHD adults receiving combined medication treatment and CBT showed significant reductions

in clinician rated ADHD symptoms with a large effect size. Clinician rated clinical global impression scores for ADHD symptoms were reduced from pre- to post-treatment with a very large effect size. Significant reductions in comorbid anxiety and depression symptoms were also observed for both self-report and clinician ratings of symptoms. It is unclear the extent to which improvements were differentially associated with medication versus CBT, however, the results demonstrate the potential efficacy of a combined treatment package for this population.

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

For these reasons, one major aim of this thesis is to examine the effects of a cognitive strategy, called Self-Alert Training (SAT), for teaching adults with

ADHD to increase their level of alertness and attention by self-alerting. A randomized controlled trial (RCT) has been conducted to this purpose. This study is a logical progression from previous study conducted in our lab by O'Connell et al. (2008), in which it was shown that a very similar training produced significant short-term improvements in a group of adults with ADHD. In Chapter 5 the randomised controlled trial in adults with ADHD is described in details.

Chapter 2 Electrophysiology (EEG) in ADHD research

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

2.1 Human Electroencephalography

Electroencephalography involves placing electrodes on the scalp over multiple areas of the brain to detect and record the patterns of electrical activity generated by neurons by means of an instrument called an electroencephalograph. The electroencephalogram (EEG) is a graphic record of the pattern of voltage variation that is revealed over time in the output from a differential amplifier that has been attached to a pair of electrodes that are, in turn, attached to the human scalp. Action potentials and postsynaptic potentials are the two main types of electrical activity associated with neurons. Due to the timing and the physical arrangement of action potentials it is not possible to detect them at the scalp surface. However there is a general acceptance that the ongoing EEG recorded on the scalp surface derives from summated postsynaptic potentials (Davidson, Jackson, & Larson, 2000). This view is supported by evidence from animal studies that compare intracellular recordings and scalp-recorded EEG (Davidson et al., 2000; Thatcher & John, 1977). Postsynaptic potentials are the voltages that arise when neurotransmitters bind to receptors on the membrane of the postsynaptic cell. Postsynaptic potentials are generally confined to the dendrites and cell body, occur instantaneously, and last for tens or hundreds of milliseconds. When postsynaptic potentials summate it is possible to record them at the scalp. Although the exact biophysical events involved are not known it is thought that current flows from the extracellular space when a neurotransmitter is released, for

example, at the apical dendrite of a cortical pyramidal cell yielding a net negativity in the region of the apical dendrite. The circuit is completed when current also flows out of the cell body and the basal dendrites producing a net positivity in this area. Together the negativity and the positivity create a tiny dipole (a pair of positive and negative electrical charges separated by a small distance). The dipoles from many neurons with a similar orientation (e.g. cortical pyramidal cells) must summate in order to be recordable at the scalp. The voltage present at any point on the scalp is dependent upon the position and orientation of the generator dipole and on the resistance and shape of the brain, skull, and scalp. Electricity spreads out through the brain, and laterally when it encounters the skull leading to a blurring of the surface distribution of voltage and poor spatial resolution. In contrast because electricity travels at the speed of light the voltage recorded at the scalp reflects the activity of the brain with millisecond accuracy. This excellent temporal resolution makes the EEG an ideal choice for studying the neural correlates of behaviour that dynamically changes over time.

The electrical activity of the brain can be described at multiple levels ranging from the currents within a single dendrite to the activity measured by the electroencephalograph (EEG) which aggregates the electrical voltage fields from millions of neurons. Different types of EEG oscillatory activity can be characterised according to whether the rhythms are spontaneous, induced or evoked (Galambos, 1992). This classification is based on the degree to which the oscillations are time locked to a stimulus. Evoked activity is time-locked to the onset of an experimental condition across trials and has the same phase in every trial; induced activity is correlated with experimental conditions but not locked to its onset, and spontaneous activity is not correlated with the occurrence of an experimental condition (Herrmann, Grigutsch, & Busch, 2005). Evoked activity or electrical potentials that show a stable relationship to a definable reference event are called Event Related Potentials (ERPs; Luck, 2005). ERP analysis involves increasing the discrimination between the ERP and the background EEG and averaging samples of the EEG that are time-locked to an event such as the

presentation of a stimulus. These ERPs are small in comparison to the ongoing EEG in which they are embedded. Electrical activity reflected in the ongoing or background EEG can be spontaneous or induced.

2.1.1 Ongoing EEG in ADHD research

In ongoing EEG, multi-electrode recordings are quantified in the frequency range of interest, which usually extends from about 1 Hz to 25 Hz. This frequency range has traditionally been separated into five frequency bands: delta: (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-15.5 Hz), beta (13-30 Hz) and gamma (30-70 Hz).

The commonly used form of EEG analysis in ADHD has been the calculation of absolute and relative power estimates (Barry et al., 2003). These provide an easily interpreted and reliable method of quantifying changes in the EEG under different conditions. Studies in children and adolescents with ADHD have consistently showed increased absolute and relative theta power, reduced beta power, and, generally, reduced alpha power during resting state tasks as well as during cognitive tasks (Bresnahan & Barry, 2002; Lazzaro et al., 1998). Fewer studies have been conducted which investigate differences in absolute and relative power between adults with ADHD and adult controls. Generally, studies suggest that the same EEG abnormalities found in children and adoloescence with ADHD decline with age but are nonetheless still apparent at maturity (Bresnahan & Barry, 2002).

Another useful form of EEG analysis is the ratio coefficients, which is the ratio between different frequency bands used to evaluate changes in the EEG that occur due to normal maturation and as a measure of cortical arousal. As arousal decreases, activity in theta and alpha bands increases while there is a gradual drop in activity in the beta band (Aeschbach & Matthews et al., 1999). Therefore the ratio of slow (theta, alpha) to fast (beta) oscillatory activity, acquired while the participant is not engaged in a particular task, is frequently used as a general measure of basal arousal levels. Research in children with ADHD has shown

increased theta/beta and alpha/beta ratios, indicative of abnormal arousal levels (Clarke et al., 2001 and 2002). Studies have also shown that the theta/beta ratio remains elevated in ADHD from children to adults (Bresnahan & Barry, 2002) and that the ratio distinguished adults who meet ADHD criteria from those with some symptoms of the disorder who failed to meet criteria, indicating some specificity for this marker in ADHD.

EEG relative and absolute power measures and ratio coefficients have been used in all experiments of this thesis as measures of arousal. In chapter 3 and 4 differences in EEG spectral power measures between adults with ADHD and controls have been investigated. In chapter 5, EEG spectral power variables have also been used to evaluate effects of training on arousal levels in adults with ADHD.

2.1.2 Event Related Potentials (ERPs)

Peaks and components are not the same thing and so it is important to draw a distinction between the observable peaks in a waveform and the unobservable latent components (Otten & Rugg, 2005). The voltage deflections observed in an ERP waveform reflect the sum of several relatively independent underlying components, in the absence of direct access to these latent components researchers can only make inferences about them from the observed waveforms (Otten & Rugg, 2005).

The concept of the component facilitates communication across experiments, paradigms and scientific fields, allows the integration of ERP data with other measures of brain activity and can act as a marker of cognitive processes (Otten & Rugg, 2005). However, there is no universally accepted definition of what constitutes an ERP component. The voltage deflections observed in a waveform may be the summation of contributions from a variety of origins and may reflect functionally heterogeneous neural or cognitive sources (Otten & Rugg, 2005). A

number of approaches to component definition that span the extremes of physiological and functional viewpoints have emerged from ERP research. Physiological proponents (Naatanen & Picton, 1987) advocate the definition of ERP components in terms of their anatomical source within the brain, an approach that necessitates the isolation of cerebral sources underlying ERP waveforms in order to facilitate component measurement. In contrast, a functional approach (Donchin, 1981) requires that the component be defined predominantly in terms of the functional processes with which it is associated. This view makes it irrelevant whether the component reflects the activity of one or multiple generators within the brain as long as these generators constitute a functionally homogenous system (Fabiani et al., 2000; Otten & Rugg, 2005). Physiological and functional/psychological approaches are not mutually exclusive and in practice components can be defined operationally as a part of a waveform with a delineated scalp distribution and delineated relationship to experimental variables (Otten & Rugg, 2005). A classic approach (Donchin, Ritter, & McCallum, 1978) defines a component by a combination of its polarity, characteristic latency, scalp distribution and its sensitivity to characteristic experimental manipulations.

The letters *P* and *N* traditionally designate positive-going and negative-going peaks respectively. At present there is no universally agreed convention for plotting ERP waveforms with some researchers plotting negative voltages up and others plotting positive voltages as up. This study adopts the latter approach because the wider scientific community uses a positive-up convention. It is important to note that the polarity of an ERP effect has no particular physiological or functional significance because it is contingent on a number of neurophysiological and non-neurophysiological factors including the baseline against which the effect is compared, the location and orientation of intra-cerebral sources, whether input is inhibitory or excitatory, or whether input is received via synapses distal or proximal to the cell bodies (Otten & Rugg, 2005; Wood, 1987). Peaks can be labelled according to their ordinal or temporal latency. When the letters P and N are followed by a single digit (e.g. N1, P3) the number simply

refers to the peak's ordinal position within the waveform. However it is also common to label components according to their exact latency (e.g. P225) or approximate latency (e.g. N100, P300). The latency of a component can vary across experiments, across conditions of an experiment and within conditions across electrodes. The final two descriptors used to define components refer to the scalp location (e.g. frontal P300) or the experimental manipulation (e.g. novelty P3 or readiness potential).

Components can also be distinguished according to whether they reflect sensory or cognitive processing. From a psychological perspective components can be characterised along a continuum that runs from exogenous, through mesogenous, to endogenous (Fabiani et al., 2000). Obligatory responses that are primarily influenced by the physical properties of an external eliciting event are referred to as exogenous or 'sensory'. In contrast endogenous potentials are thought to reflect information processing in the brain that may or may not be invoked by the event (Picton et al., 2000). These components are influenced by factors such as attention, task relevance, type of processing required by the stimulus and can even be elicited in the absence of an event, for example, when an expected target does not appear (Coles & Rugg, 2002).

Although sensory components in all modalities are considered obligatory because they are elicited in all individuals with intact sensory systems, on all occasions, they are also modifiable because they are modulated by attentional and task parameters (Coles & Rugg, 2002; De Sanctis et al., 2008; Dockree, Kelly, Robertson, Reilly, & Foxe, 2005). Scalp voltage oscillations elicited by the presentation of stimuli in visual, auditory, and somatosensory modalities are thought to be related to the transmission of the signal generated at peripheral receptors to the cortex and/or the arrival of that information in the cortex (Coles & Rugg, 2002; Fabiani et al., 2000). It is thought that extremely short deflections (e.g. <10ms) reflect the transmission of sensory information in the sensory pathways whilst later deflections (e.g. up to 100ms) reflect the arrival of the

information in the modality relevant areas of the cortex (Coles & Rugg, 2002). Only later deflections are evident in the visual modality, most probably due to the closed field configuration of the sensory relay nuclei (Coles & Rugg, 2002).

Potentials that are sensitive to both the physical properties of the stimulus and the nature of the participant event interaction can be referred to as mesogenous (Fabiani et al., 2000). The exogenous-endogenous continuum can be described as roughly coextensive with time wherein components that occur within the first 100ms post-stimulus tend to be more exogenous and those that occur later tend to be more endogenous in nature. However it should be noted that recent evidence suggests that endogenous processes can affect visual components as early as the C1 (~50ms), a component that up until very recently was thought to be purely exogenous and impenetrable to endogenous processes (Kelly, Gomez-Ramirez, & Foxe, 2008). Sensory components tend to have less individual variability when compared to later more cognitive processes which tend to demonstrate greater spatial variability across subjects (Handy, 2005). It is important to note that although components are labelled according to their polarity and position within the waveform, sensory components from different modalities given the same label are not usually functionally related (Luck, 2005). Even within a modality components given the same label in different experiments may not be the same. Components can also be classified based on their relationship to a response or on whether they precede or follow events.

ERPs provide a solution to the major limitation of testing by behavioural means alone. Simple behavioural measures, such as reaction time, can be the product of the compound contributions of several different cognitive functions. ERPs allow one to fill the gap between stimulus and response by providing a direct insight into timing of covert cognitive processing activities in the brain. The importance of this kind of information is most obvious in the case of neurological conditions such as ADHD where neuropsychologists have struggled to disentangle

overlapping cognitive deficits and to identify an accurate neuropsychological profile that distinguishes it from other disorders.

2.1.2.1 Event-Related Potentials (ERPs) studies in ADHD

Most studies of children with ADHD have focused on P3-type components. P3 components can be divided into three broad categories; the no-go P3, the P3a and the P3b (see Polich & Criado, 2006 for review). The no-go P3 is commonly seen on trials that require to withhold a preponent response and is thought to index response inhibition (Polich & Criado et al., 2005). The P3a or 'oddball P3' is elicited by unexpected or rare stimuli and reflects orienting aspects of attention. P3b components can be distinguished from P3a by their more posterior scalp distribution and can be elicited by motivationally significant stimuli or events (Polich & Criado, 2005). Different theories of the P3a and P3b suggest that they represent an updating working memory (Donchin & Coles, 1988) or a facilitation of task-related brain regions mediated by ascending sub-cortical arousal systems (Niuewenhuis et al., 2005). P3 components are largely endogenous and can be present even in response to an expected missing stimulus and have larger amplitudes under attention demanding conditions (Polich & Criado, 2006). As a result, although their function is still controversial, P3 components are frequently used as an index of the endogenous mobilisation of attentional resources in response to a critical event. Reduced P3a and P3b components have been observed on a range of different tasks in both children (Brown et al., 2005; Jonkman, 1997; Satterfield, 1990; Senderecka et al., 2012) and adolescents (Du et al., 2006; Lazzaro et al., 2001) with ADHD. In a study by Brown et al. (2005) children with ADHD exhibited a reduced P3 amplitude to both visual non-target and auditory target stimuli in a multi-modal oddball task. Another study by Du et al. (2006) showed that adolescents with combined ADHD and conduct disorder (CD) had reduced P3 latency and amplitude in an auditory single-stimulus oddball task. Studies on adults with ADHD using oddball tasks and go-nogo tasks (Barry et al., 2009; Prox et al., 2007) have revealed a tendency toward decreased P3 activity; however, in these studies differences were not significant. The latency of

the P3 component is believed to reflect the timing of stimulus evaluation processed. Mixed results have been reported in relation to ADHD (Johnstone & Barry, 1996; Lazzaro et al., 2001; Barry et al., 2009).

Recent studies have agreed that the strongest effect sizes are obtain when individuals with ADHD are asked to perform tasks that require response inhibition (Liotti et al., 2010; Seidman, 2006). Response inhibition is most frequently measured using go/no-go tasks in which participants make speeded responses to a series of go stimuli but must withhold responding on the appearance of the no-go stimulus. As would have been predicted, studies that have recorded ERPs while participants performed such tasks have found differences in componentry relating to response inhibition (no-go N2 and no-go P3). But these studies have also reported that the clearest group differences were seen on components relating to the allocation of attentional resources, response preparation processes and the orientation to no-go stimuli (Banaschewski et al., 2004; Polich & Criado et al., 2006). The behavioural deficit in response inhibition therefore appears to be preceded by deficiency in state regulation and attentional control throwing doubt on the idea that a basic inability to inhibit a preponent response is the core deficit. In this case, results relative to behavioural measures alone may have led to a misinterpretation of ADHD deficits.

Finally, other ERP studies of ADHD have examined earlier auditory and visual attention processing reflected in components such as P1, N1 and P2.
The component N1 is generally thought to represent the initial extraction of information from sensory analysis of the stimulus, or the excitation associated with allocation of a channel for information processing out of the primary cortex. Generally, studies suggest that N1 is reduced in children and adolescents with ADHD (Satterfield et al., 1994; Kemner et al., 1996). However, research also found an age-specific effect, suggesting that ADHD and control participants are differentiated by N1 at about 7-9 years of age only (Johnstone et al., 2001). Fewer

studies have been conducted on adults with ADHD. In a recent study (Barry et al., 2009) adults with ADHD were compared to matched controls in an inter-modal auditory/visual oddball task. N1 was increased in adults with ADHD compared to controls and authors suggested potential early sensory processing impairments. Increased N1/N2 complex was also found in another study on adults with ADHD using a go-nogo task (Prox et al., 2007). There is also evidence of decreased N1 amplitude, as in a study (Kenemans et al., 2005) in which adults with ADHD were compared to controls using a stop-signal task. N1 was not larger in adults with ADHD when the button press was successfully inhibited suggesting, in this case, a failure of selective attention to stop signals.

In the context of an oddball task, the P2 component may represent inhibition of sensory input from further processing via automatic stimulus identification and discrimination/classification, or inhibition of other channels of information competing for attention and further processing (Barry et al., 2003). Studies (Satterfield et al., 1994; Kemner et al., 1996) suggest that in three tone oddball tasks, P2 to novel stimulus is larger in children with ADHD compared to controls on target stimuli. These findings apply also to adolescents with ADHD (Lazzaro et al., 2001). Furthermore, in Satterfield et al.'s study (1994), P2 was also found to be increased in children and adolescents with ADHD on standard tones. Interpretations of these results include atypical inhibition of sensory input from further processing (Johnstone et al., 2001), while the larger P2 to standard stimuli suggest that these relatively unimportant stimuli are likely to be processed without competition to the response-elicitation stage (Oades et al., 1996). P2 component was significantly increased in a study on adults with ADHD using an inter-modal auditory/visual oddball task on both target and standard stimuli by Barry et al., 2009.

ERP studies which have focused on the visual attention system, have reported group differences in the early components elicited by visual stimuli. Reduced P1 responses in children with ADHD revealed a decreased attentional priming effect

on early sensory responses (Perchet et al., 2001). Studies in children and adolescents with ADHD found larger P2 amplitude to standard stimuli in oddball tasks and continuous performance task (CPT) (DeFrance et al., 1996).

This brief review of ERP studies in ADHD suggested that several ERP markers might be impaired in ADHD. N1 and P1 components that index primary sensory processing of tasks stimuli have been found to be reduced in ADHD thus indicating specific difficulties at very early stages of stimulus elaboration. These impaired primary sensory mechanisms might then affect the tasks' stimuli elaboration at later stages leading to inattention. Findings on P2 ERP component indicate increased P2 to both target and standard stimuli in different tasks. Given that the P2 component may represent inhibition of sensory input from further processing via automatic stimulus identification and discrimination/classification, or inhibition of other channels of information competing for attention and further processing (Barry et al., 2003), increased P2 on standard-irrelevant stimuli might indicate that too much attention is given to task-irrelevant information while the increased P2 on target might indicate atypical inhibition of sensory inputs. Findings related to the N2-P3 complex and the later no-go P3, that index response inhibition, also seem to suggest a central deficit in inhibition at later stages of the stimulus elaboration. This may point to a central executive deficit in inhibitory processes which might explain ADHD impaired performance, as suggested by classic cognitive models of ADHD (Barkley, 1997). Finally, it must be stressed that although findings on children and adolescences with ADHD seem quite consistent, more studies are needed to explore ERP correlated in adult ADHD. In fact fewer studies have been conducted on adults with ADHD and their results are less consistent that findings in younger population.

As this brief review of ERP studies in ADHD suggests, the use of electrophysiological measures may provide a more parsimonious representation of neuropsychological deficits in ADHD. In chapter 3, EEG and Event Related Potentials (ERPs) measures have been employed in combination with

pupillometry to investigate the neurophysiological underpinnings of sustained attention deficits in adults with ADHD. In chapter 4, the Continuous Temporal Expectancy task (CTET) was employed for the first time to compare adults with ADHD to control participants to uncover electrophysiological signatures of an upcoming attentional failure in adult ADHD. EEG and ERP measures have also been used in chapter 5 to evaluate the effects of Self-Alert Training on sustained attention in adults with ADHD.

Chapter 3. Sustained attention deficits in adult ADHD

3.1. Sustained attention deficits in ADHD

Poor sustained attention is a defining characteristic of the ADHD syndrome, as stated in the DSM-IV criteria (A.P.A., 2000): "often has difficulty sustaining attention in tasks or play activities", "avoids tasks requiring sustained effort" and "often fails to give close attention to details or makes careless mistakes in school work, work or other activities".

Sustained attention deficits in people with ADHD are evident in everyday life situations requiring attentional effort for a long period of time. For example, a child with ADHD usually experiences no difficulties in performing challenging video games for long time, but he/she struggles to sustained attention when completing maths problems (Barkley, 1998). The difference here is that the exogenous stimulation provided by the video game colours, its fast movements and exciting sound can actually capture a child's attention. As a result, the demands placed on the sustained attention system are very small. In contrast, boring and repetitive maths exercises require an extensive attentional effort, therefore making the task difficult to complete for a child with ADHD.

There is ample evidence of sustained attention deficits in ADHD within the literature. For example, in a systematic review conducted by Losier and colleagues (1996), 26 studies, in which different variants of the Continuous Performance Task (CPT) were employed to test children with ADHD, were submitted to a meta-analytic procedure. The CPT is the most popular computerised test of sustained attention and in its original version, it requires participants to respond to a target letter (e.g. X) embedded in the successive singular presentation of non-target letters. In this study, authors aimed to systematically review the pattern of CPT errors of omission and commission

exhibited by normal children and children with ADHD under no drug, placebo and methylphenidate drug conditions. In this way, it was possible to separately investigate the effect of drugs on children's performance in the CPT. The meta-analysis revealed that children with ADHD who were not receiving drug treatments, made significantly more errors of omission and commission than control children. Results also showed that children with ADHD treated with methylphenidate exhibited statistically significant reductions in the rate of both errors types. In another review study conducted by Wood and colleagues (2002), performance at the CPT in adults with ADHD were examined. It was found that overall the CPT findings in adults with ADHD were largely consistent with the paediatric and adolescent literature. In the current review, 92% of the studies that used a CPT version for testing participants reported significant differences between adults with ADHD and controls as at least one CPT variable. Significant CPT findings were most commonly reported on measures of commission errors, omissions and summary impairment indices (Wood et al., 2002).

Previous studies conducted in our research lab (Bellgrove et al., 2006; Johnson et al., 2007; Mcavinue et at., 2012; O'Connell et al., 2004 & 2006) have repeatedly shown that children with ADHD exhibited impaired performance in the Sustained Attention to Response Task (SART). The SART requires participants to respond to non-target stimuli while withholding their response in appearance to no-go targets. The simplicity of the SART tends to encourage a routine response set, placing heavy demands on the individual's ability to endogenously maintain the overall goal of withholding to the no-go target during the inter-target intervals. These demands are particularly apparent in a fixed sequence version of the task, in which the digits 1-9 are presented in a predictable and repeating sequence and participants are simply asked to withhold their response to the 3. Previous work has established the SART's sensitivity for indexing self-reports of everyday attentional failures (Dockree et al., 2004). Further, another study (Manly et al., 2003) has demonstrated that the endogenous maintenance of attention on the SART activates right fronto-parietal attentional networks that appear

dysfunctional in ADHD. Thus is can be argued that the SART is sensitive measure of momentary lapses of attention. In O'Connell et al. study (2006) it was demonstrated that children with ADHD made more errors of commission, more omissions and they also exhibited higher RT variability in the SART. Similar results were shown in Bellgrove et al. study (2006), in which children with ADHD performed poorer in the SART compared to a group of matched control children. O'Connell and colleagues (2008) also showed that the same impairments in the SART were apparent in adults with ADHD. Their study was aimed to test the efficacy of a new alertness training strategy aimed to transiently increase levels of arousal in adult controls as well as in a group of adults with ADHD. Participants in both groups were assessed before and after the training using four blocks of the SART. Comparisons of performance at the baseline pre-training assessment revealed that adults with ADHD made significantly more errors of commission and omission and they also showed higher RT variability, indicative of sustained attention deficits.

Another sensitive measure of sustained attention impairments in ADHD is the analysis of periodic changes in reaction times (RTs). This method was developed in recent years by Castellanos and colleagues (2005). The analysis technique employed, called Fast Fourier Transform (FFT) is able to measure the power of periodic changes in RT at different temporal frequencies or, in other words, the degree at which periodic patterns of certain time-scale exist within the RT data series. It was found that a group of children with ADHD performing a Flanker Task showed significantly more variability in RT within in the frequency range 0.02-0.07 Hz, compared with controls. The same method was employed in recent studies conducted in our lab by Johnson and colleagues (2007). Johnson and colleagues (2007) compared children with ADHD with control children using the fixed version of the SART and they analysed the nature of RT variability in the task using Castellanos' method. They found that children with ADHD showed greater variation in response time in the low frequency bands over the course of the 5 minutes SART than control children and they suggested that this is related to

a deficit in arousal. Furthermore, results indicate that children with ADHD showed a consistently poor performance in fast-frequency variability in RT, and in commission and omission error rates. It is argued that these deficits may be due to particular difficulties in sustaining attention over short time-periods and may be reflective of frontoparietal dysfunction.

3.2 Sustained attention and its links to the arousal system

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

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

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

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

The "alerting" component of this model bears a close relationship to the cognitive concept of sustained attention.

Sustained attention has been defined as: *'the ability to self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing qualities would otherwise lead to habituation and distraction by other stimuli'* (Roberston et al., 1997, pp 747).

In the last few decades, researchers have made use of technological advances in human brain mapping which provided a clearer understanding of the attention system. Gathering together the available evidence from more recent fMRI, PET and pharmacological studies, Sturm and Wilmes (2001) observed that an amodal sustained attention system has been consistently localised to a right lateralised cortical network that includes the ACC, the right dorsolateral prefrontal cortex and the inferior parietal lobe.

Investigation of the cytoarchitecture of the human brain stem indicates that subcortical nuclei have multiple ascending pathways each linked to different neurotransmitters and each projecting to different regions of the cortex (Olszewski & Baxter, 1982). Arousal within cortical regions is dependent on these innervatory pathways. Sustained attention has been most closely associated with the action of the neurotransmitter noradrenaline (NA) which is produced by the locus coeruleus (LC) and has its strongest projections in the right-fronto parietal regions (Foote & Morrison, 1997). Astone-Jones, Chiang and Alexinsky (1991) acquired extracellular recordings from noradrenergic neurons in the LC of the monkeys performing a visual discrimination task. It was found that LC responses varied with behavioural performance and were attenuated during periods of poor performance. LC responses became reduced in magnitude over time in parallel with a behavioural performance decrement supporting the view that LC activity is linked to sustained attention and arousal.

Additional evidence of the neuroanatomical basis for the attention-arousal coupling has been found in a relevant study by Usher and colleagues (1999). In this study it was found that LC activity correlates closely with behavioural performance when monkeys had to detect relatively rare visual targets among

foils, but optimal performance was achieved not at maximum levels of LC activity, but rather than at intermediate levels. In a comprehensive review of cathecolamine modulation of prefrontal cognitive functions, Arnsten (1998) showed that many studies have confirmed Usher and colleagues by showing a Yerkes-Dodson type of inverted U relationship between levels of noradreline release, on the one hand, and behavioural performance on the other (Arnsten, 1998). In that review Arnsten concluded that different neuropsychiatric conditions may reveal impairments in executive control of complex behaviours for reasons of either deficient or excessive levels of noradrenaline.

The influence of noradrenaline (NA) mediated arousal on sustained attention in humans was firstly demonstrated by Smith and Nutt (1996) who found that reducing NA release by administering the drug clonadine resulted in an increase in the kinds of attentional lapses characteristic of poor sustained attention.

Additional evidence of the close connection between attention and arousal can be found in a study by Paus and colleagues (1997) in which healthy participants were asked to perform a simple vigilant attention task for approximately 60 minutes. Every 10 minutes regional cerebral blood flow and EEG were measured. Significant reductions in blood flow were observed in subcortical structures, the thalamus and putamen, and right hemisphere cortical regions, including frontal and parietal cortex. These blood flow reductions were interpreted by the authors as indications of a subcortical arousal system and right cortical attentional system respectively. Increases in low theta activity, associated with a reduction in arousal were also observed on the EEG as the task progressed.

More recent evidence of the influence of the noradrenergic arousal system on sustained attention is found in a genetic study conducted in our research group (Greene et al., 2009) that demonstrates an association between a functional DBH gene polymorphism and sustained attention in healthy adult participants. DBH plays a critical role in controlling the balance of dopamine and noradrenaline

available in the cortex. A number of polymorphisms at and near the DBH gene have been associated with variation in DBH activity. In particular, it has been suggested that the T allele of C−1021T diminishes gene transcription, resulting in lower levels of DBH than the C allele (Cubells and Zabetian, 2004). In Green et al. study (2009), DBH genotype could predict sustained attention lapses. Participants with more copies of the DBH T allele committed more errors of commission in the SART, as demonstrated by fMRI studies (Manly et al., 2003), than those with fewer copies. These participants also tended to make more errors of omission and to react more quickly, but these differences were not statistically significant. The T allele leads to a slower rate of dopamine–noradrenaline conversion than the C allele (Zabetian et al., 2001), and is therefore presumed to result in higher levels of extrasynaptic dopamine and relatively lower levels of noradrenaline. It is argued that the reduced availability of noradrenaline occasioned by the T allele may have reduced participants' capacity to remain alert throughout the task. An alternative explanation may be that the T allele is linked with a faster, more impulsive style of responding than the C allele. However, in this study, a notable, though statistically insignificant, increase in errors of omission in participants with two copies of the T allele was found, supporting the notion of a drifting of attention in these participants and a general failure to stay on task.

To summarise, as the cited evidence of animal and human studies have demonstrated, the arousal and the sustained attention systems share common structures and they mutually influence one another. A crucial role seems to be played by the noradrenaline (NA), which is produced in the locus coeruleus (LC) and it regulates the arousal-alertness system. NA has been found to be associated with the sustained attention system in human studies and it has been demonstrated that NA availability in the brain influences performance of participants in sustained attention tasks.

Recently in another study conducted in our group (Bellgrove et al., 2006), the relationship between NA and sustained attention deficits in ADHD was investigated exploring the link between genetic variation in a catecholamine-related gene, dopamine beta hydroxylase (DBH) and sustained attention deficits. As explained previously for Greene et al. study (2009), DBH encodes the enzyme that converts dopamine to noradrenaline and is crucial to catecholamine regulation. Results of this study indicate that a specific variation of a polymorphism with the DBH gene was associated with ADHD. Specifically, children with ADHD possessing two copies of the ADHD-associated risk allele (A2) had significantly poorer sustained attention in the SART than those ADHD children who did not posses this allele or a non-genotyped control group. This finding is relevant as it demonstrates that sustained attention in ADHD is affected by a DBH gene variant which regulates noradrenergic availability in the brain.

As reviewed previously, sustained attention deficits have been well documented within the ADHD literature. Particularly, these attentional impairments are characteristic of the inattentive subtype of ADHD and they also become the predominant symptom of the adult form of the disorder (Seidman et al., 2006), as explained in the introduction of this thesis. This pattern of sustained attention deficits may be caused by deficiencies in brain areas linked to the sustained attention-arousal network. Abnormalities in right fronto-parietal areas which are part of the fronto-parietal attentional network, have been documented in ADHD (see Bush 2010 for a review). Furthermore, the remarkable responsiveness of these attentional deficits in ADHD to methylaphenidate or amphetamine, drugs that potentiate noradrenergic as well as dopaminergic release, also link the sustained attention and arousal system to this clinical syndrome. It is possible that the sustained attention deficit in ADHD is due to an underactive arousal system, as suggested by Zentall & Zenatll (1983). In this study it is suggested that, according to the optimal stimulation theory, children with ADHD suffer from a state of underarousal which results in hyperactive behaviours and in the inability to sustain central task attention.

In this chapter the neurophysiological underpinnings of the sustained attention deficits in adults with ADHD will be explored using EEG, Event-Related potentials (ERPs) and pupillometry. Another aim of the study is to test the hypothesis that an impairment in noradrenergic dysfunction may underlie this deficit will be explored.

3.3 Electrophysiological measures, pupil measures and sustained attention

In chapter 2, electrophysiological studies conducted in ADHD were reviewed and the usefulness of EEG and Event-Related Potentials (ERPs) measures in uncovering neuropsychological deficits in this syndrome have been demonstrated. For example, on going EEG measures cortical arousal and impaired levels of arousal have been found in ADHD, as expressed by higher rates of EEG slow waves (e.g. elevated absolute and relative theta power) and reduced EEG fast waves (reduced beta absolute and relative power) in children and adolescents with ADHD compared to matched controls (Bresnahan & Barry, 2002; Lazzaro et al., 1998). These deficits seem to persist, however attenuated, in adults with ADHD (Bresnahan & Barry, 2002). ERP have been employed in ADHD research and they gave invaluable contributions for disentangling cognitive deficits in ADHD. Particularly, consistent findings of ERP studies in children and adolescents with ADHD have pointed to significant reductions of the P3 ERP component, which is know to index endogenous maintenance of attention. Fewer studies have been conducted in adults with ADHD that, nonetheless, have reported a persistent reduction of P3 amplitudes, consistently with children and adolescents findings. However, more ERP studies are needed in adults with ADHD.

One measure of arousal which has not thus far been applied to an ADHD population is that of pupillometry. Pupil diameter has been found to be a reliable indirect measure of the activity of the locus coeruleus-noradrenergic (LC-NE)

system (Gilzenrat et al., 2010; Beatty, 1982; Aston-Jones et al., 1994) and strong relationships exist between LC activity and performance in sustained attention tasks (Aston-Jones et al., 1981 & 1988, Nieuwenhuis et al., 2005). In the next sections the close link between pupil measures and LC activity as well the link between these measures and tasks performance will be described.

3.3.1 LC-NE system, tasks performance and pupil measures

Studies have supported the notion of a role for the LC-NE system in optimising task performance and engagement. The search for good physiological candidates of the LC activity has recently become a crucial challenge, as suitable physiological measures of LC modes only are able to tap directly into the LC tonic and phasic shifts observed in this system.

The role of the LC in maintaining arousal and its involvement in the sleep-wake cycle has been documented in the literature in classic studies of the 'ascending reticular activating system' (Moruzzi & Magoun, 1949; Aston-Jones & Bloom, 1981). The LC activity has been found to be enhanced during periods of alertness and engagement in the environment and diminished during periods of quiescence or drowsiness.

Such findings focus on the so called *tonic* activity of the LC, as they describe the LC activity as a continuum, which varies depending on levels of arousal and alertness and behavioral engagement. A number of other studies, however, have revealed a distinction between such tonic activity and a *phasic* LC activation that accompanies presentation of particular kinds of stimuli. Tonic activity typically varies between 0 and 5 Hz, whereas the phasic response can be as high as 20 Hz (Nieuwenhuis, Aston-Jones, & Cohen, 2005). Studies have demonstrated that the phasic LC response is evoked following salient, behaviorally-relevant stimuli that elicit some kind of behavioral response (Aston-Jones & Bloom, 1981; Grant, Aston-Jones, & Redmond, 1988). The phasic response is also not specific to any

particular sensory attribute of such relevant stimuli and occurs even when these target-stimuli are presented on every trial of a given paradigm, while it is absent to behaviorally-irrelevant or distracter stimuli (Aston-Jones et al., 1994).

Importantly, relative levels of tonic and phasic LC activity exhibit a very strong relationship with performance on a variety of tasks requiring attentional engagement or high level of alertness.

Studies found that the phasic locus coeruleus (LC) response is largest when animals are performing well in vigilance tasks. For example, in Aston-Jones et al study (1994), monkeys performing an oddball stimulus detection task exhibit high phasic LC activity during periods of high target detection accuracy. Periods of such good performance are accompanied by moderate to low tonic levels of LC activity. In contrast, periods of elevated tonic LC activity are associated with an attenuated or absent phasic response to task-relevant stimuli and poor performance. This is congruent with previously cited observations that low tonic LC activity accompanies drowsy and disengaged behaviour (Aston-Jones & Bloom, 1981; Rajakowski et al., 1994). At the other extreme, high tonic activity is associated with more false alarms, wider RT distributions and generally poor target discrimination (Aston-Jones, Rajakowski et al., 1996; Usher er al., 1999). These findings are consistent with a role for the phasic response in facilitating task-relevant responses and optimal performance, with poor performance coincident with its diminution or absence.

Pharmacological studies in humans also supported the causal role of LC activity on participants' performance. For example, in one of the few fMRI studies to successfully isolate LC activity, Minzenberg and colleagues (2008) recently investigated the effects of modafinil administration on healthy humans on LC activity and performance during a cognitive control task. Modafinil is a non-amphetamine psychostimulant that has the indirect effect of elevating synaptic NA and dopamine (DA) levels in various areas of the prefrontal cortex and

elsewhere. Modafilin was found to induce a low tonic, high phasic mode of LC activity which, in a subset of participants, had the effect of increasing their task performance.

Early animal studies have investigated the link between the LC modes, task performance and pupil diameter measures demonstrating that pupil diameter is a good physiological candidate that can reliably reflect LC tonic and phasic shifts that occur during tasks performance.

For example in a study by Rajkowski et al. (1993), monkeys performed a simple target detection task and their pupil diameter measures were taken by a remote eye-tracking camera at each instant in time at which the monkey achieved fixation of a visual spot during the target detection task. The authors found that baseline pupil diameter (recorded at the onset of each trial of the experiment) closely tracked LC tonic discharge frequency. It was concluded that pupil diameter varies with LC mode, such that the LC tonic mode is marked by a relatively large baseline pupil diameter and the LC phasic mode is marked by a relatively smaller baseline pupil diameter.

Pupil diameter represents an ideal measure to employ also in human studies, as it is a non-invasive index and it can reliably account for changes for LC modes with minimal interference.

The validity of pupil diameter as a physiological measure of LC-NE activity in humans was demonstrated in more recent studies (Hou et al., 2005; Morad et al., 2000). Such studies have shown that baseline pupil diameter increases with tonic LC activity in humans. For example, it has been shown that spontaneous and drug-induced drowsiness and other low-arousal states, which are characterized by low tonic LC activity, are accompanied by reduced baseline pupil diameter in men (Hou et al., 2005; Morad et al., 2000). Conversely, it was shown that noradrenergic drugs that increase arousal and tonic LC activity (clonidine) also

increased baseline pupil diameter in healthy human volunteers (Phillips et al., 2000).

The relationship between phasic locus coeruleus (LC) activity and pupil diameter has been investigated in humans in a large number of studies that have shown that task processing is accompanied by rapid and dramatic pupil dilation (Beatty, 1982; Einhauser et al., 2008). In an early review of pupil diameter studies, (Beatty, 1982) it was concluded that the magnitude of pupillary dilation appears to be a function of processing or "mental effort" required to perform cognitive tasks. Studies reported in this review have repeatedly shown that pupil size variation is positively correlated with the intensity of stimuli (e.g. varying tones) or the difficulty of the task (e.g. increasing load on memory). For example, greater pupillary dilation has been found in a study using a short-term memory task (Peavler at al., 1974). In this experiment the task-evoked pupillary response for strings of 1 to 7 digits randomly intermixed in presentation were measured. During presentation of strings pupillary diameter increased as an increased function of memory load for digit 1 through 7. These results indicate that increasing memory load is reflected in increased pupillary dilation. A similar relationship between processing required to perform tasks has been demonstrated in perception studies using visual and auditory perceptual tasks (Beatty & Wagoner, 1978).

Importantly, pupil diameter seems to operate as an index for attentional fluctuations in sustained attention tasks. For example, an early study by Beatty & Wagoner (1978) explored the changes in pupil diameter in an auditory oddball task. In this experiment the task-evoked pupillary responses to non-target stimuli were recorded. Non-target stimuli were 50 msec 1 Hz tone presented at intervals of 3.2 sec and randomly intermixed with target tones. Results showed that the efficiency of target/non-target discrimination dropped as a function of time over the 48 minutes of the task. The amplitude of the task-evoked pupillary response showed a similar reduction, indicating reduced pupillary responses from the first

third of the task to the last third. Furthermore, tonic or baseline pupillary diameter exhibited no such relation with performance. These results suggest that, in this study, phasic pupil dilation could index decreased performance in a sustained attention task.

Finally, a recent study conducted in our lab has provided the first detailed examination of the relationships between single-trial measurements of the P3 potential and pupil diameter in the context of extended performance of an auditory version of the oddball task. The goals of this study were twofold: first, to further support the use of prestimulus pupil diameter as an index of fluctuations in task engagement predicted by the adaptive gain theory and, second, to establish the extent to which the P3 component shows sensitivity to these same changes. The primary analyses of this study focused on sorting and binning each participant's epochs according to different variables of interest: pretarget pupil diameter, P3 amplitude, pupil dilation amplitude, and time on task. Because the present study sought to elucidate the relationship of these measures to the hypothesized Yerkes–Dodson LC-NE arousal function, it was chosen to bin epochs into quintiles: this facilitated the investigation of possible quadratic trends in the data while also ensuring sufficient epochs per bin. Therefore, analyses of this study proceeded in four steps: the first step was aimed to examine the relationship between pretarget pupil diameter and task performance; in the second step, it was probed how phasic pupil dilations related to task performance dynamics; the third step aimed to investigate the extent to which the P3 component related to these measures; and lastly, we time on- task effects across measures were investigated. Results of the study showed that baseline, prestimulus pupil diameter exhibited a significant inverted U-shaped relationship with both P3 amplitude and task performance such that the largest P3 amplitudes and optimal performance occurred at the same intermediate level of prestimulus diameter. Therefore these results provide indirect evidence in humans that the P3 may index LC-NE mode. In addition, it was found that large phasic pupil dilations, hypothesized to be a physiological marker of the LC phasic response (Gilzenrat et al., 2010), were preceded by a

progressive degradation in task performance and immediately followed by a re-engagement in the task and P3 components of increased amplitude. These finding are relevant as they demonstrated for the first time that pupil diameter and the P3 closely mirror the changes in task engagement that are predicted by the adaptive gain theory of LC-NE function in healthy control participants.

Consistently with Beatty & Wagoner. study (1978), this study showed that during the course of a sustained attention task, reductions in phasic pupil dilation were associated with degraded tasks performance. Another important implication of this study is that, while pupil dilation is an indirect measure of LC activity and therefore it may not be directly under the control of the LC, pupil dilation may serve as a very useful 'reporter variable' of the LC-NE activity in the same way as it has previously been employed as a reliable index of cognitive processing (Beatty et al., 1982; Beatty & Wagoner, 1978).

As explained before, the purpose of the current study is to further explore neurophysiological underpinnings of sustained attention deficits in adults with ADHD using EEG, ERP and pupillometry. Particularly, pupillometry has never been used to compare adult controls with adults with ADHD.

As previous studies have shown (Bresnahan & Barry, 2002; Barry et al., 2009; Prox et al., 2007), adults with ADHD showed impairments in EEG and Event-Related Potentials (ERP) measures related to arousal and sustained attention. It is therefore hypothesised that similar deficits will emerge in our study. Particularly, it is expected to see differences between adults with ADHD and control in the key P3 ERP component, which has been related to endogenous attentional maintenance and it was suggested to represent facilitation of task-related brain regions mediated by ascending sub-cortical arousal systems (Niuewenhuis et al., 2005).

In the cited studies, the close link between sustained attention and arousal has been elucidated and evidence of the influence of the LC-NE arousal system on sustained attention in healthy participants as well as in people with ADHD (Greene et al., 2009) has been provided. In this context, a reliable indirect index of noradrenergic LC tonic and phasic shifts is pupil diameter and studies have shown that pupil diameter relates to performance in sustained attention tasks (Beatty & Wagoner, 1978; Murphy et al., 2011). Particularly, these studies have shown that decreased phasic pupil dilation, indicative of decreased phasic LC activity, was related to impaired sustained attention performance. Therefore, in the current study differences in pupil measures between adults with ADHD and a group healthy matched controls will be explored. The prediction is that significant differences in pupil measures between adults with ADHD and controls will emerge indicative of sustained attention deficits. To further corroborate the link between pupil measures and sustained attention, correlations between pupil measures and ADHD symptoms, behavioural measures and ERP measures respectively will be carried out. In light of the evidence that links the LC-NE arousal system to sustained attention, it is finally proposed that a noradrenergic dysfunction may underlie sustained attention deficits in adults with ADHD. Moreover, if significant differences will emerge, these might suggest that measures of pupil diameter represent a new and valuable psychophysiological correlate of sustained attention deficits in ADHD.

To our knowledge, no studies have investigated the relationship between pupil diameter and sustained attention deficits ADHD. Therefore this study represents the first attempt to characterise sustained attention deficits in adults with ADHD using pupillometry and it might therefore give important insights on the nature of these deficits.

3.4. Experiment 1. Psychophysiological correlates of sustained attention deficits in adults with ADHD: the influence of noradrenaline (NA) on sustained attention

Specific research questions:

1) Are there sustained attention deficits in an auditory oddball task in adults with ADHD as indicated by classic behavioural, EEG and Event-Related Potentials (ERPs) measures?

2) Can pupil measures qualitatively differentiate adults with ADHD from age matched controls and does this difference indicate sustained attention deficit in ADHD?

3) Are pupil measures linked to ADHD symptoms severity, behavioural measures and /or ERP measures?

4) If a deficit in sustained attention emerges in ADHD, how valid is an explanation which rely upon a noradrenergic dysfunction underling this deficit?

3.4.1. Materials and Methods

3.4.1.1. Participants

Non-ADHD group

Participants were recruited by poster advertisement at the university campus as well as from an existing database of our research group. Exclusion criteria were any known neurological condition, severe head trauma, mood disorders, personality disorders or learning disability. In total, twenty participants (9 female, 2 left handed; mean age=30.6 (SD= 10.3); mean years of education=17.50 (SD=1.73); mean IQ = 113,09 (SD=5.03)) were assessed and included in the

behavioural analysis. Another two additional participants were excluded from ERP analyses due to the presence of artefacts leaving twenty final participants for EEG and ERP analysis (8 female, 3 left handed; mean age=28.5 (SD=9.02); mean years of education=17.60 (SD=1.69); mean IQ = 112.91 (SD=4.29)).

ADHD group

Forty adult participants with ADHD volunteered for the present study following a telephone call or mail advertisement. All patients had existing diagnoses made by a trained clinical psychologist attached to St. Patrick's Hospital Dublin. Before inclusion in the study all participants were screened with a background questionnaire addressing personal and family history of ADHD, learning disability, psychiatric, neurological or medical disorders, use of medication and substance or alcohol abuse. Participants were excluded if they reported any previous history of psychosis, organic brain disorder, epilepsy or serious head injury. Twenty-two patients were currently taking psychostimulant medication, whereas the others had either taken stimulant medication in the past but had stopped and or were stimulant-naïve. Comorbid disorders in the ADHD group included history of depression (n = 7), current depression (n = 5), history of anxiety (n = 5), current anxiety disorder (n = 4) and substance abuse (n = 3, alcohol and cannabis use). All participants were included in behavioural analysis (11 female, 2 left handed; mean age=32.78 (SD= 10.96); mean years of education=15.56 (SD=3.63); mean IQ=111.23 (SD=6.01)), while two participants were excluded from EEG and ERP analysis based on excessive artefacts, leaving 38 final participants (7 female, 1 left handed; mean age=29.8 (SD= 10.44); mean years of education=15.5 (SD=3.51); mean IQ = 109,45 (SD=7.02)).

The two groups do not differ in terms of mean age ($t_{(62)}$ = -.812; p=.420), years of education ($t_{(35)}$ = 1.801, p =.080) or IQ ($t_{(40)}$ = 1.576; p =.123). All participants reported normal or corrected to normal vision. All participants gave written informed consent and all procedures were approved by the Ethics Committee of the School of Psychology, Trinity College Dublin. All participants completed the

Conners' Adult ADHD Rating Scale-Self Report (Conners, Erhardt, & Sparrow, 2003) before starting the testing session. Additionally, ADHD participants only completed the Wender Utah Rating Scale (WURS), a retrospective measure of ADHD symptoms in childhood (Ward, Wender, & Reimherr, 1993) and observers versions of the CAARS and the WURS were also administered to a close family member or partner. Means and standard deviations for each variable and significant difference between groups for CAARS self-rated symptoms scores are summarised in Table 3.1.

Table 3.1. Participants' scores in the Conners' Adult ADHD Rating Scale – Self Report (CAARS – S: L) and Wender Utah Rating Scale (WURS)

	ADHD group [a]	Control group [a]	$T_{(65)}$	p
CAARS-E-DSM-IV inattention self	80.54(11.52)**	46.88(12.12)	-12.004	<.001*
CAARS-F-DSM-IV hyperactivity self	65.73(13.89)**	42.53(10.68)	-6.959	<.001*
CAARS-G-DSM-IV total	77.71(12.70)**	44.21(13.24)	-10.567	<.001*
CAARS-E-DSM-IV inattention other	69.10(11.65)**			
CAARS-F-DSM-IV hyperactivity other	63.81(11.35)			
CAARS-G-DSM-IV total other	68.74(11.27)**			
WURS self	55.39(21.04)**			
WURS other	19.15(8.23)			

T-scores are reported for each of the Conners' Adult ADHD Rating Scale (CAARS) measures. [a] Values are mean (SD); *Statistically significant difference. **Clinically significant symptom

3.4.1.2 Auditory oddball task paradigm and procedure

The auditory oddball task is a simple and well established paradigm for the investigation of sustained attention and arousal effects on cognitive performance and has been shown to reliably evoke both pupillary dilations (Beatty, 1982) and robust P3 components (Polich, 2007). Therefore, EEG and pupil measures were

acquired in task simultaneously. Stimuli were presented through headphones using the 'Presentation' software suite (NeuroBehavioural Systems, San Francisco, CA). They consisted of 60ms-duration sinusoidal tones of frequencies 1000Hz ('targets') and 500Hz ('standards'). Targets were pseudo-randomly interspersed throughout the task and constituted 20% of the total number of trials. Participants were instructed to press the left key of the mouse to target tones with a right index finger as quickly and accurately as possible, while ignoring presentation of the non-target standard tones. Participants completed a practice run of the task to ensure that they were well acquainted with the instructions before beginning. They were seated comfortably at a distance of ~50cm from a 20" LED monitor (Dell P2011H; Dell Inc., Ireland) with their head supported by a chin rest and were instructed to maintain gaze on a white fixation cross presented over a black background at the centre of the monitor (font size = 48). The tasks were conducted in a dark room with the only ambient light provided by the fixation cross and it lasted for approximately 15 minutes. Tones were presented at an inter-stimulus interval (ISI) which varied pseudo-randomly between 2.1-2.9 seconds, with an average of 66 target tones and 267 standard tones over the whole task. In order to allow target-evoked pupil responses to return to baseline the stimuli were ordered such that at least three standard tones were presented between targets, leaving a minimum inter-target interval of 8 seconds.

3.4.2 Data Acquisition and Processing

3.4.2.1 EEG and ERPs

Continuous EEG was acquired using an ActiveTwo system (BioSemi, The Netherlands) from 32 scalp electrodes, configured to the standard 10/20 setup and digitized at 512Hz. Vertical and horizontal eye movements were recorded using two vertical electro-occulogram (EOG) electrodes placed above and below the left eye and two horizontal EOG electrodes placed at the outer canthus of each eye, respectively. Continuous EEG data were re-referenced offline to the average

reference, high-pass filtered to 0.50 Hz and low-pass filtered up to 35 Hz. Data from the 32 scalp electrodes for each participant were then subjected to temporal independent component analysis (ICA) using FASTER v1.2b (Nolan et al., 2010) for removal of EOG and other noise transients.

Event markers emitted by the stimulus presentation computer were recorded simultaneously during EEG and pupil diameter acquisition. Three seconds epochs were extracted for EEG datasets around each stimulus marker from -1 to +2 seconds and epochs were baseline corrected relative to the mean activity in the 100ms directly preceding stimulus presentation, whereas. All further processing was carried out using a combination of in-house MATLAB scripting and EEGLAB (Delorme and Makeig, 2004).

EEG datasets were subject to further artefact rejection criteria applied between -100 and +800ms relative to the stimulus for the EEG epochs. Any epochs with an EEG amplitude > 90μVwere rejected. All epochs on which participants responded to standard tones (false alarms), failed to respond to target tones (misses) or responded within the first 100ms after target presentation (quick responses) were also removed from the data.

3.4.2.2 Pupil

Continuous pupil diameter was recorded using an Eyestart eye-tracker (ASL, Bedford, MA). Pupil diameter in the left eye was sampled at a rate of 50Hz with a spatial resolution of greater than 0.01mm. As a preliminary pre-processing measure, artefacts and blinks were interpolated using a linear interpolation algorithm in the ASL Results software suite. All participants' data were visually inspected after interpolation, and those with excessive artefacts still remaining (e.g. blinks of long duration or excessively noisy periods of data) were excluded from further analyses. For pupil datasets, 7 second epochs were extracted around each stimulus marker from -2 to +5 seconds relative to stimulus presentation and epochs from the pupil datasets were baseline corrected to the pre-stimulus interval

of 1 second. Pupil diameter datasets were subject to further artefact rejection criteria applied between -1 and +2 seconds for the pupil epochs. Any epoch with a pupil diameter deflection > 2mm were rejected. To eliminate instances of brief, high amplitude noise in the up-sampled pupil data, any epoch in which the difference between two consecutive samples exceeded +/- 0.03mm was rejected. Each dataset was also removed of epochs in which any pupil diameter data point exceeded the combined mean of that epoch plus two neighbouring epochs to either side by 4 standard deviations or more (for a similar approach, see Porter et al., 2010). Additionally, all epochs on which participants responded to standard tones (false alarms) failed to respond to target tones (misses) or responded within the first 100ms after target presentation (quick responses) were also removed from the data.

3.4.2.3 Measures

3.4.2.3.1 Behavioural measures

Percentage of accuracy, omission errors, reaction time (RT; ms) and RT Coefficient of Variation (CV) on target tones were extracted. CV is a stringent measure of performance variability that has demonstrated sensitivity to the efficiency of frontal top-down control networks (Bellgrove et al., 2004; Stuss et al., 2003), calculated by dividing the standard deviation in RTs for a group of epochs by their mean. Separate averages were also calculated for omission errors, reaction times and CV for the first and second half of the auditory oddball task. Each one lasted approximately 7 minutes and 30 seconds. This step was aimed to evaluate the effect of time on participants' performance. Group (ADHD vs controls) by time (first half vs second half) mixed model repeated measures ANOVAs were carried out to compare differences between groups.

3.4.2.3.2 EEG and Event-Related Potentials (ERPs) measures

EEG

The average EEG power spectrum was calculated for each participant using the discrete fast Fourier transform. Each participant's tonic theta, alpha and beta power was calculated as the power in the 4-7 Hz, 8-12 Hz and 13-29 Hz ranges respectively in the 1 second preceding each target stimulus onset. Theta/Beta and Alpha/Beta ratios were subsequently calculated. Independent sample t-tests were employed for comparing groups differences.

Event-Related Potentials (ERPs)

ERP component structure was confirmed by visual inspection of grand-average waveforms. The width of the latency window used to measure component amplitude was based on the duration and spatial extent of each component. Target stimuli evoked an auditory N1 component with a central topography. N1 amplitudes and maximal peak measures were extracted from three central electrodes (Cz, C3 and C4) between 100ms and 200ms post-stimulus presentation. N1 latency measures were also obtained. A large positive component over centro-parietal scalp areas was elicited by target tones (the posterior P3). P3 amplitudes and maximal peak amplitudes were maximal at central sites and therefore were extracted from three central sites (Cz, C3 and C4) in the interval of 250ms to 450ms post-stimulus presentations. P3 latency values were also calculated. ERP components were not analysed for errors of omission, as the total rate of omission errors was too low to allow ERP analysis (mean= 2.1; SD=1.8). The same ERP measures were extracted for standard tones. As for target tones, P3 was maximal at central sites and therefore it was extracted from 3 central sites (Cz, C3 and C4) and a shorter latency interval of 200-350 ms was used. N1 was also extracted from the same central sites (Cz, C3 and C4) in the interval 100-180 ms. Independent sample t-tests were used to compare group differences.

3.4.2.3.3 Pupil measures

Pupil measures were extracted for targets and standard tones. Target tones elicited significant dilatory responses. Pupil dilations (mm) were extracted and defined as

the peak-to-peak measure of the maximum dilation between 0.4-2 seconds post-stimulus minus the minimum pupil diameter 0-0.4 seconds post-stimulus. The baseline pupil diameter pre-stimulus on each epoch was also extracted and calculated by averaging the 1 second of pupil diameter data preceding tone presentation on that epoch. Thus our analyses included both baseline and stimulus-evoked or phasic changes in pupil diameter. Measures of pupil latency (defined as the latency of the dilation peak in the interval 500-2000ms) and pupil variability (defined as the standard deviation of pupil dilation) were also extracted. Independent sample t-tests were used to compare groups differences. Additionally, measures of pupil dilations, baseline pre-stimulus pupil diameter, pupil latency and pupil variability were extracted for the first and second half of the auditory oddball task respectively. As for behavioural measures, this step allows to investigate the effect of time on participants' pupil measures. Extracted values for each variable were entered into a group (ADHD vs controls) by time (first half vs second half) repeated measures ANOVA to investigate groups differences.

3.4.3 Results

3.4.3.1 Behavioural results

Independent sample t-tests revealed no significant difference in reaction times between adults with ADHD and controls ($t_{(58)}$ = -.807, p =.423). Coefficient of Variation (CV) was significantly different ($t_{(58)}$ = -3.637, p =.001), indicating significantly larger variability in adults with ADHD compared to controls. Accuracy ($t_{(58)}$ = -1.706, p =.102) did not differ in the two groups, while a marginal significant difference was found in omission errors ($t_{(58)}$ = -1.768, p =.083). Mean values for each variable in the two groups are reported in table 3.2.

Table 3.2. Reaction Times (RT), Coefficient of Variation (CV), Accuracy and Omission errors in the ADHD group and in the control group.

	ADHD group [a]	Control group [a]	$t_{(58)}$	p
RT (ms)	499.51(105.54)	433.98(163.54)	-0.81	0.423
Coefficient of Variation (CV)	0.31(0.11)	0.23(0.06)	-3.64	.001*
Accuracy (%)	91.51(29.26)	98.15(5.04)	-1.71	0.102
Omission errors	0.64(1.35)	0.16(0.70)	-1.77	.083

[a] Values are mean (SD) *Significant difference between groups

A repeated measures ANOVA on reaction times revealed a significantly main effect of time ($F_{(1,57)} = 4.638$, $p = .036$) and a marginal time by group interaction ($F_{(1,57)} = 3.351$, $p = .072$). This result seems to suggest a larger increase in reaction time from the first half to the second half in the ADHD group compared to the control group. However, the effect was a trend and therefore did not indicate a significant difference between groups. No main effect of group was found ($F_{(1,57)} = 1.307$, $p = .258$). There was no main effect of time in a repeated measures ANOVA for Coefficient of Variation (CV) ($F_{(1,55)} = 1.498$, $p = .226$) and there was a marginal significant time by group interaction ($F_{(1,55)} = 2,963$, $p = .091$), suggesting higher variability in the second half of the task than in the first half in the ADHD group only. Coefficient of Variation (CV) seems to reduce as a function of time in the control group. No main effect of group emerged ($F_{(1,55)} = 1.481$, $p = .228$). A repeated measures ANOVA on percentage of accuracy revealed a main effect of time ($F_{(1,51)} = 5.072$, $p = .029$) and no significant time by group interaction ($F_{(1,51)} = .124$, $p = .726$). No main effect of group emerged ($F_{(1,51)} = .124$, $p = .726$). A main effect of time ($F_{(1,52)} = 5.321$, $p = .025$) and no significant time by group interaction ($F_{(1,52)} = .008$, $p = .852$) emerged in a repeated measures ANOVA on omission errors. No main effect of group emerged ($F_{(1,52)} = .123$, $p = .727$). Figure 3.1 shows differences in behavioural measures in the two groups between the first and second half of the task.

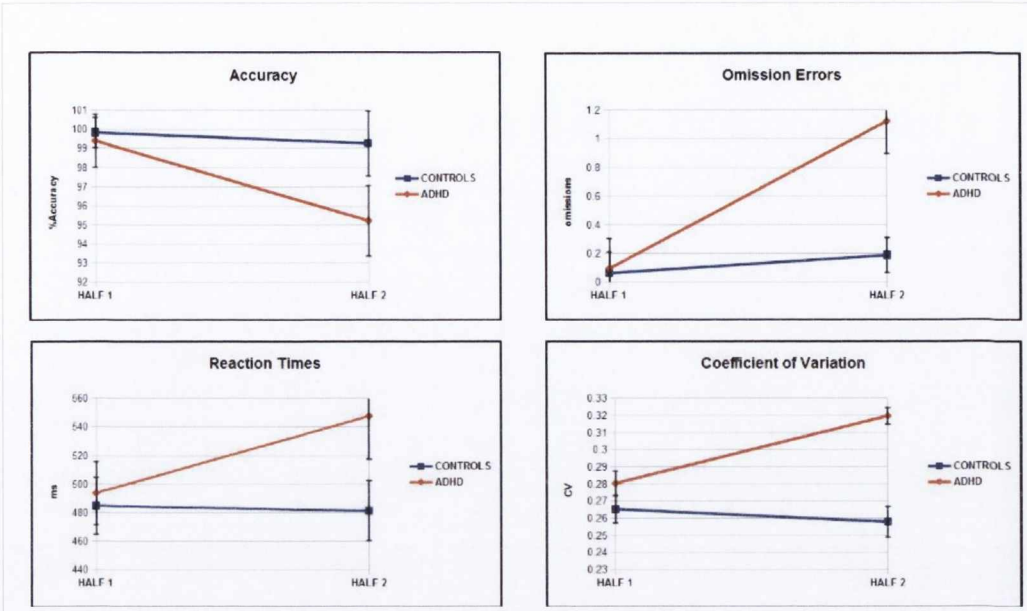


Figure 3.1. Differences in behavioural measures

Note: From the top left: Percentage of Accuracy, Omission errors, Reaction Times (ms) and Coefficient of variation (Coefficient of Variation (CV) in ADHD and control participants in the first and second half of the auditory oddball task. Errors bars represent the standard error. A marginal time by group interaction emerged for RT only (p=.072).

3.4.3.2 Event-Related potentials (ERPs) results

Independent sample t-tests on target tones revealed a significant between groups difference for mean P3 amplitude at central sites ($t_{(58)}$ = 1.942, p =.047), indicating smaller P3 amplitude in the ADHD group compared to the control group. A significant difference between groups was also found for P3 maximal amplitude ($t_{(56)}$ = 2.275 p =.027) which suggest that the maximal P3 amplitude was smaller in the ADHD group compared to the control group. No significant between group difference in P3 latency was found ($t_{(58)}$ = -.816, p =.418). P3 waveforms and topographies are presented in figure. No significant difference emerged for N1 amplitude ($t_{(56)}$ =.122, p =.903) and for N1 latency ($t_{(56)}$ = -1.763, p =.083) on central sites. N1 waveforms and topographies are presented in figure 3.2.

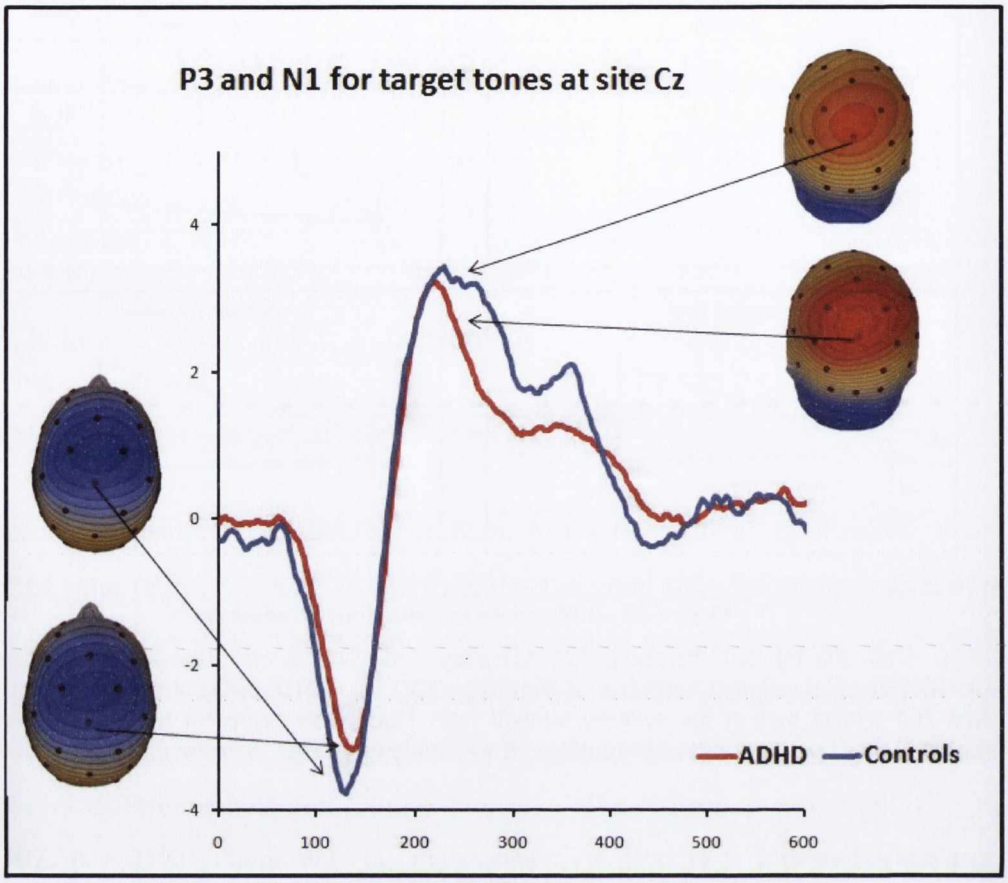


Figure 3.2. Differences in ERPs measures on target tones.

Note: N1 and P3 waveforms for target tones for ADHD and control participants and relative topographies. A significant difference between groups in P3 mean amplitude (p= .047) and P3 maximal amplitude (p=.027) were found. No significant differences emerged for N1 measures.

Independent sample t-tests were also carried out on standard tones. A marginal significant difference emerged for mean P3 amplitude ($t_{(54)}$ = 1.996, p =.051), indicating smaller P3 amplitude in the ADHD group compared to the control group. No significant difference was found for P3 maximal amplitude ($t_{(56)}$ = 1.011, p =.316). No between groups difference emerged for P3 latency ($t_{(58)}$ = -1.238, p =.221). P3 waveforms and topographies are presented in figure. N1 amplitude ($t_{(56)}$ =.599, p =.552) and N1 latency ($t_{(58)}$ =.004, p =.997) were not significantly different between the ADHD group and the control group. N1 waveforms and topographies are presented in figure 3.3.

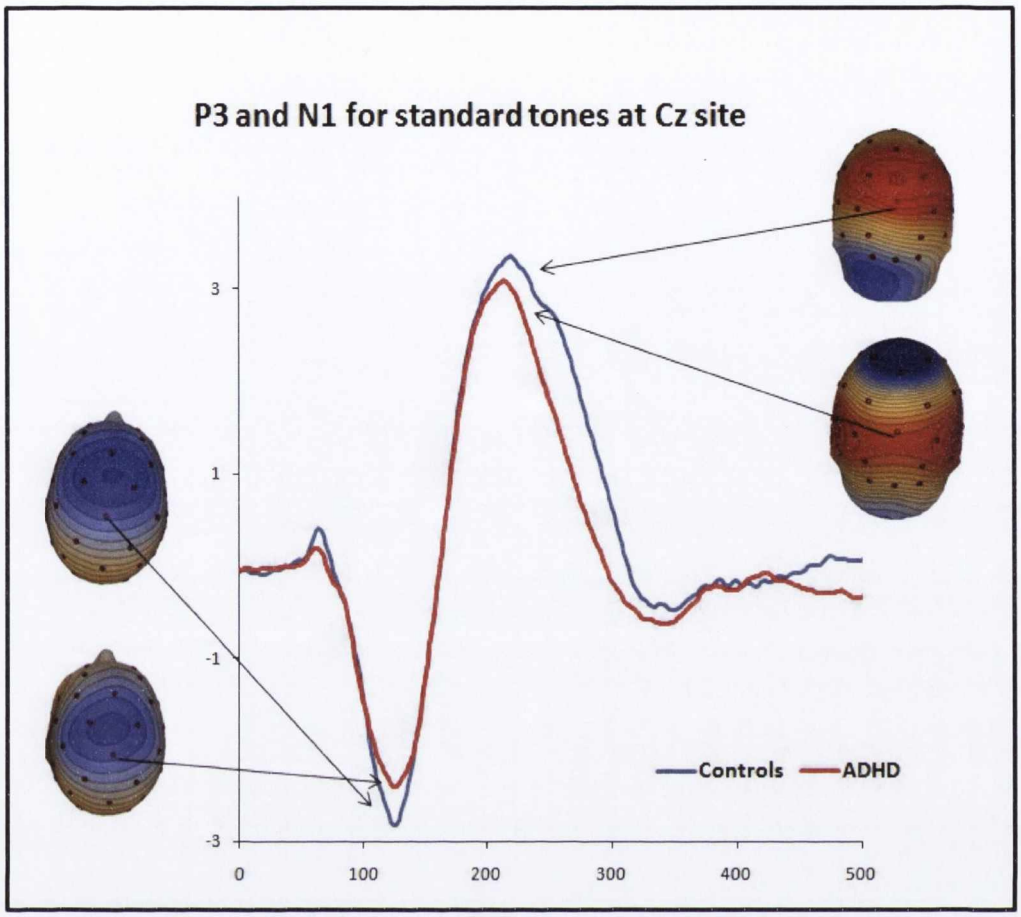


Figure 3.3. Differences in ERPs measures on standard tones.

Note: N1 and P3 waveforms for standard tones for ADHD and control participants and relative topographies. A marginal difference between groups emerged for P3 mean amplitude (p=.051). No significant differences were found for N1 measures.

3.4.3.3 EEG spectral power results

Independent samples t-tests showed no significant group differences were found for EEG spectral power in the theta ($t_{(54)}$ = -.348, p =.729), alpha ($t_{(54)}$ = -.340, p =.735) or beta ($t_{(54)}$ = -1.312, p =.196) bands and there were no differences in theta/beta ($t_{(55)}$ = 1.102, p =.275) or alpha/beta ratios ($t_{(57)}$ =.022, p =.982). These data indicated that there were equivalent levels of cortical arousal during the auditory oddball task performance.

3.4.3.4 Pupil results

Independent sample t-tests revealed no significant difference in pupil dilation on target tones ($t_{(54)}$ =.601, p =.550) and no significant difference in pupil dilation on standard tones ($t_{(54)}$ = -.738, p =.463) between the two groups. No significant difference between groups was found in pupil latency on targets ($t_{(54)}$ = -1.703, p =.099) while latency on standards was significantly different ($t_{(54)}$ = 3.521 p =.001). No significant between groups differences emerged on pupil pre-stimulus baseline on targets ($t_{(54)}$ =.590, p =.558) and on standards ($t_{(54)}$ =.623, p =.536) and no differences were found in pupil variability on targets ($t_{(54)}$ = -.244, p =.808) and standards ($t_{(54)}$ = -1.353, p =.114). Mean pupil dilation waveforms in each group are presented in figure. Mean values for pupil measures are reported in table 3.4. Figure 3.4 shows mean pupil dilation on target and standard tones in the ADHD group and in the control group.

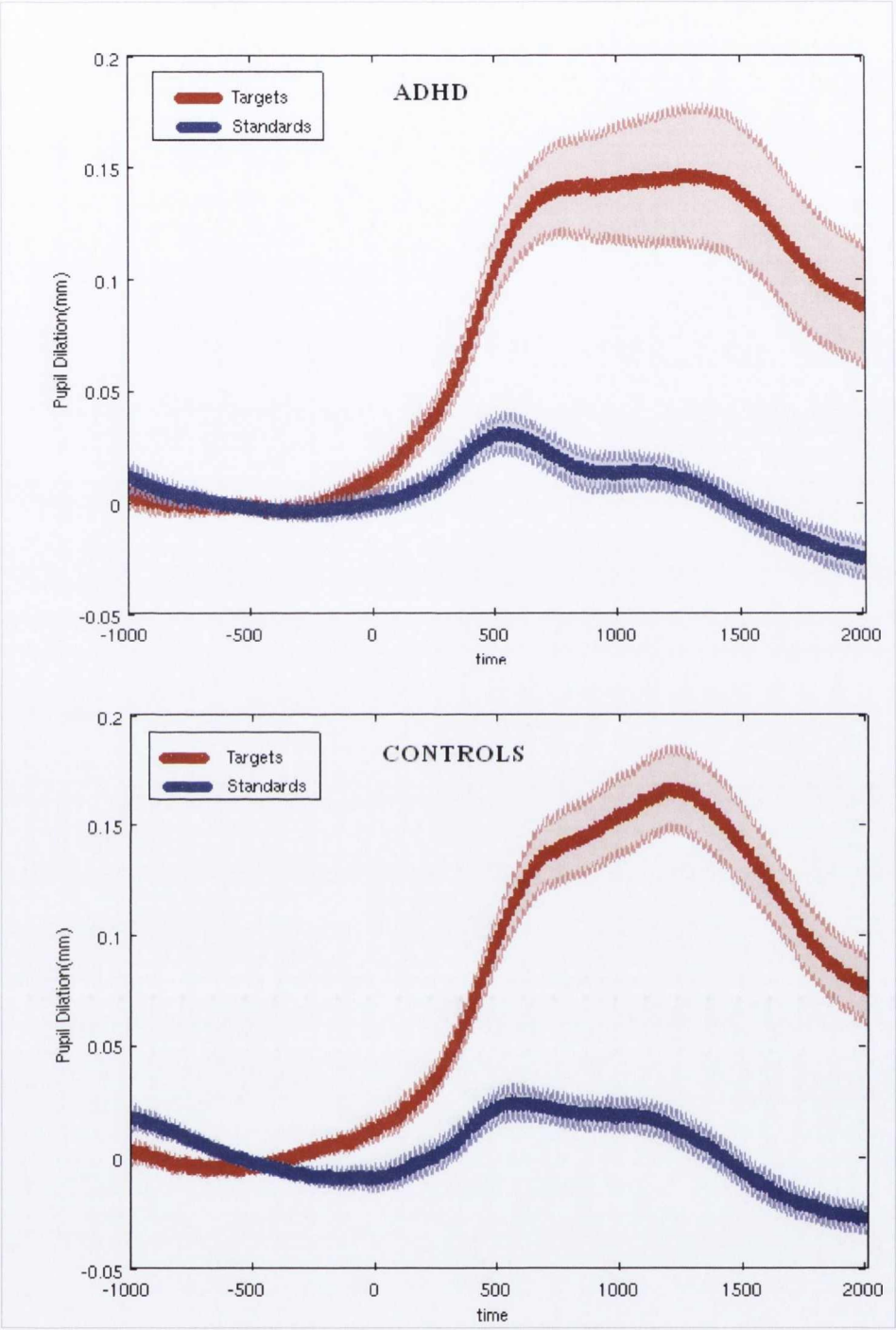


Figure 3.4. Differences in pupil measures.

Note: Mean pupil dilation waveforms for target and standard tones in the ADHD group (top) and the control group (bottom).No significant differences between groups in pupil dilations on both target and standard tones emerged.

Table 3.3. Mean values for pupil dilation, pupil baseline, pupil latency and pupil variability for target and standard tones in the ADHD group and in the control group

	ADHD group [a]	Control group [a]	T	p
Dilation on targets (mm)	0.19(0.10)	0.21(0.11)	0.6	0.55
Latency on targets (ms)	1039.32(338.8)	783.51(369.32)	-1.7	0.1
Pre-target baseline (mm)	5.13(0.83)	5.23(1.48)	0.59	0.56
Pupil variability on targets	0.25(0.09)	0.24(0.06)	-.244	.808
Dilation on standards (mm)	0.05(0.03)	0.04(0.02)	-.738	.463
Latency on standards (ms)	765.12(299.1)	1135.6(220.1)	3.521	.001*
Pre-standard baseline (mm)	5.17(0.83)	5.28(1.48)	.623	.536
Pupil variability on standards	0.25(0.09)	0.20(0.07)	-1.35	.114

[a] Values are mean (SD) *Significant difference between groups

A repeated measures ANOVA for pupil dilation on target tones revealed no main effect of time ($F_{(1,52)}$ = 2,468, p =.122), while there was a significant time by group interaction ($F_{(1,52)}$ = 11.579, p =.001). Post-hoc paired samples t-tests revealed that the interaction effect was driven by significantly reduced pupil dilation in the second half of the task in the ADHD group ($t_{(36)}$ = 4.655, p <.001). No significant difference in pupil dilation between the first half and the second half emerged in the control group ($t_{(19)}$=-.723, p =.479). No main effect of group was found ($F_{(1,52)}$ =.675, p = 415). A repeated measures ANOVA for pupil latency on targets revealed no main effect of time ($F_{(1,55)}$ =.205, p =.652) and no time by group interaction ($F_{(1,55)}$ = 1.007, p =.320). A significant main effect of group was found ($F_{(1,55)}$ = 4.887, p =.031). No main effect of time ($F_{(1,56)}$ = 1.053, p =.309) and no time by group interaction ($F_{(1,56)}$ =.049, p =.825) emerged in a repeated measures ANOVA for baseline pre-stimulus pupil diameter on target tones. Neither did a main effect of group emerged ($F_{(1,55)}$ =.051, p =.822). A repeated measures ANOVA on pupil variability found a significant main effect of time ($F_{(1,58)}$ =

5.778, p =.019) and no significant time by group interaction ($F_{(1,58)}$ = 1.780, p =.19). A main effect of group was also found ($F_{(1,58)}$ = 5.780, p =.019). Table 3.4 reported mean values for pupil measures for target tones. Figure 3.5 shows mean pupil dilation for pupil variables on target tones.

Table 3.4. Mean values for pupil dilation, pupil's latency, pupil baseline and variability for target tones

		H1	H2	F	p
Dilation targets	ADHD	0.23(0.12)	0.16(0.11)	11.58	**.001***
	Controls	0.19(0.11)	0.19(0.12)		
Latency on targets	ADHD	1242.58(141.88)	1216.99(156.65)	1.01	0.32
	Controls	1100.99(391.06)	1130.89(407.27)		
Pre-target baseline	ADHD	5.23(0.83)	5.09(0.99)	0.05	0.83
	Controls	5.10(1.25)	5.02(1.37)		
Pupil variability on targets	ADHD	0.24(0.09)	0.25(0.10)	1.78	0.19
	Controls	0.21(0.06)	0.23(0.11)		

*Significant group by time interaction effect

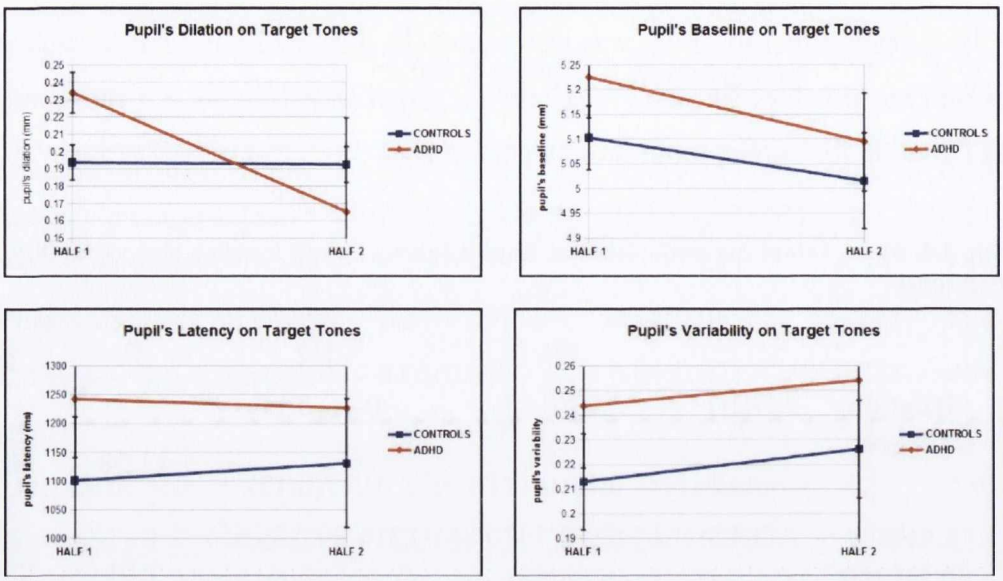


Figure 3.5. Differences in pupil's measures on target tones

Note: From the top left: Pupil dilation, pupil pre-target baseline, pupil latency and pupil variability on target tones in the ADHD group and in the control group in the first and second half of the auditory oddball task. Error bars represent the standard error. A significant time by group interaction was found for pupil dilation (p=.001)

A repeated measures ANOVA for pupil dilation on standard tones revealed no main effect of time ($F_{(1,54)}$ =.220, p =.641) and no time by group interaction ($F_{(1,54)}$ = 2.522, p =.118). No main effect of group was found too ($F_{(1,54)}$ = 2.743, p =.104). A repeated measures ANOVA for pupil latency on standards revealed a main effect of time ($F_{(1,55)}$ = 5.827, p =.019) and no time by group interaction ($F_{(1,55)}$ =.466, p =.498). A significant main effect of group was found (F(1,55) = 6.003, p =.017). A repeated measures ANOVA for baseline pre-stimulus pupil diameter revealed a main effect of time ($F_{(1,57)}$ = 14.242, p <.001) and no time by group interaction ($F_{(1,57)}$ =.098, p =.756). No main effect of group was found too ($F_{(1,57)}$ = 1.329, p =.254). Finally, a repeated measures ANOVA on pupil dilation variability indicated a main effect of time ($F_{(1,53)}$ = 7.810, p =.007) and no time by group interaction ($F_{(1,53)}$ =.001, p =.975). There was no main effect of group ($F_{(1,53)}$ = 2.743, p =.104). Table 3.5 reported mean values for pupil measures for standard tones. Figure 3.6 shows mean pupil dilation for pupil variables on standard tones.

Table 3.5. Mean values for pupil dilation, pupil latency, pupil baseline and variability for standard tones

		H1	H2	F	p
Dilation standards	ADHD	0.06(0.03)	0.05(0.03)	2.52	0.12
	Controls	0.07(0.08)	0.08(0.09)		
Latency on standards	ADHD	1175.60(66.31)	1206.54(77.15)	0.47	0.5
	Controls	1171.66(68.51)	1191.22(68.68)		
Pre-standard baseline	ADHD	5.27(0.83)	5.13(0.98)	0.098	0.76
	Controls	5.00(0.09)	4.76(0.09)		
Pupil variability on standards	ADHD	0.23(0.09)	0.26(0.09)	0.001	0.975
	Controls	0.21(0.07)	0.22(0.06)		

*Significant group by time interaction effect

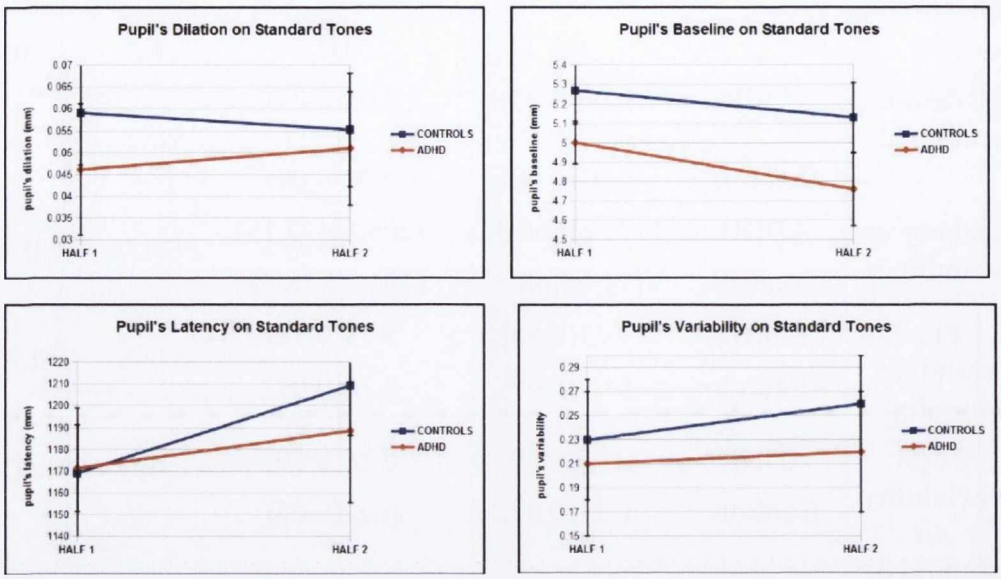


Figure 3.6. Differences in pupil's measures on standard tones.

Note: From the top left: Pupil dilation, pupil pre-standard baseline, pupil latency and pupil variability on standard tones in the ADHD group and in the control group in the first and second half of the auditory oddball task. Errors bars represent the standard error. No significant time by group interactions emerged.

3.4.3.4 Correlations

Partial correlations, controlling for the effect of group, were carried out between pupil variables (pupil dilation, pupil pre-stimulus baseline, pupil latency and pupil variability) and the following measures for target tones:

- Behavioural measures of the auditory oddball task: Reaction Time (RT), Coefficient of Variation (CV), percentage of accuracy and percentage of omission errors
- ADHD symptoms severity: Conners' Adult ADHD Rating Scale (CAARS)-Self Report
- Event-Related Potentials (ERPs) measures: P3 amplitude, P3 maximal amplitude and P3 latency
- Power spectral measures: theta, alpha and beta power and theta/beta and alpha/beta ratios

The only significant correlation or marginal correlations that emerged are reported in the table below:

Table 3.6. Correlations between pupil dilation on target tones and percentage of accuracy, omission errors and P3 amplitude

Variables	$r_{(44)}$	p-value
Pupil dilation on targets and percentage of accuracy	.265	.086
Pupil dilation on targets and percentage of omissions	-.265	.086
Pupil dilation on targets and P3 amplitude	.316	.032*

* Significant value

No significant correlations emerged between pupil measures on standard tones and any other variables.

3.4.4 Discussion

The aim of the study was to examine the neurophysiological underpinnings sustained attention deficits in adults with ADHD, using EEG, ERP and pupillometry and to address the hypothesis that this sustained attention deficit is underpinned by a deficit in neurophysiological arousal.

Behavioural results of the study suggest a pattern of sustained attention deficits. ADHD participants showed significantly increased variability, as expressed by higher Coefficient of Variation (CV) compared to controls, and a marginal, however not significant higher number of omission errors. Furthermore, analysis of effects of time on task performance revealed a trend toward a significant time by group interaction on reaction times, which may indicate that adults with ADHD had significantly slower reaction times in the second half of the task compared to the first one, while this effect is not evident in controls. A very close to significance time by group interaction effect was also found in performance variability, suggesting increased CV in the second half of the task compared to the

first half in the ADHD group, while control participants seem to show the opposite effect as they reduced CV in the last part of the task. Nonetheless, these were just trends and therefore they do not indicate a significant difference between groups.

Event-Related Potential (ERP) results showed no differences in basic sensory processing between adults with ADHD and controls, as suggested by the absence of groups differences in N1 amplitude and latency. Importantly, P3 amplitude on target tones was significantly reduced in adults with ADHD compared to controls. Reduced P3 amplitude in adults with ADHD extends one of the most common findings in ERP studies of children with ADHD to an adult sample (Barry et al., 2003). As explained in chapter 2, the precise function of P3 is still controversial. However, since P3 is reliably enhanced under attention demanding conditions, this component is frequently used as an index of endogenous mobilisation of attentional resources in response to significant task stimuli (Polich & Criado, 2006). Therefore it can be argued that, in this experiment, decreased P3 indexed reduced sustained attention in adults with ADHD.

Comparisons of EEG spectral power revealed no differences between the groups in terms of theta, alpha and beta power and no differences for theta/beta and alpha/beta ratios, suggesting that the two groups don't differ in measures of cortical arousal. A longitudinal study by Bresnahan et al. (1999) demonstrated that differences in these measures between people with ADHD and controls decrease linearly with age. Our findings are consistent with this study suggesting that abnormalities in these measures are not a persistent aspect of ADHD. The absence of any group difference in EEG measure despite behavioural differences suggests that sustained attention failures might be attributable to more localised or focal changes in activity at cortical level that may not be reflected in these global EEG measures.

Results of pupil comparisons suggest that overall pupil dilation and baseline pre-stimulus pupil diameter do not differ between adults with ADHD and controls for

both target and standard tones. Pupil variability was also not different on both types of stimuli while pupil latency was significantly increased on standard tones in the ADHD group compared to the control group. Investigations of the effect of time on pupil measures revealed some important differences. For target tones, a significant time by group interaction emerged for phasic pupil dilation which suggests that pupil dilation on task-relevant stimuli significantly decreased as a function of time. This effect is not present in the control group. A main effect of time also emerged for pupil variability on target tones, suggesting higher variability in the second half of the task in both groups. No significant interactions emerged for standard tones, while a significant main effect of time emerged for baseline pre-stimulus pupil diameter, which increases in both groups as a function of time. Main effects of time on pupil variability and pupil latency were also found -both measures increased in the second half of the task compared to the first one.

Partial correlation also revealed interesting findings. Marginal significant correlations emerged between pupil dilation on target tones and behavioural measures of accuracy and omission errors. A significant correlation emerged between pupil target dilation and P3 amplitude. No correlations emerged between pupil measures and EEG spectral power measures of cortical arousal.

As explained in the introduction of this chapter, to our knowledge, no studies have investigated differences in pupil measures between ADHD participants and controls. In the current study, the most relevant finding is the interaction effect on pupil dilation on target tones. Previous studies (Beatty & Wagoner, 1978; Murphy et al., 2011) have shown that decreased pupil dilation was linked to diminished behavioural performance in sustained attention tasks. The current results have shown that in adults with ADHD pupil dilation significantly decreased from the first half to the second half of the auditory oddball task, while no such difference was evident in the control group. Results of partial correlations also suggest that phasic pupil dilations on target tones are related to P3 amplitudes on target

stimuli, that have been shown before to index decreased sustained attention. Therefore, consistent with previous studies, this result suggests that the ADHD group experienced a reduction in sustained attention during the course of the task. This effect is not present in the control group. Alternatively, classic pupil studies (Beatty, 1982) found that pupil dilation is an indicator of mental effort and good task processing in a range of different tasks and decreased pupil dilation has been associated with decreased task-processing. Our results may indicate that people with ADHD became less efficient in processing task-relevant information, while control participants do not exhibit such difficulties. In this case, a diminished task-processing might also be a direct consequence of decreased sustained attention.

Comparisons of pupil measures on standard tones revealed that baseline pupil diameter decreased for task-irrelevant stimuli as a function of time in both groups. Additionally, variability and latency increased in both groups. No effects emerged for pupil dilation on standard tones. These results are consistent with previous descriptions of locus coeruleus (LC) tonic mode as a continuum which decreases with diminished alertness and task-engagement (Nieuwenhuis, Aston-Jones, & Cohen, 2005). The reduction found here in both groups in baseline pupil diameter in the second half of task might indicate that processing of standard task-irrelevant stimuli decreased over the course of the task in both groups.

Another aim of the current study was to explore the hypothesis that a noradrenergic dysfunction might underlie sustained attention deficits in adults with ADHD. Studies have extensively shown that people with ADHD exhibit sustained attention deficits and evidence of the link between sustained attention and the arousal system have been provided in the introduction of this chapter. In this context, the remarkable responsiveness of these attentional deficits in ADHD to methylaphenidate or amphetamine, drugs that potentiate noradrenergic as well as dopaminergic release, also link the sustained attention and arousal system to this clinical syndrome. Additionally, one of our study has shown that NA is linked to sustained attention deficits in children with ADHD (Greene et al., 2009).

In the current study, the hypothesis that a noradrenergic (NA) dysfunction underlies sustained attention deficits might be partially supported by deficits that emerged in some specific neurophysiological measures. As mentioned before, a significant decreased P3 amplitude was found for adults ADHD compared to controls in relation to target tones only, while N1 measures on target tones as well as P3 and N1 measures on standard tones were not impaired. This result suggests a specific impairment at the attentional level of target stimuli elaboration, while primary sensory processes of target tones and elaboration of task-irrelevant information remain intact. It has been demonstrated that posterior P3 originates from the same tempo-parietal regions that are part of the sustained attention-arousal system (Polich et al., 2007). Furthermore, a comprehensive review of the wide-ranging P3 neuropharmacology literature suggests that the locus coeruleus-noradrenergic (LC-NE) system underlies parietal P3 generation for target detection tasks and reduced NA availability results in decreased parietal P3 amplitudes (Nieuwenhuis et al., 2005). This supports the hypothesis that a NA dysfunction may explain P3 amplitude deficits in ADHD participants in the current study.

Physiological measures of pupil dilations also revealed impairments in adults with ADHD, as expressed by significant decreased phasic pupil dilations on target stimuli over the course of the auditory oddball task. This impairment was absent in the control group. No such difference was found for baseline pre-target pupil diameter on target tones. In this regard, it has been shown that phasic pupil dilation increased in response to increased LC phasic activity while diminished pupil dilations are linked to decreased LC phasic response. Furthermore, LC phasic response has also been shown to index performance in vigilance tasks, where low LC phasic activity is related to poor accuracy (Beatty et al., 1982; Murphy et al., 2011). No such relationship emerged for baseline pupil diameter on target stimuli in the cited studies. Finally, pharmacological studies suggest that diminished LC phasic response has been related to decreased levels of NA

availability in the brain (Minzenberg et al., 2008). In light of these evidences, it might be suggested that decreased phasic pupil dilation in the ADHD group in this study may index altered NA function which in turn has given rise to the reported sustained attention lapses. However, this is still an hypothesis and it should be stressed that pupil dilation is an indirect index of LC activity. Therefore additional studies using more direct measures, such as fMRI, are needed to confirm this proposal.

Additionally, another limitation of this study might be that the auditory oddball task used in this experiment to assess participants was relatively short (it lasted for 17 minutes). Longer tasks would place higher demand on sustained attention and therefore might be preferable to assess these deficits in ADHD.

To conclude, evidence of sustained attention deficits in ADHD have been provided, as showed in both behavioural and ERP impaired performance. In this study, pupil dilation related to target task-relevant stimuli appeared to be able to qualitatively distinguish adults with ADHD from control participants, suggesting that pupil dilation might be a good physiological correlate of sustained attention deficits in adults with ADHD. Furthermore, the specific neurophysiological deficits that emerged from this study seem to support the idea that a noradrenergic dysfunction might underlie the current sustained attention deficits in adults with ADHD.

Future studies should employ pupillometry as a valuable technique for investigating psychophysiological correlates of attentional deficits in the ADHD population to explore potential differences in pupil measures between ADHD subtypes. Ultimately, as pupil measures are relatively simple to acquire and are completely non-invasive, they can be easily used to investigate psychophysiological changes in sustained attention arising, for example, from non-pharmachological treatments in ADHD. This is be attempted in this thesis in chapter 5.

Chapter 4. Exploring the neurophysiological precursors of lapses in attention in ADHD

4.1 Introduction

In real life settings, performance errors arising from transient inattention can have negative consequences. This is particularly critical for people with ADHD and for individuals with other clinical syndromes that are characterised by an increased frequency of these attentional failures.

In this context, the knowledge of the neural underpinnings responsible for attentional failures is critical for understanding the brain mechanisms that caused these lapses giving rise to difficulties experienced in every day life. As explained in chapter 2, EEG and Event-Related Potentials (ERPs), because of their excellent temporal resolution, can be ideal for capturing the precise pattern of physiological changes in the brain that might underpin attentional failures. Furthermore, in chapter 3, the neurophysiological underpinnings of sustained attention deficits in adults with ADHD were investigated and, as predicted and in line with the literature, pupil and ERP measures revealed a pattern of sustained attention deficits in adults with ADHD.

However, the majority of ERP studies have adopted event-related approaches that focus on the downstream consequences of attentional failures on transient target processing (O'Connell et al., 2009). The inter-trial period before a target, when continuous attentional control is important, has received less investigation. Relatively few recent studies have started to look at physiological markers that *precede* attentional failures in healthy control volunteers and they have indeed demonstrated the existence of maladaptive patterns of neurophysiological precursors of errors arising from lapsing attention.

4.1.1 The neuropshysiological precursors of attentional failures in healthy individuals

Maladaptive neurophysiological responses preceding performance errors have been investigated in a very recent study conducted by Eichele and colleagues (2010). In this study seventy control participants were assessed using a modified visual Eriksen flanker task in which participants were asked to to respond as fast as possible and as accurately as possible with either a left or a right mouse button press following the direction of a central target arrow that appeared 100 ms after the flankers. EEG was recorded while participants performed the task. Event-Related Potential (ERP) data was analysed using single trial analysis, known to be a sensitive technique to capture dynamics of brain activity on a moment-to-moment basis. A pattern of behavioural and physiological phenomena preceding errors was identified. Participants increased the speed of their reaction times before committing an error. Furthermore, a gradual decrease in N2 ERP amplitude, known to index conflict processing (Debener et al., 2005; Gentsch et a., 2009), was also found across trials. It was argued that these markers indicate a reduction in attentional effort which gave rise to performance errors. To analyse maladaptive changes in event-related brain networks, the same group also conducted an fMRI study in which 13 young healthy volunteers underwent fMRI while they performed the same flanker task used in the previous study (Eichele et al., 2007). Results of the study showed that activations of particular brain regions predicted an upcoming error up to 30 seconds before the error was committed. Interestingly, results showed decreased activation in brain areas related to task engagement and a simultaneous increase in the so called "default mode network" (DMN), which comprises brain areas known to be more active during a resting condition. It was concluded that participants during the course of the task shifted from effortful motivated involvement toward a mental state more similar to resting condition. This increasing task-disengagement from task-related brain activity ultimately caused errors.

The neural correlates which precede errors were investigated in another recent study (Mazaheri et al., 2009) in which the oscillatory brain activity was recorded using magnetoecephalography (MEG) in young healthy volunteers while they performed a go/no-go task. Results showed that an increase in occipital alpha and sensorimotor activity immediately prior to the presentation of the stimuli predicted an upcoming error. These studies demonstrated that, by examining the state of the brain before the presentation of a stimulus, it is indeed possible to predict lapses of attention before they actually occur in young healthy participants.

A relevant study was recently conducted in our research group (O'Connell et al., 2009), which constitutes a comprehensive and systematic analysis of the psychophysiological precursors of lapses of sustained attention in young healthy participants using the Continuous Temporal Expectancy Task (CTET). In this task participants had to monitor a continuous stream of patterned stimuli centrally presented and flickering which changed at regular intervals. Their task was to detect "target" frames with duration that was longer than the standard frame. The CTET is particularly challenging when performed over a long period of time and it places significant demands on the sustained attention system. In Eichele et al. study (2007) it was found that specific fMRI activations could predict an upcoming error up to 30 seconds before the error was committed. O'Connell et al. (2009) aimed to establish if these patterns of cortical activity were detectable using EEG, which provides a more direct measure of cortical activity. Specifically, the first aim of this study was to establish how far back in time an attentional lapse is reflected in EEG. To accurately investigate the timing of the predictive error changes, EEG data was analysed on three distinct time-scales relative to a target stimulus: post-target processing, which referred to a time frame of 1 second after the onset of a target stimulus; immediate pre-target processing, that was extracted in a time frame of 4 seconds before a target; and long-term pre-target processing which referred to a time frame up to 30 seconds preceding a target. The second aim of the study was to establish whether lapsing attention

produced effects at all stages of stimulus processing, including "bottom-up" stimulus processing or only on endogenous, higher-order process. For this purpose, stimuli were presented at a 25 Hz flicker eliciting a steady-state visual-evoked potential (SSVEP), which provided a basic measure of visual processing. SSVEP as well as early visual components (i.e. P1) within the 30-second frame preceding a response were computed to assess long-term effects of attentional lapses on bottom-up stimulus evoked processes. Late higher order ERP components and EEG ongoing rhythms were also analysed to explore the effects of lapsing attention on endogenous processes. Results of this study revealed new and very interesting patterns. The alpha band activity was the strongest electrophysiological predictor of a lapse of attention. A maladaptive increase in alpha activity was evident up to 20 seconds before an error, followed then by a disruption of task-related time monitoring mechanisms indexed by reduced P3 amplitude in the short term pre-target epoch and diminished CNV amplitude during target processing (1 second after target presentation). Bottom-up stimulus processing indicted by SSVEP and P1 early visual ERP component were not affected, suggesting that lapsing attention affects endogenous processes only. In this regard, it's been shown that alpha activity is sensitive to changes in visual cortical excitability (Romei et al., 2008). However, the absence of any changes in SSVEP and P1 amplitudes suggested that the current alpha effects did not reflect changes in baseline visual activity. Importantly, this finding is also consistent with results of Mazaheri et al. (2009) in pointing to a relevant role of alpha in predicting an upcoming error. Ultimately, it was also argued that because there was a gradual decay over the 20 second pre-target frame in the alpha bands, alpha band states could be used as an early warning system to avert critical lapses of attention.

The cited studies suggest that the state of the brain is important for how incoming stimuli are processed and for how subjects respond. As it was argued before, it is therefore of particular interest to investigate the brain mechanisms underlying

syndromes characterised by increased errors in task performance as a result of poor sustained attention; one such disorder being ADHD.

To our knowledge, no studies have investigated neurophysiological underpinnings preceding attentional failures in ADHD. Investigating potential brain precursors of lapses in attention will significantly contribute to our knowledge of dysfunctional brain mechanisms responsible for impaired performance in people with ADHD.

In this chapter, the neural precursors of attentional failures in adults with ADHD will be investigated using the CTET. As cited before, O'Connell and colleagues (2009) have shown that in healthy control participants, the CTET revealed a precise pattern of physiological indices that anticipated and predicted errors. Therefore the aim of this experiment is to investigate differences in behavioural and neurophysiological measures, that can qualitatively differentiate adults with adults from controls using the CTET.

Specifically, the current study will address the following research questions:

- Can the Continuous Temporal Expectancy task (CTET) behaviourally differentiate adults with ADHD from control participants?
- Are there neurophysiological markers that qualitatively distinguish normal controls from adults with ADHD?
- If so, how can these markers contribute to better explain clinical attention deficits in adults with ADHD?

The current experiment represents the first attempt at characterising predictive brain patterns of lapsing attention in ADHD. The presence of qualitatively significant differences between adults with ADHD and controls will give valuable and novel contributions for explaining the neurophysiological bases of attentional failures in ADHD.

4.2 Materials and Methods

4.2.1 Participants

Non-ADHD group

Participants were recruited by poster advertisement at the university campus. Exclusion criteria were any known neurological condition, severe head trauma, mood disorders, personality disorders or learning disability. Thirty total participants were assessed. Four participants were excluded because they made an insufficient number of hits (less than 20%) leaving a final sample of twenty-six participants (8 female, 3 left handed; mean age=27.8; SD= 8.53; mean years of education=17.6) for behavioural analyses. An additional two participants were excluded from ERP analyses due to the presence of artefacts leaving twenty-four final participants for EEG and ERP analysis (8 female, 3 left handed; mean age=28.5; SD=9.02; mean years of education=17.6).

ADHD group

Twenty-two participants with ADHD volunteered for the present study following a telephone call or mail advertisement. All patients had existing diagnoses made either by a trained clinical psychologist attached to Saint Patrick's Hospital Dublin. Before inclusion in the study all participants were screened with a background questionnaire addressing personal and family history of ADHD, learning disability, psychiatric, neurological or medical disorders, use of medication and substance or alcohol abuse. Participants were excluded if they reported any previous history of psychosis, organic brain disorder, epilepsy or serious head injury. Eleven patients were currently taking psychostimulant medication, whereas the others had either taken stimulant medication in the past but had stopped and or were stimulant-naïve. Comorbid disorders in the ADHD group included history of depression (n = 3), current depression (n = 1), history of anxiety (n = 3), current anxiety disorder (n = 3) and substance abuse (n = 2, alcohol and cannabis use). All participants were included in behavioural analysis

(7 female, 1 left handed; mean age=29.3; SD= 10.27; mean years of education=15.2), while two participants were excluded from EEG and ERP analysis based on excessive artefacts, leaving twenty final participants (7 female, 1 left handed; mean age=29.8; SD= 10.44; mean years of education=15.5).

All participants reported normal or corrected to normal vision. All participants gave written informed consent and all procedures were approved by the ethical board of the School of Psychology, Trinity College Dublin. All participants completed the Conners' Adult ADHD Rating Scale-Self Report (Conners, Erhardt, & Sparrow, 2003) before starting the testing session. Additionally, ADHD participants only completed the Wender Utah Rating Scale (WURS), a retrospective measure of ADHD symptoms in childhood (Ward, Wender, & Reimherr, 1993) and observers versions of the CAARS and the WURS were also administered to a close family member or partner. Means and standard deviations for each variable and significant difference between groups for CAARS self-rated symptoms scores are summarised in Table 4.1.

Table 4.1. ADHD and control participants' scores in the Conners' Adult ADHD Rating Scale – Self Report (CAARS) and in the Wender Utah Rating Scale (WURS)

	ADHD group [a]	Control group [a]	T	p
CAARS-E-DSM IV inattention self	79.52(11.16)	48.67(9.48)	-10.87	<.001*
CAARS-F-DSM IV hyperactivity self	64.26(12.49)	44.33(9.14)	-6.71	<.001*
CAARS-G-DSM IV total self	76.31(12.27)	46.73(10.26)	-9.55	<.001*
CAARS-E-DSM IV inattention other	67.81(11.30)			
CAARS-F-DSM IV hyperactivity other	63.55(8.57)			
CAARS-G-DSM IV total other	67.64(10.06)			
WURS self	56.55(17.88)			
WURS other	23.5(7.31)			

T-scores are reported for each of the Conners' Adult ADHD Rating Scale (CAARS) measures
[a] Values are mean (SD); *Statistically significant difference

4.3 Continuous Temporal Expectancy Task (CTET)

In the continuous temporal expectancy task (CTET) (Figure 4.1), a centrally presented patterned stimulus underwent a change at regular intervals, resulting in a continuous stream of "frames." The key requirement of the task was to monitor the temporal duration of each stimulus frame and to identify the minority of "target" frames with a duration that was 40% longer than the standard. The CTET was designed such that the temporal judgements that were required were unchallenging when performed in isolation but demanding when participants were asked to continuously perform these judgements over an extended period. It was predicted that this task scenario would lead to more frequent lapses than the more common stimulus classification tasks that are used in attention research, thus facilitating EEG analysis. The pattern stimulus consisted of a single 8 cm^2 large

square divided into a 10 × 10 grid of identical square tiles (0.8 mm^2), each one diagonally split into black and white halves. The tile orientation shifted by 90° in a random direction (clockwise or counter-clockwise) on each frame change yielding four distinct patterns. To reduce eye movement, participants were instructed to fixate on a white cross that was continuously presented at the centre of the large square. All stimuli were presented on a grey background.

Standard (nontarget) stimuli were presented for 800 ms, and target stimuli were presented for 1120 ms. Stimuli were pseudo-randomly presented such that there were between 7 and 15 (average of 11) standard trials or 5.6–12 s (average 8.8 s) between each target presentation. To generate an SSVEP, the stimulus stream flickered on and off at a constant rate of 25 Hz. The SSVEP represents synchronous neuronal activity in early visual areas elicited by repetitive visual stimulation (Muller and Hillyard, 2000). Here, the SSVEP provided us with a continuous measure of basic visual stimulus processing. Participants were required to press a response key as quickly as possible when they detected a frame of longer duration (target). Each block consisted of 225 trials (frames) with a total duration of ~3 min and 5 s. The number of targets varied between 18 and 22 per block. All participants completed 8 blocks of the task and were given a rest break in between each block.

To verify that the target/standard comparison was well above individual detection thresholds, all participants were required to exhibit 100% accuracy during an initial practice session. The practice session consisted of two separate practice blocks. In the first block, three targets were randomly interspersed among 25 standard stimuli. At this early stage, the stimuli were presented without the 25 Hz flicker to facilitate target identification. In the second practice block, an identical number of stimuli were presented, this time with the 25 Hz flicker. Participants were required to identify all target stimuli before advancing to the experimental trials. If participants missed one or more target stimuli, the practice was performed again. If the participant still failed to identify all the targets, they were

excluded from the experiment. All tested participants could successfully perform the initial practice.

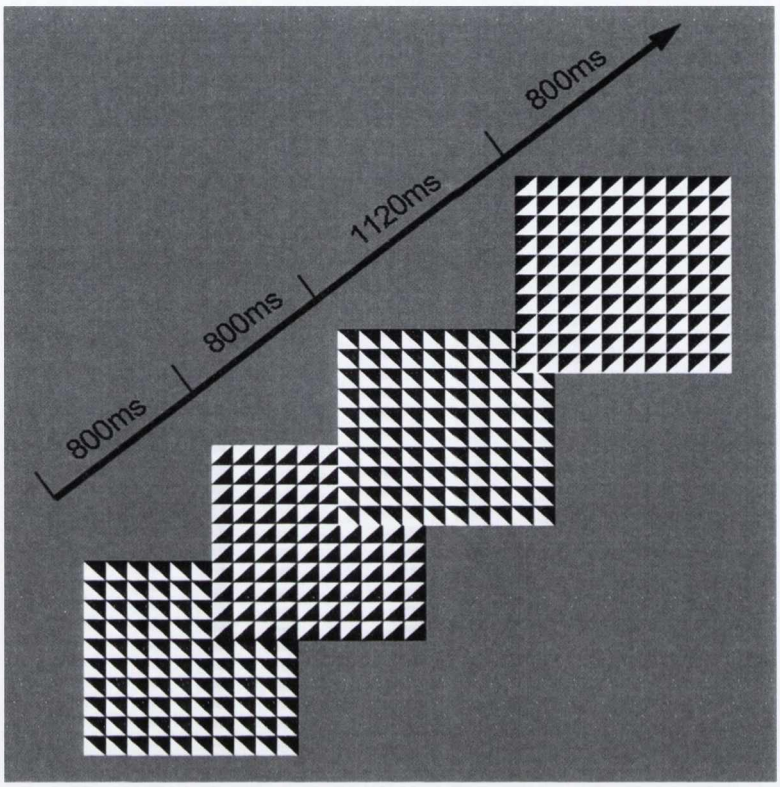


Figure 4.1. Contingent Temporal Expectancy Task (CTET).

Note: Participants monitored a continuous stream of patterned stimuli centrally presented and flickering at a rate of 25 Hz. Standard stimuli were presented for 800 ms, and participants were required to monitor for the occurrence of target stimuli defined by their longer duration (1120 ms) relative to other stimuli.

4.4 Data analysis

4.4.1 Behavioural analysis

Variables analysed included accuracy, errors of omission, false alarms, reaction times and variability. Variability of reaction times for correct responses was expressed as coefficient of variation, calculated as the ratio between reaction time and standard deviation. Independent samples t-tests were employed to investigate

differences between groups. Separate averages were also calculated for accuracy, reaction times and variability for each of the eight blocks to evaluate the effect of time on participants' performance. Each variable was entered into a repeated measures ANOVA with two levels of group (ADHD vs control) and eight levels of time (block 1 to block 8). The ADHD group and the control group were matched for key demographic variables (age, gender and years of education).

4.4.2 EEG and Event-Related Potentials (ERPs) analysis

Continuous EEG was acquired through the ActiveTwo Biosemi electrode system from 64 scalp electrodes, digitized at 512 Hz. Vertical eye movements were recorded with two vertical electrooculogram (EOG) electrodes placed below the left and right eye, while electrodes at the outer canthus of each eye recorded horizontal movements. Data were analysed in Matlab R2009a. Data were re-referenced off-line to the mastoids and low-pass filtered up to 40 Hz. All electrode channels were subjected to an artefact criterion of ±90 mV to reject trials with excessive EOG or other noise transients. To exclude errors that may have arisen from blinking rather than true failures of attention, a 4 s window before each target trial was scanned, and any trial that included an artefact (±90 mV) that was evident across eight or more channels was excluded from all analyses. In all analyses of transient ERP, baseline and component intervals of a multiple of 40 ms were used, encapsulating an integer number of SSVEP cycles, to protect against contamination by residual SSVEP power remaining after notch-filtering.

The analysis proceeded in three stages: examining immediate target-related processing, short-term epochs preceding targets (4 sec), and long-term epochs preceding targets (30 sec). In all stages, we examined differences in activity between the ADHD group and the control group in a specific time interval relative to target trials (onset of longer-duration frame), comparing correctly detected trials (hits) to undetected trials (misses).

4.4.2.1 Immediate target processing

We examined the discrete event-related activity elicited by the detection of a target in each group by deriving ERP for an epoch encapsulating the target interval (800–1120 ms) and beyond. A notch filter centred on 25 Hz was applied to eliminate the SSVEP activity in transient ERP. Stimulus-locked data were segmented into epochs of −100 ms before to 1800 ms after target frame onset and averaged separately for correctly detected targets and missed targets. Artefact rejection was based on a much broader preceding time frame starting from −3200, so that trials that were missed on account of preceding blinks or eye movement, as opposed to lapsing attention, were excluded. Target epochs were baseline corrected relative to the interval 560–640 ms, i.e., an 80 ms window centred on contingent negative variation (CNV) onset.

In each group, ERP component structure was confirmed by visual inspection of grand-average waveforms and associated scalp maps. The width of the latency window used to measure component amplitudes was based on the duration and spatial extent of each component. The target interval elicited the following components (Fig. 4.2): an early ERP component maximal at central scalp sites starting at ~200 ms and peaking ~300 ms, a strong negative shift over central scalp sites with onset ~600 ms and peaking at 1000 ms (CNV) and a late positive wave with fronto-central (1200 ms; frontal target P3) and parietal maxima (1400 ms; parietal target P3).

We measured the early central ERP component from three electrodes (C3, C4 and Cz) within the interval 200-400 ms preceding target presentation (i.e., up until onset of the first post-target standard frame). The CNV from the same three electrodes centred on central (Cz) within the interval of 900–1100 ms. The late positive wave was measured around its dominant peak in the interval of 1300–1450 ms at both frontal and parietal sites.

To investigate differences between groups, we conducted a repeated measures ANOVA for each component with two levels of group (ADHD vs control) and two levels of detection (hit vs miss).

4.4.2.2 Short-term pretarget processing

In the next step of our analysis, the goal was to look for differences between the ADHD group and the control group in electrophysiological markers within a relatively discrete time frame of 4 s. This window was selected to isolate activity that would be uncontaminated by the occurrence of other preceding target trials since the minimum inter-target interval was 5.6 s. For this time frame, we examined both the broadband transient ERP and spectral measures.

For the broadband ERP analysis, stimulus-locked data were segmented into epochs of −3200 ms before to 800 ms after target stimulus onset (i.e., until the beginning of the target interval). A notch filter of 25 Hz (width, 2 Hz) was applied to eliminate the SSVEP activity. Amplitude measures for the ERP components elicited by each of the four preceding standard frames and the target frame itself were acquired using separate baselines of −80 to 0 before the onset of each stimulus. Note that because a target frame cannot be identified as such until the 800 ms time point, we regarded it as the fifth pre-target standard frame here.

To select latency windows for the measurement of ERP components, a grand-average standard frame ERP was generated in each group by averaging across the five frames preceding the target interval and without distinguishing between hits and misses (Figure 4.2). Standard frames elicited three principal ERP components: first, the early visual P1, maximal over occipital regions and peaking ~120 ms after stimulus onset. Second, a frontal positivity, peaking at ~300–350 ms. Finally, as in the target–interval waveform, we observed a CNV component with onset ~600 ms and lasting until the following transient response. We performed independent sample t-tests to compare differences in components' amplitudes between ADHD participants and controls. Results showed marginal significant differences between groups for P1 amplitudes ($t_{(38)} = 2.043$, $p = .050$)

and P3 amplitudes ($t_{(38)}$ = 1.967, p =.057) and no significant differences on CNV amplitudes ($t_{(38)}$ = -.982, p =.333). To reduce the likelihood that differences between detection conditions could be contaminated by activity differences at the prestimulus baseline, ERP component amplitudes were calculated by subtracting the amplitude at component onset from the peak amplitude (Table 4.2; Figure 4.2). Amplitude measures for each component were entered into a repeated measures ANOVA with two levels of group (ADHD vs control) two levels of detection (hit vs miss) and five levels of trial (standard −4, standard −3, standard −2, standard −1, and target).

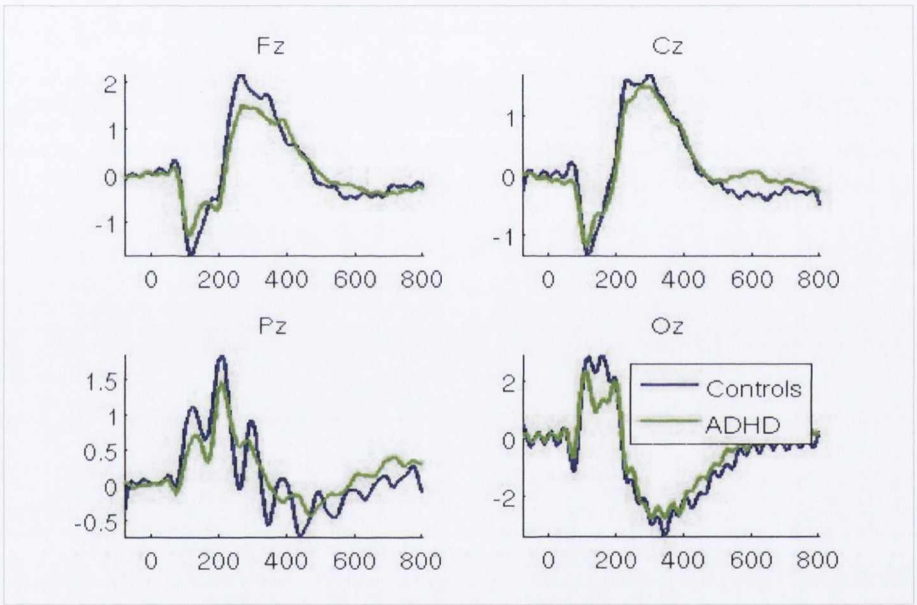


Figure 4.2. Short-term pre-target epoch.

Note: Grand-average ERP waveforms for the ADHD and control group for the five frames immediately preceding the target interval (ITI) and collapsed around outcome. This waveform was used as basis for defining component measurement intervals for the short- and long-term pre-target analysis.

Table 4.2. Latency intervals and electrodes sites used for measurement of ERP in the short-term pretarget epoch

Component	Onset interval (ms)	Peak interval (ms)	Electrodes
P1	-20 to 60	95-135	Oz, O1,O2
Standard P3	80-160	280-400	Fz, F3, F4
CNV	560-640	760-840	Pz, P3, P4

To measure effects on activity within discrete spectral bands in each group, we used the Fast-Fourier transform to compute the amplitude spectrum across a 4 s epoch extending from −3200 to +800 ms relative to target frame onset. Three dominant peaks were observed in grand average spectra collapsed across conditions: a relatively narrow spectral peak was identified within the theta band mainly over frontal sites; this was measured by integrating amplitude across the band 5–6.5 Hz. Alpha was measured in the broader standard band of 8–14 Hz, whereas SSVEP amplitude was measured at the discrete frequency of 25 Hz. Spectral amplitude measures were acquired individually from three electrodes centred on frontal (F3, F4, Fz), Cz (C3, C4, Cz), parietal (P3, P4, Pz), and occipital (O1, O2, Oz) scalp sites and entered into a repeated measures ANOVA with two levels of group (ADHD vs control), two levels of detection (hit vs miss) and four levels of region (frontal, central, parietal, and occipital). A separate ANOVA was carried out for each of the three bands. For each group, theta/alpha and theta/beta ratios were also extracted as measures of arousal and independent sample t-tests were carried out to compare differences between groups.

4.4.2.3 Long-term pretarget processing

The next step in our analysis was designed to explore differences between the ADHD group and the control group in the longer-term temporal dynamics of the electrophysiological markers identified in the previous step and their relationship to performance on an upcoming target. On the basis of the findings of Eichele et al. (2008), we examined a 30 s long pretarget epoch. For the P3, we extracted an amplitude measure from each of 40 consecutive frames ending on the target frame (starting 39 frames, or 31.2 s before target frame onset). P3 amplitude was computed as the integrated amplitude in the interval 280–400 ms minus that in the onset period from 80 to 160 ms relative to the onset of each frame (as in analysis step 2). Because of the rarity of 30 s periods of data that are free of blinks or other artefacts, we rejected a target trial only if an artefact was detected in the preceding 4 s using a 90 μV criterion as before. For all preceding frames, artefact rejection was carried out on a frame-by-frame basis. Because artefacts were distributed evenly across frames, this did not result in appreciably lower sweep counts for earlier frames than frames closer to the target. The average sweep count was in the range 42–49 for all frames. A smoothed series of 19 P3 amplitude measures, derived by averaging across windows of four frames in steps of 2, were entered into a repeated measures ANOVA with two levels of group (ADHD vs controls), two levels of detection (hit vs miss) and 19 levels of time (corresponding to the 19 time points preceding a target).

For the spectral measures of alpha and SSVEP, 2 s segments of data were extracted to provide reasonable frequency resolution. Starting with an epoch defined by the interval −1200 to 800 ms relative to target frame onset, we derived spectral measures at parietal and occipital sites for alpha (8–14 Hz) and SSVEP (25 Hz), respectively. We then proceeded in steps of two frames (1.6 s) back to 30 s before the target, resulting in 20 time points. To match the temporal smoothing applied to the P3, each pair of consecutive time bins was averaged, and, again, a repeated measures ANOVA with two levels of group and 19 levels of time was carried out for each spectral measure. For the measures that showed an effect of

detection in the short-term pretarget time frame, it was of interest to characterize the timing of the effect. Paired t-tests were carried out for each of the 19 bins to determine the time bin at which each measure ceased to dissociate hits from misses.

4.5 Results

4.5.1 Behavioural data

Independent sample t-tests revealed a very close to significance difference between groups for accuracy ($t_{(46)}$ = 1.983, p =.054) and number of omission errors ($t_{(46)}$ = -1.977, p =.054). These trends suggest that ADHD participants are on average less accurate and they commit more errors of omission compared to control subjects. Results indicate that ADHD participants made more false alarms and they appear slightly slower and more variable that the control group too. However, no significant differences emerged in false alarms ($t_{(46)}$ = -1.052, p =.298), reaction times ($t_{(46)}$ = 1.239, p =.223) and variability ($t_{(46)}$ = -1.273, p =.209). Behavioural results are summarised in Table 4.3.

Table 4.3. Percentage of accuracy, errors of omission and false alarms, mean reaction time and Coefficient of Variation (CV) for each group.

	ADHD	Control
Accuracy (%)	57.7	66.3
Omission errors (%)	42.3	33.1
False alarms (%)	3.3	2.4
Reaction time (ms)	138.09(21.16)	135.76(17.55)

Coefficient of Variation (CV)	0.16	0.14

A repeated measures ANOVA for accuracy revealed a significant main effect of time ($F_{(7,322)} = 3.801$, $p = .005$). No significant time by group interaction was found ($F_{(7,322)} = 1.385$, $p = .240$) and there was a marginal main effect of group ($F_{(7,322)} = 3.390$, $p = .072$). No significant main effects or interactions emerged for reaction times (main effect of time: $F_{(7,322)} = 0.738$, $p = .640$; group by time interaction: $F_{(7,322)} = 1.629$, $p = .126$; main effect of group: $F_{(7,322)} = 1.756$, $p = .192$) and variability (main effect of time: $F_{(7,322)} = 1.111$, $p = .356$; group by time interaction: $F_{(7,322)} = 1.567$, $p = .144$; main effect of group: $F_{(7,322)} = .489$, $p = .488$). Figure 4.3 shows participants' performance for accuracy, reaction times and variability across the eight blocks.

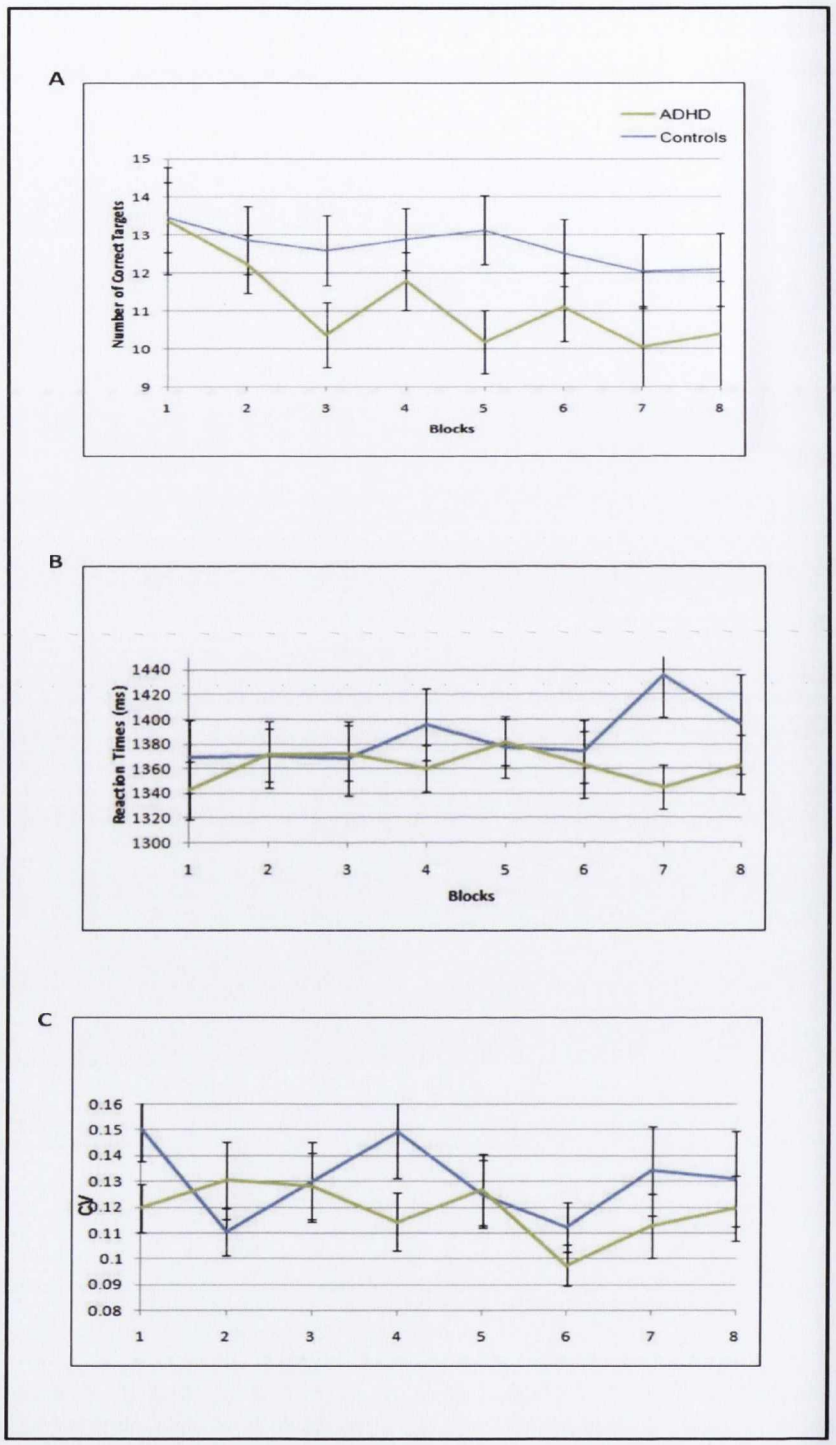


Figure 4.3. Behavioural results across the eight blocks.

Note: Accuracy (A), Reaction times (B) and Coefficient of Variation (CV) (C) across the eight blocks in the ADHD and control group. Error bars represent the standard error.

4.5.2 Immediate target processing

Since target stimuli are identical to standards, except for their increased duration, a target stimulus cannot be identified until its duration has exceeded that of a standard. Therefore, in our analyses of the electrophysiological data, we made the distinction between "target onset," which is the time point at which the target frame begins (0 ms) and "target interval" (800–1120 ms), which is the window of time during which target identification is possible. All of the following analysis steps adhere to this convention whereby the zero time point corresponds to target frame onset.

The early ERP component wave was measured on central sites in the interval of 200-400 ms preceding target presentation. A repeated measures ANOVA revealed significant group by detection interaction ($F_{(1,38)} = .006$). There were no significant main effects of detection ($F_{(1,38)} = .123$) or group ($F_{(1,38)} = .323$). T-tests were employed to investigate the interaction effect. Paired samples t-tests showed a significant difference between hit trials and missed trials in the ADHD group ($t_{(19)} = .006$), indicating that the early component was significantly reduced on missed trials compared to hit trials. No significant difference between hit trials and missed trials was found in the control group ($t_{(19)} = .349$). Independent samples t-tests also revealed a significant difference on the early component between the two groups on missed trials only ($t_{(19)} = .030$), driven by significantly higher early component on a miss in the ADHD group compared to the control group.

CNV was extracted from three central electrodes in the interval of 900-1100 ms (Figure 4.4). There was no significant main effects of detection ($F_{(1,38)} = .833$) or group ($F_{(1,38)} = .674$) or detection by group interaction ($F_{(1,38)} = .267$).

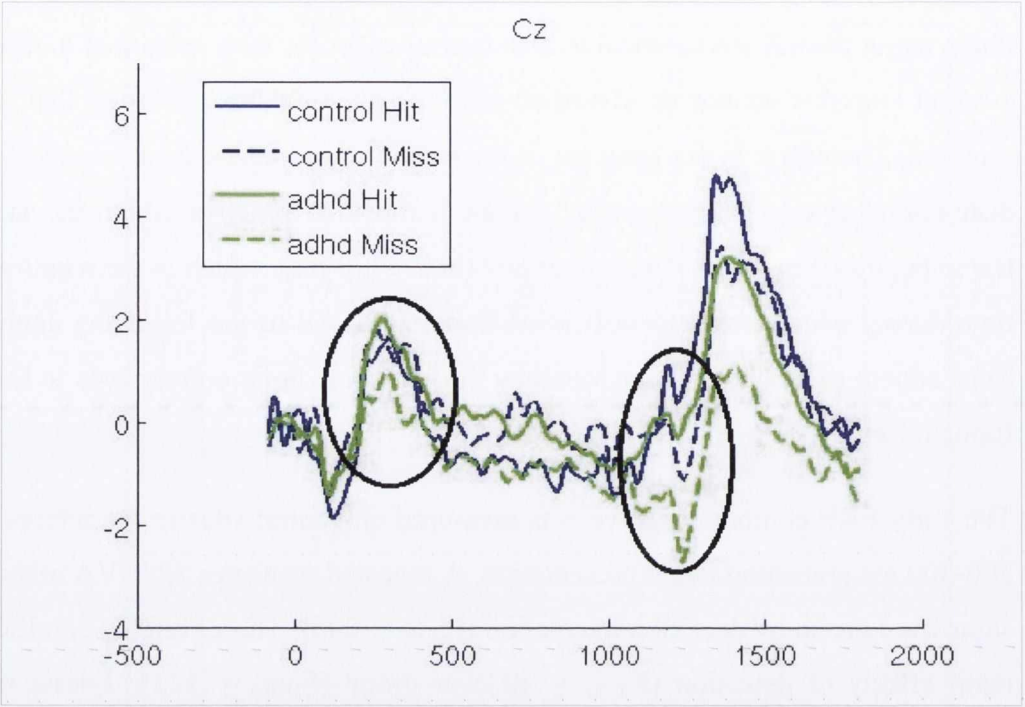
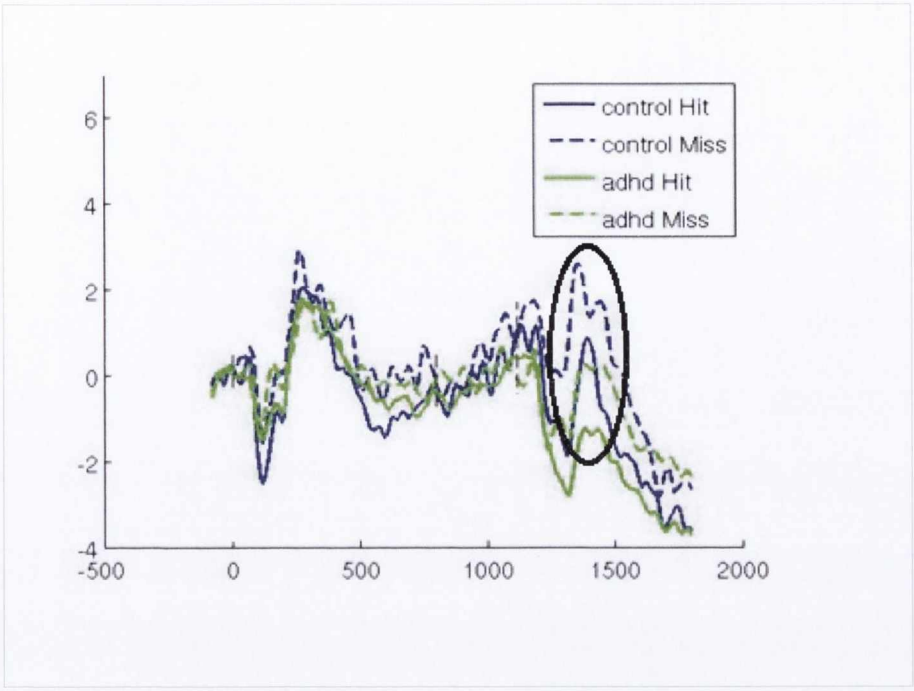


Figure 4.4. Early positivity and CNV in the immediate target processing.

Note: Grand average ERP waveforms focused on the target detection interval and averaged separately for the ADHD group and the controls group respectively for hits and misses. The target interval elicited a central early positivity between 200 and 400 ms preceding the target presentation (in the circle on the left) that was significantly smaller in the ADHD group only for misses compared to hits. A central negativity (CNV) is generated between 900 and 1100 ms (in the circle on the right). No interaction effect was found in the CNV.

The late positivity wave was measured around its dominant peak in the interval of 1330-1500 ms at both frontal and parietal sites. A repeated measures ANOVA revealed a significant main effect of detection ($F_{(1,38)} = .002$) in the frontal P3, driven by larger P3 amplitude before a missed trial. No main effect of group ($F_{(1,38)} = .673$) or detection by group interaction ($F_{(1,38)} = .149$) emerged. Another repeated measures ANOVA showed a significant main effect of detection ($F_{(1,38)} = .002$) on the parietal P3, indicative of higher P3 amplitudes before correct target detection. There was no main effects of group ($F_{(1,38)} = .318$) or detection by group interaction ($F_{(1,38)} = .871$). Figure 4.5 shows ERP waveforms in the ADHD group and in the controls group for the late positivity on frontal and parietal sites.



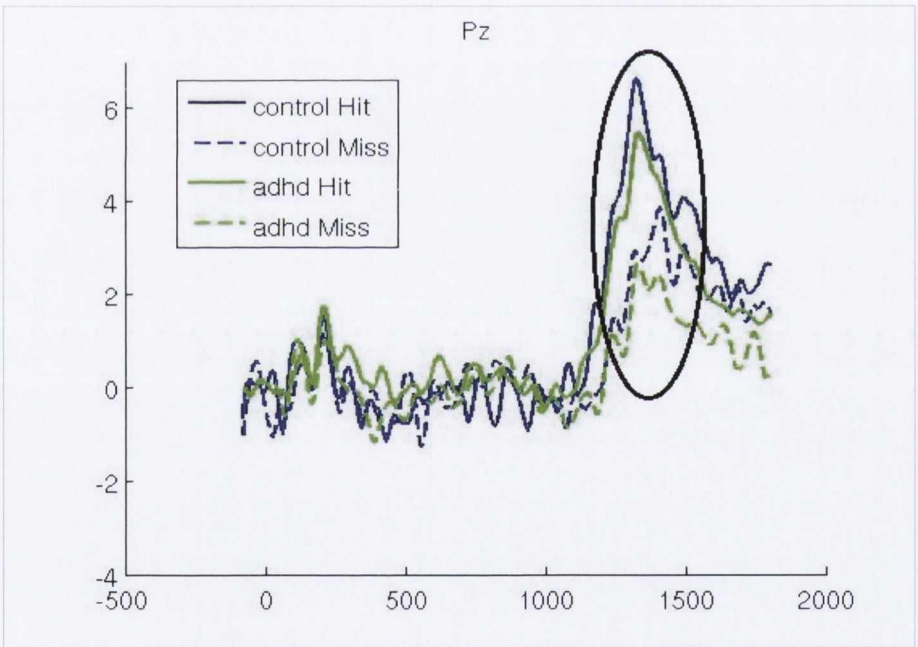


Figure 4.5. Frontal and parietal P3 in the immediate target processing.

Note: Grand average ERP waveforms for the ADHD group and the control group averaged separately for hits and misses. On the top, the late frontal positivity maximal at ~1200 ms. The late positivity at parietal sites was maximal at ~1400 and it is shown on the bottom. There were no significant interaction effects for both components.

4.5.3 Short-term pretarget processing

Differences in electrophysiological markers between ADHD participants and control subjects were examined within a time frame of 4 s before the onset of the target interval.

Early sensory processing

The P1 was measured from three occipital electrodes (O1, O2 and Oz). No significant main effects (main effect of detection: $F_{(1,38)} = 1.087$, $p = .304$; main effect of trial: $F_{(4,152)} = .747$, $p = .561$; main effect of group: $F_{(1,38)} = 2.426$, $p = .128$) or interactions (detection by group: $F_{(1,38)} = 2.847$, $p = 1.0$; trials by group: $F_{(4,152)} = .572$, $p = .683$; detection by trial: $F_{(4,152)} = .615$, $p = .652$; detection by trial by group: $F_{(4,152)} = .449$, $p = .773$) were found. Figure 4.6 shows P1 amplitudes within the 4 s time frame for the ADHD group and the control group averaged separately for hit and missed trials.

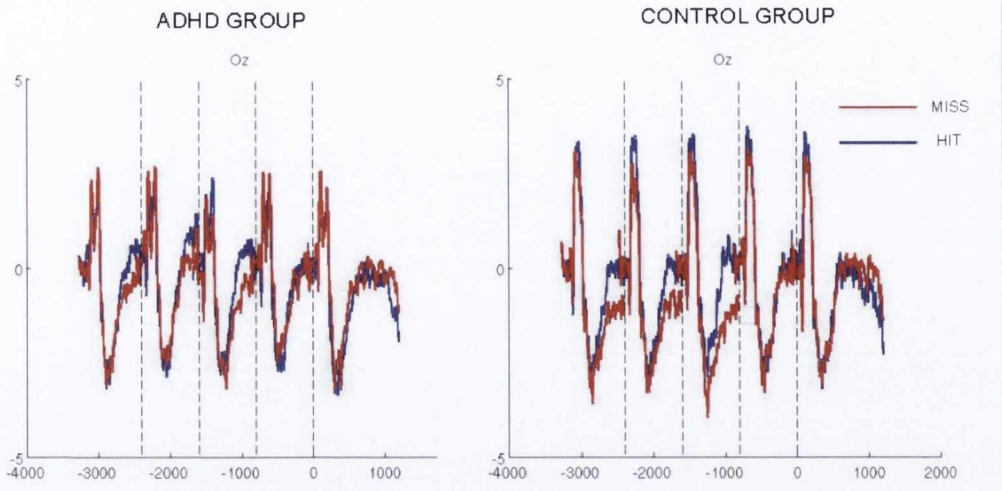


Figure 4.6. P1 in the short-term pretarget epoch.

Note: Grand-average ERP waveforms for P1 within the epoch of -4000 ms preceding target interval for the ADHD group (left) and the control group (right), averaged separately according to subsequent target identification performance (hit, miss). There were no significant differences between groups in P1.

Standard P3

The standard P3 was extracted from three frontal sites (F3, F4 and Fz). For the standard P3, there were no significant main effects of detection ($F_{(1,38)} = .247$, $p = .622$), trial ($F_{(4,152)} = 668$, $p = 615$) or group ($F_{(1,38)} = 2.390$, $p = 130$). There was a marginal detection by trial interaction ($F_{(4,152)} = 2.462$, $p = .057$), driven by higher P3 amplitudes before hit trials compared to missed trials. No other significant interactions were found (detection by group interaction: $F_{(1,38)} = .247$, $p = .622$: trial by group interaction: $F_{(4,152)} = .850$, $p = .496$; detection by trial by group: $F_{(4,152)} = .479$, $p = .751$). Figure 4.7 represents P3 amplitudes within the 4 s epoch in each group averaged separately for hit and misses trials.

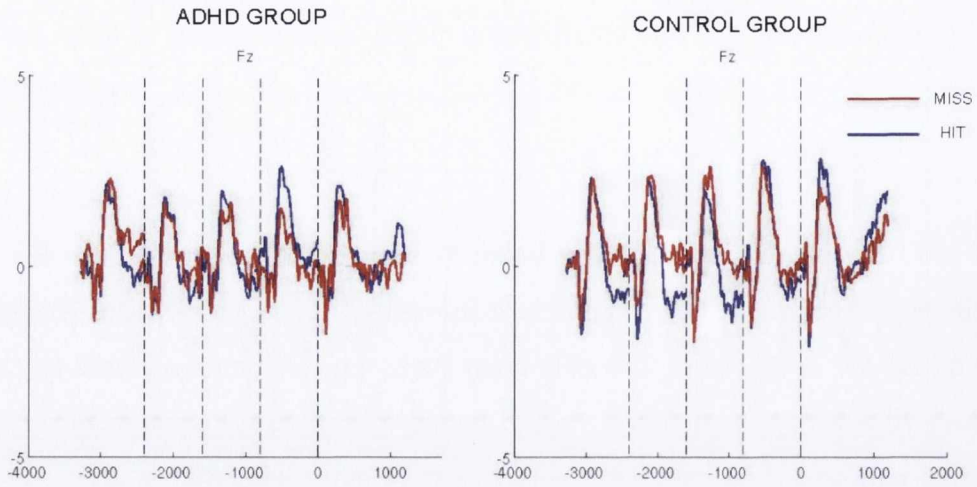


Figure 4.7. P3 in the short-term pre-target epoch

Note: Grand-average ERP waveforms within the epoch of -4000 ms preceding target interval for the ADHD group (left) and the control group (right), averaged separately for hit and missed trials. Each standard stimulus elicited a strong P3 component over fronto-central sites. No significant differences emerged between ADHD participants and controls subjects.

CNV

CNV measures were extracted from central sites. A repeated measures ANOVA showed a significant detection by group interaction ($F_{(1,38)} = 7.096$, $p = .011$). T-tests revealed that CNV amplitudes are larger before a hit trial compared to a miss trial in the ADHD group only ($t_{(19)} = -2.162$, p .044 (minus 3); $t_{(19)} = -3.116$, $p = .006$ (minus 2)). There were no other significant main effects (main effect of detection: $F_{(1,38)} = .001$, $p = .973$; main effect of trial: $F_{(4,152)} = 2.524$, $p = .114$; main effect of group: $F_{(1,38)} = .273$, $p = .604$) or interactions (detection by trial: $F_{(4,152)} = .090$, $p = .765$; trial by group: $F_{(4,152)} = 1.038$, $p = .115$; detection by trial by group: $F_{(4,152)} = 1.859$, $p = .181$). Figure 4.8 shows CNV amplitudes in the 4 s epoch for ADHD and control participants respectively averaged separately for hits and misses.

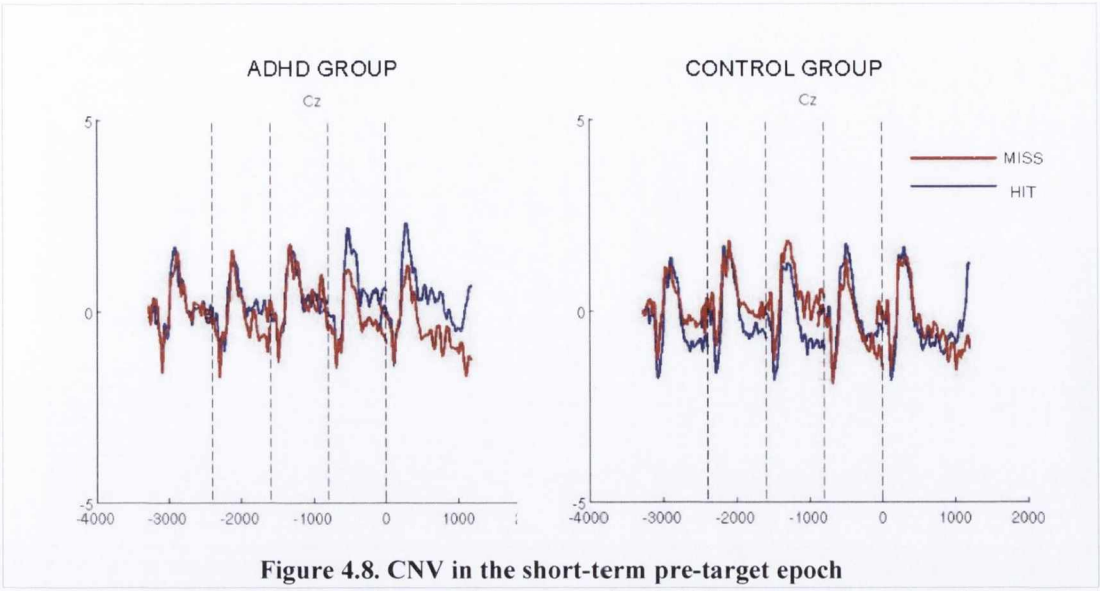


Figure 4.8. CNV in the short-term pre-target epoch

Note: Grand-average ERP waveforms within the epoch of -4000 ms preceding target interval for the ADHD group (left) and the control group (right), averaged separately according to subsequent target identification performance (hit, miss). CNV amplitudes were extracted from central sites. There was a significant detection by group.

EEG amplitude spectrum

The continuous EEG amplitude spectrum was also calculated for the 4 s pretarget epoch.

Theta (5-6.5 Hz). A repeated measures ANOVA showed a marginal main effect of detection ($F_{(1,38)}$ = 3.278, p = .078), driven by higher theta on missed trials compared to hits. There was no detection by group interaction ($F_{(1,38)}$ = .332 p = . 568) and no main effect of group ($F_{(1,38)}$ = 1.316, p = .259). Theta/alpha and theta/beta ratios were also extracted in each group as measures of arousal. Independent samples t-tests revealed significantly higher theta/alpha ratio on hit trials ($t_{(38)}$ = -2.081, p =.044) as well as missed trials ($t_{(38)}$ = -2.430, p = .020) and significantly higher theta/beta ratio on hit trials ($t_{(38)}$ = -2.272, p = .030) as well as missed trials ($t_{(38)}$ = -2.415, p = .022) in the ADHD group compared to the control group.

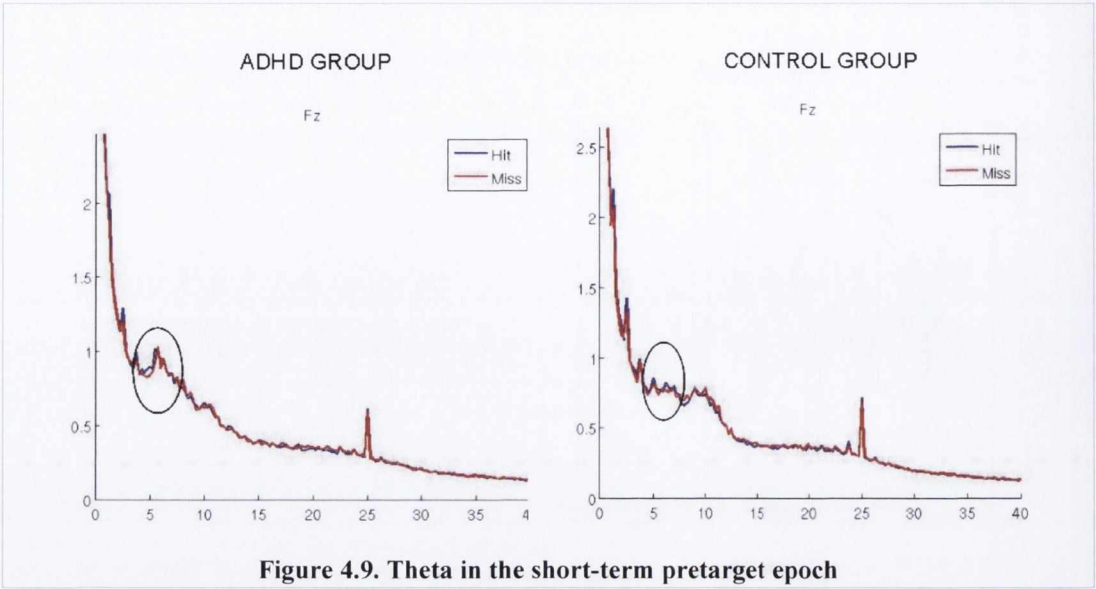


Figure 4.9. Theta in the short-term pretarget epoch

Note: Amplitude spectrum difference between the ADHD group (left) and the control group (right) before hits and misses for Theta (5-6.5 Hz) measured at Fz. No significant difference emerged between ADHD and control participants.

Alpha (8-14 Hz). Alpha was extracted from parietal sites. A repeated measures ANOVA revealed a significant detection by group interaction ($F_{(1,38)}$ = 7.696, p =.009). There was no significant main effect of detection ($F_{(1,38)}$ = 1.188, p = .283) and group ($F_{(1,38)}$ = 2.964, p = .093). Post-hoc paired samples t-tests revealed that alpha amplitude was significantly higher before a miss relative to a hit in the control group ($t_{(19)}$ = -2.670, p = .015). No such effect was found in the ADHD group ($t_{(19)}$ = 1.220, p =.237). An independent samples t-test revealed a marginal difference on missed trials between ADHD participants and controls ($t_{(38)}$ = 1.940, p = .060), driven by higher alpha in the control group compared to the ADHD group.

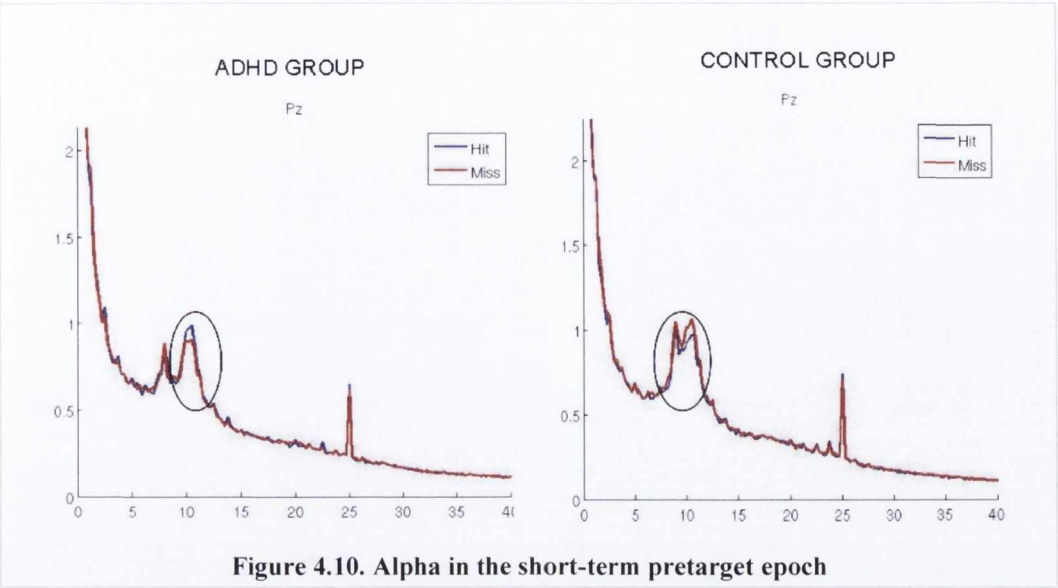


Figure 4.10. Alpha in the short-term pretarget epoch

Note: Amplitude spectrum difference between the ADHD group (left) and the control group (right) before hits and misses for alpha (8-14 Hz) measured at Pz. There was a significant detection by group interaction. The ADHD group did not show increased alpha before a miss.

SSVEP (25 Hz). SSVEP was measured form three occipital sites. A repeated measures ANOVA revealed a significant main effect of detection ($F_{(1,38)} = 5.114$, $p = .030$), but no significant detection by group interaction ($F_{(1,38)} = .067$, $p = .797$) and marginal main effect of group ($F_{(1,38)} = 3.563$, $p = .067$).

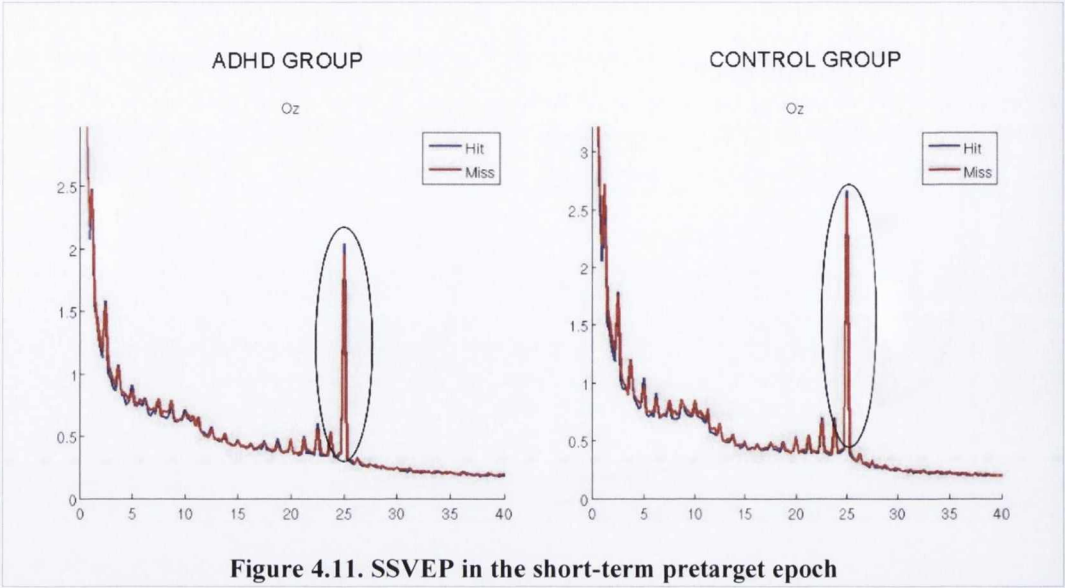


Figure 4.11. SSVEP in the short-term pretarget epoch

Note: Amplitude spectrum difference between the ADHD group (left) and the control group (right) before hits and misses for SSVEP (25 Hz) measured at Oz. No significant interaction was found.

4.5.4 Long-term pretarget epoch

Electrocortical markers were then extracted within a 30 s epoch before the target interval and differences in these markers were compared between ADHD and controls. A series of 19 values were extracted for each variable and entered in a repeated measures ANOVA to investigate differences between the ADHD group and the control group between hit and missed trials. On the basis of analyses of the short term pretarget epoch, alpha was the only marker that distinguished ADHD participants from control participants. However, differences have been investigated on all neurophysiological components.

Standard P3. No significant main effects (main effect of detection: $F_{(1,36)} = 2.520$, $p = .121$; main effect of time: $F_{(18,648)} = 1.688$, $p = .095$; main effect of group: $F_{(1,36)} = 1.488$, $p = .230$) or interactions (detection by group: $F_{(1,36)} = 1.520$, $p = .226$; detection by time: $F_{(18,648)} = 1.099$, $p = .349$; detection by time by group: $F_{(18,648)} = .997$, $p = .460$) emerged in the standard P3.

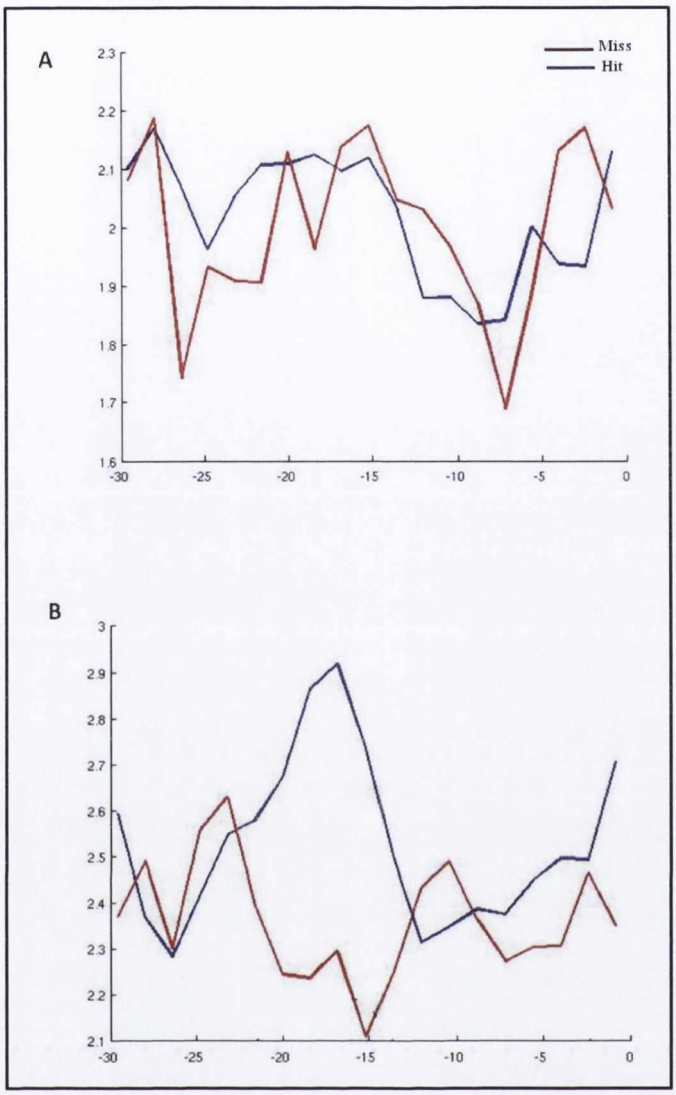


Figure 4.12. P3 in the long-term pretarget epoch.

Note: Standard P3 measures in the ADHD group (A) and in the control group (B) calculated over the 30 s period preceding target onset and averaged separately for hits and misses. No significant differences were found.

CNV. There were no significant main effects (main effect of detection: $F_{(1,36)}$ = 2.205, p = .146; main effect of time: $F_{(18,648)}$ = .787, p = .717; main effect of group: $F_{(1,36)}$ = .841, p = .365) or interactions (detection by group: $F_{(1,36)}$ = 1.002, p = .324; detection by time: $F_{(18,648)}$ = .888, p = .594; detection by time by group: $F_{(18,648)}$ = . 794, p = .708) on CNV.

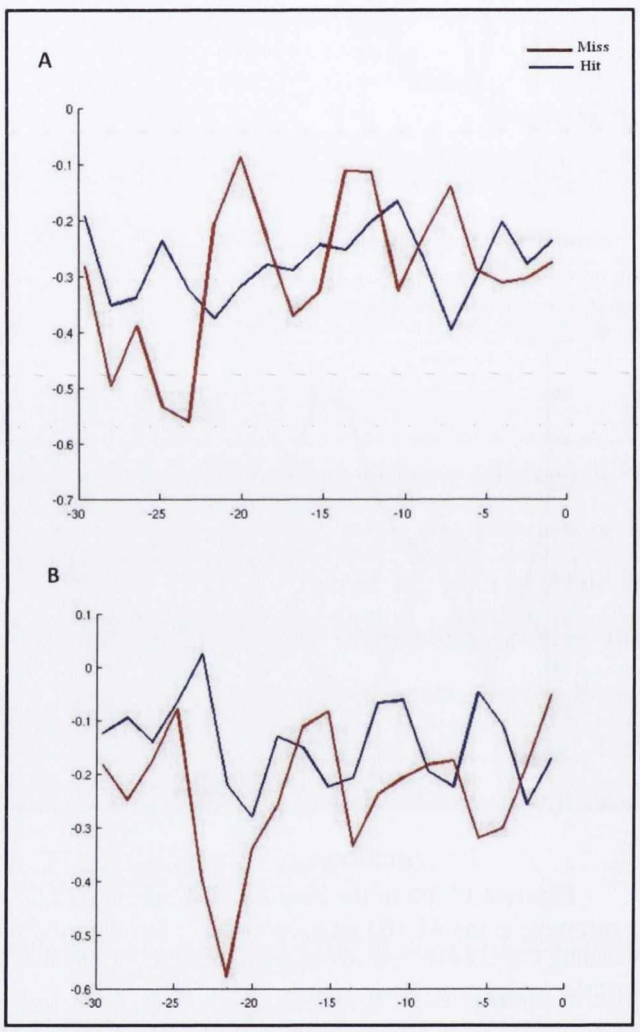


Figure 4.13. CNV in the long-term pretarget epoch.

Note: CNV measures in the ADHD group (A) and in the control group (B) calculated over the 30 s period preceding target onset and averaged separately for hits and misses. No significant differences were found.

Theta (5-6.5 Hz). No significant main effects emerged (main effect of detection: $F_{(1,36)}$ = 1.187, p = .283; main effect of time: $F_{(18,648)}$ = .653, p = .858; main effect

of group: $F_{(1,36)} = 1.091$, $p = .303$). Interactions were not significant too (detection by group: $F_{(1,36)} = .761$, $p = .389$; time by group: $F_{(18,648)} = .619$, $p = .887$; detection by time: $F_{(18,648)} = .980$, $p = .481$; detection by time by group: $F_{(18,648)} = 1.178$, $p = .273$).

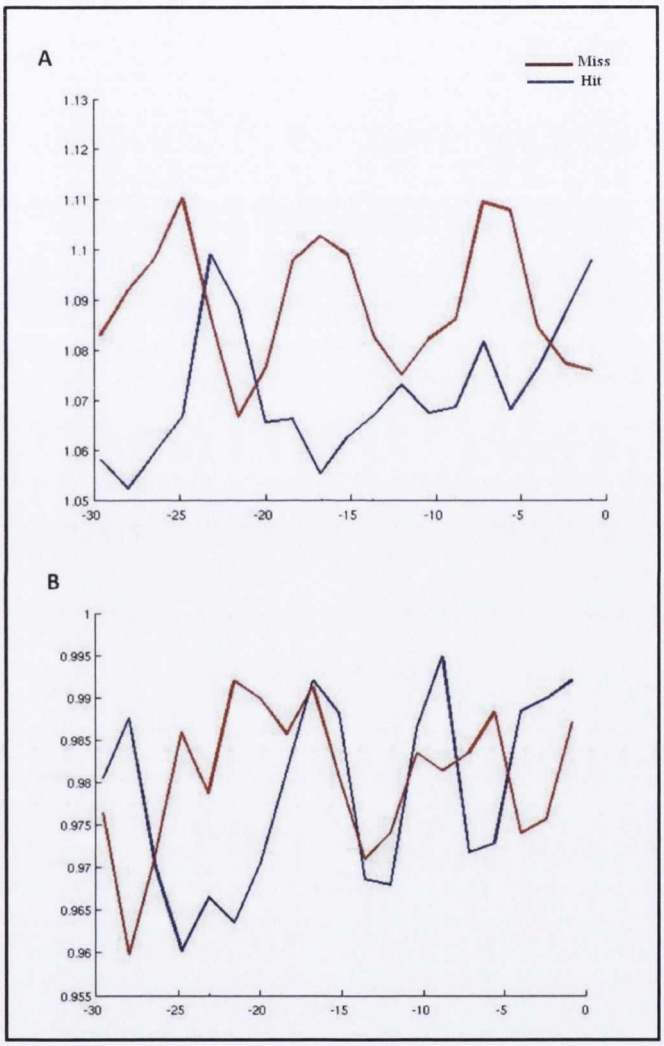


Figure 4.14. Theta in the long-term pretarget epoch.

Note: Theta measures in the ADHD group (A) and in the control group (B) calculated over the 30 s period preceding target onset and averaged separately for hits and misses. No significant differences were found.

Alpha (8-14 Hz). There was a significant main effect of detection ($F_{(1,36)} = 11.507$, $p = .002$) and a significant detection by group interaction ($F_{(1,36)} = 7.807$, $p = .008$)

on posterior alpha, driven by an increased alpha over time before a miss in the control group. No gradual increase of alpha was evident in the ADHD group. There was no significant time by group ($F_{(18,648)} = 1.265$, $p = .205$), detection by time ($F_{(18,648)} = 1.413$, $p = .118$) or detection by time by group ($F_{(18,648)} = 1.362$, $p = .143$) interaction.

Paired samples point by point t-tests were conducted to examine the course of the alpha activity preceding a hit and a miss in the control group and in the ADHD group respectively. In the control group significant differences were evident for the 15 of 19 total pre-target time points tested, corresponding to approximately the 25 seconds immediately preceding a target in which alpha amplitude was significantly larger before a miss (.054<p>.001). In the ADHD group instead paired samples t-tests showed that there was no significant increase of pre-error alpha. Significant differences between pre-hit and pre-error alpha emerged for the following time point: time point 15 corresponding to ~ 7 s preceding a target in which alpha was larger prior to an error, and time point 18 corresponding to ~ 3 s preceding a target, in which alpha was higher preceding a correct response compared to an error.

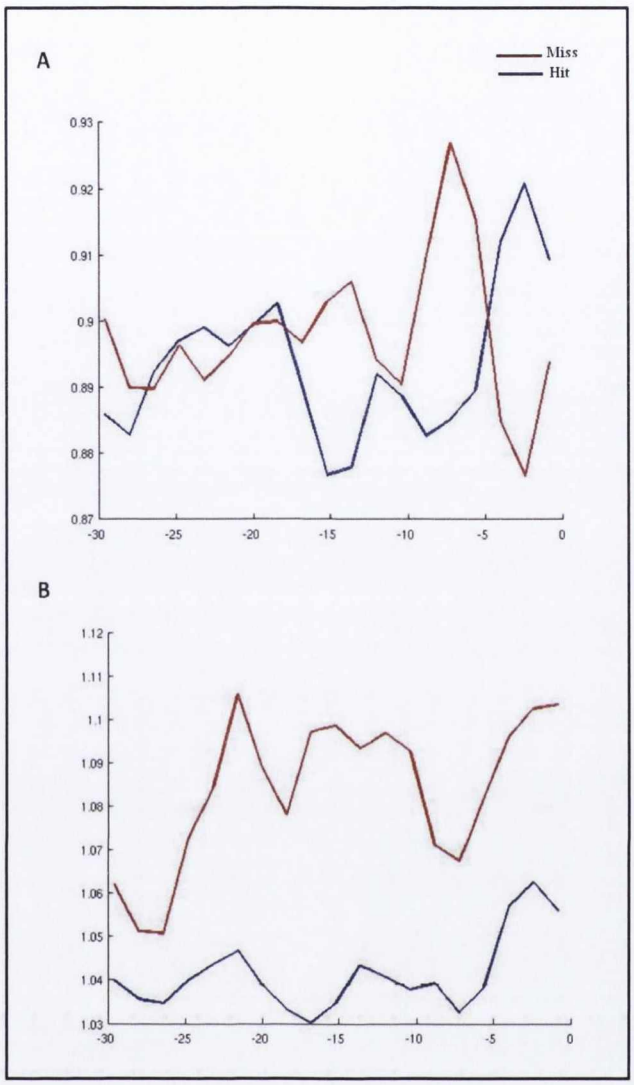


Figure 4.15. Alpha in the long-term pretarget epoch.

Note: Alpha measures in the ADHD group (A) and in the control group (B) calculated over the 30 s period preceding target onset and averaged separately for hits and misses. There was a significant detection by group interaction, driven by higher alpha preceding a miss in the control group. No such effect was found in the ADHD group.

SSVEP (25 Hz). There was no significant main effect of detection ($F_{(1,36)} = .001$, $p = .973$) or time ($F_{(18,648)} = .427$, $p = .982$). However, there was a significant main effect of group ($F_{(1,36)} = 5.523$, $p = .024$), driven by overall higher SSVEP in the control group compared to the ADHD group. No significant detection by group

($F_{(1,36)}$ = .004, p = .950), time by group ($F_{(18,648)}$ = .943, p = 526) or detection by time by group ($F_{(18,648)}$ = .735, p = .776) interaction was found. ANOVA revealed a significant detection by time interaction ($F_{(18,648)}$ = 2.266, p = .029), driven by higher SSVEP preceding a hit trial compared to a missed trial.

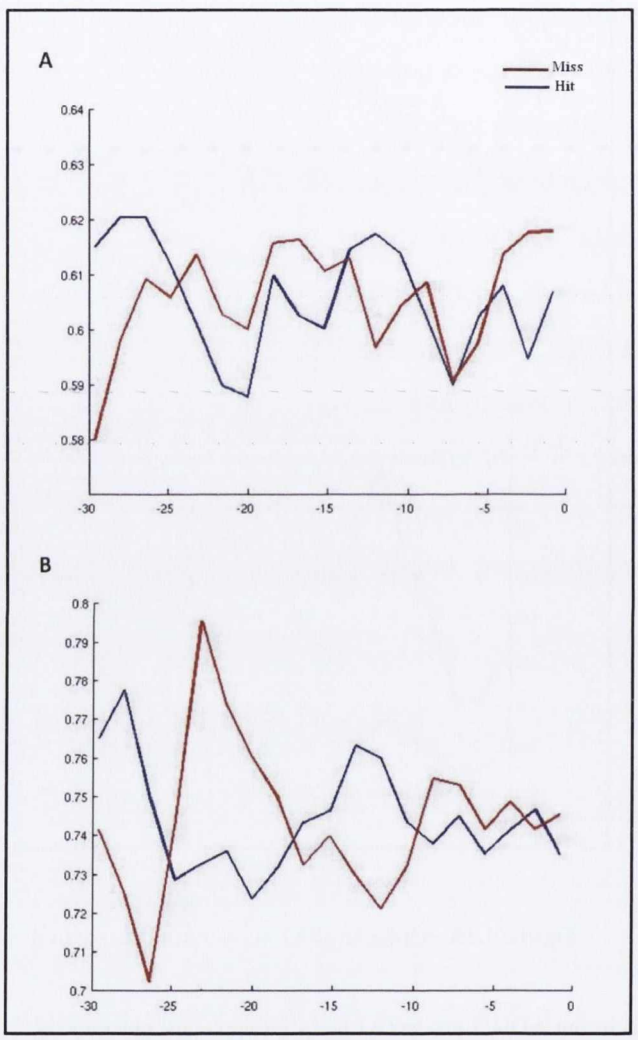


Figure 4.16. SSVEP in the long-term pretarget epoch.

Note: SSVEP measures in the ADHD group (A) and in the control group (B) calculated over the 30 s period preceding target onset and averaged separately for hits and misses. There was a significant main effect of group and a significant detection by time interaction.

4.5.5 Correlations

Pearsons partial correlations to exclude the effect of group have been carried out to investigate links between significant neurophysiological findings and behavioural results as well ADHD symptoms severity.

In immediate target processing, a significant interaction on the early ERP component revealed that in the ADHD group the early ERP component was significantly reduced on missed trials compared to hit trials. No such difference was evident in the control group. A significant negative correlation was found between the early ERP component on misses and hyperactivity/impulsivity symptoms measured by The Conners' Adult ADHD rating Scale (CAARS) subscale F ($r_{(37)}$= -.393, p =.013) as well as total ADHD symptoms, measured by CAARS subscale G ($r_{(37)}$ = -.401, p =.011).

In the short term pretarget epoch of 4 seconds, a significant interaction emerged in posterior alpha. Alpha was significantly increased before missed trials compared to hit trials in controls. The ADHD group does not show this effect. There was a significant positive correlation between posterior alpha amplitudes preceding hits and CAARS subscale F measuring hyperactivity/impulsivity ($r_{(37)}$ =.333, p =.038) as well as CAARS subscale G indicative of total ADHD symptoms ($r_{(37)}$ =.384, p =.016).

Finally, there were significant positive correlations between theta/alpha ratios measured in the short term pretarget epoch on hits and reaction times ($r_{(37)}$ =.298, p =.065), standard deviation ($r_{(37)}$ =.434, p =.006) and coefficient of variation ($r_{(37)}$ =.425, p =.007). Similarly, significant positive correlations also emerged between theta/beta ratios in the 4 s pretarget epoch on hits and reaction times ($r_{(37)}$ =.507, p =.001), standard deviation ($r_{(37)}$ =.463, p =.003) and coefficient of variation ($r_{(37)}$ =.398, p =.012) respectively.

4.6 Summary of significant results

4.6.1 Behavioural results

Comparisons of behavioural results revealed an effect on accuracy and number of omission errors which was close to significance (p =.054 for both variables). Repeated measures ANOVAs on the percentage of accuracy across blocks showed that there is a time on task effect in both groups, suggesting gradual decrease in performance over time in both groups.

4.6.2 Immediate target processing

An interaction effect on the early ERP component was found, indicating that in the ADHD group only, the early ERP component was significantly reduced on missed trials compared to hit trials. No difference in this component was found in the control group. Partial correlation also revealed a significantly negative correlation between the early ERP component's amplitudes on misses and ADHD symptoms' severity. No difference emerged in CNV, while parietal P3 was significantly higher on hits compared to misses in both groups.

4.6.3 Short term pretarget epoch

A repeated measures ANOVA revealed a significant detection by group interaction, driven by increased CNV amplitudes preceding a hit compared to a miss in the ADHD group only. No significant results emerged for P1 and P3. A repeated measures ANOVA revealed a significant detection by group interaction in the short-term pretarget epoch on alpha measures. This was driven by significantly higher alpha preceding a miss compared to a hit in the control group. No such effect was evident in the ADHD group. A partial correlation indicated a significant positive correlation between alpha preceding a hit and severity of ADHD symptoms. Comparisons of theta/alpha and theta/beta ratios suggest higher ratios in the ADHD group compared to the control group. Moreover, correlations revealed a significant positive relationship between theta/alpha ratios and reaction time, standard deviation and coefficient of variation as well as a positive correlation between theta/beta ratios and reaction time, standard deviation

and coefficient of variation. SSVEP was significantly higher preceding hit trials compared to missed trial in both groups. No significant differences emerged for theta.

4.6.4 Long term pretarget epoch

No significant results emerged for the standard P3, CNV. A repeated measures ANOVA revealed a significant detection by group interaction in the long term pretarget epoch of 30 s on alpha, driven by higher alpha measures preceding a missed trial in the control group only. Another repeated measures ANOVA suggested a main effect of group on SSVEP, indicative of overall higher SSVEP in the control group compared to the ADHD group. No significant differences emerged in theta amplitudes.

4.7 Discussion

One aim of this study was to investigate behavioural differences in the Continuous Temporal Expectancy Task (CTET) between adults with ADHD and controls to explore sustained attention deficits. Based on the study findings, it emerges that the CTET is able to behaviourally distinguish ADHD participants from control participants. Results in fact suggest that there is a very close to significance difference between groups in terms of accuracy and the number of omission errors, suggesting that people with ADHD show impaired performance in this task. This pattern of deficits clearly indicates a difficulty in sustained attention. Both groups also show decreased performance over time, as expressed by significantly reduced accuracy across the eight blocks of the task.

Another aim of the study was to investigate electrophysiological markers accompanying and preceding errors that could differentiate ADHD participants from control participants. It emerged that two electrophysiological markers can distinguish ADHD subjects from controls. The first one is the alpha band in the short-term time-frame of 4 seconds preceding the target. Results relating to the

short-term pre-target epoch showed alpha to be significantly increased 4 seconds before an error in the control group, while no such difference emerged in the ADHD group. The second marker is an early ERP component in the immediate target processing frame which was maximal in the interval of 200-400ms preceding the onset of a target stimulus. The early ERP component appeared to significantly increase on correct trials compared to missed trials in the ADHD group, while no such difference emerged in the control group.

The finding of a significant interaction in the alpha band in the short-term time frame is of particular interest as it is consistent with O'Connell et al.'s (2009) previous findings which demonstrated a gradual increase in alpha up to 20 seconds prior to the commission of an error, thus allowing the prediction of an upcoming error. Interestingly, the gradual increase in alpha in the long-term pre target epoch is also present in the control group in the current study. As evident from figure 4.15 and from the results of point-by-point t-tests, the control group showed increased alpha in the 30 seconds preceding a missed trial. This result is consistent with previous results (O'Connell et al., 2009; Mazaheri et al., 2009) that refer to healthy control subjects. The gradual increase in alpha in the long-term pre target epoch is instead not present in the ADHD group. In fact, the alpha trend in the ADHD group, is not homogeneous, showing a similar level of alpha on both misses and hits up to 15 seconds preceding the target, followed by an increase in alpha on misses, maximal at around 7 seconds before the target, and finally, by the end of the task (~3 sec), the pattern appeared to be the opposite, as alpha became higher before hit trials than missed trials.

Furthermore, some correlations emerged between alpha and ADHD symptoms severity that suggests that ADHD symptoms of inattention and impulsivity are positively correlated with alpha measures on hit trials. In the case of the ADHD group, there was no significant difference between alpha preceding a hit or a miss, however it is evident from figure 4.15 that alpha was slightly higher on hit trials compared to missed trials. The opposite pattern was found in the control group.

The results of the study also showed a significant interaction effect in an early ERP component. The early ERP component appeared to significantly increase on correct trials compared to missed trials in the ADHD group, while no such difference emerged in the control group. Additionally, there was also a significant negative correlation between the amplitude of this early ERP component and the severity of ADHD symptoms. This correlation suggests that smaller amplitudes on missed trials are associated with higher ADHD symptoms' severity. No differences between groups emerged for later components such as P3 and CNV.

The electrophysiological results of the study suggest that control participants are able to desynchronise alpha, as alpha in the long-term epoch appear relatively stable and suppressed before a hit. Conversely, there is a maladaptive drifting trend in alpha before a miss prior to a missed trial. The ADHD group do not therefore suppress and they maintain a stability of alpha thus failing to dissociate pre-hit and pre-error alpha power. The second electrophysiological mechanism that differentiated the ADHD group from the control group was an early ERP component in the target time-frame that was significantly reduced on error trials compared to correct trials in the ADHD group only. This reduced early positivity in the ADHD group might indicate poor anticipatory processes that maybe caused by inattention due to the preceding maladaptive alpha states.

A final relevant finding of the study was the increased theta/alpha and theta/beta ratios in the ADHD compared to the control group that may be indicative of diminished arousal. This result is not consistent with the results of chapter 3, as, in that case, no significant differences between ADHD participants and control participants emerged for measures of cortical arousal. This discrepancy might originate from different tasks characteristics. The CTET is in fact longer and more difficult compared to the 15 minutes auditory oddball task that was employed in chapter 3. CTET might therefore have placed higher demands on the vigilance and sustained attention system thus resulting in impaired levels of arousal in the ADHD group.

To summarise, the use of the CTET to assess adults with ADHD has provided new and interesting findings on dysfunctional brain mechanisms involved in ADHD. The most relevant finding was the absence of the alpha increase on missed trials in the ADHD group, which was instead replicated in the control group. Another dysfunctional mechanism is evident later during the immediate target processing on the early ERP component which precedes the target onset. Additionally, decreased levels of arousal have been found before an error in ADHD. Altogether, these findings suggest dysfunctional alpha states in the long-term pre-target epoch in the ADHD group, who did not dissociate pre-hit form pre-error alpha power. This may have caused inattention and poor anticipatory processes, as evident in the differences between the two groups in the early ERP positivity.

It is finally important to highlight a few possible limitations of the current study. It must be said that this study represents the first attempt at investigating predictive brain correlates which precede lapses in attention in ADHD. Although the CTET is ideal task for investigating electrophysiological patterns preceding lapsing attention, it might be considered very demanding for people with ADHD. The CTET places high demands on the sustained attention system as it requires participants to continuously focus their attention on strings of patterns for an extensive period of time. It should also be added that the nature of the EEG testing, which requires participants to minimise movements and blinking, made the task even more challenging, especially considering the nature of the ADHD symptoms. This was reflected in the presence of many artefacts in original datasets and, in some cases, it lead to the exclusion of some participants from final analysis. Despite these difficulties, the current study gave new and explanatory insights into the brain processes responsible for attentional failures in ADHD.

Chapter 5. A single-blind randomized controlled trial (RCT) to investigate the effects of Self-Alert Training on attention and impulsivity in adults ADHD

As cited before, the second and main part of this thesis is aimed to examine the effects of a training programme for adults with ADHD to improve attention and impulsivity. A single blind randomized controlled trial (RCT) is conducted to investigate these effects and detailed descriptions of the methodological approach as well as comprehensive results are presented in this chapter. This challenging study represents a logical progression from a previous study conducted in our research group by O'Connell and colleagues (O'Connell et al., 2008). In this study, a new alertness training strategy called Self-Alert Training (SAT – Robertson et al., 1995) was developed and its very short-term efficacy was assessed in a group of healthy individuals and then, independently tested in a group of adults with ADHD. The current RCT is aimed to test the efficacy of an extended version of a similar SAT protocol, using a partially home-based SAT and biofeedback strategy in adults with ADHD.

5.1 Background

As reviewed in the introduction to this thesis, at present, there are just two well-established treatments for ADHD: psychostimulant medication and behavioural therapy. Psychostimulant treatments have proven efficacy in dealing with behavioural symptoms of ADHD. However, stimulant medications such as methylphenidate and atomoxetine, that increase dopaminergic and noradrenergic levels in the brain, produce only short-term improvements in ADHD symptoms, without altering affected cortical networks in a long lasting manner (Castellanos et al., 2002). Furthermore, stimulant medications are effective with a proportion of individuals with ADHD, while for others their effectiveness is very limited. Stimulant drugs also have high associated costs, as they require long term

prescription by a consultant psychiatrist with costly associated medical screening to monitor associated side effects, such as insomnia and anxiety. Side effects represent another limitation to drug treatments and, in a proportion of people with ADHD, associated side effects, such as insomnia, anxiety and depression, are particularly severe, affecting quality of life. Behavioural interventions for ADHD have also been developed and their efficacy in reducing primary and secondary behavioural symptoms has been demonstrated (MTA Cooperative Group, 2001; Pelham et al., 2000). However, as for psychostimulant medications, these positive effects are not long-lasting. This may explain why, despite long-term treatments behavioural and neuropsychological abnormalities associated with ADHD persist into adulthood in a significant proportion of cases (Castellanos et al., 2002; Woods et al., 2002).

Recognition of such limitations of isolated pharmachological or behavioural treatments of ADHD has prompted a move toward multi-modal treatment strategies that seek to address the underlying, cognitive, behavioural and environmental roots of the disorder.

5.2 The development of Self-Alert Training (SAT) for the remediation of sustained attention deficits

As reviewed in the introduction and in chapter 3, ADHD is associated with abnormal neurotransmitter function, particularly dopaminergic and noradrenergic (Arnsten, 2006), abnormal neuroanatomical brain structures and altered function (Valera et al., 2007) and a number of genes confer risk for ADHD (Bellgrove et al., 2006). Although ADHD is primarily a behavioural disorder, cognitive functions such as working memory and attention are integral to psychological development and may play a causal role in the emergence of behavioural symptoms (Barkley et al., 1997; Nigg et al., 2001).

In experiments 1 and 2 it was demonstrated that adults with ADHD experience difficulties when a task is particularly reliant upon the endogenous maintenance of

sustained attention. These difficulties manifested themselves in the form of increased attentional lapses and higher variability (Experiment 1 and 2). In Experiment 1, these behavioural findings were accompanied by a reduction in phasic pupil dilations over the course of the task in the ADHD group, indicative of reduced attention as well as ERP evidence indicating reduction of goal maintenance. Furthermore, a pattern of dysfunctional brain correlates preceding failures in sustained attention was identified in Experiment 2, suggesting dysfunctional task-engagement mechanisms in ADHD. In the same experiment diminished level of arousal was also associated with attentional lapses in ADHD.

Behavioural methods to increase levels of alertness/arousal have been developed in previous research conducted in our group (Manly et al., 2002; O'Connell et al., 2006). These behavioural methods have exploited the existing relationships between the sustained attention system and the arousal system. As demonstrated in previous experiments in chapter 3 and 4 and as recent literature reviews suggested (Bush, 2010), impaired sustained attention is a key symptom of ADHD. The sustained attention system is subject to bottom-up influences mediated by ascending thalamic-mesencephalic projections (Usher et al., 1999). Similarly, sub-cortical arousal systems are particularly sensitive to exogenous stimulation, such as noise, temperature or light received form the peripheral sensory systems via thalamic relay nuclei (Olszewski & Baxter, 1982). Therefore, these two systems are related and they share common structures.

One of our previous study (Manly et al., 2002), patients with frontal pathology following brain injury were tested using the Hotel Task, which is a complex task that mimic a real-life setting and it provides a measure of executive functions. In this task, participants are given 15 minutes to try and do some of each of five sub-tasks. As the total time to complete all the tasks would exceed an hour, the measure emphasises patients' ability to monitor the time, switch between the tasks and keep track of their intentions, all abilities that require good executive skills. The aim of the experiment was to examine whether the provision of a brief auditory stimuli, acting to interrupt current activity and to cue patients to consider

their overall goal, would improve performance in the Hotel Task. Without the external auditory cues, patients performed the task significantly more poorly than age- and IQ-matched control volunteers, a common error being to continue to perform one task to the detriment of beginning or allocating sufficient time to the other tasks. When exposed to the interrupting tones, however, the patients' performance was both significantly improved and no longer significantly different from the control group. These results demonstrated that providing an external bottom-up cue could improve performance in brain injured patients and may facilitate monitoring and behavioural flexibility. Furthermore, these findings suggest that the introduction of brief auditory alerts may have had their effect of improving arousal via ascending thalamic mesencephalic projections, thus re-orienting attention to the task at hand (Robertson et al., 1995).

Another relevant study was conducted in our research group by O'Connell et al. (2006) using a similar behavioural strategy. In this experiment, 15 children with ADHD and 15 control children performed four blocks of a modified version of the Sustained Attention to Response Task (SART). Non contingent alerts were randomly introduced on two of these blocks as a cue for participants to adopt a more supervisory stance to their performance. Results showed that while the alerting cues did not alter the total number of commission errors made by ADHD children over a task block, they did produce a significant short-term reduction in commission errors in the period immediately following an alerting cue. These findings suggest that sustained attention performance can be enhanced in children with ADHD using simple cognitive training strategy.

The findings from these studies suggest that bottom-up influences on the sustained attention network can be exploited to compensate for reduced top-down control of attention and a fundamental question is whether is it possible to train such top-down control of attention.

In the last few years our research group has been developing a new endogenous technique, called Self Alert Training (SAT), which seeks to capitalise the known

relationship between sustained attention and arousal (O'Connell et al., 2008). Instead of reducing arousal, the goal of SAT is to teach participants to transiently increase their arousal at regular intervals in order to offset the periodic decreases in endogenous control that are major determinants of momentary lapses of attention, impulsive slips and disorganized behaviour.

The behavioural strategies involved in SAT arose from an earlier intervention developed by Robertson and colleagues (Robertson et al., 1995) which was designed to remediate sustained attention deficits of a group of patients with right-hemisphere lesions arising from stroke. The 5 hours intervention occurred while patients performed a variety of routine everyday tasks (e.g. reading or sorting). While patients were performing these tasks, the experimenters re-directed the patients' attention to the task by combining a loud sound with an instruction to attend. Thus, as in O'Connell et al. Study (2006), the intact bottom-up alerting pathways were used to re-orient attention. Patients were then gradually taught to initiate this alerting procedure themselves, using a self-generated verbal cue. By the end of the task patients learned to self-alert without needing to generate verbal sues at all. Thus patients acquired to ability to activate the sustained attention network in a covert- self-initiated and therefore endogenous manner without requiring any external cue. Importantly, this technique is not task-specific but has the potential to enhance performance on a variety of tasks that require sustained attention. After training, all patients showed clinically significant improvements on the training tasks and on a number of untrained simulated real life behaviour tasks. The duration of these training effects ranged from 24 hours to 14 days.

SAT extends Robertson at al.'s original training protocol by teaching participants to modulate their arousal during each 'self-alert' using a biofeedback protocol. Participants learn to produce transient increases in arousal, as indexed by SCRs, in order to offset the periodic decreases in top-down modulation of arousal that have been associated with failures of sustained attention. Unlike Robertson et al.'s (1995) original training technique, participants do not perform any particular tasks during SAT other than observing and modulating their EDA. The objective of

SAT is to gradually acquire the ability to control one's alertness levels in a task-independent manner that can be applied to a variety of real-life settings.

Essential to assisting control of alertness is awareness of the current state of alertness. For this reason, as explained above, biofeedback of a signal known to be hugely sensitive to alertness –SCR- was included, as part of the SAT. Similar biofeedback has been used in many other domains. In biofeedback individuals receive real time visual or auditory information conveying the current level of an otherwise covert biomarker and they learn to to exert volitional control over that particular process (Nagai et al., 2004). One arousal biomarker that can be reliably modulated during biofeedback is electrodermal activity (EDA), a measure of covert modulation of autonomic system activity that is linked to emotional and cognitive states. The autonomic system is subject to descending cortical and subcortical influences on hypothalamic and brainstem mechanisms. Studies have found that volitional modulation of skin SCR during biofeedback activates many of the same control regions that have been implicated in top-down sustained attention (Critchley et al., 2002 – see HRB). For example, Nagai and colleagues (Nagai et al., 2004 – see redm) tested healthy participants with fMRI while they performed a visual EDA-biofeedback task in which they were taught relaxation strategies in order to reduce transient SCRs. The fMRI data revealed a neuroanatomical network that included the ACC, lateral prefrontal cortices, the thalamus and the hypothalamus. In addition, Patterson et al. (2002) have identified a region incorporating ventromedial prefrontal cortices and rostral ACC that is consistently activated irrespective of the task being performed. Thus, there is evidence to suggest that volitional modulation of SCRs would activate frontal control regions that are also implicated in sustained attention.

This overlap, together with the other studies cited above, provides a basis for hypothesising that training participants to modulate their alertness suing a number of methods, including SCR feedback, should lead to improvements in sustained attention with associated impulsive and disorganized behaviours.

The efficacy of SAT was examined in a study previously conducted in our research group by O'Connell and colleagues (O'Connell et al., 2008). In this study, the SAT protocol was first validated in a group of 23 neurologically healthy participants and then independently in a group of 18 adults with ADHD to determine its clinical validity. All participants underwent a pre-training baseline assessment as well as a post-training assessment, both consisted of four blocks of a modified version of the SART. Half of the participants in each group were assigned to a placebo condition to control for non-specific effects. The SAT protocol was delivered following three main steps. In Step 1, participants were presented with a loud alerting sound in order to demonstrate the responsiveness of their SCRs to changes in arousal. This step was repeated 5 times and each time participants were able to view increases in the EDA waveform online. In Step 2, the external cue was removed and the aim of participants was to begin producing internally driven increases in response to a verbal cue from the experimenter (the word 'now' spoken at a normal volume). This step was repeated until participants could generate at least 5 clear increases in SCR amplitude. Finally in Step 3, participants learned to take complete control of their EDA trace without any prompting from the experimenters. First, participants were asked to say the word 'now' when they were initiating a self-alert and, as before, this step was repeated, with visual feedback, until participants could generate at least 5 increases in amplitude. In the last phase, the same procedure was then repeated but this time visual feedback was withdrawn and participants were not able to view their EDA trace. This final step was repeated until participants could generate at least 5 increases in amplitude. Participants in the placebo-training group were trained on the video game 'Tetris'. Both training procedures lasted for approximately 30 minutes. Results showed that control participants and ADHD participants that received SAT showed improvements on key behavioural indices of sustained attention. Both participant groups showed a reduction of commission errors in the post training assessment and additionally, ADHD participants also maintained a consistent level of RT variability. In contrast, participants in the training-placebo condition showed no significant change in commission error rates and exhibited a

gradual increase in RT variability. Comparison of SCR amplitudes before and after training indicated that the non-ADHD group who received SAT showed an increase in arousal post-training while participants in the placebo condition experienced a gradual drop in arousal. A similar trend was observed in the ADHD groups. Block-by-block analysis revealed in fact that the ADHD SAT group clearly showed increased arousal during the first two blocks of SART post-training, however these effects dissipated by the third and fourth blocks. This last finding might suggest that increasing length and intensity of the training session might be necessary to achieve lasting effects in ADHD. Results of this study are shown in figure 5.1.

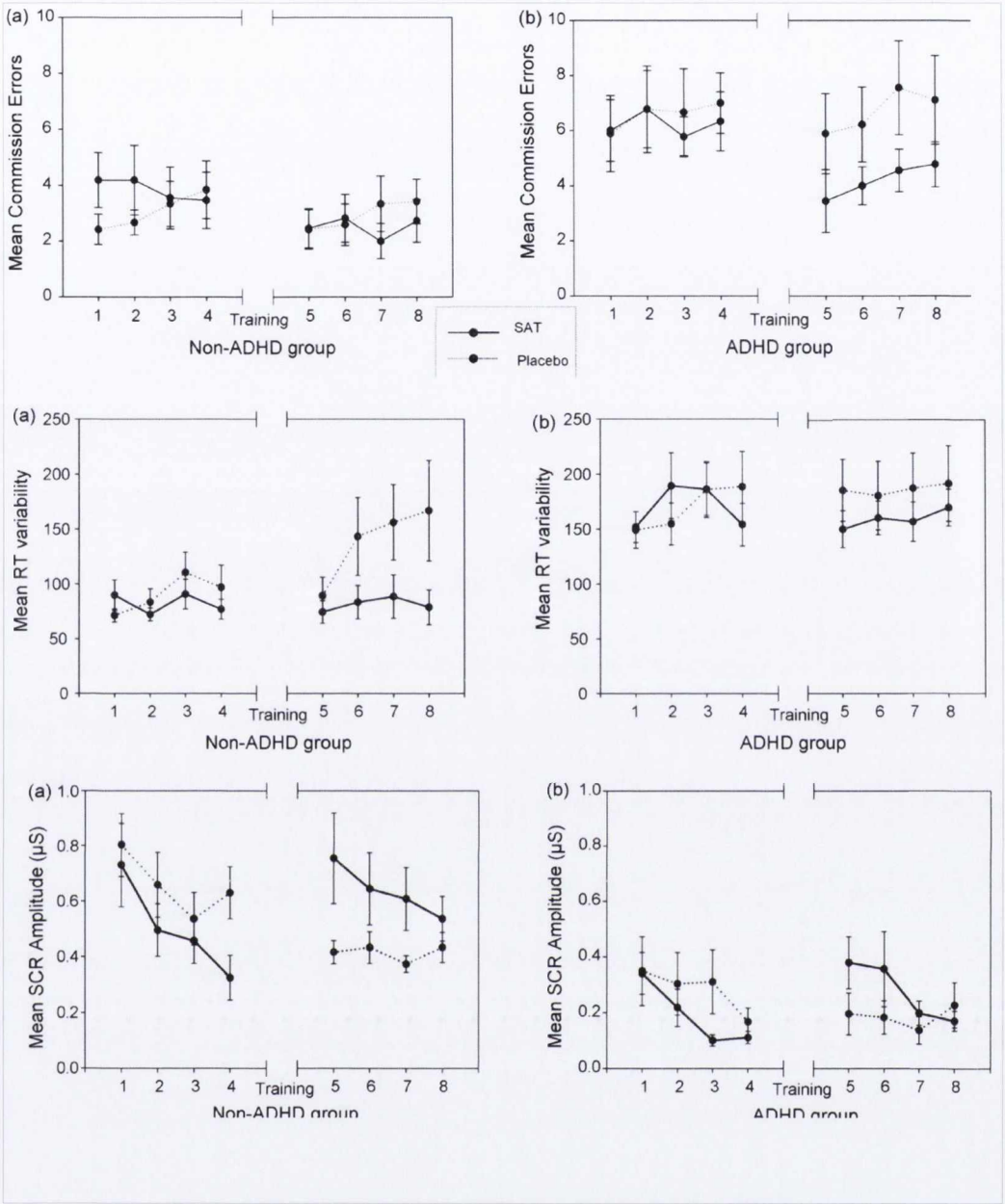


Figure 5.1. Results of O'Connell et al study (2008).

Note: From the top: comparisons of SAT and placebo groups for mean commission errors, RT variability and SCR amplitude in the non-ADHD groups and in the ADHD groups (figure from O'Connell et al., 2008).

In summary, results of the study are consistent with the hypothesis that volitional control of arousal would lead to improvements in sustained attention. While previously cited studies (Manly et al., 2002; O'Connell et al., 2006) have targeted the sustained attention network via its bottom-up influences, SAT targeted

sustained attention via its top-down influences. SAT might be particularly beneficial for adults suffering from ADHD since this disorder produces subtle neuropsychological abnormalities that do not preclude direct training within the affected domains.

Importantly, this experiment has demonstrated that a relatively simple cognitive intervention can lead to substantial neuropsychological improvements. From a rehabilitation perspective, the use of alerts that are independent of task or participant characteristics provides a highly flexible means of triggering controlled behaviour that is potentially applicable to a range of real-world settings (see Fish et al., 2007; Levine et al., 2000).

The possibility that extended SAT and implementation of training strategies in everyday life would lead to lasting improvement in frontally mediated cognitive function is an interesting possibility worthy of further investigation. Future work is therefore needed to test the efficacy of extended SAT protocol in a systematic and rigorous way. Further work is also required to establish whether or not these gains can be transferred to real world settings.

These points are addressed in this chapter by testing the efficacy of an extended SAT protocol in a partially home based biofeedback based training programme for adults with ADHD. Furthermore, emphasis is given to the application of SAT in real life settings through the use of individualized everyday life selected goals.

5.3. Experimental Design

The design of the study is a single blind randomised controlled trail (RCT) comparing SAT with a control attention training procedure involving equal amounts of computer practice and trainer contact. The study followed Consort guidelines (Altman et al, 2001). Adults who met DSM-IV criteria for Attention Deficit Hyperactivity Disorder (combined type or inattentive subtype) were recruited for the study, on the basis of a standardised structured interview

(Conners' Adult ADHD Diagnostic Interview for DSM-IV – CAAID, Epstein et al., 2001), corroborative evidence from an informant about childhood and current symptoms and a neuropsychological assessment. Following informed consent, participants were randomly allocated to either to SAT or to a control attention training procedure using a minimisation method (Altman and Bland, 2005) which ensured that the two groups did not differ significantly in a) gender; b) prescribed psychotropic medication status; c) alcohol and illegal drug use (sorted according to: alcohol consumption less than 35 units per week *and* no illegal drug more than once per month use *versus* alcohol consumption more than 35 units per week *OR* illegal drug use more than once per month). Measures of cognitive, social, psychiatric function were taken pre-training, post-training (after five weeks of home based training) and at 3 months follow up. EEG/ERP measures and pupil's measures were recorded at these three times. MRI scans were also conducted before the start of the training period.

5.4. General procedure and participants' schedule

The study included three assessments: a pre-training assessment, a post-training assessment after five weeks and a three months follow-up assessment, and two training sessions. Participants who were willing and suitable also underwent an fMRI assessment before and after the five-week training period. The figure below shows the typical participant's schedule.

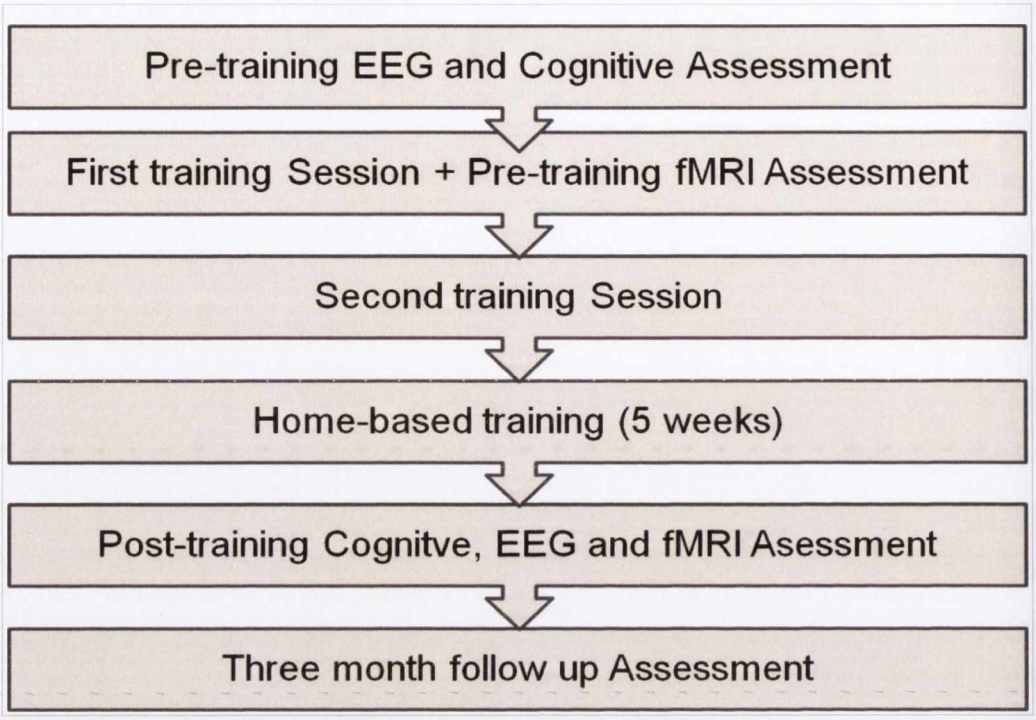


Figure 5.2. Participants' typical training schedule

Each assessment involved two stages. During the first stage of participants' assessment subjects underwent a neuropsychological evaluation during which their performance on a number of behavioural tasks was measured. These tasks emphasised ecological validity as they simulated typical day-to-day activities and were designed to assess a range of cognitive abilities, including selective, divided, and shifting processes of attention, time management and other real-life executive functions. Additionally, patients were asked to complete self-report measures of their attention and memory related difficulties– corroborative reports from a close friend or relative were also obtained. This first stage of testing lasted approximately 45 minutes. After completing the neuropsychological assessment, each participant was given a ten minutes break and after that the second part of the assessment was conducted which involved an EEG and pupillometry assessment. Participants completed a resting state task, which lasted for 3 minutes followed by two blocks of a two-stimuli auditory oddball task, each block lasting 15 minutes. EEG and pupil's diameter changes were recorded during both blocks of the auditory oddball task. This second phase lasted for approximately 1 hour and 15

minutes.

Following the first baseline assessment, participants were asked to attend Trinity College Institute of Neuroscience for two training sessions. Each session was carried out on separate days and lasted approximately 1 hour and 30 minutes.

Participants who were willing and suitable for fMRI also underwent a pre-training fMRI assessment, which was conducted after the first training session. The pre-training fMRI session lasted for approximately 1 hour and 40 minutes.

After the completion of both training sessions and assessments, participants were asked to practice the training at home for five weeks.

Following the 5 week training period participants were asked to attend a follow up assessment during which the same neuropsychological, EEG and pupillometry assessment was repeated. Their performance on the original behavioural tasks as well as neurophysiological measures could be evaluated. Self-report measures were also obtained, thus affording the opportunity to compare patients' personal experience of their cognitive and behavioural difficulties at the beginning and end of the 5 week training programme. A brief interview was also held with the patient, during which they were asked to reflect on and relay both their positive and negative experiences of using the training. They were also asked to complete a feedback questionnaire to that effect.

Participants that underwent a pre-training fMRI assessment were also required to attend Trinity College Institute of Neuroscience for a post-training fMRI session, which was conducted after the post-training neuropsychological and EEG assessment and it lasted for approximately 1 hour.

Finally, all participants were asked to return after 3 months for a final assessment, to evaluate whether or not any immediate improvements following the training had been long-lasting. In this session the same neuropsychological and EEG tests were repeated for the last time.

A subset of participants underwent pre and post-training fMRI, but these data are

not included in this thesis.

5.5. Description of experimental Self-Alert Training and control attention training protocols

Prior to the five-week training period, participants from both experimental groups attended two sessions of training with a member of the research team. These training sessions were a means of providing patients with psychoeducation regarding sustained attention, arousal, and the role of noradrenaline in mediating levels of cognitive alertness. Participants were then familiarised with the programme and the tasks they were required to practice during the proceeding five-week period.

The role of the trainer was to *facilitate* and *encourage* patients' development over the course of the training. Significantly, this treatment programme combined intervention with psychoeducation, so that participants were both informed and in control of their own progress. Emphasis was thus placed on the role of the participants themselves in what is essentially a 'self-training' scheme.

Both training programmes are completely automated and had been installed on laptops we provided to participants. The home page of both training programmes contained the structure of the training. Each training programme included several steps which were displayed in a drop-down menu on the left side of the laptop's screen. Participants could read content of each step simply by clicking on the drop down menu. Although training programmes' interfaces were designed to appear very similar, the content of each step differed between the two training versions.

Detailed descriptions of the SAT and control attention training are presented in the next two sections.

5.5.1 Self-Alert Training (SAT) group protocol

In the case of the SAT group, training materials include: a written manual, a laptop with the training programme, a biofeedback device consisting of two

electrodes to place on the index and middle finger and a usb cable to connect the biofeedback device to the laptop's usb port (VERIM 3.0, http://www.verim.info/index_en.php) and a goals diary.

Training session 1

Phase 1: The basis of SAT: the notion of alertness and modulatory arousal

This first phase of the first training session provided SAT participants with the basic concepts of SAT. This phase introduced to the participant, in simple language, the nature of alertness, arousal and attention. Examples of problematic situations in which lacks alertness usually cause deficits in day to day situations were presented. Participants were also asked to provide examples themselves from their own life problems that have arisen -in the domains of forgetfulness, disorganization and impulsivity for instance- and which have caused them problems. The linkage between these problems and the difficulties the participant has in maintaining the optimal levels of brain activation was then explained. Participants were then introduced to the basic concepts of SAT. Participants focussed on the concept of modulatory arousal and basic SAT strategies to control that, such as breaths and correct posture, were explained. Participants were invited to try such strategies. The trainer asked participants to try to focus by taking a deep breath and sitting up straight. The trainer then asked to try these strategies few times and every time to focus as much as possible. Participants were encouraged to provide their feedback on their feelings and current state of alertness.

If the participant was using medication, such as Ritalin or other stimulants, the trainer briefly showed the analogy between what a biofeedback training attempts him/her to do in terms of raising the levels of noradrenaline without the aid of medication, and how similar this is to the effects of medications. The trainer then gave the participant the option of continuing or discontinuing his/her medication during the training, but we asked to all participants to avoid taking any medication for at least 24 hours before every training or assessment session. Stimulant

medication has a typical wash-out period of under 24 hours and temporary withdrawal carries no known risk to the participant.

Phase 2: The Self-Alert Training (SAT)

As explained before, SAT embedded a biofeedback protocol which was used as an additional means to help participants understand the concept of alertness and how to increase it at will. Therefore, in this phase, participants started to familiarize with the biofeedback software and devices.

The biofeedback package is presented and the use of the biofeedback device is briefly explained to participants.

This step was followed by the explanation of the actual SAT. During SAT participants are taught to gain volitional control of their electrodermal activity (EDA) trace following three main steps:

Step1: Eliciting SCRs by external alerting

1. Participants were allowed to view the EDA reading on-line and the meaning of this measurement was briefly explained:

'The white line (the EDA trace) measures minute changes in levels of sweat in your skin which tells you how alert is your brain when you perform a task'

2. Illustration of EDA sensitivity to arousal: The participant was presented with a loud sound played on the laptop in order to demonstrate the responsiveness of SCRs to changes in arousal. After the SCR has returned to baseline the trainer said:

' Do you see how your skin showed that you woke up? That is an example of how you can experience a fast increase of how alert you are because of some external event. However, it is also possible to cause increases in how alert you are without any external events. Although we may not always be aware of it, we are able to change how alert we are by ourselves and this ability helps us in our everyday lives to stay focused on tasks and to avoid making absent-minded errors. This is

what we are going to try and work on during the next few minutes. I'm going to play the loud sound on the laptop a few more times and I want you to concentrate on how it feels every time. Try to make a link between what you feel inside and the increase you see in the while line'

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

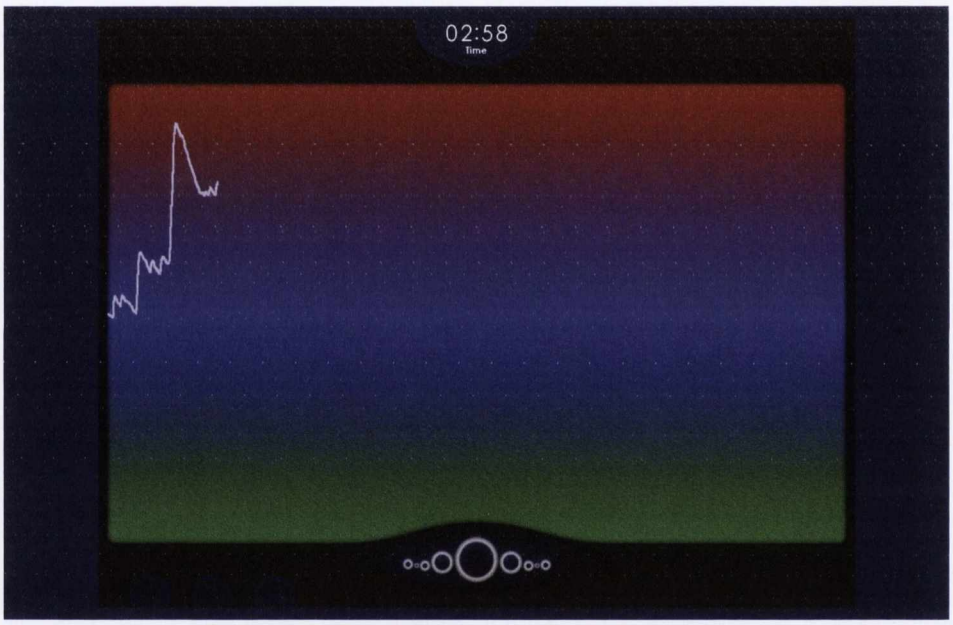


Figure 5.5. The biofeedback software's interface.

Note: An examples of a participant's SCR online following the presentation of a loud sound.

Step2: Cues internally generated SCRs

3. In the second step, the sound was removed and the aim was for participants to begin producing internally driven increases in arousal without a loud sound alerting cue. The trainer said:

' Now I want you to try to wake yourself up without the loud sound to help you. When I say 'now', you try to recreate what it was that you felt earlier (when I

played the loud sound on the laptop) that made the white line go up. You need to concentrate on the internal process of switching to a highly alert state on my cue and try and get as large an increase in the white line as you can each time. Good (or, ok let's try again, try to recreate that sudden increase in alertness you felt the first time that you heard the loud sound)'.

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

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

Step3: Self-initiated control over arousal responses

5. In the final step of SAT, participants learned to take complete control of their EDA trace without any external prompt from the trainer. The trainer said:

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

The experimenter left the laptop in front of the participant so that both of then were able to observe the trace on line.

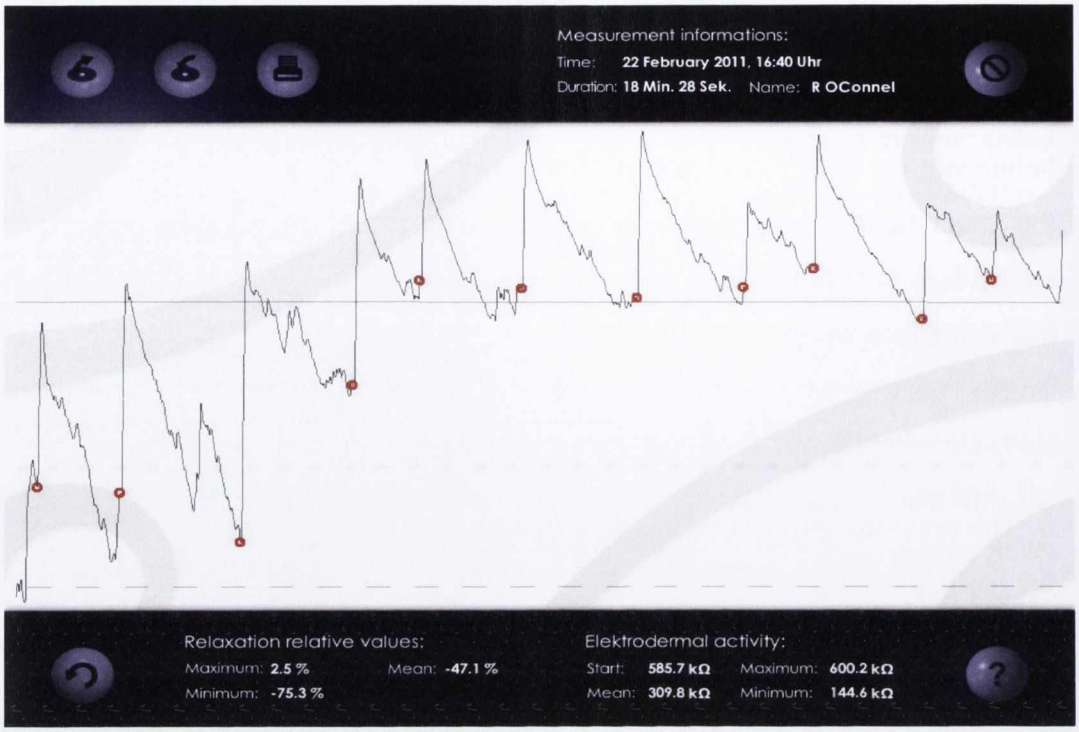
'Well done – you see you decided there to make the line move up, and there it moved up. This time you have managed to do it without any external cue whatsoever'

This step is repeated, with visual feedback, until the participant can generate at least 5 increases in amplitude. The participant was instructed to relax in order to reduce number of non-specific SCRs and thus ensure that an increase in arousal

was readily observable.

Participants were then instructed to press the "F1" key on the laptop's keyboard before starting a self-alert attempt. This allowed the biofeedback software to mark the exact point where participants started self-alerting. Participants were also shown how to save biofeedback sessions on the laptop. As the training was home-based for five weeks, this procedure allowed enable participants practices to be saved. This was very important as it allowed us to obtain, at the end of the training period, a complete record of the five-week practice for each participant.

6. The previous step is repeated but this time visual feedback was removed and the participant was not able to view the EDA trace. The participant was asked to say 'now' when they are self alerting and the trainer only was able to observe the trace online. This step was central as it was aimed to teach participants to self-alert in an automatic fashion, without any visual feedback from the biofeedback software. This step was repeated until the participant could generate at least 5 increases in amplitude. Examples of successful self-alerting during training are provided in figure 5.6.



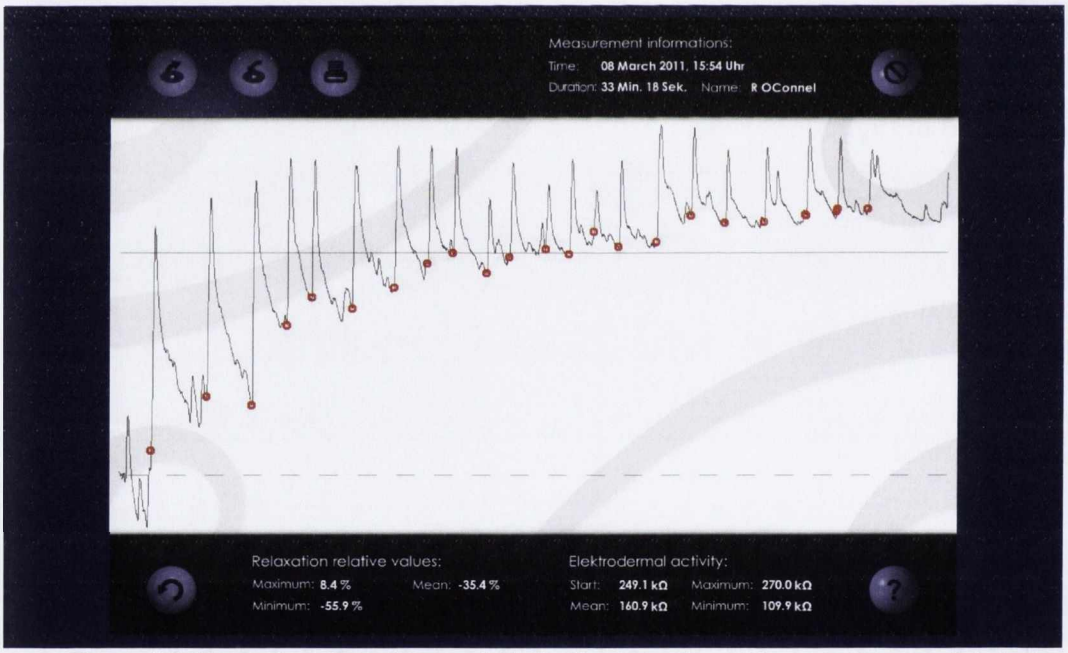


Figure 5.6. Examples of participants' biofeedback session with several successful alerts.
Note: The red dots indicate the start of a self-alert episode, which is followed by a clear increase (peak) in participants' SCR.

Training session 2

Phase1: Attentional Exercises

During the first phase of the second training session, participants were presented with different types of attentional exercises, which were part of the training programme and were included in 'homework' sessions. Each type of exercise was introduced and briefly demonstrated. Participants were encouraged to try a one minute practice of each type of exercises to familiarize with the tasks. Each exercise complete practice lasted for approximately 3 minutes and 30 seconds. Participants were instructed to practice complete versions of the exercises at home. Importantly, participants were encouraged to apply SAT while practising the exercises to try to improve their performance. In this way participants learned to control their alertness levels without visual feedback from their EDA trace, in a task-independent manner.

The following computerized exercises were included in the training programme:

- *Sustained Attention to Response Task (SART).* Three versions of this task were included. In the Number SART, numbers from 1 to 9 were visually randomly presented on the laptop's screen. Participants were asked to press the space bar for every number except for number 3s. In the Auditory SART, numbers from 1 to 9 were called out loud from a recorded voice and presented on the laptop. As for the Number SART, participants had to press the space bar for every pronounced number except 3s. In the Animal SART, animals shapes were presented on the laptop's screen and participants had to press the space bar for every animal's shape except for the kangaroo.

- *Choice Reaction Time task.* Two versions of this task were included. In the first version (Arrow Choice Reaction Time Task) arrows pointing either to the left or to the right were presented on the laptop's screen and participants had to

press the arrow pointing to the left or to the right, according with the presented stimuli. The second version of the task (Letter Choice Reaction Time Task) was very similar to the previous version, but this time either the letter O or X were presented on the laptop's screen and people were asked to press the correspondent letter on the laptop's keyboard.

- *Listening task.* In this task, participants had to listen to audio files which consisted of recorded weather forecasts. Audio files were downloaded from RTE website (www.rte.ie) and they were implemented in the training programme. Participants had to count the number of times a particular word was presented during the forecasts. Four different audio files were included.

- *Stop Signal Task.* Two versions of this task were implemented (Arrows Stop Signal Task and Letter Stop Signal Task). The stimuli were the same used in the Choice Reaction Times Tasks (arrows pointing right or left and letter O and X). In this task a tone was randomly presented before a given stimulus. Every time a stimulus was preceded by a tone, participants had to withhold their responses.

Each practice of an attentional exercise was automatically saved by the training software in a database on the laptop. As for SAT-biofeedback sessions, this step allowed us to get a complete database containing each participants' practice schedule during the five week training.

Phase 2: Planning for application of SAT to key situations in everyday life

This final phase of the training has the key aim of transferring SAT abilities acquired so far to real life settings, thus achieving the ultimate goal of SAT to help people with ADHD increasing alertness and concentration in day to day

situations. In the last part of the training session, participants identified a number of key situations where they had difficulty in everyday life. With the help of the trainer, participants were then asked to select up to three key therapeutic goals and problems. Each participant was then asked to type each selected goal in specific spaces into the training programme on the laptop and to save them (figure). Participants were also given the option of adding more goals during the course of the five weeks training, if they wanted.

Participants visualised everyday life situations that they identified as problematic and practised the self-alerting during these imagined scenarios. This was designed to establish the habit and to ensure that they learned to self-alert in a range of situations. Participants were then asked to rate their current performance of their specified goals/ problem areas, and their satisfaction with that performance, on a scale of one to ten. A printed number chart was given to participants in order to aid in their visualisation of these goal ratings. Number charts were taken from the Goal Attainment Scaling (Kiresuk, Smith & Cardillo, 2009). Participants were asked to rate their performance and satisfaction of their chosen goals in the post-training testing session too. These subjective goal ratings formed the basis for investigating whether or not there had been any perceived benefits of the SAT in participants' day-to-day lives.

Finally participants were given a goals diary and they were instructed to record their progress in the diary during the five week training. On each page of the diary participants could write the selected goal and a brief description of how they applied SAT to each specific day-to-day situation. There was also a space to record the outcome of their attempts, in terms of how successful self-alerting was in each situation.

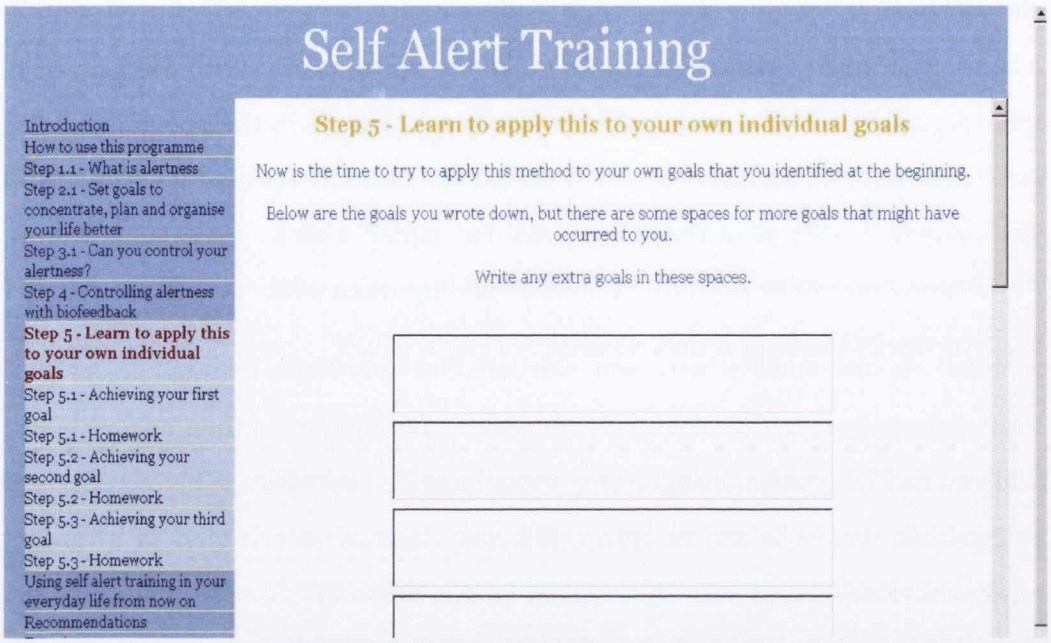


Figure 5.7. Self-Alert Training Programme.

Note: In the step of the training, participants are required to select everyday life goals and type them into boxes where these goals are recorded.

Typical duration of each training session was approximately 1 hour and 30 minutes.

Participants in the SAT group were asked to practice 20 minutes of SAT-biofeedback exercises and 10 minutes of computerised exercises per day. They were also asked to apply the self-alerting to their selected goals in everyday life situations and to record their attempts and results into their goals diary.

5.5.2. Control attention training group protocol

The aim of the control training procedure was to control for key non-specific elements of SAT, including interaction with the trainer, positive feedback and the placebo effect. Therefore, the attention training group attended Trinity College for the same number of training sessions as the experimental group. Training materials of this group included a laptop with the training programme and a manual

Training session 1

Phase 1: Background and Education

In this phase participants were educated about sustained attention and were asked to reflect on their everyday life problematic situations arisen from poor attention, absentmindness or disorganization. The trainer then explained to participants that research has shown that it is possible to improve attention by practising certain attentional exercises and that this is the aim of the current training. The same option on continuing or discontinuing medication was provided to each participant. Figure showed the home page of the attention training programme in which participants could read and learn about key notion of sustained attention.

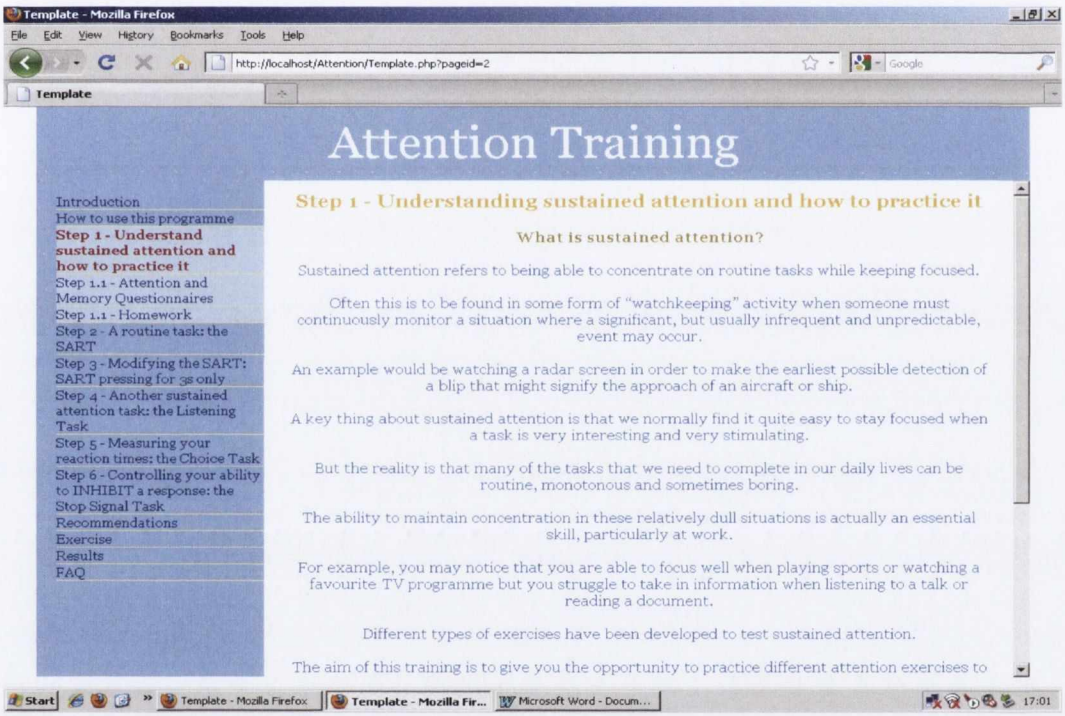


Figure 5.9. Home page of the attention training programme.

Phase 2: Attentional Exercise – part 1

Attentional exercises in the attention training group were the same as in the SAT group.

Participants were presented with the first two types of attentional exercises (*Sustained Attention to Response Task (SART) and Choice Reaction Time Task*).

Participants were told:

'Research suggests that constantly practising certain attentional exercises over an extended period of time can actually increase one's ability to concentrate over time. If you perform a task intensively for sustained periods of time, it can actually improve your ability to concentrate in everyday life situations which you may find problematic'.

Each of the two types of attentional exercise was then explained, specifying the particular ability that each exercise was aimed to measure and train. The emphasis was placed on the fact that improvements could be obtained from repeated and constant practice. Each exercise was then demonstrated and participants were asked to perform a short practice for each exercise. Participants continued to practice attentional exercises until the end of the first training session and the experimenter encouraged them to try and do their best, giving positive feedback when improvements were evident.

Training session 2

Phase 1: Attentional Exercises – part 2

The last two type of exercises (*Stop Signal Task and Listening Task*) were presented and, as in the previous step, the trainer explained to participants that each type of exercises was designed to measure a specific ability and that improvements could be reached by constant and intensive practice of these exercises. Each type of exercise was then demonstrated and participants were asked to perform a practice of each exercises.

Phase 2: Focusing attention in everyday life

In the last part of the attention training programme, participants were invited to think about high risk situations for attentional failures in their everyday life and they were encouraged to 'focus attention' in these situations. They were also prompted to be more aware of their levels of attention and concentration in day-to-day settings and they were encouraged to pay attention to any improvements

following each training practice.

Typical duration of each training session was approximately 1 hour and 30 minutes.

Participants in this group are asked to practice 10 minutes of attentional computerised exercises per day over the five-week period and to try and focus attention in everyday life problematic situations.

5.6. Materials and Procedures

5.6.1. Participants

Adult participants with ADHD were recruited from the Dean Clinic of Dr Jessica Bramham at St Patrick's Hospital in Dublin and from various ADHD support groups in Ireland. Participants who attended Dean Clinic and received a clinical assessment, were given an information sheet and they were asked to directly contact Trinity College Institute of Neuroscience if they were interested in taking part in the study. Participants who attended ADHD support groups were given the same information sheet with Trinity College Institute of Neuroscience contact details. Participants recruited from ADHD support groups who expressed interest in taking part in the study were additionally contacted by Dr Jessica Bramham for a phone interview to assess the reliability of their ADHD diagnosis.

All participants that contacted Trinity College Institute of Neuroscience were preliminarily screened for inclusion and exclusion criteria. The following criteria were applied:

Inclusion criteria:

- Age 18-55 years;
- Full Scale IQ > 85 (assessed using Wechsler Adult Intelligence Scale – 3rd Edition);

- Informed consent given;
- Diagnosis of ADHD according to DSM-IV criteria in both childhood and at present in adulthood (using the Conners' Adult ADHD Diagnostic Inventory for DSM-IV, 2001).
- Self-reported clinically significant problems in daily life attributable to attentional, executive or arousal deficits (based on interview by Dr. Bramham).

Exclusion criteria:

- History of pervasive developmental disorders (e.g. Asperger's syndrome, autism) or intellectual disability (IQ<80);
- History or current diagnosis of epilepsy or other neurological condition (e.g. multiple sclerosis, motor neuron disease);
- History or current diagnosis of schizophrenia, bipolar disorder or other equivalently severe psychiatric condition;
- Current primary diagnosis of substance misuse which requires treatment with priority (i.e. dependent on alcohol or other illicit substances), however individuals with recreational alcohol and drug use will be included as they are representative of the adult ADHD population.

Participants who agreed to participate in the fMRI part of the study had also to satisfy the standard screening criteria for undergoing MRI that pertain in Trinity College Institute of Neuroscience; those patients who failed to meet these criteria (for example because of metal in body) underwent the study, but not the fMRI assessment.

Patients who meet the main criteria were randomly assigned using an automated procedure devised by Dr Cathal Walsh, Statistician in Trinity College Dublin according to a minimisation randomisation procedure (Altman and Bland, 2005)

which ensured that the two groups did not differ significantly in a) gender; b) prescribed psychotropic medication status; c) alcohol and illegal drug use (sorted according to: alcohol consumption less than 35 units per week *and* no illegal drug more than once per month use *versus* alcohol consumption more than 35 units per week *OR* illegal drug use more than once per month).

It must be stressed that the study was a single blind randomized controlled trial in which ADHD participants and the researcher involved in participants testing and data analysis remained blind for the whole duration of the study. Participants were told at the start of the study that they would be assigned to either a biofeedback based training group or another attention training group and efforts were made to keep participants blind to group assignment during their participation in the study. Participants' randomization was conducted by a clinical psychologist who worked outside Trinity College and a research assistant was responsible for conducting participants' training sessions and follow-up calls. The researcher who was responsible for conducting assessments and subsequent final analysis was blind to participants' conditions.

Sixty-two participants expressed interest in taking part in the study. Out of these eleven were excluded (nine declined to participate while two did not meet the inclusion criteria). Fifty-one participants were randomized to either the SAT group or the attention training group. There were twenty-four participants in the biofeedback training group (16 males, 8 females) and twenty-seven in AT group (20 males, 7 females). Participants did not differ in terms of age ($t_{(49)}$=-.408, p=.685; SAT = 31.38, AT = 32.81), IQ ($t_{(23)}$=.941, p=.356; SAT=110, AT = 109) and years of education ($t_{(29)}$=.389, p=.700; SAT=16.25, AT=14.92). Eight participants in the SAT group and six participants in the AT group were taking medication. Nine participants in the SAT group had comorbid disorders (one insomnia, one dyslexia and seven anxiety and depression) while four AT participants reported comorbid conditions (one depression and three anxiety and depression). Table 5.1 shows participants' CAARS and WURS scores. Fourteen

participants dropped out leaving thirty-seven participants that underwent the post-training assessment, eighteen in the SAT group (mean age= 32.7; mean years of education= 15.9; mean IQ= 112) and nineteen in the AT group (mean age= 31.9; mean years of education=13.4; mean IQ= 109). Eight participants were lost at the three-month follow up, so that twenty-nine participants underwent the final three-month follow up assessment, fourteen in the SAT group (mean age= 32.6; mean years of education= 15.9; mean IQ= 112) and fifteen in the AT group (mean age= 31.6; mean years of education= 14.7; mean IQ= 108). Figure 5.10 shows the study detailed consort flow diagram.

Table 5.1. CAARS and WURS scores

	SAT group [a]	AT group [a]	T	p
CAARS-E- DSM IV inattention self ($t_{(49)}$)	81.33 (9.38)	80.22 (13.20)	.342	.734
CAARS-F- DSM IV hyperactivity self ($t_{(49)}$)	65.92 (13.21)	66.00 (14.02)	.022	.983
CAARS-G- DSM IV total self ($t_{(49)}$)	78.38 (9.05)	77.56 (14.73)	.236	.815
CAARS-E- DSM IV inattention other ($t_{(38)}$)	68.05 (10.64)	70.90 (11.63)	.424	-.809
CAARS-F- DSM IV hyperactivity other ($t_{(38)}$)	63.80 (11.11)	64.55 (12.75)	-.200	.842
CAARS-G- DSM IV total other ($t_{(38)}$)	68.20 (10.61)	70.05 (12.09)	-.515	.610
WURS self ($t_{(48)}$)	48.43 (19.33)	49.46 (29.45)	-.088	.930
WURS other ($t_{(33)}$)	16.82 (6.54)	21.11 (7.70)	-1.570	.120

T-scores are reported for each of the Conners' Adult ADHD Rating Scale (CAARS) measures. [a] Values are mean (SD); *Statistically significant difference. **Clinically significant symptom

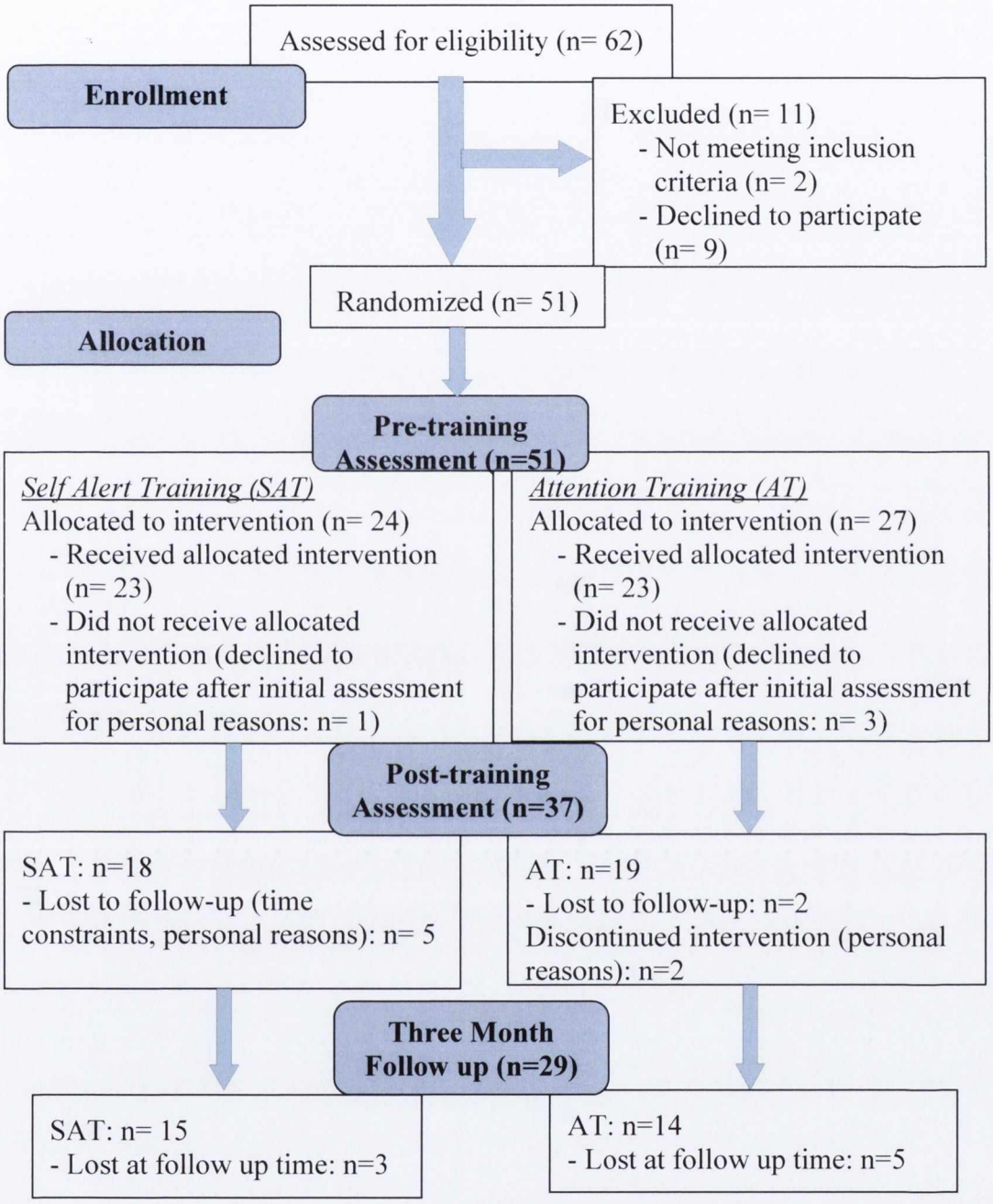


Figure 5.10. CONSORT Flow Diagram

5.6.2. Testing Procedure and Materials

5.6.2.1 Pre-training Assessment

In the first phase of the assessment, participants were firstly asked to complete some scales and questionnaires. Observer forms for a close relative or friend were also given to participants in this first phase. Participants were asked to return these forms by post as soon as the chosen relative or friend have completed them. After that, participants. underwent a neuropsychological assessment. This first phase of the assessment lasted for approximately 45 minutes.

The complete list of scales and questionnaires followed by the list of neuropsychological tests, are presented below:

Scales and Questionnaires (appendix 3):

- *The Conners' Adult ADHD Rating Scale Self Report: Long version* (CAARS-S: L - Conners et al., 2001) and *the Conners' Adult ADHD Rating Scale Observer Form: Long Version* (CAARS-O: L, Conners et al., 2001). Both scales include 66 items which consist of the DSM-IV ADHD symptoms and other items measuring everyday life problems of attention, impulsivity, emotional lability and problems with self-concept. The observer form is given to a parent or a close relative or friend chosen by each participant.

- *The Wender Utah Rating Scale (WURS* - Ward, Wender, & Reimherr, 1993*).* The WURS is a retrospective measure of ADHD symptoms in childhood. The self-report version of the scale includes 25 items, while the observer form included 10 items only.

- *The General Health Questionnaire* (GHQ – Goldberg, 1988, look at GK paper for ref). The General Health Questionnaire (GHQ) includes 28 items that measure anxiety and insomnia, depression, somatic symptoms and

social dysfunction. Norms indicate that a score higher than 23 is indicative of impairment.

- *The Attention-Related Cognitive Errors Questionnaire (*ARCEQ – adapted from Cheyn, Carriere & Smilek, 2006) and the *Memory Failures Questionnaire* (EMFQ – adapted from Cheyn et al., 2006). These questionnaires measure reported lapses in attention, memory and absentmindedness experienced in everyday life.

- *The Beck Depression Inventory* (BDI-II, Beck, Steer & Brown, 1996, look at manual). This scale is composed by 21 items and it gives a measure of severity of depression. A score between 0 and 13 indicates minimal level of depression.

- *The Beck Anxiety Inventory* (BAI, Beck & Steer, 1993). The BAI includes 21 items which measure severity of anxiety symptoms. A score between 0 and 7 is considered minimal.

- *The Self Efficacy Scale* (SES- Schwarz and Jerusalem, 1993, look on the scale at the bottom). This scale is used as a measure of self-efficacy.

Neuropsychological measures (appendix 4):

- *The National Adult Reading Test* (NART – Nelson, 1982). In this test, participants were given a list of words they were asked to read out loud to the tester. Participants' premorbid intelligence score was then calculated on the basis of the total number of errors.

- *The Test of Everyday Attention* (TEA- Robertson et al., 1994). This battery provides norm-referenced scores on eight different subtests that are sensitive to selective attention, sustained attention and attentional switching respectively. There is also a divided attention test in the battery. The following three subtests were

administered:

The Elevator Counting with Distraction, which had been designed as test of auditory selective attention. Participants had to imagine they were on an elevator and they had to establish which floor they had arrived by counting a series of computer-presented tones. Low as well as high pitched tones were presented and participants were asked to count low pitched tones only. Ten series of tones of increasing length were presented and the final score was the total number of correctly counted strings of tones out of ten.

The Telephone Search, which loads on the selective attention factor. Participants' task was to look for key symbols while searching through pages in a simulated telephone directory and to circle every key symbol they find. The score was the total number of corrected circled symbols out of twenty.

The Telephone Search While Counting. This test gives a measure of divided attention. The final score is called "dual task decrement" and it is obtained by combining the score at this subtest with the "Telephone Search's" score. In this subtest participants had to search again in the telephone directory, similarly as in the "Telephone Search" subtest, while simultaneously counting strings of tones.

- *The Hotel task* (Manly et al., 2002). This task is a measure of executive functions and it is designed to simulate typical day-to-day activities. The Hotel task comprised five distinct activities that would plausibly be completed in the course of running a hotel (i.e. checking guests' bills, proofreading a leaflet on the hotel's facilities, ordering labels with guests' names in alphabetical order, sorting money, etc.). Materials were arranged on a desk in front of each participant and instructions are given. Participants were told

to imagine they were working in a hotel and that they had to try each of the five activities. Their main job was to try and do at least some of all five tasks over the next 1o minutes. Instructions emphasized that the most important thing was to try and do something from each task, spending as much time on each as possible within the total time available. The details of each task were then described using the materials to demonstrate. Before staring the task participants were asked to explain each task to the examiner and to summarise their overall goals. A clock was also placed on the table with a cover and participants were told that they could check the time as many times as they wanted by taking the cover off the clock. During the task the examiner sitted out of view of the participant and noted down the time at which activity started and stopped and the number of time the clock was consulted. Performance on the Hotel task is scored within the following categories: number of attempted tasks out of five and time allocation. Participants were told to spend as long as possible on each of the five tasks. The optimal allocation to each across the 10 minutes was therefore 2 minutes. Deviation in seconds from this optimal level were calculated for each of the task and then summed. Total time spent in activity is also calculated by summing time spent in practicing each of the five tasks.

- *The Sustained Attention to Response Task – Fixed and Random* (SART- Robertson et al, 1997). In the SART numbers from 1 to 9 were presented on a computer screen and participants were asked to press the left key of a mouse for every number except for 3s. In the fixed version of the SART, numbers appeared in a fixed order (from 1 to 9 every time). Fixed SART gave a measure of response inhibition. In a random version of the SART, numbers appeared in a random order. This version measured sustained attention. Each

version lasted for approximately 5 minutes and performance were measured in terms of total number of commission errors, total number of omissions, reaction times on corrected responses and variability.

After completing the first phase of the assessment, participants were given a short 10 minutes break and then they were taken to the EEG lab to carry out the second part of the session. This second phase of the assessment lasted for approximately 1 hour and 15 minutes, including participants' EEG set up.

The following tasks were performed:

- *Resting State Task.* At the start of the EEG assessment, EEG recordings were taken from participants during an eyes condition lasting three minutes. Participants were instructed to sit on a chair with their eyes closed and to stay as still as possible. The task was conducted in a dark room.

- *Auditory Oddball Task.* Following the resting state task, participants underwent a two-stimuli auditory oddball task. The auditory oddball task is a simple and well established paradigm for the investigation of arousal effects on cognitive performance and has been shown to reliably evoke both pupillary dilations (Beatty, 1982) and robust P3 components (Polich, 2007). Participants were given two blocks of the same auditory oddball task. Stimuli were presented through headphones using the 'Presentation' software suite (NeuroBehavioural Systems, San Francisco, CA). They consisted of 60ms-duration sinusoidal tones of frequencies1000Hz ('targets') and 500Hz ('standards'). Targets were pseudo-randomly interspersed throughout the task and constituted 20% of the total number of trials. In the first block of the task, participants were instructed to press the left key of the mouse to target tones with a right index finger as quickly and accurately as possible, while ignoring presentation of the non-target standard tones. In the second block of the task, participants were

told to press the left key of the mouse for target tones with their right-index finger and the right key of the mouse for every standard tone with their right-middle finger. Participants completed a practice run of the task to ensure that they were well acquainted with the instructions before beginning. They were seated comfortably at a distance of ~50cm from a 20" LED monitor (Dell P2011H; Dell Inc., Ireland) with their head supported by a chin rest and were instructed to maintain gaze on a white fixation cross presented over a black background at the centre of the monitor (font size = 48). The tasks were conducted in a dark room with the only ambient light provided by the fixation cross. Each block of the task lasted 15 minutes. After completing the first block participants were given a 5 minutes break and then the second block of the task was performed. The total duration of the task was approximately 40 minutes. Tones were presented at an inter-stimulus interval (ISI) which varied pseudo-randomly between 2.1-2.9 seconds, with an average of 66 target tones and 267 standard tones over the whole task. In order to allow target-evoked pupil responses to return to baseline the stimuli were ordered such that at least three standard tones were presented between targets, leaving a minimum inter-target interval of 8 seconds.

5.6.2.2 Post-training assessment

The first post-training assessment was conducted after 5 weeks of home-based training. In the first phase of the assessment, a short interview was conducted with each participants. During this interview participants were asked to reflect on and relay both their positive and negative experiences of using the training. Participants were also asked to complete a feedback questionnaire to that effect (appendix). Participants in the SAT group only were then asked to rate their selected everyday life goals, in terms of performance and satisfaction, as they did before starting the training. The trainer recorded each participant post-training goals ratings in a form.

After that participant was given the same scales and questionnaires to complete, as in the pre-training session. Importantly, before starting the neuropsychological testing, participants in both training groups were given the same following instructions:

'Now we are going to start the testing session in few minutes, but before starting I want to ask you to use the technique or strategies you have learned during the five weeks training to help you stay alert. You can use your technique every time you feel you need to re-focus or to increase your level of attention and concentration. Please use this technique to help you performing tasks as best as you can'

These instructions were given to assure that participants applied the training technique during the course of the testing session to try and increase their levels of alertness, when needed.

The same neuropsychological tests were then repeated, using parallel versions of each test.

In the second phase of the assessment, participants repeated the same EEG and pupillometry assessment. Again, before staring the first task in the EEG lab, the same instructions were given to participants. The trainer said:

'Now, we are going to start the first task of the testing session in few minutes, but before starting I want to remind you again to use whatever technique or strategies you have learned during your training period to help you stay alert. Use your technique every time you feel your levels of attention and concentration are decreasing to help you staying focus. As you probably remember from your first testing session, during EEG recordings, you have to try to stay as still as you can while you perform tasks and this might be particularly hard for you. Use your technique to help you in that too'

5.6.2.3 Three-months follow up assessment

The last assessment was conducted after 3 months from the previous post-training

assessment. The same procedure was used to conduct the assessment and the same neuropsychological tests and EEG tasks were repeated. The aim of this final follow-up assessment was to evaluate whether or not any immediate improvements following the training had been long-lasting.

5.7 Data Acquisition & Processing

5.7.1 EEG and Event-Related Potentials (ERPs)

Continuous EEG was acquired using an ActiveTwo system (BioSemi, The Netherlands) from 32 scalp electrodes, configured to the standard 10/20 setup and digitized at 512Hz. Vertical and horizontal eye movements were recorded using two vertical electro-occulogram (EOG) electrodes placed above and below the left eye and two horizontal EOG electrodes placed at the outer canthus of each eye, respectively. Continuous EEG data were re-referenced offline to the average reference, high-pass filtered to 0.50 Hz and low-pass filtered up to 35 Hz. Data from the 32 scalp electrodes for each participant were then subjected to temporal independent component analysis (ICA) using FASTER v1.2b (Nolan et al., 2010) for removal of EOG and other noise transients.

Event markers emitted by the stimulus presentation computer were recorded simultaneously during EEG and pupil diameter acquisition. Three seconds epochs were extracted for EEG datasets around each stimulus marker from -1 to +2 seconds and epochs were baseline corrected relative to the mean activity in the 100ms directly preceding stimulus presentation, whereas. All further processing was carried out using a combination of in-house MATLAB scripting and EEGLAB (Delorme and Makeig, 2004).

EEG datasets were subject to further artefact rejection criteria applied between -100 and +800ms relative to the stimulus for the EEG epochs. Any epochs with an EEG amplitude > 90μVwere rejected. In the first block of the task, where participants had to respond to target tones only, all epochs on which participants

responded to standard tones (false alarms), failed to respond to target tones (misses) or responded within the first 100ms after target presentation (quick responses) were also removed from the data. In the second block of the task in which participants were required to respond to target and standard tones, all epochs on which participants press the right key of the mouse to target tones (false alarms on target) or the left key of the mouse on standard tones (false alarms on standard), failed to response to either target (misses on targets) or standard tones (misses on standard) or responded within the first 100ms after target/standard tones presentation (quick responses) were removed from the datasets

5.7.2 Pupil

Continuous pupil diameter was recorded using an Eyestart eye-tracker (ASL, Bedford, MA). Pupil diameter in the left eye was sampled at a rate of 50Hz with a spatial resolution of greater than 0.01mm. As a preliminary pre-processing measure, artefacts and blinks were interpolated using a linear interpolation algorithm in the ASL Results software suite. All participants' data were visually inspected after interpolation, and those with excessive artefacts still remaining (e.g. blinks of long duration or excessively noisy periods of data) were excluded from further analyses. For pupil's datasets, 7 second epochs were extracted around each stimulus marker from -2 to +5 seconds relative to stimulus presentation and epochs from the pupil datasets were baseline corrected to the pre-stimulus interval of 1 second. Pupil diameter datasets were subject to further artefact rejection criteria applied between -1 and +2 seconds for the pupil epochs. Any epoch with a pupil diameter deflection > 2mm were rejected. To eliminate instances of brief, high amplitude noise in the up-sampled pupil data, any epoch in which the difference between two consecutive samples exceeded +/- 0.03mm was rejected. Each dataset was also removed of epochs in which any pupil diameter data point exceeded the combined mean of that epoch plus two neighbouring epochs to either side by 4 standard deviations or more (for a similar approach, see Porter et al., 2010). In the first block of the task, where participants had to respond to target

tones only, all epochs on which participants responded to standard tones (false alarms) failed to respond to target tones (misses) or responded within the first 100ms after target presentation (quick responses) were also removed from the data. In the second block of the task in which participants were required to respond to target and standard tones, all epochs on which participants pressed the right key of the mouse to target tones (false alarms on target) or the left key of the mouse on standard tones (false alarms on standard), failed to response to either target (misses on targets) or standard tones (misses on standard) or responded within the first 100ms after target/standard tones presentation (quick responses) were removed from the datasets.

5.7.3 EEG and Event-Related Potentials (ERPs) measures

5.7.3.1 EEG

The average EEG power spectrum was calculated for each participant for the resting state task using the discrete fast Fourier transform. Each participant's tonic theta, alpha and beta power was calculated as the power in the 4-7 Hz, 8-12 Hz and 13-29 Hz ranges respectively. Theta/Beta and Alpha/Beta ratios were subsequently calculated.

The extracted EEG variables were entered into a group (SAT vs. AT) by time (pre-training vs. post-training/three month follow up) repeated measures ANOVA to investigate training's effects at five weeks after training and at the three-month follow up.

5.7.3.2 Event-Related Potentials (ERPs)

ERP component structure was confirmed by visual inspection of grand-average waveforms. The width of the latency window used to measure component amplitude was based on the duration and spatial extent of each component. Target stimuli evoked an auditory N1 component with a central topography. N1

amplitude and latency measures were extracted from three central electrodes (Cz, C3, C4) between 100ms and 200ms post-stimulus presentation. A large positive component over centro-parietal scalp areas was elicited by target tones (the posterior P3). P3 amplitudes and maximal peak amplitudes were extracted from three central-parietal sites (CPz, CP5 and CP6) in the interval of 300ms to 500 ms post-stimulus presentation. P3 latency values were also calculated. ERP components were not analysed for errors of omission, as the total rate of omission errors was too low to allow ERP analysis (mean=0.85, SD=1.78)

In the second block of the auditory oddball task, participants were required to press a button for target tones as well as standard tones. The same procedure employed in the first block of the task was used to extract ERP components in the second block of task. Auditory N1 and parietal P3 were extracted for target and standard stimuli. For each component mean amplitudes, maximal peak amplitudes and latencies were extracted. ERP components were not analysed for false alarms (mean false alarms on target=5.29, SD=4.21; mean false alarms on standard=2.53, SD=3.59) and omission errors (mean omissions on target=0.90, SD=2.67; mean omissions on standard=4.32, SD=4.67) as the total error rates were too low, similarly to the previous task.

The extracted ERP variables were entered into a group (SAT vs. AT) by time (pre-training vs. post-training/three month follow up) repeated measures ANOVA to investigate training's effects at five weeks after training and at the three-month follow up.

5.7.4 Pupil measures

In the first block of the oddball task, target tones elicited significant dilatory responses. Pupil's dilations (mm) were extracted and defined as the peak-to-peak measure of the maximum dilation between 0.4-2 seconds post-stimulus minus the minimum pupil diameter 0-0.4 seconds post-stimulus. The baseline pupil diameter

pre-stimulus pupil diameter on each epoch was also extracted and calculated by averaging the 1 second of pupil diameter data preceding tone presentation on that epoch. For the second block of the auditory oddball task, pupil dilation measures and baseline values of pupil pre-stimulus diameter were obtained for target and standard tones. Thus our analyses included both baseline and stimulus-evoked or phasic changes in pupil diameter.

The extracted pupil variables were entered into a group (SAT vs. AT) by time (T1 vs. post-training/three month follow up) repeated measures ANOVA to investigate training's effects at five weeks after training and at the three-month follow up.

5.7.5 Auditory oddball task's behavioural measures

For the first block of the oddball task, Accuracy, Omissions, Reaction Time (RT; ms) and RT Coefficient of Variation (CV) on target tones were calculated. CV is a stringent measure of performance variability that has demonstrated sensitivity to the efficiency of frontal top-down control networks (Stuss et al., 2003; Bellgrove et al., 2004), calculated by dividing the standard deviation in RTs for a group of epochs by their mean. In the second block of the oddball task, Reaction Time on target (RT target; ms) and standard tones (RT standard; ms) and RT Coefficient of Variation on target tones (CV target) and standard tones (CV standard) were calculated. Accuracy, Total number of Omissions and False Alarms were also extracted on target and standard tones (omissions on target and omissions on standard; false alarms on target and false alarms on standard).

The extracted behavioural variables were entered into a group (SAT vs. AT) by time (pre-training vs. post-training/three month follow up) repeated measures ANCOVA using pre-training scores ad covariate, to investigate training's effects at five weeks after training and at the three-month follow up.

5.8. Primary outcome measures

The following measures were considered primary outcome measures in the current study:

- *ADHD symptoms*

These were assessed using the CAARS Self Report form (Conners et al., 1999). An informant-version of this form (CAARS – Observer Form) was also given to a close friend or relative where available.

- *Co-morbid symptoms and psychosocial function*

These were assessed using the General Health Questionnaire (GHQ)-28. This allows measurement of anxiety and insomnia, depression, somatic symptoms and social dysfunction.

- *Everyday life problems with attention and memory*

The Attention-Related Cognitive Errors Questionnaire (ARCEQ) and the Memory Failures Questionnaire (EMFQ).

- *Anxiety and Depression*

These were measured by the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI).

- *Self-efficacy.* It was measured using the Generalised Self-Efficacy Scale.

- *Test of Everyday Attention (TEA)*

The TEA subtests (Elevator Counting with Distraction, Telephone Search, and Telephone Search While Counting) assess selective attention, divided attention and shifting respectively with an ecologically valid format to reflect typical day-to-day activities. Three parallel forms of these subtests were administered in order to reduce practice effects. Importantly, improvements in these tasks indicate

generalisation of training effects to untrained tasks.

- *SART*

The SART was used as a measure of sustained attention (SART fixed) and behavioural response inhibition (SART random).

- *Hotel Task*

This task simulated work situation is a well-validated measure of real life executive function (Manly et al., 2002). Improvements in this test following the training period indicate generalisation of training effects to an untrained task.

Before performing repeated measures ANCOVAs data were checked for normality and outliers (participants that performed +/- 1.5 SD) were excluded from the data. Two participants were excluded from analysis of the SART Fixed and Random reaction time because their reaction times were either too fast or too slow and one participant was excluded because of his score in the Dual Task Decrement.

Each of the primary measure was entered into a Group (SAT vs. AT) by Time (pre-training vs. post-training/three month follow up) repeated measures ANCOVA, using pre-training scores as the covariate to investigate training's effects.

5.7.1. Other measures

The following measures were considered secondary outcome measures:

- Qualitative measures*: Everyday life goals ratings*

Each individual in the SAT group identified individually-tailored goals that they were failing to reach during the last part of their second training session and these goals were rated on two ten-point rating scales assessing performance and

satisfaction at all 3 assessment periods. Participants were also asked to complete a diary and, where possible, qualitative feedback from participants' diaries was also evaluated as an outcome measure.

EEG & Event-Related Potentials (ERPs)

The psychophysiological effects of the SAT were investigated via a number of well-established electrocortical signals of sustained attention and arousal. These include:

Alpha (8-14Hz) and theta (4-7Hz) EEG rhythms. Internally-generated rhythms, such as alpha and theta, provide a highly sensitive index of cortical arousal. Power in both the alpha and theta band is inversely related to the level of arousal as established in studies of the wake-sleep cycle (Danos et al., 2001). Abnormalities in both alpha and theta have been highlighted amongst children and adults with ADHD (Clarke et al., 2002). Comparisons in term of theta/beta and alpha/beta ratios were also carried out as measures of cortical arousal.

P300 amplitude and latency. P300 is a well established event-related marker of sustained attention (Polich 2007; Polich & Kok, 1995; Dockree et al., 2005). P300 amplitudes and latencies measures were extracted in the two blocks of the auditory oddball task for target and standard tones.

Pupillometry

Pupil's dilatory response and pupil's pre-stimulus baseline diameter were extracted for target and standard stimuli. As reviewed in chapter 3 of this thesis, stimulus evoked pupil's dilation is a reliable index of phasic LC activity, while baseline pupil's diameter has been found to index LC tonic activity (Gilzenrat et al., 2010, Murphy et al., 2011). Therefore, both measures represent reliable indirect markers of arousal levels. Furthermore, other studies have also demonstrated that pupil's diameter can be reliably used as physiological correlates of stimulus processing and 'mental effort' required to perform a cognitive task.

5.8 Aims and specific hypothesis

The proposed study aims to evaluate the effectiveness of a partly home based Self-Alerting method for adults with ADHD, and to examine the effects of this training on key cognitive, social and psychiatric variables. If successful, this would pave the way for a further study with children and adolescents with ADHD, where the possibility of using this method as a preventative strategy for some or all of the negative outcomes associated with ADHD arises.

A second aim of the study is to study whether changes in brain function, using EEG and pupillometry, occurred as a result of the training. However, given that Self-Alert Training (SAT) involves teaching a strategy to self-alert in key real life situations, a failure to show brain changes would not be incompatible with any behavioural or cognitive changes found.

The specific hypotheses are as follows:

1. SAT will help reducing ADHD symptoms' severity, as measured by the CAARS Self Report form and the CAARS Observer form.
2. SAT will result in improved cognitive, social and psychiatric functioning in the treated as compared to the control group, based on scores in scales and questionnaires.
3. SAT will improve neuropsychological functions and, more importantly, improvements will generalize to untrained neuropsychological tests (i.e. selective attention and executive functions).
4. SAT will help people improving their attention levels and/or reducing levels of impulsivity and distractibility in day-to-day settings, as reflected in participants' selected goal's ratings.
5. SAT may result in improved levels of arousal measured by EEG and

pupillometry in the treated group compared to the control training group.

6. SAT improvements may also be reflected in key ERP marker of sustained attention, such as the P300.

5.9 Results

5.9.1 Participants training data

Participants in the AT group spent 76.5 hours in training and did 1282 total exercises. The mean time spent in training was 4.2 hours and the mean number of exercises was 67.5. (SD=68.8) Participants in the SAT group spent 54.1 hours in training and they did 884 total exercises. Their mean time spent in training was 3.3 hours and they did 49.1 mean exercises (SD=48.5). SAT participants spent 106.6 hours in biofeedback practice and they did 696 total biofeedback sessions. The mean number of biofeedback sessions was 36.6 and the mean time spent in biofeedback practice was 5.5 hours. The mean duration of a biofeedback session was 9.2 minutes. SAT participants made 8.2 (SD=9.4) mean alerts per biofeedback session and 6.7 (SD=7.4) mean successful alerts per session (peaks in SCR). Independent sample t-tests were carried out to investigate differences between groups in the training time. Participants in the AT group spent more time in exercises practice, however a t-test showed that the there was no significant difference between groups ($t_{(29)}$=-1.076, p=.291). Although SAT participants spent more mean total time time in training (3.3 hours in exercise practice and 5.5 hours in biofeedback practice), a t-test showed that there was no significant difference between groups in the total amount of practice ($t_{(31)}$=1.554, p=.130). An analysis of participants home-based practice during the five week training revealed that some participants did very little practice. Therefore, a cut off of ten exercises was established and participants who practised less than ten exercises during the five week period were excluded. Five total participants in the SAT group (number of exercises: 6,3,5,5 and 7) and two participants in the AT group (number of

exercises: 7 and 3) were excluded. After excluding these seven participants, it resulted that participants in the AT group made 75.2 mean exercises (SD=68.5), spending a mean of 4.5 hours in training and SAT participants did 71 mean exercises (SD=47.1), spending 4.1 hours in training. Analysis was conducted first including all participants and then a sub-analysis was carried out on smaller groups after excluding the seven participants that did less than ten exercises. Results of both analyses are described in the following sections.

5.9.2 Relationship between variables

Partial correlations have been carried out to investigate relationships between variables at the baseline assessment. Three significant negative correlations emerged between CAARS Self Report form and neuropsychological tests. A significant correlation was found between CAARS D – Self Report that measures problems with self concept and scores of the Elevator Counting with Distraction (TEA) ($r_{(51)}$=-.276, p=.050). Significant correlation emerged also between CAARS D - Self Report that measures problems with self concept and reaction times in the Fixed Sustained Attention to Response Task (SART) ($r_{(50)}$=-.306, p=.029) and between CAARS D – Self Report that measures problems with self concept and omission errors in the Random SART ($r_{(45)}$=-.308, p=.039). No significant correlations emerged between behavioural variables and any of the neurophysiological measures.

5.9.3 Post-training effects

Repeated measures ANCOVAs were carried out to investigate differences between groups after five weeks of training on primary outcome measures.

5.9.3.1 Post-training effects on primary outcome measures

CAARS Self Report Form (CAARS – S: L)

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no significant main effect of time ($F_{(1, 34)}$=2.273, p=.141), a significant main effect of group ($F_{(1,34)}$=5.370, p=.027) and a significant time by

group interaction($F_{(1,34)}$=5.370, p=.027). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(17)}$=4.018, p=.001) that was absent in the AT group ($t_{(18)}$=1.136, p=.271). No significant main effect of time ($F_{(1,34)}$=.853, p=.362) and group ($F_{(1,34)}$=.459,p=.503) and no significant interaction ($F_{(1,34)}$.459, p=.503) were found for CAARS-B- Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed a marginal main effect of time ($F_{(1,34)}$=3.831, p=.059), a significant main effect of group ($F_{(1,34)}$=9.068, p=.005) and a significant time by group interaction ($F_{(1,34)}$=9.068, p=.005). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(17)}$=2.836, p=.011) that was absent in the AT group ($t_{(18)}$=-.549, p=.590). There was no significant main effect of time ($F_{(1, 34)}$=4.292, p=.46), a significant main effect of group ($F_{(1,34)}$=5.324, p=.027) and a significant group by time interaction ($F_{(1,34)}$=5.324, p=.027) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(17)}$=2.556, p=.020) that was not present in the AT group ($t_{(18)}$= -.207, p=.838). A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed a significant main effect of time ($F_{(1,34)}$=8.109, p=.007), a significant main effect of group ($F_{(1,34)}$=9.726, p=.004) and a significant time by group interaction ($F_{(1,34)}$=9.726, p=.004). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(17)}$=5.329, p=.000) that was absent in the AT group ($t_{(18)}$= -.109, p=.914). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed a significant main effect of time ($F_{(1,34)}$=8.026, p=.008), no significant main effect of group ($F_{(1,34)}$=1.778, p=.191) and no significant interaction effect ($F_{(1,34)}$=1.778, p=.191). There was a significant main effect of time ($F_{(1,34)}$=5.427, p=.026), a significant main effect of group ($F_{(1,34)}$= 6.090, p=.019) and a significant time by group interaction ($F_{(1,34)}$= 6.090, p=.019) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(17)}$=3.428, p=.003) that was not present in the AT group ($t_{(18)}$= -.141, p=.889). A repeated measures ANCOVA for CAARS-H - ADHD Index revealed

no significant main effect of time ($F_{(1,34)}$=1.662, p=.206), a significant main effect of group ($F_{(1,34)}$=6.570, p=.015) and a significant time by group interaction ($F_{(1,34)}$=6.570, p=.015). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(17)}$=3.507, p=.003) that was absent in the AT group ($t_{(18)}$= -.032, p=.975). Significant group by time interactions in the CAARS – Self Report are shown in figure 5.11.

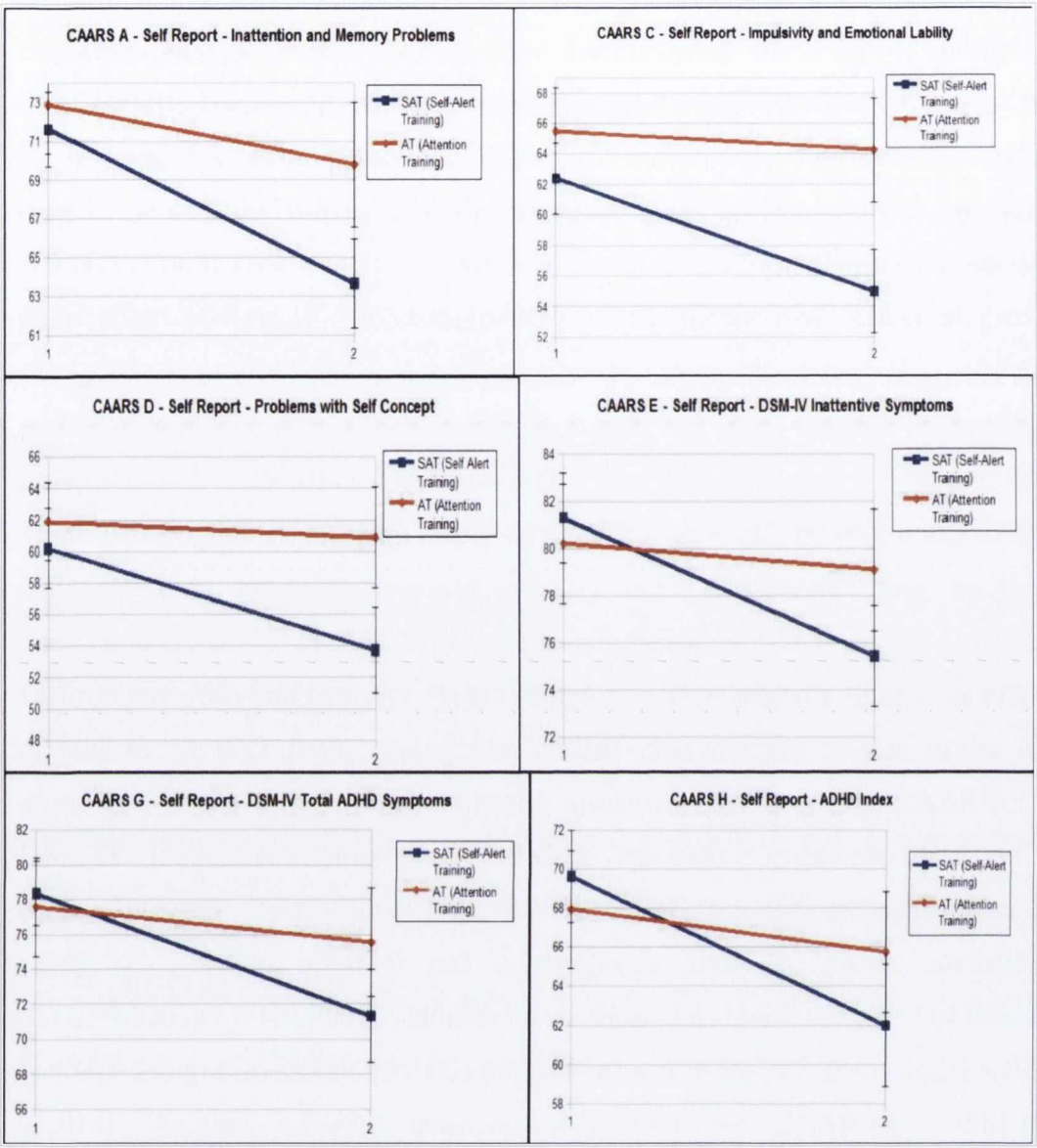


Figure 5.11. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale Self Report (CAARS – S: L) at pre and post-training. Error bars represent the standard error.

Note: Participants in the SAT group significantly improved in several CAARS measures after training, indicating decreased symptoms of inattention and hyperactivity.

CAARS Observer Form (CAARS – O: L)

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no main effect of time ($F_{(1, 14)}$=2.097, p=.170), a marginal significant main effect of group ($F_{(1,14)}$=3.948, p=.067) and a marginal time by group interaction ($F_{(1,14)}$=3.948, p=.067). Paired samples t-tests revealed a

significant effect of time in the SAT group ($t_{(8)}$=3.107, p=.015) that was absent in the AT group ($t_{(7)}$=1.821, p=.111). No significant main effect of time ($F_{(1,14)}$=.431, p=.522) and group ($F_{(1,14)}$=.051, p=.825) and no significant interaction ($F_{(1,14)}$.051, p=.825) were found for CAARS-B- Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed a significant main effect of time ($F_{(1,14)}$=7.429, p=.016), no significant main effect of group ($F_{(1,14)}$=1.174, p=.297) and no significant time by group interaction ($F_{(1,14)}$=1.174, p=.297). There was no significant main effect of time ($F_{(1,14)}$= 1.228, p=.286), no significant main effect of group ($F_{(1,14)}$=.647, p=.435) and a significant group by time interaction ($F_{(1,14)}$=.647, p=.435) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed a significant main effect of time ($F_{(1,14)}$=7.180, p=.018), no significant main effect of group ($F_{(1,14)}$=.784, p=.391) and no significant time by group interaction ($F_{(1,14)}$=.784, p=.391). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed no significant main effect of time ($F_{(1,14)}$=3.059, p=.102), no significant main effect of group ($F_{(1,14)}$=2.774, p=.118) and no significant interaction effect ($F_{(1,14)}$=2.774, p=.118). There was a significant main effect of time ($F_{(1,14)}$=9.667, p=.008), no significant main effect of group ($F_{(1,14)}$= 2.187, p=.161) and no significant time by group interaction ($F_{(1,14)}$= 2.187, p=.161) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed a marginal main effect of time ($F_{(1,14)}$=4.513, p=.052), no significant main effect of group ($F_{(1,14)}$=.000, p=.994) and a significant time by group interaction ($F_{(1,14)}$=7.188, p=.020). Figure 5.12 shows the marginal group by time interaction in CAARS A – Inattention and Memory Problems - Observer Form.

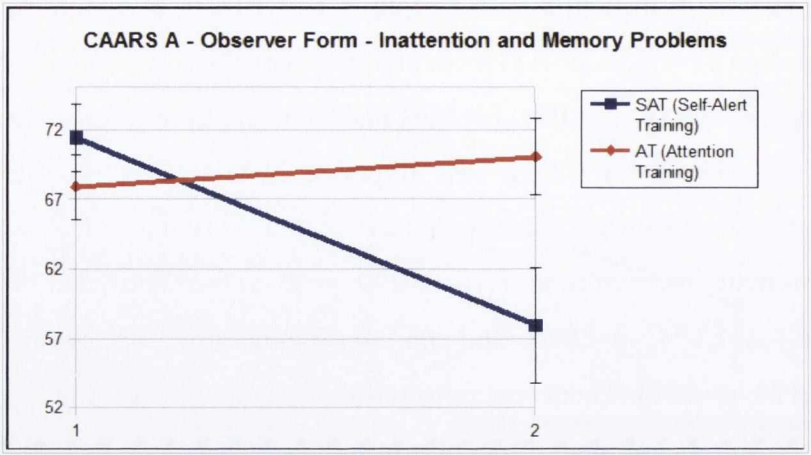


Figure 5.12.Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale Observer Form – Inattention and Memory Problems (CAARS A– O: L) at pre and post-training. Error bars represent the standard error.

Note: A marginal interaction emerged indicating marginal improvements in inattention and memory problems in the SAT group after training. Samples size were very small (SAT: N= 10; AT: N= 8)

Other Scales and Questionnaires

A repeated measures ANCOVA for the Attention-Related Cognitive Errors Questionnaire (ARCEQ) revealed a significant main effect of time ($F_{(1,18)}$=6.118, p=.024), no significant main effect of group ($F_{(1,18)}$=2.7, p=.118) and no significant time by group interaction ($F_{(1,18)}$=2.7, p=.118). A significant main effect of time ($F_{(1,18)}$=17.467, p=.001), no significant main effect of group ($F_{(1,18)}$=1.688, p=.21) and no significant interaction effect ($F_{(1,18)}$=1.688,p=.21) emerged in a repeated measures ANCOVA for the Everyday Memory Failures Questionnaire (EMFQ). A repeated measures ANCOVA for the General Health Questionnaire (GHQ) showed a significant main effect of time ($F_{(1,32)}$=6.770, p=.014), no significant main effect of group ($F_{(1,32)}$=.077, p=.783) and no significant time by group interaction ($F_{(1, 32)}$=.077, p=.783). There was a significant main effect of time ($F_{(1, 33)}$=13.747, p=.001), a marginal main effect of group ($F_{(1,33)}$=3.073, p=.089) and a marginal time by group interaction ($F_{(1, 33)}$=3.073, p=.089) in a repeated measures ANCOVA for the Self Efficacy Scale (SES). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(16)}$= -3.740, p=.002) that was absent in the AT group ($t_{(18)}$= -1.144, p=.267). A repeated measures ANCOVA for the Beck Depression Inventory (BDI) revealed no significant main effect of time

($F_{(1,33)}$=2.091, p=.158), no significant main effect of group ($F_{(1,33)}$=.371, p=0.547) and no significant interaction ($F_{(1,33)}$=.371, p=.547). Another repeated measures ANCOVA for Beck Anxiety Inventory (BAI) showed no significant main effect of time ($F_{(1,34)}$=2.596, p=.116), no significant main effect of group ($F_{(1,34)}$=.33, p=.57) and no significant time by group interaction ($F_{(1,34)}$=.33, p=.57). Figure 5.13 shows the marginal time by group interaction in the Self Efficacy Scale (SES).

Figure 5.13. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Self Efficacy Scale (SES) at pre and post-training. Error bars represent the standard error.

Note: A significant interaction emerged showing that SAT participants significantly increased their self-efficacy after training compared to AT participants.

Neuropsychological tests

A repeated measures ANCOVA was carried out on the scores in the Elevator Counting with Distraction (TEA) and it revealed a significant main effect of time ($F_{(1,34)}$=22.508, p=.000), a significant main effect of group ($F_{(1, 34)}$=6.920, p=.013) and a significant time by group interaction ($F_{(1,34)}$=6.920, p=.013). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(17)}$= -3.630, p=.002) that was absent in the AT group ($t_{(18)}$= -.159, p=.875). A repeated measures ANCOVA was performed on the Raw Score in The Telephone Search and a significant main effect of time ($F_{(1,34)}$=5.208, p=.029), no main effect of group ($F_{(1,,34)}$=.006, p=.938) and no time by group interaction ($F_{(1,,34)}$=.006, p=.938) were found. Another repeated measures ANCOVA was conducted on the Dual Task Decrement in the Telephone Search While Counting (TEA) which showed a

significant main effect of time ($F_{(1,33)}$=8.337, p=.007), a significant main effect of group ($F_{(1,33)}$=6.583, p=.015) and a significant time by group interaction ($F_{(1,33)}$=6.583, p=.015). Paired samples t-test showed a significant effect of time in the SAT group ($t_{(16)}$=.213, p=.039) that was absent in the AT group ($t_{(18)}$= -.319, p=.754). Significant group by time interactions are shown in figure 5.14.

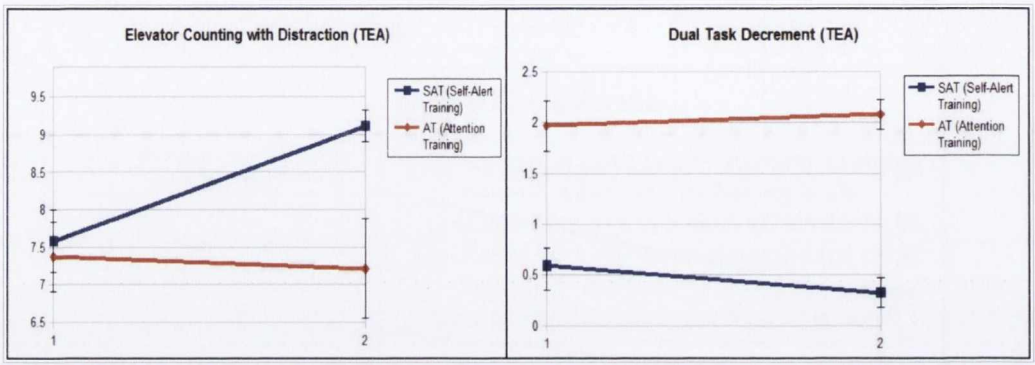


Figure 5.14. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Elevator Counting with Distraction (TEA), a measure of selective attention, and in the Dual Task Decrement (TEA), measuring divided attention, at pre and post-training. Error bars represent the standard error.

Note: SAT participants significantly increased in both tests after training compared to AT participants.

A repeated measures ANCOVA on the number of attempted tasks in the Hotel Task revealed a significant main effect of time ($F_{(1, 34)}$=13.542, p=.001), no significant main effect of group ($F_{(1, 34)}$=.031, p=.861) and no significant time by group interaction ($F_{(1, 34)}$=.031, p=.861). A repeated measures ANCOVA for the total deviation time in the Hotel Task showed no significant main effect of time ($F_{(1,34)}$=1.11, p=.299), a significant main effect of group ($F_{(1,34)}$=5.093, p=.031) and a significant time by group interaction ($F_{(1,34)}$=5.093, p=.031). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(17)}$=3.742, p=.002) that was absent in the AT group ($t_{(18)}$=.528, p=.604). There was a significant main effect of time ($F_{(1, 34)}$=86.198, p=.000) but no significant main effect of group ($F_{(1,34)}$=.52, p=.821) and no significant interaction effect ($F_{(1,34)}$=.52, p=.821) in a repeated measures ANCOVA for the total time spent in activity in the Hotel Task. The significant group by time interaction in the Total Deviation Time is shown in figure 5.15.

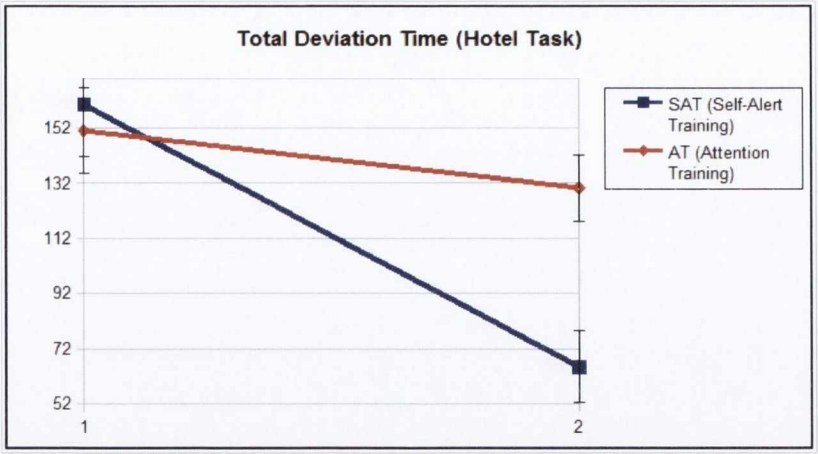


Figure 5.15. Self-Alert Training group (SAT) and Attention Training group (AT)'s Total Deviation Time in the Hotel Task, a measure of executive functions, at pre and post-training. Error bars represent the standard error.

Note: SAT participants significantly decreased their total deviation time, indicating improved task performance, after training compared to AT participants.

Sustained Attention to Response Task (SART) Fixed and Random

A repeated measures ANCOVA on Omissions in the Fixed SART revealed a significant main effect of time ($F_{(1,30)}$=4.385, p=.045), no significant main effect of group ($F_{(1,30)}$=.003, p=.960) and no significant time by group interaction ($F_{(1,30)}$=.003, p=.960). There was a significant main effect of time ($F_{(1,27)}$=16.490, p=.000), no significant main effect of group ($F_{(1,27)}$=.358, p=.555) and no significant interaction effect ($F_{(1,27)}$=.358, p=.555) in a repeated measures ANCOVA on Commission Errors in the Fixed SART. A repeated measures ANCOVA on Reaction Times (RT) in the Fixed SART showed a significant main effect of time ($F_{(1,28)}$=28,828, p=.000), no significant main effect of group ($F_{(1,28)}$=.085, p=.773) and no significant time by group interaction ($F_{(1,28)}$=.085, p=.773). There was a significant main effect of time ($F_{(1,28)}$=16.739, p=.000), no significant main effect of group ($F_{(1,28)}$=.779, p=.385) and no significant time by group interaction ($F_{(1,28)}$=.779, p=.385) for SD in the Fixed SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Fixed SART revealed a significant main effect of time ($F_{(1,30)}$=11.009, p=.002), no significant main effect of group ($F_{(1,30)}$=.039, p=.845) and no significant time by group interaction ($F_{(1,30)}$=.039, p=.002).

A repeated measures ANCOVA on Omissions in the random SART revealed no significant main effect of time ($F_{(1,26)}$=.531, p=.473), no significant main effect of group ($F_{(1,26)}$=2.529 p=.124) and no significant time by group interaction ($F_{(1,26)}$=2.529, p=.124). There was a significant main effect of time ($F_{(1,29)}$=5.766, p=.023), no significant main effect of group ($F_{(1,29)}$=.008, p=.929) and no significant interaction effect ($F_{(1,29)}$=.008, p=.929) in a repeated measures ANCOVA on Commission Errors in the Random SART. A repeated measures ANCOVA on Reaction Times (RT) in the Random SART showed a significant main effect of time ($F_{(1,32)}$=14.431, p=.001), no significant main effect of group ($F_{(1,32)}$=1.650, p=.208) and no significant time by group interaction ($F_{(1,32)}$=1.650, p=.208). There was a significant main effect of time ($F_{(1,26)}$=9.166 p=.006), no significant main effect of group ($F_{(1,26)}$=2.143, p=.155) and no significant time by group interaction ($F_{(1,26)}$=2.143, p=.155) for Standard Deviation (SD) in the Random SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Random SART revealed a significant main effect of time ($F_{(1,24)}$=4.378, p=.047), no significant main effect of group ($F_{(1,24)}$=.091, p=.765) and no significant time by group interaction ($F_{(1,24)}$=.091, p=.765).

Auditory Oddball Task – Behavioural Measures

Repeated measures ANCOVAs were carried out for each variable in the first block of the auditory oddball task in which participants were required to press the left key of the mouse on target tones only. A repeated measures ANCOVA on Accuracy revealed a significant main effect of time ($F_{(1,32)}$=43.799, p=.000), no significant main effect of group ($F_{(1,32)}$=1.273, p=.269) and no significant interaction effect ($F_{(1,32)}$=1.223, p=.259). A repeated measures ANCOVA on Omission Errors showed a significant main effect of time ($F_{(1,32)}$=4.779, p=.037), no significant main effect of group ($F_{(1, 32)}$=.425, p=0.520) and no significant time by group interaction ($F_{(1,32)}$=.425, p=.520). There was a significant main effect of time ($F_{(1,32)}$ =7.158, p=.012), no significant main effect of group ($F_{(1,32)}$=.183, p=.672) and no significant interaction ($F_{(1,32)}$=.183, p=.672) in a repeated measures ANCOVA on Reaction Times. A repeated measures ANCOVA on Coefficient of

Variation (CV) revealed a significant main effect of time ($F_{(1,32)}$=11.851, p=.002), no significant main effect of group ($F_{(1,32)}$=.250, p=0.621) and no significant time by group interaction ($F_{(1,32)}$=.250, p=.621).

Repeated measures ANCOVAs were conducted on the second block of the auditory oddball task for each variable on target and standard tones. A repeated measures ANCOVA on Accuracy on target tones revealed a significant main effect of time ($F_{(1,32)}$=15.268,p=.001), no significant main effect of group ($F_{(1,32)}$=.396, p=.534) and no significant time by group interaction ($F_{(1,32)}$=.396, p=.534). A repeated measures ANCOVA on Omission Errors on target tones revealed no significant main effect of time ($F_{(1,32)}$ =2.304, p=.141), no significant main effect of group ($F_{(1,32)}$=.921, p=.346) and no significant interaction effect ($F_{(1,32)}$=.921, p=.346). A significant main effect of time ($F_{(1,32)}$=22.143, p=.000), no significant main effect of group ($F_{(1,32)}$=.005, p=.945) and no significant time by group interaction ($F_{(1,32)}$=.005, p=.945) were found for Commission Errors on target tones. A repeated measures ANCOVA on Reaction Times on target tones revealed a significant main effect of time ($F_{(1,32)}$=6.142, p=.019), no significant main effect of group ($F_{(1,32)}$=.312, p=.581) and no significant time by group interaction ($F_{(1,32)}$=.312, p=.581). A repeated measures ANCOVA on Coefficient of Variation (CV) for target tones showed a significant main effect of time ($F_{(1,32)}$=8.387, p=.008), no significant main effect of group ($F_{(1,32)}$=1.946, p=.176) and no significant time by group interaction ($F_{(1,32)}$=1.946, p=.176).

A repeated measures ANCOVA on Accuracy on standard tones revealed a significant main effect of time ($F_{(1,32)}$=32.435, p=.000), no significant main effect of group ($F_{(1,32)}$=.195, p=.662) and no significant time by group interaction ($F_{(1,32)}$=.195, p=.662). A repeated measures ANCOVA on Omission Errors on standard tones revealed no significant main effect of time ($F_{(1,32)}$ =.414, p=.524), no significant main effect of group ($F_{(1,32)}$=1.361, p=.251) and no significant interaction effect ($F_{(1,32)}$=1.361, p=.251). A significant main effect of time ($F_{(1,32)}$=16.214, p=0.000), no main effect of group ($F_{(1,32)}$=1.518, p=.230) and no time by group interaction ($F_{(1,32)}$=1.518, p=.230) were found for commission errors

on standard tones. A repeated measures ANCOVA on Reaction Times on standard tones revealed a significant main effect of time ($F_{(1,32)}$=5.284, p=.029), no significant main effect of group ($F_{(1,32)}$=.006, p=.938) and no significant time by group interaction ($F_{(1,32)}$=.006, p=.938). A repeated measures ANCOVA on Coefficient of Variation (CV) for standard tones showed no significant main effect of time ($F_{(1,32)}$=.955, p=.337), no significant main effect of group ($F_{(1,32)}$=.055, p=.944) and no significant interaction effect ($F_{(1,32)}$=.055, p=.944).

5.9.3.2 Post-training effects on neurophysiological measures

Repeated measures ANOVAs were carried for pupil, EEG power spectral and Event Related Potentials (ERPs) measures to investigate differences between groups after the five week training.

Pupil

Pupil's variables were analysed in the first block of the auditory oddball task. A repeated measures ANOVA on mean pupil's dilation on targets revealed no significant main effect of time ($F_{(1,28)}$=.016, p=.900), no significant main effect of group ($F_{(1,28)}$=.083, p=.776) and no significant time by group interaction ($F_{(1,28)}$=.663, p=.422). No significant main effect of time ($F_{(1,24)}$=.728, p=.402), no significant main effect of group ($F_{(1,24)}$=.121, p=.731) and no significant time by group interaction ($F_{(1,24)}$=.007, p=.909) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,28)}$=.022, p=.883), no significant main effect of group ($F_{(1,28)}$=2.663, p=.112) and no significant time by group interaction ($F_{(1,28)}$=.628, p=.435). No significant main effect of time ($F_{(1,29)}$=.291, p=.594), no significant main effect of group ($F_{(1,29)}$=.138, p=.713) and no significant time by group interaction ($F_{(1,29)}$=2.767, p=.107) emerged in a repeated measures ANOVA on pupil's variability.

The same statistical analysis was performed for target and standard tones in the second block of the auditory oddball task. A repeated measures ANOVA on mean

pupil's dilation on targets revealed no significant main effect of time ($F_{(1,26)}$=1.380, p=.251), no significant main effect of group ($F_{(1,26)}$=.007, p=.932) and no significant time by group interaction ($F_{(1,26)}$=1.156, p=.292). No significant main effect of time ($F_{(1,25)}$=1.115, p=.301), no significant main effect of group ($F_{(1,25)}$=.046, p=.886) and no significant time by group interaction ($F_{(1,25)}$=.180, p=.675) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,26)}$=.498, p=.487), no significant main effect of group ($F_{(1,26)}$=1.621, p=.214) and no significant time by group interaction ($F_{(1,26)}$=1.860, p=.184). No significant main effect of time ($F_{(1,25)}$=2.285, p=.143), no significant main effect of group ($F_{(1,25)}$=.364, p=.552) and no significant time by group interaction ($F_{(1,25)}$=1.018, p=.323) emerged in a repeated measures ANOVA on pupil's variability. A repeated measures ANOVA on mean pupil's dilation on standard revealed no significant main effect of time ($F_{(1,26)}$=.625, p=.419), no significant main effect of group ($F_{(1,26)}$=.888, p=.355) and no significant time by group interaction ($F_{(1,26)}$=.091, p=.765). No significant main effect of time ($F_{(1,25)}$=1.259, p=.272), no significant main effect of group ($F_{(1,25)}$=.053, p=.821) and no significant time by group interaction ($F_{(1,25)}$=.220, p=.643) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,26)}$=1.434, p=.242), a marginal main effect of group ($F_{(1,26)}$=3.286, p=.081) and no significant time by group interaction ($F_{(1,26)}$=.012, p=.912). No significant main effect of time ($F_{(1,25)}$=2.900, p=.101), no significant main effect of group ($F_{(1,25)}$=.119, p=.733) and no significant time by group interaction ($F_{(1,25)}$=1.033, p=.319) emerged in a repeated measures ANOVA on pupil's variability.

EEG power spectra

A repeated measures ANOVA on theta power revealed a significant main effect of time ($F_{(1,34)}$=.19.143, p=.000) no significant main effect of group ($F_{(1,34)}$=1.918, p=.175) and no significant time by group effect ($F_{(1,34)}$=.391, p=.536). A repeated

measures ANOVA on alpha power revealed a significant main effect of time ($F_{(1,34)}$ =23.519, p=.000), no significant main effect of group ($F_{(1,34)}$=2.171, p=.150) and no significant time by group interaction ($F_{(1,34)}$= .392, p=.535). A repeated measures ANOVA on beta power showed a significant main effect of time ($F_{(1,34)}$=14.363, p=.001), no significant main effect of group ($F_{(1,34)}$=.837, p=.367) and no significant time by group effect ($F_{(1,34)}$=1.597, p=.215). Another repeated measures ANOVA on theta/beta ratio revealed a main effect of time ($F_{(1,34)}$=31.241, p=.000), no main effect of group ($F_{(1,34)}$=.557, p=.461) and no significant time by group interaction ($F_{(1,34)}$=.018, p=.895). A repeated measures ANOVA on alpha/beta ratio showed a significant main effect of time ($F_{(1,34)}$=31.466, p=.000), a marginal main effect of group ($F_{(1,34)}$=1.176,p=.286) and no significant time by group interaction ($F_{(1,34)}$=.362, p=.552).

Event Related Potentials (ERPs)

P3 amplitude, peak and latency values were extracted on target tones in the first block of the auditory oddball task at central-parietal sites. N1 amplitude and latency were also extracted on target stimuli at central sites.

A repeated measures ANOVA on P3 amplitude showed no significant main effect of time ($F_{(1,24)}$=2.202, p=.151), no significant main effect of group ($F_{(1,24)}$=.063, p=.804) and no significant time by group interaction ($F_{(1,24)}$=.860, p=.363). No significant main effect of time ($F_{(1,24)}$=.532, p=.473), no significant main effect of group ($F_{(1,24)}$=.639, p=.432) and no significant time by group interaction ($F_{(1,24)}$=1.641, p=.212) emerged in a repeated measures ANOVA on P3 peak at parietal sites. A repeated measures ANOVA on P3 latency at parietal sites revealed a significant main effect of time ($F_{(1,24)}$=4.653, p=.041), no significant main effect of group ($F_{(1,24)}$=1.615, p=.215) and no significant time by group interaction ($F_{(1,24)}$=.224, p=.640).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,24)}$=.009, p=.925), no significant main effect of group ($F_{(1,24)}$=.145, p=.706) and no significant time by group interaction

($F_{(1,24)}$=.478, p=.496). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,24)}$=.234, p=.633), no significant main effect of group ($F_{(1,24)}$=.030, p=.863) and no significant time by group interaction ($F_{(1,24)}$=1.233, p=.278).

The same P3 variables were extracted in the second block of the auditory oddball task on target and standard stimuli respectively. N1 amplitude and latency were also extracted on target and standard stimuli at central sites.

A repeated measures ANOVA on P3 amplitude on target tones at CPz showed no significant main effect of time ($F_{(1,30)}$=2.006, p=.167), no significant main effect of group ($F_{(1,30)}$=.240, p=.628) and no significant time by group interaction ($F_{(1,30)}$=2.010, p=.112). A significant main effect of time ($F_{(1,30)}$=50.149, p=.000), no significant main effect of group ($F_{(1,30)}$=.042, p=.838) and no significant time by group interaction ($F_{(1,30)}$=2.750, p=.108) emerged in a repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,30)}$=.318, p=.577), no significant main effect of group ($F_{(1,30)}$=.012, p=.912) and no significant time by group interaction ($F_{(1,30)}$=.016, p=.900).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,30)}$=2.092, p=.158), no significant main effect of group ($F_{(1,30)}$=.429, p=.517) and no significant time by group interaction ($F_{(1,30)}$=.912, p=.347). A repeated measures ANOVA on N1 latency at central sites revealed a marginal main effect of time ($F_{(1,30)}$=4.123, p=.051), no significant main effect of group ($F_{(1,30)}$=.042, p=.839) and no significant time by group interaction ($F_{(1,30)}$=.432, p=.516).

A repeated measures ANOVA on P3 amplitude on standard tones at CPz site showed no significant main effect of time ($F_{(1,29)}$=.073, p=.789), no significant main effect of group ($F_{(1,29)}$=.156, p=.696) and no significant time by group interaction ($F_{(1,29)}$=1.281, p=.267). No significant main effect of time ($F_{(1,29)}$=.253,

p=.619), no significant main effect of group ($F_{(1,29)}$=1.387, p=.249) and no significant time by group interaction ($F_{(1,29)}$=1.833, p=.186) emerged in a repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,29)}$=.377, p=.544), no significant main effect of group ($F_{(1,29)}$=2.698, p=.111) and no significant time by group interaction ($F_{(1,29)}$=2.101, p=.158).

A repeated measures ANOVA on N1 amplitude at central sites revealed a significant main effect of time ($F_{(1,29)}$=4.627, p=.040), no significant main effect of group ($F_{(1,29)}$=1.411, p=.245) and no significant time by group interaction ($F_{(1,29)}$=1.274, p=.268). A repeated measures ANOVA on N1 latency at central sites revealed a marginal main effect of time ($F_{(1,29)}$=3.919, p=.057), no significant main effect of group ($F_{(1,29)}$=.017, p=.896) and no significant time by group interaction ($F_{(1,29)}$=.051, p=.823).

5.9.4 Three-month follow up effects

5.9.4.1 Three-month follow up effects on primary outcome measures

Repeated measures ANOVAs were performed to investigate differences between groups at the three-month follow up on the study primary outcomes measures.

CAARS Self Report Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no significant main effect of time ($F_{(1, 28)}$=.108, p=.745), no significant main effect of group ($F_{(1,28)}$=.895, p=.352) and no significant time by group interaction($F_{(1,28)}$=.895, p=.352). A significant main effect of time ($F_{(1,28)}$=6.938, p=.014) and group ($F_{(1,28)}$=.206, p=.653) and no significant interaction ($F_{(1,28)}$=.206, p=.653) were found for CAARS-B - Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed no significant main effect of time ($F_{(1,28)}$=2.259, p=.144), a significant main effect of group ($F_{(1,28)}$=5.287, p=.029) and a significant time by

group interaction ($F_{(1,28)}$=5.287, p=.029). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(15)}$=3.012, p=.009) that was absent in the AT group ($t_{(14)}$=-.326, p=.749). There was a marginal main effect of time ($F_{(1,28)}$=3.985, p=.056), a significant main effect of group ($F_{(1,28)}$=9.231, p=.005) and a significant group by time interaction ($F_{(1,28)}$=9.231, p=.005) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(15)}$=2.989, p=.009) that was not present in the AT group ($t_{(14)}$= -.624, p=.543). A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed no main effect of time ($F_{(1,28)}$=1.196, p=.283), a significant main effect of group ($F_{(1,28)}$=4.270, p=.048) and a significant time by group interaction ($F_{(1,28)}$=4.270, p=.048). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(15)}$=2.946, p=.010) that was absent in the AT group ($t_{(14)}$=.331, p=.749). Another repeated measures ANCOVA for CAARS-F-DSM-IV Hyperactive Symptoms showed a significant main effect of time ($F_{(1,28)}$=6.189, p=.019), no significant main effect of group ($F_{(1,28)}$=.814, p=.375) and a significant time by group interaction ($F_{(1,28)}$=.814, p=.375). There was no significant main effect of time ($F_{(1,28)}$=1.405, p=.246), no significant main effect of group ($F_{(1,28)}$= 2.722, p=.11) and no significant time by group interaction $F_{(1,28)}$= 2.722, p=.11) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed a marginal main effect of time ($F_{(1,28)}$=3.453, p=.074), a significant main effect of group ($F_{(1,28)}$=10.623, p=.003) and a significant time by group interaction ($F_{(1,28)}$=10.623, p=.003). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(15)}$=3.684, p=.002) that was absent in the AT group ($t_{(14)}$= -1.079, p=.299). See figure 5.16 below to visualise significant time by group interactions at the three-month follow up.

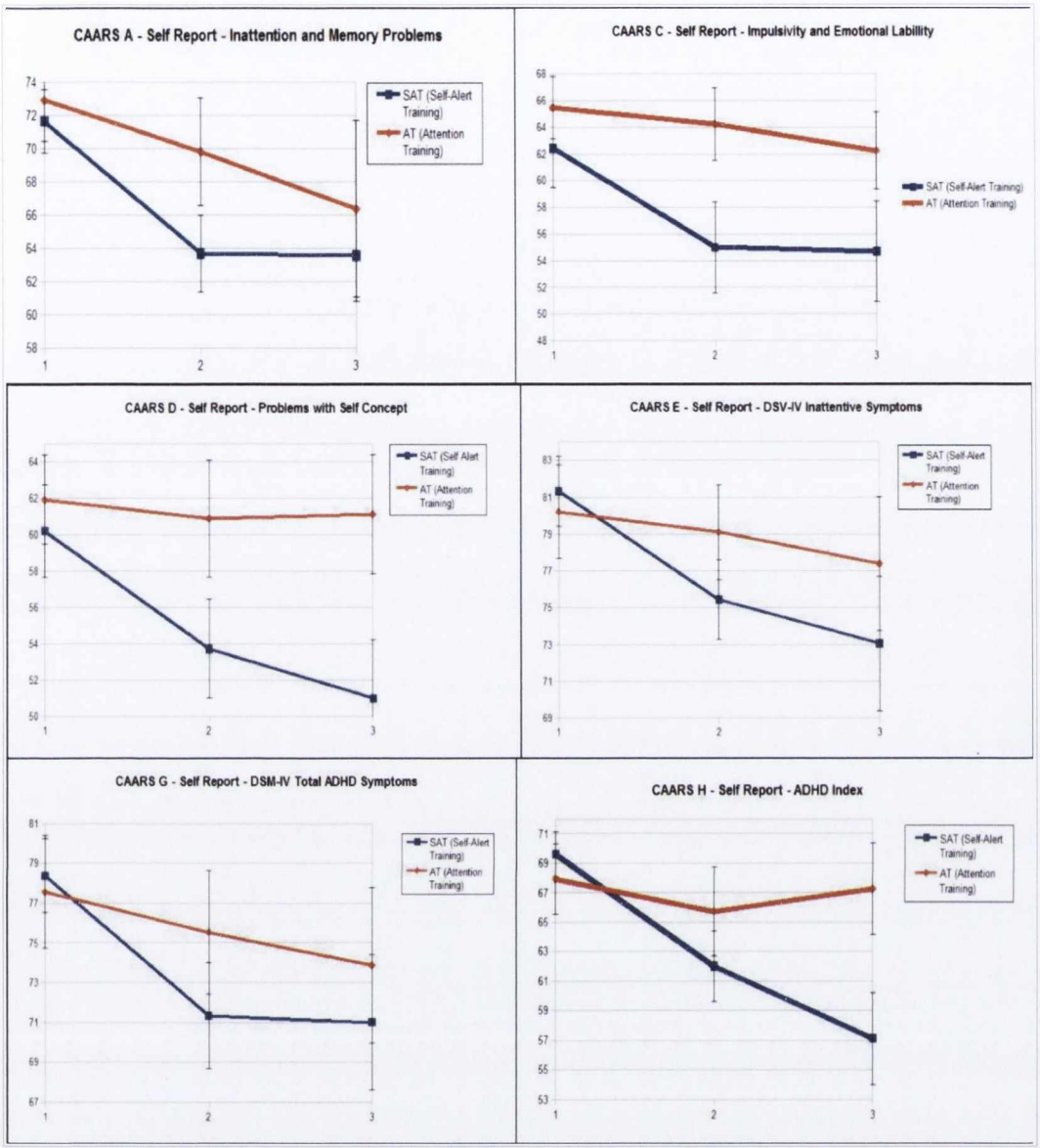


Figure 5.16. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale – Self Report (CAARS- S: L) at pre and post-training and at the three-month follow up. Error bars represent the standard error.

Note: SAT participants significantly improved their ADHD symptoms compared to AT participants at the three-month follow up.

CAARS Observer Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no main effect of time ($F_{(1, 13)}$=.351, p=.564), no significant main effect of group ($F_{(1,13)}$=.094, p=.764) and no significant time by group interaction ($F_{(1,13)}$=.094, p=.764). No significant main effect of time ($F_{(1,13)}$=1.663,

p=.220) and group ($F_{(1,13)}$=.016, p=.900) and no significant interaction ($F_{(1,13)}$=.016, p=.900) were found for CAARS-B. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed no significant main effect of time ($F_{(1,13)}$=.045, p=.836), no significant main effect of group ($F_{(1,13)}$=.441, p=.518) and no significant time by group interaction ($F_{(1,13)}$=.441, p=.518). There was a significant main effect of time ($F_{(1,13)}$= 8.324, p=.013), no significant main effect of group ($F_{(1,13)}$=.811, p=.384) and a significant group by time interaction ($F_{(1,13)}$=.811, p=.384) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed no significant main effect of time ($F_{(1,13)}$=.194, p=.667), no significant main effect of group ($F_{(1,13)}$=.104, p=.752) and no significant time by group interaction ($F_{(1,13)}$=.104, p=.752). Another repeated measures ANCOVA for CAARS-B- Impulsivity - DSM-IV hyperactive symptoms showed no significant main effect of time ($F_{(1,13)}$=1.169, p=.311), no significant main effect of group ($F_{(1,13)}$=2.105, p=.207) and no significant interaction effect ($F_{(1,13)}$=2.105, p=.207). There was no significant main effect of time ($F_{(1,13)}$=.394, p=.541), no significant main effect of group ($F_{(1,13)}$=.244, p=.63) and no significant time by group interaction ($F_{(1,13)}$=.244, p=.63) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed no main effect of time ($F_{(1,13)}$=.035, p=.855), no significant main effect of group ($F_{(1,13)}$=.048, p=.831) and a significant time by group interaction ($F_{(1,13)}$=.048, p=.831).

Other Scales and Questionnaires

A repeated measures ANCOVA for the Attention-Related Cognitive Errors Questionnaire (ARCEQ) revealed no significant main effect of time ($F_{(1,16)}$=.01, p=.921), a significant main effect of group ($F_{(1,16)}$=7.921, p=.012) and a significant time by group interaction ($F_{(1,16)}$=7.921, p=.012). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(10)}$=12.235, p=.000) that was absent in the AT group ($t_{(7)}$=2.212, p=.063). A significant main effect of time

($F_{(1,16)}$=16.028 p=.000), no main effect of group ($F_{(1,16)}$=.032, p=.861) and a marginal interaction effect ($F_{(1,16)}$=.032, p=.861) emerged in a repeated measures ANCOVA for the Everyday Memory Failure Questionnaire (EMFQ). A repeated measures ANCOVA for the General Health Questionnaire (GHQ) showed a significant main effect of time ($F_{(1,26)}$=9.124, p=.006), no significant main effect of group ($F_{(1,26)}$=.415, p=.525) and no significant time by group interaction ($F_{(1,26)}$=.415, p=.525). There was a significant main effect of time ($F_{(1,24)}$=10.874, p=.003), a significant main effect of group ($F_{(1,24)}$=4.335, p=.048) and a significant time by group interaction ($F_{(1,24)}$=4.335, p=.048) in a repeated measures ANCOVA for the Self Efficacy Scale (SES). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(14)}$=-4.042, p=.001) that was absent in the AT group ($t_{(1)}$=-1.316, p=.215). A repeated measures ANCOVA for the Beck Depression Inventory (BDI) revealed a significant main effect of time ($F_{(1,26)}$=5.063, p=.033), a significant main effect of group ($F_{(1,26)}$=4.454, p=.045) and a significant time by group interaction ($F_{(1,26)}$=4.454, p=.045). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(14)}$=2.807, p=.014) that was absent in the AT group ($t_{(13)}$=-1.342, p=.203). Another repeated measures ANCOVA for Beck Anxiety Inventory (BAI) showed a significant main effect of time ($F_{(1,26)}$=4.605, p=.041), no significant main effect of group ($F_{(1,26)}$=.451, p=.508) and no significant time by group interaction ($F_{(1,26)}$=.451, p=.508). Figures 5.17 show significant time by group interactions in Attention-Related Cognitive Errors Questionnaire (ARCEQ), in the Beck Depression Inventory (BDI) and in the Self Efficacy Scale (SES)

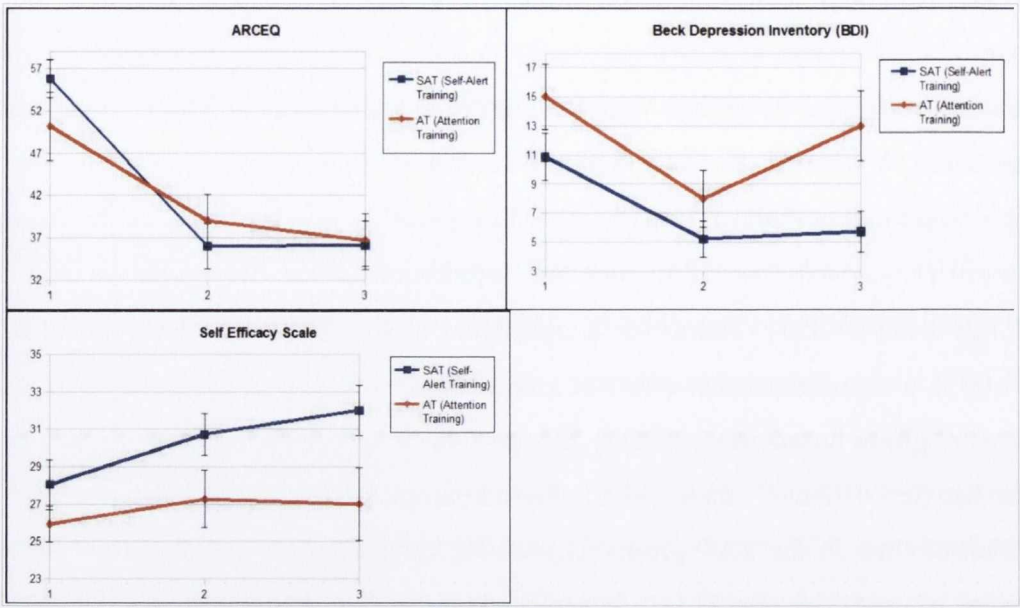


Figure 5.17. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Attention-Related Cognitive Errors Questionnaire (ARCEQ) and in the Beck Depression Inventory (BDI) at pre and post-training and at the three-month follow up. Error bars represent the standard error.

Note: SAT participants significantly improved their scores in both scales compared to AT participants at the three-month follow up, indicating improved social and psychiatric functioning.

Neuropsychological tests

A repeated measures ANCOVA was carried out for the scores in the Elevator Counting with Distraction and it revealed a significant main effect of time ($F_{(1,28)}$=25.031, p=.000), no main effect of group ($F_{(1,28)}$=.972, p=.333) and no significant time by group interaction ($F_{(1,28)}$=.972, p=.333). A repeated measures ANCOVA was performed on the Raw Score in the Telephone Search and a significant main effect of time ($F_{(1,28)}$=7.855, p=.009), no main effect of group ($F_{(1,,28)}$=.558, p=.461) and no time by group interaction ($F_{(1,,28)}$=.558, p=.461) were found. Another repeated measures ANCOVA was conducted on the Dual Task Decrement in the Telephone Search While Counting which showed no significant main effect of time ($F_{(1,27)}$=2.215, p=.148), no significant main effect of group ($F_{(1,27)}$=.041, p=.841) and no significant time by group interaction ($F_{(1,27)}$=.041, p=.841).

A repeated measures ANCOVA for the number of attempted tasks in the Hotel

task revealed no significant main effect of time ($F_{(1,28)}$=1.115, p=.30), no significant main effect of group ($F_{(1, 28)}$=1.544, p=.224) and no significant time by group interaction ($F_{(1, 28)}$=1.544, p=.224). A repeated measures ANCOVA for the total deviation time in the Hotel Task showed a significant main effect of time ($F_{(1,27)}$=8.233, p=.008), no significant main effect of group ($F_{(1,27)}$=.381, p=.542) and no significant time by group interaction ($F_{(1,27)}$=.381, p=.542). There was a marginal main effect of time ($F_{(1, 28)}$=3.155, p=.087) but no significant main effect of group ($F_{(1,28)}$=1.36, p=.253) and no significant interaction effect ($F_{(1,28)}$=1.36, p=.253) in a repeated measures ANCOVA for the total time spent in activity in the Hotel Task.

Sustained Attention to Response Task (SART) Fixed and Random

A repeated measures ANCOVA on Omissions in the Fixed SART revealed a marginal main effect of time ($F_{(1,21)}$=.908, p=.352), no significant main effect of group ($F_{(1,21)}$=.414, p=.527) and no significant time by group interaction ($F_{(1,21)}$=.414, p=.527). There was a significant main effect of time ($F_{(1,20)}$=5.555, p=.029), no significant main effect of group ($F_{(1,20)}$=.569, p=.460) and no significant interaction effect ($F_{(1,20)}$=.569, p=.460)in a repeated measures ANCOVA on Commission Errors in the Fixed SART. A repeated measures ANCOVA on Reaction Times (RT) in the Fixed SART showed a significant main effect of time ($F_{(1,24)}$=9.072, p=.006), a significant main effect of group ($F_{(1,24)}$=4.311, p=.049) and a significant time by group interaction $F_{(1,24)}$=4.311, p=.049). Paired samples t-tests showed that there was no main effect of time in the SAT group ($t_{(13)}$=-1.515, p=.154) and in the AT group ($t_{(12)}$=1.350, p=.202). There was a marginal main effect of time ($F_{(1,21)}$=4.163, p=.054), no significant main effect of group ($F_{(1,21)}$=.002, p=.969) and no significant time by group interaction ($F_{(1,21)}$=.002, p=.969) for SD in the Fixed SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Fixed SART revealed a significant main effect of time ($F_{(1,23)}$=6.357, p=.019), no significant main effect of group ($F_{(1,23)}$=.164, p=.689) and no significant time by group interaction ($F_{(1,23)}$=.164, p=.689). Figure 5.18 below shows the significant time by group interaction in

Reaction Times (RT) in the Fixed SART

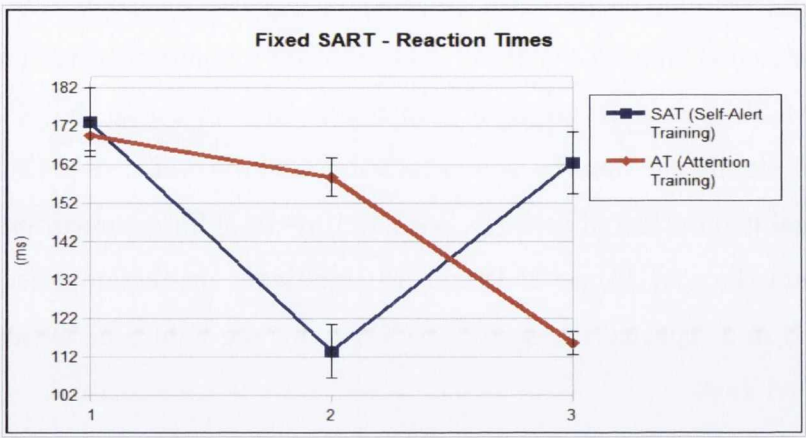


Figure 5.18. Self-Alert Training group (SAT) and Attention Training group (AT)'s reaction times (RTs) in the Sustained Attention to Response Task (SART) Fixed version, at pre and post-training and at the three-month follow up. Error bars represent the standard error.

Note: SAT participants significantly increased their RTs compared to AT participants at the three-month follow up.

A repeated measures ANCOVA on Omissions in the random SART revealed no significant main effect of time ($F_{(1,17)}$=2,854, p=.109), no significant main effect of group ($F_{(1,17)}$=.134, p=.719) and no significant time by group interaction ($F_{(1,17)}$=.134, p=.719). There was no significant main effect of time ($F_{(1,23)}$=.441, p=.513), no significant main effect of group ($F_{(1,23)}$=.083, p=.776) and no significant interaction effect ($F_{(1,23)}$=.083, p=.776) in a repeated measures ANCOVA on Commission Errors in the Random SART. A repeated measures ANCOVA on Reaction Times (RT) in the Random SART showed a significant main effect of time ($F_{(1,24)}$=29.924, p=.000), a significant main effect of group ($F_{(1,24)}$=4.784, p=.039) and a significant time by group interaction ($F_{(1,24)}$=4.784, p=.039). Paired samples t-tests revealed that there was no main effect of time in the SAT group ($t_{(12)}$=-1.449, p=.160) and in the AT group ($t_{(13)}$=-.161, p=.875).There was no significant main effect of time ($F_{(1,20)}$=1.927, p=.180), no significant main effect of group ($F_{(1,20)}$=2.441, p=.134) and no significant time by group interaction ($F_{(1,20)}$=2.441, p=.134) for SD in the Random SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Random SART

revealed no significant main effect of time ($F_{(1,19)}$=.051, p=.824), no significant main effect of group ($F_{(1,19)}$=.132, p=.720) and no significant time by group interaction ($F_{(1,19)}$=.132, p=.720). Figure 5.19 shows the significant time by group interaction in Reaction Times (RT) in the Random SART.

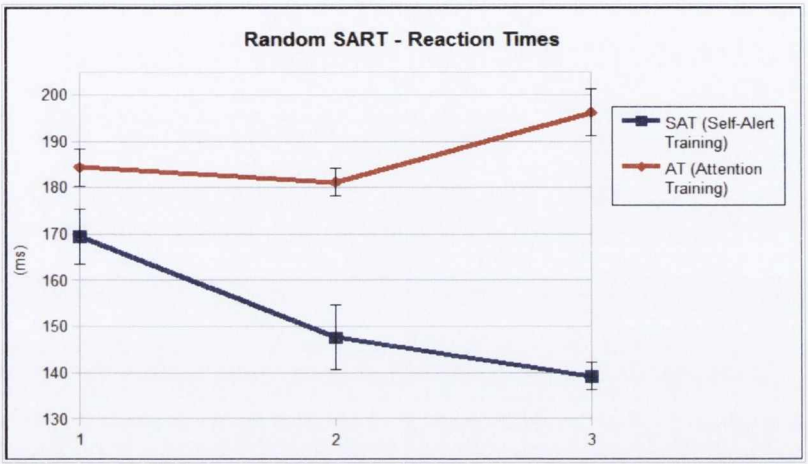


Figure 5.19. Self-Alert Training group (SAT) and Attention Training group (AT)'s reaction times (RTs) in the Sustained Attention to Response Task (SART) Random version, at pre and post-training and at the three-month follow up. Error bars represent the standard error.

Note: SAT participants significantly decreased their RTs compared to AT participants at the three-month follow up.

Auditory Oddball Task – Behavioural Measures

Repeated measures ANCOVAs were carried out for each variable in the first block of the auditory oddball task. A repeated measures ANCOVA on Accuracy revealed a significant main effect of time ($F_{(1,18)}$=35.007, p=0.000), no significant main effect of group ($F_{(1,18)}$=.628, p=.438) and no significant interaction effect ($F_{(1,18)}$=.628, p=.438). A repeated measures ANCOVA on Omission Errors showed a significant main effect of time ($F_{(1, 18)}$=4.578, p=.046), no significant main effect of group ($F_{(1, 18)}$=.628, p=.438) and no significant time by group interaction ($F_{(1,18)}$=.628, p=.438). There was no significant main effect of time ($F_{(1,18)}$ =2.535, p=.129), no significant main effect of group ($F_{(1,18)}$=.385, p=.542) and no significant interaction ($F_{(1,18)}$=.385, p=.542) in a repeated measures ANCOVA on Reaction Times. A repeated measures ANCOVA on Coefficient of Variation (CV) revealed a significant main effect of time ($F_{(1,18)}$=7.816, p=.012), no significant

main effect of group ($F_{(1,18)}$=.301, p=.59) and no significant time by group interaction ($F_{(1,18)}$=.301, p=.59).

Repeated measures ANCOVAs were conducted on the second block of the auditory oddball task for each variable on target and standard tones. A repeated measures ANCOVA on Accuracy on target tones revealed no significant main effect of time ($F_{(1,18)}$=.277, p=.605), no significant main effect of group ($F_{(1,25)}$=.964, p=.339) and no significant time by group interaction ($F_{(1,25)}$=.964, p=.339). A repeated measures ANCOVA on Omission Errors on target tones revealed no significant main effect of time ($F_{(1,19)}$ =1.559, p=.228), no significant main effect of group ($F_{(1,19)}$=.507, p=.486) and no significant interaction effect ($F_{(1,19)}$=.507, p=.486). No significant main effect of time ($F_{(1,18)}$=1.542, p=.23), no significant main effect of group ($F_{(1,19)}$=1.756, p=.202) and no significant time by group interaction ($F_{(1,19)}$=1.756, p=.202) were found for Commission Errors on target tones. A repeated measures ANCOVA on Reaction Times on target tones revealed a significant main effect of time ($F_{(1,19)}$=.211, p=.651), no significant main effect of group ($F_{(1,19)}$=.061, p=.807) and no significant time by group interaction ($F_{(1,19)}$=.061, p=.807). A repeated measures ANCOVA on Coefficient of Variation (CV) for target tones showed a significant main effect of time ($F_{(1,19)}$=3.012, p=.100), no significant main effect of group ($F_{(1,19)}$=.439, p=.515) and no significant time by group interaction ($F_{(1,19)}$=.439, p=.515).

A repeated measures ANCOVA on Accuracy on standard tones revealed no significant main effect of time ($F_{(1,18)}$=.046, p=.832), no significant main effect of group ($F_{(1,18)}$=.953, p=.342) and no significant time by group interaction ($F_{(1,18)}$=.953, p=.342). A repeated measures ANCOVA on Omission Errors on standard tones revealed no significant main effect of time ($F_{(1,19)}$ =.000, p=.987), no significant main effect of group ($F_{(1,19)}$=.049, p=.827) and no significant interaction effect ($F_{(1,19)}$=.049, p=.827). A significant main effect of time ($F_{(1,19)}$=1.394, p=.253), no main effect of group ($F_{(1,19)}$=1.05, p=.319) and no time by group interaction ($F_{(1,19)}$=1.05, p=.319) were found for Commission Errors on standard tones. A repeated measures ANCOVA on Reaction Times on standard

tones revealed a significant main effect of time ($F_{(1,19)}$=6.103, p=.023), no significant main effect of group ($F_{(1,19)}$=.177, p=.678) and no significant time by group interaction ($F_{(1,19)}$=.177, p=.678). A repeated measures ANCOVA on Coefficient of Variation (CV) for standard tones showed no significant main effect of time ($F_{(1,19)}$=.251, p=.622), no significant main effect of group ($F_{(1,19)}$=.287, p=.598) and no significant interaction effect ($F_{(1,19)}$=.287, p=.598).

5.9.4.2 Three-month follow up effects on neurophysiological measures

Repeated measures ANOVAs were performed on pupil, EEG power spectra and Event-Related Potentials (ERPs) measures to investigate differences between groups at the three-month follow up.

Pupil

In the first block of the auditory oddball task, a repeated measures ANOVA on mean pupil's dilation on targets revealed no significant main effect of time ($F_{(1,28)}$=.455, p=.505), no significant main effect of group ($F_{(1,28)}$=1.606, p=.215) and no significant time by group interaction ($F_{(1,28)}$=.642, p=.430). Another repeated measures ANOVA on pupil's baseline on target tones showed no significant main effect of time ($F_{(1,18)}$=.210, p=.653), no significant main effect of group ($F_{(1,18)}$=.321, p=.577) and no significant time by group interaction ($F_{(1,18)}$=.574, p=.458). A marginal main effect of time ($F_{(1,22)}$=3.765, p=.065), no significant main effect of group ($F_{(1,22)}$=.318, p=.570) and no significant time by group interaction ($F_{(1,22)}$=1.439, p=.243) emerged in a repeated measures ANOVA on pupil's latency. No significant main effect of time ($F_{(1,24)}$=1.027, p=.319), no significant main effect of group ($F_{(1,24)}$=.809, p=.375) and no significant time by group interaction ($F_{(1,24)}$=2.767, p=.107) emerged in a repeated measures ANOVA on pupil's variability.

The same statistical analysis was performed for target and standard tones in the second block of the auditory oddball task. A repeated measures ANOVA on mean pupil's dilation on targets revealed a significant main effect of time ($F_{(1,23)}$=8.746,

p=.007), no significant main effect of group ($F_{(1,23)}$=.021, p=.885) and no significant time by group interaction ($F_{(1,23)}$=.665, p=.423). No significant main effect of time ($F_{(1,23)}$=1.335, p=.260), no significant main effect of group ($F_{(1,23)}$=1.829, p=.189) and no significant time by group interaction ($F_{(1,23)}$=.125, p=.727) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,24)}$=.358, p=.555), no significant main effect of group ($F_{(1,24)}$=1.732, p=.112) and no significant time by group interaction ($F_{(1,24)}$=1.518, p=.230). A marginal main effect of time ($F_{(1,24)}$=3.464, p=.075), no significant main effect of group ($F_{(1,24)}$=.100, p=.755) and no significant time by group interaction ($F_{(1,24)}$=.139, p=.713) emerged in a repeated measures ANOVA on pupil's variability. A repeated measures ANOVA on mean pupil's dilation on standard revealed a significant main effect of time ($F_{(1,23)}$= 4.315, p=.049), no significant main effect of group ($F_{(1,23)}$=.234, p=.633) and no significant time by group interaction ($F_{(1,23)}$=.011, p=.885). No significant main effect of time ($F_{(1,23)}$=1.335, p=.260), no significant main effect of group ($F_{(1,23)}$=1.189, p=.189) and no significant time by group interaction ($F_{(1,23)}$=.125, p=.727) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,24)}$=.000, p=.987), a marginal main effect of group ($F_{(1,24)}$=3.226, p=.085) and no significant time by group interaction ($F_{(1,24)}$=.244, p=.626). No significant main effect of time ($F_{(1,23)}$=.666, p=.423), no significant main effect of group ($F_{(1,23)}$=.131, p=.720) and no significant time by group interaction ($F_{(1,23)}$=.431, p=.518) emerged in a repeated measures ANOVA on pupil's variability.

EEG power spectra

A repeated measures ANOVA on theta power revealed a significant main effect of time ($F_{(1,28)}$=11.154, p=.002), no significant main effect of group ($F_{(1,28)}$=.007, p=.933) and no significant time by group effect ($F_{(1,28)}$=.495, p=.487). A repeated measures ANOVA on alpha power revealed a significant main effect of time ($F_{(1,28)}$=14.082, p=.001), no significant main effect of group ($F_{(1,28)}$=.005, p=.944)

and no significant time by group interaction ($F_{(1,28)}$=.744, p=.396). A repeated measures ANOVA on beta power showed a significant main effect of time ($F_{(1,28)}$=17.385, p=.000), no significant main effect of group ($F_{(1,28)}$=.053, p=.820) and no significant time by group effect ($F_{(1,28)}$=1.068, p=.310). Another repeated measures ANOVA on theta/beta ratio revealed a main effect of time ($F_{(1,28)}$=15.889, p=.000), no main effect of group ($F_{(1,28)}$=1.432, p=.241) and no significant time by group interaction ($F_{(1,28)}$=.046, p=.832). A repeated measures ANOVA on alpha/beta ratio showed a significant main effect of time ($F_{(1,28)}$=13.188, p=.001), no significant main effect of group ($F_{(1,28)}$=1.744,p=.197) and no significant time by group interaction ($F_{(1,28)}$=.000, p=.988).

Event-Related Potentials (ERPs)

P3 variables were extracted on target tones in the first block of the auditory oddball task. N1 amplitude and latency were also extracted on target tones.

A repeated measures ANOVA on P3 amplitude at CPz site showed no significant main effect of time ($F_{(1,17)}$=.841, p=.372), no significant main effect of group ($F_{(1,17)}$=.954, p=.342) and no significant time by group interaction ($F_{(1,17)}$=.001, p=.975). No significant main effect of time ($F_{(1,17)}$=.092, p=.766), no significant main effect of group ($F_{(1,17)}$=1.013, p=.328) and no significant time by group interaction ($F_{(1,17)}$=1.063, p=.317) emerged in a repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed a significant main effect of time ($F_{(1,17)}$=21.447, p=.000), no significant main effect of group ($F_{(1,17)}$=.439, p=.516) and no significant time by group interaction ($F_{(1,17)}$=.456, p=.509). A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,19)}$=.032, p=.862), no significant main effect of group ($F_{(1,19)}$=.301, p=.595) and no significant time by group interaction ($F_{(1,19)}$=.694, p=.424). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,19)}$=2.677, p=.133), no significant main effect of group ($F_{(1,19)}$=.636, p=.444) and no significant time by group interaction ($F_{(1,19)}$=1.989, p=.189).

The same P3 variables were extracted in the second block of the auditory oddball task on target and standard stimuli respectively. N1 measures were also extracted on target and standard tones.

A repeated measures ANOVA on P3 amplitude on target tones at CPz site showed no significant main effect of time ($F_{(1,19)}$=.056, p=.816), no significant main effect of group ($F_{(1,19)}$=.006, p=.941) and no significant time by group interaction ($F_{(1,19)}$=.489, p=.493). No significant main effect of time ($F_{(1,19)}$=.269, p=.610), no significant main effect of group ($F_{(1,19)}$=.643, p=.432) and no significant time by group interaction ($F_{(1,19)}$=2.055, p=.168) emerged in a repeated measures ANOVA on P3. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,19)}$=.167, p=.688), no significant main effect of group ($F_{(1,19)}$=1.561, p=.227) and no significant time by group interaction ($F_{(1,19)}$=.007, p=.933).

A repeated measures ANOVA on N1 amplitude at central sites revealed a marginal main effect of time ($F_{(1,18)}$=3.495, p=.078), no significant main effect of group ($F_{(1,18)}$=.228, p=.639) and no significant time by group interaction ($F_{(1,18)}$=.228, p=.639). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,18.)}$=.067, p=.799), no significant main effect of group ($F_{(1,18)}$=.005, p=.947) and no significant time by group interaction ($F_{(1,18)}$=.005, p=.947).

A repeated measures ANOVA on P3 amplitude on standard tones at CPz site showed no significant main effect of time ($F_{(1,18)}$=2.327, p=.145), no significant main effect of group ($F_{(1,18)}$=.060, p=.810) and no significant time by group interaction ($F_{(1,18)}$=.164, p=.690). A marginal main effect of time ($F_{(1,18)}$=4.266, p=.054), no significant main effect of group ($F_{(1,18)}$=.378, p=.546) and no significant time by group interaction ($F_{(1,18)}$=2.594, p=.125) emerged in a repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,18)}$=1.018, p=.326), no significant main effect of group ($F_{(1,18)}$=1.540, p=.231) and no significant time by group

interaction ($F_{(1,18)}$=.093, p=.764).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,19)}$=.780, p=.388), no significant main effect of group ($F_{(1,19)}$=.000, p=.988) and no significant time by group interaction ($F_{(1,19)}$=.008, p=.929). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,19)}$=1.780, p=.199), no significant main effect of group ($F_{(1,19)}$=.170, p=.685) and no significant time by group interaction ($F_{(1,19)}$=.170, p=.685).

5.9.5 Sub-analysis excluding low-participation participants

As explained before in this chapter, a sub-analysis was conducted on the primary outcome measures and on neurophysiological measures excluding participants who did less than ten exercises during the five week training period to investigate effects of training after five week and at the three-month follow up. Therefore, seven participants were excluded from the analysis (five participants in the SAT group and two participants in the AT group). The same statistical analyses were carried out.

5.9.5.1 Post-training effects

5.9.5.1.1 Post-training effects on primary outcome measures

Repeated measures ANCOVAs were performed to investigate differences between the Self-Alert Training group and the Attention Training group after five weeks after excluding seven low-participation participants

CAARS Self Report Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no significant main effect of time ($F_{(1, 29)}$=2.273, p=.516), a significant main effect of group ($F_{(1,29)}$=7.406, p=.011) and a significant time by

group interaction($F_{(1,29)}$=7.406, p=.011). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(13)}$=4.746, p=.000) that was absent in the AT group ($t_{(17)}$=1.767, p=.095). No significant main effect of time ($F_{(1,29)}$=1.147, p=.293) and group ($F_{(1,29)}$=.992,p=.328) and no significant interaction ($F_{(1,29)}$ =.992, p=.328) were found for CAARS-B- Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed no significant main effect of time ($F_{(1,29)}$=1.773, p=.193), a significant main effect of group ($F_{(1,29)}$=10.268, p=.003) and a significant time by group interaction ($F_{(1,29)}$=10.278, p=.003). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(13)}$=3.189, p=.007) that was absent in the AT group ($t_{(17)}$=--.268, p=.792). There was no significant main effect of time ($F_{(1,29)}$=2.048, p=.163), a significant main effect of group ($F_{(1,29)}$=5.061, p=.032) and a significant group by time interaction ($F_{(1,29)}$=5.061, p=.032) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(13)}$=2.795, p=.015) that was not present in the AT group ($t_{(17)}$= .197, p=.846). A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed a significant main effect of time ($F_{(1,29)}$=7.025, p=.013), a significant main effect of group ($F_{(1,29)}$=8.963, p=.006) and a significant time by group interaction ($F_{(1,29)}$=8.683, p=.006). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(13)}$=4.917, p=.000) that was absent in the AT group ($t_{(17)}$= -.109, p=.914). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed a significant main effect of time ($F_{(1,29)}$=9.425, p=.005), a significant main effect of group ($F_{(1,29)}$=4.176, p=.038) and a significant time by group interaction ($F_{(1,29)}$=4.176, p=.038). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(13)}$=2.104, p=.050) that was absent in the AT group ($t_{(17)}$=.279, p=.784). There was a significant main effect of time ($F_{(1,29)}$=6.480, p=.016), a significant main effect of group ($F_{(1,29)}$= 9.179, p=.005) and a significant time by group interaction ($F_{(1,29)}$= 9.179, p=.005) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. Paired samples t-tests showed a significant effect of time in the

SAT group ($t_{(13)}$=3.685, p=.003) that was not present in the AT group ($t_{(17)}$=.169, p=.867). A repeated measures ANCOVA for CAARS-H - ADHD Index revealed no significant main effect of time ($F_{(1,29)}$=.647, p=.428), a significant main effect of group ($F_{(1,29)}$=6.963, p=.013) and a significant time by group interaction ($F_{(1,29)}$=6.963, p=0.015). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(13)}$=3.385, p=.005) that was absent in the AT group ($t_{(17)}$= .307, p=.762). Significant time by group interactions in the CAARS – Self Report are shown in figure 5.20.

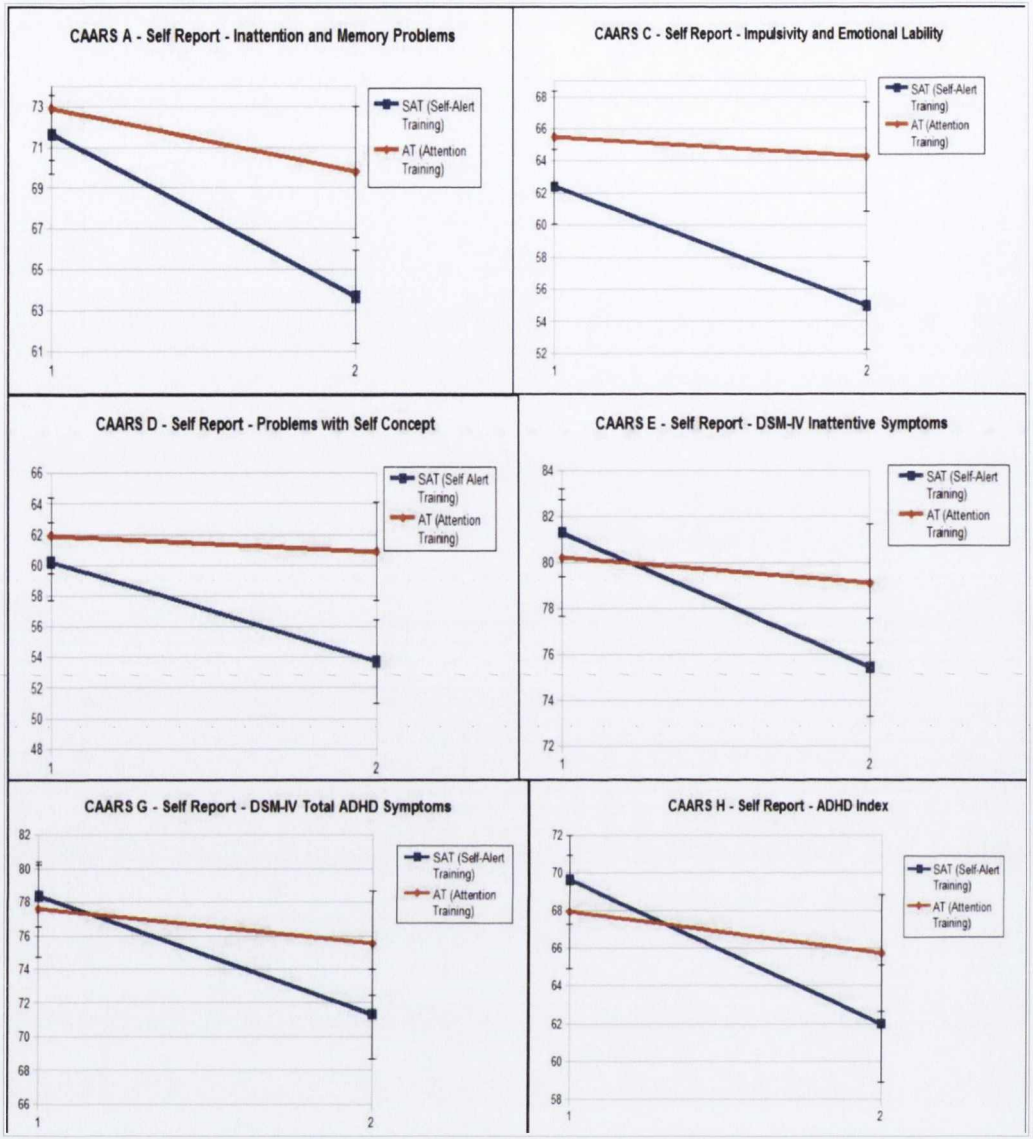


Figure 5.20. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale – Self Report (CAARS-S: L), at pre and post-training in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their ADHD symptoms after training compared to AT participants.

CAARS Observer Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no main effect of time ($F_{(1, 14)}$=2.097, p=.170), a marginal significant main effect of group ($F_{(1,14)}$=3.948, p=.067) and a marginal significant

time by group interaction ($F_{(1,14)}$=3.948, p=.067). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(8)}$=3.107, p=.015) that was absent in the AT group ($t_{(7)}$=1.821, p=.111). Figure 5.20 shows the marginal time by group interaction in the CAARS – A. No significant main effect of time ($F_{(1,14)}$=.431, p=.522) and group ($F_{(1,14)}$=.051, p=.825) and no significant interaction ($F_{(1,14)}$=.051, p=.825) were found for CAARS-B- Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed a significant main effect of time ($F_{(1,14)}$=7.429, p=.016), no significant main effect of group ($F_{(1,14)}$=1.174, p=.297) and no significant time by group interaction ($F_{(1,14)}$=1.174, p=.297). There was no significant main effect of time ($F_{(1,14)}$= 1.228, p=.286), no significant main effect of group ($F_{(1,14)}$=.647, p=.435) and a significant group by time interaction ($F_{(1,14)}$=.647, p=.435) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed a significant main effect of time ($F_{(1,14)}$=7.180, p=.018), no significant main effect of group ($F_{(1,14)}$=.784, p=.391) and no significant time by group interaction ($F_{(1,14)}$=.784, p=.391). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed no significant main effect of time ($F_{(1,14)}$=3.059, p=.102), no significant main effect of group ($F_{(1,14)}$=2.774, p=.118) and no significant interaction effect ($F_{(1,14)}$=2.774, p=.118). There was a significant main effect of time ($F_{(1,14)}$=9.667, p=.008), no significant main effect of group ($F_{(1,14)}$= 2.187, p=.161) and no significant time by group interaction ($F_{(1,14)}$= 2.187, p=.161) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed a marginal main effect of time ($F_{(1,14)}$=4.513, p=.052), no significant main effect of group ($F_{(1,14)}$=.000, p=.994) and a significant time by group interaction ($F_{(1,14)}$=.000, p=.994).

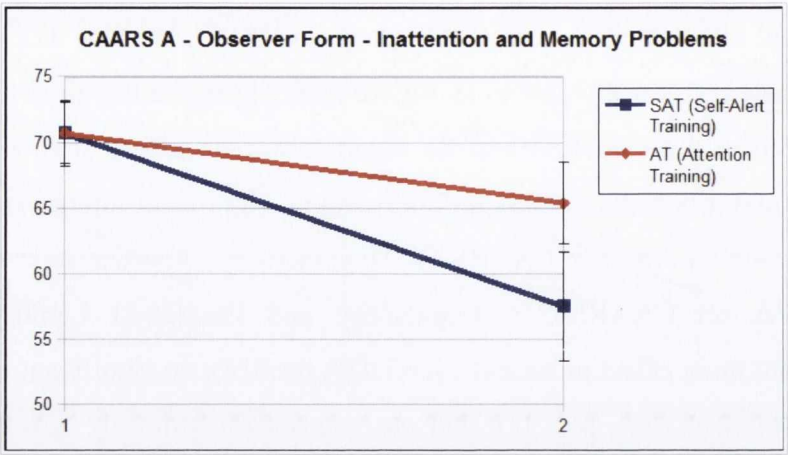


Figure 5.21. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale – Observer Form – Inattention and memory Problems (CAARS A-O: L), at pre and post-training in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants marginally reduced inattention and memory problems after training compared to AT participants. Samples size were very small (SAT: N=10; AT: N=8)

Other Scales and Questionnaires

A repeated measures ANCOVA for the Attention-Related Cognitive Errors Questionnaire (ARCEQ) revealed a significant main effect of time ($F_{(1, 13)}$=5.587, p=.034), no significant main effect of group ($F_{(1,13)}$=1.165, p=.264) and no significant time by group interaction ($F_{(1,13)}$=1.165, p=.264). A significant main effect of time ($F_{(1,13)}$=13.516, p=0.003), a marginal main effect of group ($F_{(1,13)}$=3.936,p=.069) and no marginal interaction effect ($F_{(1,13)}$=2.136, p=.169) emerged in a repeated measures ANCOVA for the Everyday Memory Failure Questionnaire (EMFQ). A repeated measures ANCOVA for the General Health Questionnaire (GHQ) showed a significant main effect of time ($F_{(1,29)}$=6.376, p=.018), no significant main effect of group ($F_{(1,29)}$=2.665, p=.113) and no significant time by group interaction ($F_{(1, 29)}$=2.665, p=.113). There was a significant main effect of time ($F_{(1,29)}$=9.872, p=.004), a significant main effect of group ($F_{(1,29)}$=1.665, p=.033) and a significant time by group interaction ($F_{(1,29)}$=1.665, p=.033) in a repeated measures ANCOVA for the Self Efficacy Scale (SES). Paired samples t-tests revealed that there was a significant effect of

time in the SAT group ($t_{(7)}$=-2.616, p=.046) that was absent in the AT group ($t_{(7)}$=-1.216, p=.157). A repeated measures ANCOVA for the Beck Depression Inventory (BDI) revealed no significant main effect of time ($F_{(1,27)}$=1.297, p=.264), no significant main effect of group ($F_{(1,27)}$=.000, p=.986) and no significant interaction ($F_{(1,27)}$=.000, p=.986). Another repeated measures ANCOVA for Beck Anxiety Inventory (BAI) showed a marginal main effect of time ($F_{(1,27)}$=3.583, p=.068), no significant main effect of group ($F_{(1,27)}$=.143, p=.708) and no significant time by group interaction ($F_{(1,27)}$=.143, p=.708). Figure 5.22 shows the significant interaction in the Self Efficacy Scale (SES)

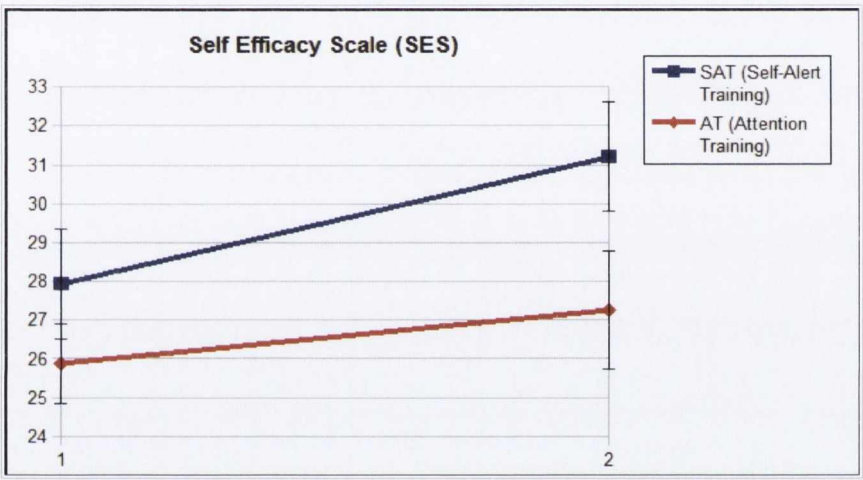


Figure 5.22. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Self Efficacy Scale (SES), at pre and post-training in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their self-efficacy scores after training compared to AT participants.

Neuropsychological tests

A repeated measures ANCOVA was carried out for the scores in the Elevator Counting with Distraction and it revealed a significant main effect of time ($F_{(1,29)}$=18.212, p=.000), a significant main effect of group ($F_{(1,29)}$=4.312, p=.047) and a significant time by group interaction ($F_{(1,29)}$=4.312, p=.047). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(13)}$= -2.936, p=.011) that was absent in the AT group ($t_{(17)}$= -.740, p=.470). A repeated measures ANCOVA was performed on the Raw Score in the Telephone Search and a

significant main effect of time ($F_{(1,29)}$=4.415 p=.044), no main effect of group ($F_{(1,,29)}$=.109, p=.743) and no time by group interaction ($F_{(1,,29)}$=.109, p=.743) were found. Another repeated measures ANCOVA was conducted on the Dual Task Decrement in the Telephone Search While Counting which showed a significant main effect of time ($F_{(1,28)}$=6.503, p=.017), a significant main effect of group ($F_{(1,28)}$=6.680, p=.014) and a significant time by group interaction ($F_{(1,28)}$=6.680, p=.014). Paired samples t-test showed a significant effect of time in the SAT group ($t_{(12)}$=2.213, p=.049) that was absent in the AT group ($t_{(17)}$= -.192, p=.850). Figure 5.23 shows significant time by group interactions.

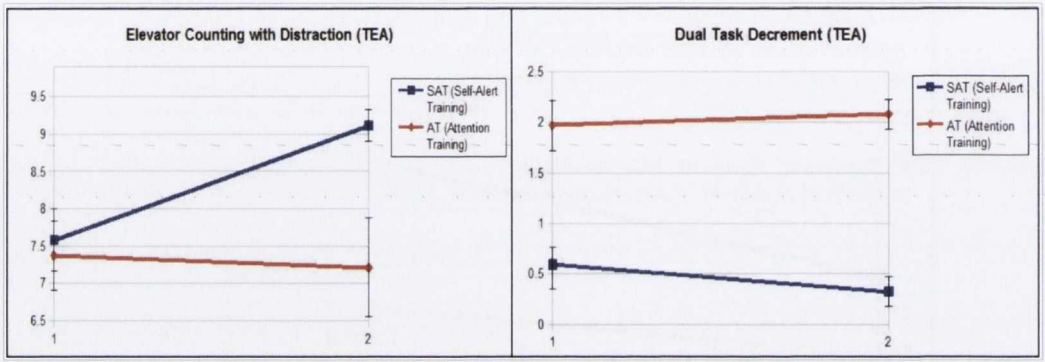


Figure 5.23. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Elevator Counting with Distraction (TEA) and in the Dual Task Decrement (TEA), at pre and post-training in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their performance in both tasks after training compared to AT participants.

A repeated measures ANCOVA for the number of attempted tasks in the Hotel task revealed a significant main effect of time ($F_{(1,29)}$=42.95, p=.000), no significant main effect of group ($F_{(1, 29)}$=.381, p=.542) and no significant time by group interaction ($F_{(1, 29)}$=.381, p=.542). A repeated measures ANCOVA for the total deviation time in the Hotel Task showed no significant main effect of time ($F_{(1,29)}$=1.088, p=.305), a significant main effect of group ($F_{(1,29)}$=4.745, p=.042) and a significant time by group interaction ($F_{(1,29)}$=4.745, p=.042). T-tests showed that there was a significant main effect of time in the SAT group ($t_{(13)}$=2.729, p=.017) that was absent in the AT group ($t_{(18)}$=.528, p=.604). There was a significant main effect of time ($F_{(1, 29)}$=32.614, p=0.000) but no significant main

effect of group ($F_{(1,29)}$=0.29, p=.866) and no significant interaction effect ($F_{(1,29)}$=0.29, p=.866) in a repeated measures ANCOVA for the total time spent in activity in the Hotel Task. Figure 5.24 shows significant group by time interaction in the Total Deviation Time.

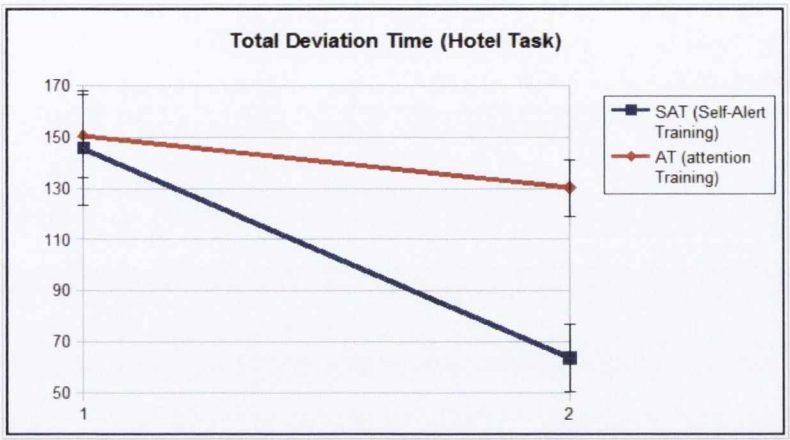


Figure 5.24. Self-Alert Training group (SAT) and Attention Training group (AT)'s Total Deviation Time in the Hotel Task, at pre and post-training in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their performance after training compared to AT participants.

Sustained Attention to Response Task (SART) Fixed and Random

A repeated measures ANCOVA on Omissions in the Fixed SART revealed a marginal main effect of time ($F_{(1,26)}$=3.152, p=.088), no significant main effect of group ($F_{(1,26)}$=.003, p=.956) and no significant time by group interaction ($F_{(1,26)}$=.003, p=.956). There was a significant main effect of time ($F_{(1,26)}$=9.353, p=.005), no significant main effect of group ($F_{(1,26)}$=.034, p=.856) and no significant interaction effect ($F_{(1,26)}$=.034, p=.856) in a repeated measures ANCOVA on Commission Errors in the Fixed SART. A repeated measures ANCOVA on Reaction Times (RT) in the Fixed SART showed a significant main effect of time ($F_{(1,26)}$=28,828, p=.000), no significant main effect of group ($F_{(1,28)}$=.085, p=.773) and no significant time by group interaction ($F_{(1,28)}$=.085, p=.773). There was a significant main effect of time ($F_{(1,26)}$=6.276, p=.019), no significant main effect of group ($F_{(1,26)}$=.013, p=.912) and no significant time by

group interaction ($F_{(1,26)}$=.013, p=.912) for SD in the Fixed SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Fixed SART revealed a significant main effect of time ($F_{(1,26)}$=7.003, p=.014), no significant main effect of group ($F_{(1,26)}$=.000, p=.999) and no significant time by group interaction ($F_{(1,26)}$=.000, p=.999).

A repeated measures ANCOVA on Omissions in the random SART revealed no significant main effect of time ($F_{(1,26)}$=.777, p=.386), no significant main effect of group ($F_{(1,26)}$=1.574, p=.221) and no significant time by group interaction ($F_{(1,26)}$=1.574, p=.221). There was no significant main effect of time ($F_{(1,26)}$=.553, p=.464), no significant main effect of group ($F_{(1,26)}$=1.492, p=.233) and no significant interaction effect ($F_{(1,26)}$=1.492, p=.233) in a repeated measures ANCOVA on Commission Errors in the Random SART. A repeated measures ANCOVA on Reaction Times (RT) in the Random SART showed a significant main effect of time ($F_{(1,26)}$=14.431, p=.001), no significant main effect of group ($F_{(1,26)}$=1.650, p=.208) and no significant time by group interaction ($F_{(1,26)}$=1.650, p=.208). There was a significant main effect of time ($F_{(1,26)}$=5.368 p=.029), no significant main effect of group ($F_{(1,26)}$=1.758, p=.196) and no significant time by group interaction ($F_{(1,26)}$=1.758, p=.196) for SD in the Random SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Random SART revealed a significant main effect of time ($F_{(1,26)}$=23.776, p=.000), no significant main effect of group ($F_{(1,26)}$=2.502, p=.126) and no significant time by group interaction ($F_{(1,26)}$=2.502, p=.126).

Auditory Oddball Task – Behavioural Measures

Repeated measures ANCOVAs were carried out for each variable in the first block of the auditory oddball task. A repeated measures ANCOVA on Accuracy revealed a significant main effect of time ($F_{(1,25)}$=22.338, p=.000), no significant main effect of group ($F_{(1,25)}$=.891, p=.354) and no significant interaction effect ($F_{(1,25)}$=.891, p=.354). A repeated measures ANCOVA on Omission Errors showed a significant main effect of time ($F_{(1, 25)}$=5.799, p=.024), no significant main effect

of group ($F_{(1, 25)}$=.048, p=.829) and no significant time by group interaction ($F_{(1, 25)}$=.048, p=.829). There was a significant main effect of time ($F_{(1,25)}$ =5.476, p=.028), no significant main effect of group ($F_{(1,25)}$=.149, p=.703) and no significant interaction ($F_{(1,25)}$=.149, p=.703) in a repeated measures ANCOVA on Reaction Times. A repeated measures ANCOVA on Coefficient of Variation (CV) revealed a significant main effect of time ($F_{(1,25)}$=13.542, p=.001), no significant main effect of group ($F_{(1,25)}$=.003, p=.959) and no significant time by group interaction ($F_{(1,25)}$=.003, p=.959).

Repeated measures ANCOVAs were conducted on the second block of the auditory oddball task for each variable on target and standard tones. A repeated measures ANCOVA on Accuracy on target tones revealed a significant main effect of time ($F_{(1,25)}$=16.112, p=.001), no significant main effect of group ($F_{(1,25)}$=.007, p=.936) and no significant time by group interaction ($F_{(1,25)}$=.007, p=.936). A repeated measures ANCOVA on Omission Errors on target tones revealed no significant main effect of time ($F_{(1,24)}$ =3.889, p=.06), no significant main effect of group ($F_{(1,24)}$=.408, p=.529) and no significant interaction effect ($F_{(1,24)}$=.408, p=.529). A significant main effect of time ($F_{(1,25)}$=20.961, p=.000), no significant main effect of group ($F_{(1,25)}$=.176, p=.679) and no significant time by group interaction ($F_{(1,25)}$=.176, p=.679) were found for Commission Errors on target tones. A repeated measures ANCOVA on Reaction Times on target tones revealed a significant main effect of time ($F_{(1,25)}$=7.882, p=.01), no significant main effect of group ($F_{(1,25)}$=.006, p=.938) and no significant time by group interaction ($F_{(1,25)}$=.006, p=.938). A repeated measures ANCOVA on Coefficient of Variation (CV) for target tones showed a significant main effect of time ($F_{(1,25)}$=17.711, p=.009), no significant main effect of group ($F_{(1,25)}$=2.100, p=.160) and no significant time by group interaction (($F_{(1,25)}$=2.100, p=.160).

A repeated measures ANCOVA on Accuracy on standard tones revealed a significant main effect of time ($F_{(1,25)}$=30.655, p=.000), no significant main effect of group ($F_{(1,25)}$=.757, p=.393) and no significant time by group interaction ($F_{(1,25)}$=.757, p=.393). A repeated measures ANCOVA on Omission Errors on

standard tones revealed no significant main effect of time ($F_{(1,25)}$ =2.334, p=.137), no significant main effect of group ($F_{(1,25)}$=.207, p=.653) and no significant interaction effect ($F_{(1,25)}$=.207, p=.653). A significant main effect of time ($F_{(1,24)}$=12.851, p=0.001), no significant main effect of group ($F_{(1,24)}$=1.502, p=.220) no significant time by group interaction ($F_{(1,24)}$=1.502, p=.220) were found for Commission Errors on standard tones. A repeated measures ANCOVA on Reaction Times on standard tones revealed a significant main effect of time ($F_{(1,25)}$=10.031, p=.004), no significant main effect of group ($F_{(1,25)}$=.846, p=.367) and no significant time by group interaction ($F_{(1,25)}$=.846, p=.367). A repeated measures ANCOVA on Coefficient of Variation (CV) for standard tones showed no significant main effect of time ($F_{(1,25)}$=.646, p=.429), no significant main effect of group ($F_{(1,25)}$=.003, p=.955) and no significant interaction effect ($F_{(1,25)}$=.003, p=.955).

5.9.5.1.2 Post-training effects on neurophysiological measures

Differences between groups after training on pupil, EEG spectral power and Event-Related Potentials (ERPs) measures were investigated in repeated measures ANOVAs in a sub-analysis excluding low-participation subjects

Pupil

In the first block of the auditory oddball task, a repeated measures ANOVA on mean pupil's dilation on targets revealed no significant main effect of time ($F_{(1,2)}$=.052, p=.822), no significant main effect of group ($F_{(1,25)}$=.343, p=.564) and no significant time by group interaction ($F_{(1,25)}$=.309, p=.583). No significant main effect of time ($F_{(1,21)}$=1.710, p=.205), no significant main effect of group ($F_{(1,21)}$=.538, p=.471) and no significant time by group interaction ($F_{(1,21)}$=.001, p=.981) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,21)}$=.016, p=.900), no significant main effect of group ($F_{(1,21)}$=1.543, p=.226) and no significant time by group interaction

($F_{(1,21)}$=1.206, p=.283). No significant main effect of time ($F_{(1,27)}$=.273, p=.606), no significant main effect of group ($F_{(1,27)}$=.148, p=.703) and no significant time by group interaction ($F_{(1,27)}$=1.318, p=.261) emerged in a repeated measures ANOVA on pupil's variability.

The same statistical analysis was performed for target and standard tones in the second block of the auditory oddball task. A repeated measures ANOVA on mean pupil's dilation on targets revealed no significant main effect of time ($F_{(1,19)}$=.795, p=.384), no significant main effect of group ($F_{(1,19)}$=.060, p=.809) and no significant time by group interaction ($F_{(1,19)}$=.061, p=.807). No significant main effect of time ($F_{(1,18)}$=2.125, p=.162), no significant main effect of group ($F_{(1,18)}$=.480, p=.497) and no significant time by group interaction ($F_{(1,18)}$=.009, p=.927) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,19)}$=.259, p=.616), no significant main effect of group ($F_{(1,19)}$=.108, p=.746) and no significant time by group interaction ($F_{(1,19)}$=1.858, p=.189). No significant main effect of time ($F_{(1,18)}$=2.463, p=.134), no significant main effect of group ($F_{(1,18)}$=.085, p=.775) and no significant time by group interaction ($F_{(1,18)}$=.226, p=.640) emerged in a repeated measures ANOVA on pupil's variability. A repeated measures ANOVA on mean pupil's dilation on standard revealed no significant main effect of time ($F_{(1,19)}$=.828, p=.374), no significant main effect of group ($F_{(1,19)}$=.192, p=.666) and no significant time by group interaction ($F_{(1,19)}$=1.814, p=.194). No significant main effect of time ($F_{(1,18)}$=2.239, p=.152), no significant main effect of group ($F_{(1,18)}$=.512, p=.484) and no significant time by group interaction ($F_{(1,18)}$=.010, p=.920) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,19)}$=1.270, p=.274), no main effect of group ($F_{(1,19)}$=1.883, p=.186) and no significant time by group interaction ($F_{(1,19)}$=.008, p=.931). No significant main effect of time ($F_{(1,18)}$=3.107, p=.100), no significant main effect of group ($F_{(1,18)}$=.267, p=.612) and no significant time by group

interaction ($F_{(1,18)}$=.972, p=.337) emerged in a repeated measures ANOVA on pupil's variability.

EEG power spectra

A repeated measures ANOVA on theta power revealed a significant main effect of time ($F_{(1,29)}$=16.502, p=.000) no significant main effect of group ($F_{(1,29)}$=.460, p=.503) and no significant time by group effect ($F_{(1,29)}$=.003, p=.954). A repeated measures ANOVA on alpha power revealed a significant main effect of time ($F_{(1,29)}$ =20.002, p=.000), no significant main effect of group ($F_{(1,29)}$=.701, p=.409) and no significant time by group interaction ($F_{(1,29)}$=.002, p=.965). A repeated measures ANOVA on beta power showed a significant main effect of time ($F_{(1,29)}$=9.803, p=.00), no significant main effect of group ($F_{(1,29)}$=.533, p=.471) and no significant time by group effect ($F_{(1,29)}$=.002, p=.965). Another repeated measures ANOVA on theta/beta ratio revealed a main effect of time ($F_{(1,29)}$=28.567, p=.000), no main effect of group ($F_{(1,29)}$=.003, p=.956) and no significant time by group interaction ($F_{(1,29)}$=.414, p=.525). A repeated measures ANOVA on alpha/beta ratio showed a significant main effect of time ($F_{(1,24)}$=13.108, p=.001), a marginal main effect of group ($F_{(1,24)}$=.233, p=.634) and no significant time by group interaction ($F_{(1,24)}$=.125, p=.727).

Event-Related Potentials (ERPs)

P3 amplitude, peak and latency values were extracted in the first of the auditory oddball task on target tones from central-parietal sites. N1 amplitude and latency were also extracted on target tones.

In the first block of the auditory oddball task, a repeated measures ANOVA on P3 amplitude showed a marginal main effect of time ($F_{(1,22)}$=3.100, p=.092), no significant main effect of group ($F_{(1,22)}$=.054, p=.819) and no significant time by group interaction ($F_{(1,22)}$=1.108, p=.324). No significant main effect of time ($F_{(1,22)}$=.643, p=.431), no significant main effect of group ($F_{(1,22)}$=.639, p=.432) and no significant time by group interaction ($F_{(1,22)}$=1.854, p=.187) emerged in a

repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed a significant main effect of time ($F_{(1,22)}$=8.844, p=.007), a significant main effect of group ($F_{(1,22)}$=6.666, p=.215) and no significant time by group interaction ($F_{(1,22)}$=.086, p=.772).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,22)}$=.022, p=.883), no significant main effect of group ($F_{(1,22)}$=.229, p=.637) and no significant time by group interaction ($F_{(1,22)}$=.165, p=.688). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,22)}$=.114, p=.739), no significant main effect of group ($F_{(1,22)}$=.002, p=.964) and no significant time by group interaction ($F_{(1,22)}$=1.276, p=.271).

The same P3 variables were extracted in the second block of the auditory oddball task on target and standard stimuli respectively. N1 measures were also extracted on target and standard tones.

A repeated measures ANOVA on P3 amplitude on target tones at CPz site showed no significant main effect of time ($F_{(1,27)}$=2.234, p=.147), no significant main effect of group ($F_{(1,27)}$=.004, p=.950) and no significant time by group interaction ($F_{(1,27)}$=2.366, p=.136). No significant main effect of time ($F_{(1,27)}$=.796, p=.380), no significant main effect of group ($F_{(1,27)}$=.234, p=.633) and a marginal time by group interaction ($F_{(1,27)}$=3.163, p=.087) emerged in a repeated measures ANOVA on P3 peak at parietal sites. P3 peak amplitude increased in the SAT group while it decreased in the AT group. T-tests showed that there was a significant effect of time in the AT group ($t_{(16)}$=2.382, p=.030) that was absent in the SAT group ($t_{(14)}$=-.933, p=.367). A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,27)}$=1.138, p=.296), no significant main effect of group ($F_{(1,27)}$=.003, p=.954) and no significant time by group interaction ($F_{(1,27)}$=.153, p=.699).

A repeated measures ANOVA on N1 amplitude at central sites revealed no

significant main effect of time ($F_{(1,27)}$=2.112, p=.158), no significant main effect of group ($F_{(1,27)}$=.241, p=.627) and no significant time by group interaction ($F_{(1,27)}$=.000, p=.988). A repeated measures ANOVA on N1 latency at central sites revealed a marginal main effect of time ($F_{(1,27)}$=4.106, p=.053), no significant main effect of group ($F_{(1,27)}$=.541, p=.468) and no significant time by group interaction ($F_{(1,27)}$=2.293, p=.142).

A repeated measures ANOVA on P3 amplitude on standard tones showed no significant main effect of time ($F_{(1,26)}$=.138, p=.713), no significant main effect of group ($F_{(1,26)}$=.266, p=.610) and a marginal time by group interaction ($F_{(1,26)}$=3.143, p=.088). P3 amplitude increased in the SAT group while it decreased in the AT group, however there was no significant effect of time in either groups (AT: $t_{(15)}$=1.011, p=.328; SAT: $t_{(14)}$=-.598, p=.559). No significant main effect of time ($F_{(1,26)}$=.064, p=.802), no significant main effect of group ($F_{(1,26)}$=1.680, p=.206) and no significant time by group interaction ($F_{(1,26)}$=2.779, p=.108) emerged in a repeated measures ANOVA on P3 peak. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,26)}$=2.099, p=.159), no significant main effect of group ($F_{(1,26)}$=2.708, p=.112) and a marginal time by group interaction ($F_{(1,26)}$=3.565, p=.070). P3 latency increased in the AT group while it decreased in the SAT group. However, t-tests showed that there was no effect of time in the AT group ($t_{(15)}$=-.724, p=.480) as well as in the SAT group ($t_{(14)}$=1.244, p=.234).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,26)}$=1.369, p=.253), no significant main effect of group ($F_{(1,26)}$=.920, p=.346) and no significant time by group interaction ($F_{(1,26)}$=1.873, p=.183). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,26)}$=1.923, p=.177), no significant main effect of group ($F_{(1,26)}$=.010, p=.920) and no significant time by group interaction ($F_{(1,26)}$=.005, p=.947).

5.9.5.2 Three-month follow up effects

Repeated measures ANCOVAs were performed to investigate differences between groups after three months on primary outcomes measures in a sub-analysis, excluding seven low-participation participants.

5.9.5.2.1 Three-month follow up effects on primary outcome measures

CAARS Self Report Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no significant main effect of time ($F_{(1, 244)}$=2.09, p=.161), no significant main effect of group ($F_{(1,24)}$=.621, p=.438) and no significant time by group interaction ($F_{(1,24)}$=.621, p=.438). A significant main effect of time ($F_{(1,24)}$=6.908, p=.015), no significant main effect of group ($F_{(1,24)}$=.269, p=.603) and no significant interaction ($F_{(1,24)}$=.269, p=.603) were found for CAARS-B-Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed no significant main effect of time ($F_{(1,24)}$=.315, p=.58), a significant main effect of group ($F_{(1,24)}$=6.16, p=.020) and a significant time by group interaction ($F_{(1,24)}$=6.16, p=.020). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(12)}$=3.850, p=.002) that was absent in the AT group ($t_{(13)}$=.535, p=.602). There was no main effect of time ($F_{(1,24)}$=2.882, p=.103), a significant main effect of group ($F_{(1,24)}$=6.186, p=.043) and a significant group by time interaction ($F_{(1,24)}$=6.186, p=.043) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(12)}$=2.680, p=.020) that was not present in the AT group ($t_{(13)}$= -.079, p=.938). A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed no main effect of time ($F_{(1,24)}$=.552, p=.465), a significant main effect of group ($F_{(1,24)}$=4.571, p=.043) and a significant time by group interaction ($F_{(1,24)}$=4.571, p=.043). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(12)}$=3.096, p=.009) that was absent in the AT group ($t_{(13)}$=.330,

p=.747). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed a significant main effect of time ($F_{(1,24)}$=5.411, p=.029), no significant main effect of group ($F_{(1,24)}$=.880, p=.358) and a significant time by group interaction ($F_{(1,24)}$=.880, p=.358). There was no significant main effect of time ($F_{(1,24)}$=1.208, p=.321), no significant main effect of group ($F_{(1,24)}$= 2.741, p=.111) and no significant time by group interaction ($F_{(1,24)}$= 2.741, p=.111) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed no main effect of time ($F_{(1,24)}$=1.385, p=.251), a significant main effect of group ($F_{(1,24)}$=9.729, p=.005) and a significant time by group interaction ($F_{(1,24)}$=9.729, p=.005). Paired samples t-tests revealed a significant effect of time in the SAT group ($t_{(12)}$=3.439, p=.005) that was absent in the AT group ($t_{(13)}$= -.524, p=.609). See figure 5.25 to visualise significant group by time interactions in the CAARS – Self Report.

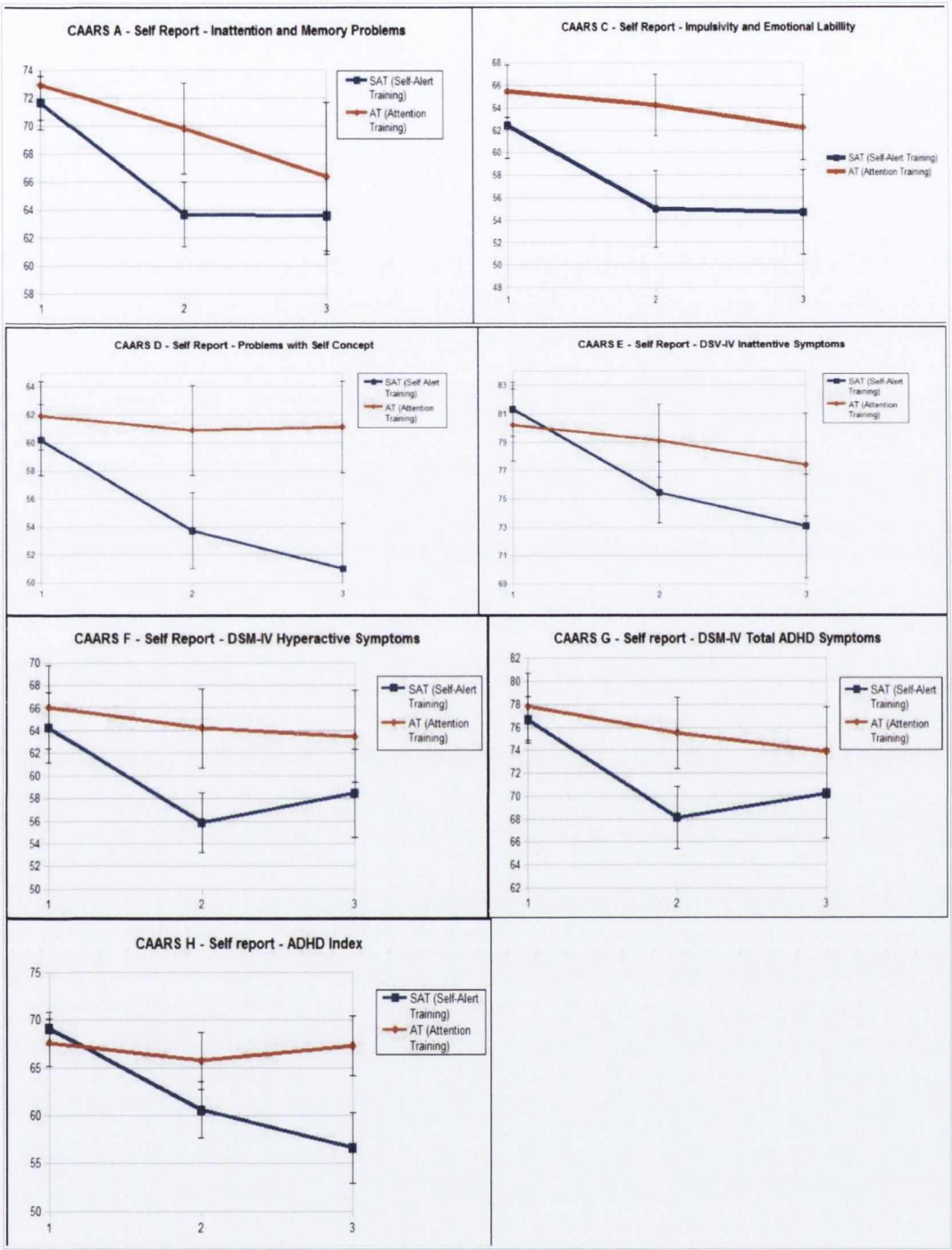


Figure 5.25. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Conners' Adult ADHD Rating Scale – Self Report (CAARS-S: L), at pre -training and at the three-month follow up in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their ADHD symptoms after training compared to AT participants.

CAARS Observer Form

A repeated measured ANCOVA on CAARS-A - Inattention and Memory Problems revealed no main effect of time ($F_{(1, 13)}$=.369, p=.554), no significant main effect of group ($F_{(1,13)}$=.301, p=.593) and no significant time by group interaction ($F_{(1,13)}$=.301, p=.593). No significant main effect of time ($F_{(1,13)}$=.731, p=.408) and group ($F_{(1,13)}$=.001, p=.976) and no significant interaction ($F_{(1,13)}$=.001, p=.976) were found for CAARS-B- Hyperactivity. Another repeated measures ANCOVA on CAARS-C - Impulsivity and Emotional Lability showed no significant main effect of time ($F_{(1,13)}$=.043, p=.839), no significant main effect of group ($F_{(1,13)}$=.408, p=.534) and no significant time by group interaction ($F_{(1,13)}$=.408, p=.534). There was a significant main effect of time ($F_{(1,13)}$= 8.399, p=.012), no significant main effect of group ($F_{(1,13)}$=.434, p=.521) and a significant group by time interaction ($F_{(1,13)}$=.434, p=.521) in a repeated measures ANCOVA for CAARS-D- Problems with Self Concept. A repeated measures ANCOVA on CAARS-E - DSM-IV Inattentive Symptoms - DSM-IV inattentive symptoms revealed no significant main effect of time ($F_{(1,13)}$=.217, p=.649), no significant main effect of group ($F_{(1,13)}$=.807, p=.385) and no significant time by group interaction ($F_{(1,13)}$=.807, p=.385). Another repeated measures ANCOVA for CAARS-F- DSM-IV Hyperactive Symptoms showed no significant main effect of time ($F_{(1,13)}$=.761, p=.412), a marginal main effect of group ($F_{(1,13)}$=5.346, p=.054) and a marginal time by group interaction ($F_{(1,13)}$=5.346, p=.054). Paired sampled t-tests revealed a main effect of time in the AT group ($t_{(6)}$=4.932, p=.022) that was absent in the SAT group ($t_{(7)}$=.791, p=.465). There was no significant main effect of time ($F_{(1,13)}$=.472, p=.504), no significant main effect of group ($F_{(1,13)}$=1.124, p=.308) and no significant time by group interaction ($F_{(1,13)}$=1.124, p=.308) in a repeated measures ANCOVA for CAARS-G - DSM-IV total ADHD symptoms. A repeated measures ANCOVA for CAARS-H - ADHD Index revealed no main effect of time ($F_{(1,13)}$=.223, p=.644), no significant main effect of group ($F_{(1,13)}$=.058, p=.813) and a significant time by group interaction ($F_{(1,13)}$=.058, p=.813).

Other Scales and Questionnaires

A repeated measures ANCOVA for the Attention-Related Cognitive Errors Questionnaire (ARCEQ) revealed no significant main effect of time ($F_{(1,12)}$=.014, p=.906), a significant main effect of group ($F_{(1,12)}$=5.264, p=.031) and a significant time by group interaction ($F_{(1,12)}$=5.264, p=.031). Paired samples t-tests showed a significant effect of time in the SAT group ($t_{(7)}$=9.861, p=.000) that was absent in the AT group ($t_{(6)}$=1.794, p=.123). A significant main effect of time ($F_{(1,12)}$=4.932 p=.046), no main effect of group ($F_{(1,12)}$=.004, p=.952) and no interaction effect ($F_{(1,12)}$=.004, p=.952) emerged in a repeated measures ANCOVA for the Everyday Memory Failure Questionnaire (EMFQ). A repeated measures ANCOVA for the General Health Questionnaire (GHQ) showed a significant main effect of time ($F_{(1,22)}$=8.969, p=.007), a marginal main effect of group ($F_{(1,22)}$=3.063, p=.094) and a marginal time by group interaction ($F_{(1,22)}$=3.063, p=.094). Paired samples t-tests showed a significant main effect of time in the AT group ($t_{(11)}$=2.812, p=.017) that was absent in the SAT group ($t_{(12)}$=.197, p=.847). There was a significant main effect of time ($F_{(1,21)}$=7.290, p=.013), a significant main effect of group ($F_{(1,21)}$=4.940, p=.040) and a significant time by group interaction ($F_{(1,21)}$=4.940, p=.040) in a repeated measures ANCOVA for the Self Efficacy Scale (SES). Paired samples t-tests showed a significant main effect of time in the SAT group ($t_{(11)}$=2.912, p=.009) that was absent in the AT group ($t_{(12)}$=.241, p=.789). A repeated measures ANCOVA for the Beck Depression Inventory (BDI) revealed no significant main effect of time ($F_{(1,22)}$=2.455, p=.131), a significant main effect of group ($F_{(1,22)}$=4.963, p=.038) and a significant interaction ($F_{(1,22)}$=4.963, p=.038). Paired samples t-tests showed a significant main effect of time in the SAT group ($t_{(11)}$=3.413, p=.037) that was absent in the AT group ($t_{(12)}$=.332, p=.689).Another repeated measures ANCOVA for Beck Anxiety Inventory (BAI) showed a marginal main effect of time ($F_{(1,22)}$=3.162, p=.089), no significant main effect of group ($F_{(1,22)}$=.014, p=.905) and no significant time by group interaction ($F_{(1,22)}$=.014, p=.905). Figure 5.26 shows significant interactions in the Attention-Related Cognitive Questionnaire (ARCEQ), Beck Depression Inventory (BDI)

and Self-Efficacy Scale (SES).

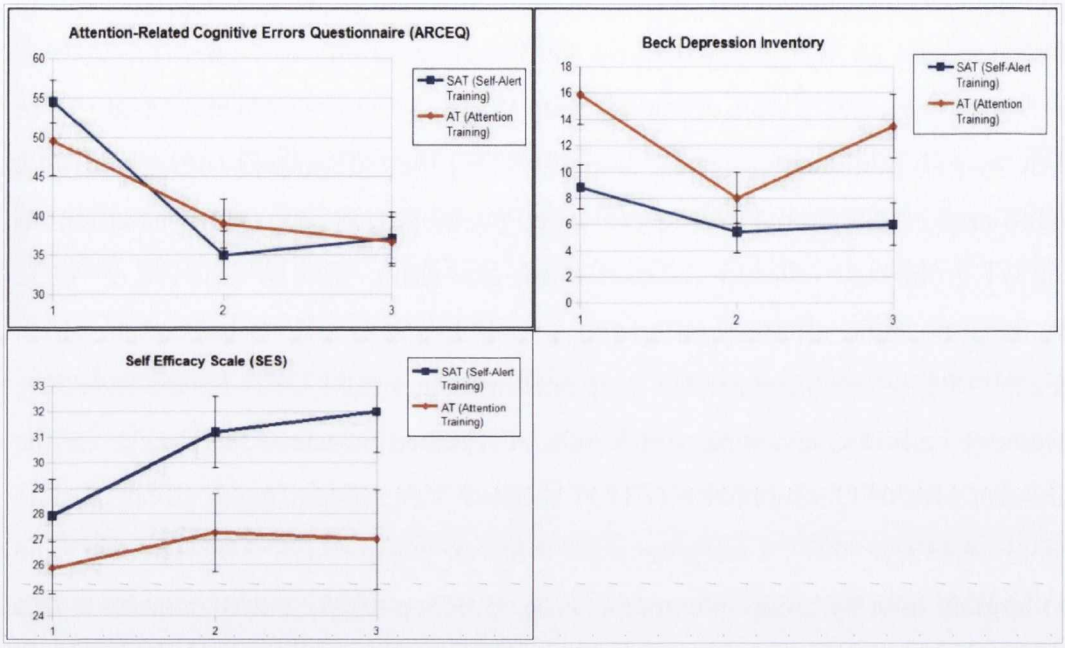


Figure 5.26. Self-Alert Training group (SAT) and Attention Training group (AT)'s scores in the Attention Related Cognitive Failures Questionnaire (ARCEQ), Beck Depression Inventory (BDI) and Self Efficacy Scale (SES), at pre and at the three-month follow up in a sub-analysis carried out excluding low-participation subjects. Error bars represent the standard error.

Note: SAT participants significantly improved their scores in the three scales compared to AT participants.

Neuropsychological tests

A repeated measures ANCOVA was carried out for the scores in the Elevator Counting with Distraction and it revealed a significant main effect of time ($F_{(1,24)}$=20.999, p=.000), no main effect of group ($F_{(1,24)}$=.763, p=.391) and no significant time by group interaction ($F_{(1,24)}$=.763, p=.391). A repeated measures ANCOVA was performed on the Raw Score in the Telephone Search and a significant main effect of time ($F_{(1,24)}$=7.466, p=.012), no main effect of group ($F_{(1,,24)}$=.749, p=.395) and no time by group interaction ($F_{(1,,24)}$=.749, p=.395) were found. Another repeated measures ANCOVA was conducted on the Dual Task Decrement in the Telephone Search While Counting which showed no significant main effect of time ($F_{(1,23)}$=1.673, p=.209), no significant main effect of group

($F_{(1,23)}$=.307, p=.585) and no significant time by group interaction ($F_{(1,23)}$=.307, p=.585).

A repeated measures ANCOVA for the number of attempted tasks in the Hotel task revealed a significant main effect of time ($F_{(1,24)}$=12.086, p=.002), no significant main effect of group ($F_{(1, 24)}$=.301, p=.588) and no significant time by group interaction ($F_{(1, 24)}$=.301, p=.588). A repeated measures ANCOVA for the total deviation time in the Hotel Task showed a significant main effect of time ($F_{(1,23)}$=10.076, p=.004), no significant main effect of group ($F_{(1,23)}$=.387, p=.54) and no significant time by group interaction ($F_{(1,23)}$=.387, p=.54). There was no main effect of time ($F_{(1, 24)}$=1.097, p=.305) but no significant main effect of group ($F_{(1,24)}$=1.095, p=.306) and no significant interaction effect ($F_{(1,24)}$=1.095, p=.306) in a repeated measures ANCOVA for the total time spent in activity in the Hotel Task.

Sustained Attention to Response Task (SART) Fixed and Random

A repeated measures ANCOVA on Omissions in the Fixed SART revealed no main effect of time ($F_{(1,18)}$=.531, p=.476), no significant main effect of group ($F_{(1,18)}$=1.438, p=.246) and no significant time by group interaction ($F_{(1,18)}$=1.438, p=.246). There was a significant main effect of time ($F_{(1,18)}$=6.653, p=.019), no significant main effect of group ($F_{(1,18)}$=.406, p=.532) and no significant interaction effect ($F_{(1,18)}$=.406, p=.532) in a repeated measures ANCOVA on Commission Errors in the Fixed SART. A repeated measures ANCOVA on Reaction Times (RT) in the Fixed SART showed a significant main effect of time ($F_{(1,18)}$=17.004, p=.001), no significant main effect of group ($F_{(1,18)}$=.224, p=.641) and no significant time by group interaction ($F_{(1,18)}$=.224, p=.641). There was a significant main effect of time ($F_{(1,18)}$=4.703, p=.042), no significant main effect of group ($F_{(1,18)}$=.051, p=.500) and no significant time by group interaction ($F_{(1,18)}$=.051, p=.500) for SD in the Fixed SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Fixed SART revealed a significant main effect of time ($F_{(1,20)}$=13.135, p=.002), no significant main effect of group

($F_{(1,20)}$=.472, p=.500) and no significant time by group interaction ($F_{(1,20)}$=.472, p=.500).

A repeated measures ANCOVA on Omissions in the random SART revealed no significant main effect of time ($F_{(1,17)}$=2,681, p=.120), no significant main effect of group ($F_{(1,17)}$=.000, p=.988) and no significant time by group interaction ($F_{(1,17)}$=.000, p=.988). There was no significant main effect of time ($F_{(1,20)}$=.378, p=.546), no significant main effect of group ($F_{(1,20)}$=.087, p=.771) and no significant interaction effect ($F_{(1,20)}$=.087, p=.771) in a repeated measures ANCOVA on Commission Errors in the Random SART. A repeated measures ANCOVA on Reaction Times (RT) in the Random SART showed a significant main effect of time ($F_{(1,21)}$=21.088, p=.000), no significant main effect of group ($F_{(1,21)}$=2.520, p=.127) and no significant time by group interaction ($F_{(1,21)}$=2.520, p=.127). There was no significant main effect of time ($F_{(1,17)}$=1.209, p=.287), no significant main effect of group ($F_{(1,17)}$=2.889, p=.102) and no significant time by group interaction ($F_{(1,17)}$=2.889, p=.102) for SD in the Random SART. A repeated measures ANCOVA on Coefficient of Variation (CV) in the Random SART revealed no significant main effect of time ($F_{(1,17)}$=.085, p=.775), no significant main effect of group ($F_{(1,17)}$=.295, p=.594) and no significant time by group interaction ($F_{(1,17)}$=.295, p=.594).

Auditory Oddball Task – Behavioural Measures

Repeated measures ANCOVAs were carried out for each variable in the first block of the auditory oddball task. A repeated measures ANCOVA on Accuracy revealed a significant main effect of time ($F_{(1,16)}$=105.144, p=0.000), no significant main effect of group ($F_{(1,16)}$=.002, p=.962) and no significant interaction effect ($F_{(1,16)}$=.002, p=.962). A repeated measures ANCOVA on Omission Errors showed a marginal main effect of time ($F_{(1,16)}$=3.946, p=.064), no significant main effect of group ($F_{(1,16)}$=.097, p=.759) and no significant time by group interaction ($F_{(1,16)}$=.097, p=.759). There was no significant main effect of time ($F_{(1,16)}$ =1.161, p=.215), no significant main effect of group ($F_{(1,16)}$=.145, p=.708) and no

significant interaction ($F_{(1,16)}$=.145, p=.708) in a repeated measures ANCOVA on Reaction Times. A repeated measures ANCOVA on Coefficient of Variation (CV) revealed a significant main effect of time ($F_{(1,16)}$=6.999, p=.018), no significant main effect of group ($F_{(1,16)}$=.388, p=.542) and no significant time by group interaction ($F_{(1,16)}$=.388, p=.542).

Repeated measures ANCOVAs were conducted on the second block of the auditory oddball task for each variable on target and standard tones. A repeated measures ANCOVA on Accuracy on target tones revealed no significant main effect of time ($F_{(1,16)}$=1.41, p=.252), no significant main effect of group ($F_{(1,16)}$=2.02, p=.174) and no significant time by group interaction ($F_{(1,16)}$=2.02, p=.174). A repeated measures ANCOVA on Omission Errors on target tones revealed no significant main effect of time ($F_{(1,16)}$ =.790, p=.387), no significant main effect of group ($F_{(1,16)}$=.765, p=.390) and no significant interaction effect ($F_{(1,16)}$=.765, p=.390). No significant main effect of time ($F_{(1,16)}$=1.6, p=.224), no significant main effect of group ($F_{(1,16)}$=2.038, p=.173) and no significant time by group interaction ($F_{(1,16)}$=2.038, p=.173) were found for Commission Errors on target tones. A repeated measures ANCOVA on Reaction Times on target tones revealed a significant main effect of time ($F_{(1,17)}$=.301, p=.59), no significant main effect of group ($F_{(1,17)}$=.007, p=.934) and no significant time by group interaction ($F_{(1,17)}$=.007, p=.934). A repeated measures ANCOVA on Coefficient of Variation (CV) for target tones showed a significant main effect of time ($F_{(1,17)}$=13.231, p=.002), no significant main effect of group ($F_{(1,17)}$=.016, p=.900) and no significant time by group interaction ($F_{(1,16)}$=.016, p=.900).

A repeated measures ANCOVA on Accuracy on standard tones revealed no significant main effect of time ($F_{(1,16)}$=.874, p=.364), no significant main effect of group ($F_{(1,16)}$=1.852, p=.192) and no significant time by group interaction ($F_{(1,16)}$=1.852, p=.192). A repeated measures ANCOVA on Omission Errors on standard tones revealed no significant main effect of time ($F_{(1,17)}$ =.974, p=.338), no significant main effect of group ($F_{(1,17)}$=.818, p=.378) and no significant interaction effect ($F_{(1,17)}$=.818, p=.378). A significant main effect of time

($F_{(1,16)}$=1.565, p=.229), no main effect of group ($F_{(1,16)}$=1.280, p=.275) and no time by group interaction ($F_{(1,16)}$=1.280, p=.275) were found for Commission Errors on standard tones. A repeated measures ANCOVA on Reaction Times on standard tones revealed a significant main effect of time ($F_{(1,17)}$=6.614, p=.02), no significant main effect of group ($F_{(1,17)}$=.000, p=.996) and no significant time by group interaction ($F_{(1,17)}$=.000, p=.996). A repeated measures ANCOVA on Coefficient of Variation (CV) for standard tones showed no significant main effect of time ($F_{(1,17)}$=.749, p=.399), no significant main effect of group ($F_{(1,17)}$=.080, p=.781) and no significant interaction effect ($F_{(1,17)}$=.080, p=.781).

5.9.5.2.2 Three-month follow up effects on neurophysiological measures

Differences between groups at the three-month follow up on pupil, EEG spectral power and Event-Related Potentials (ERPs) measures were investigated in repeated measures ANOVAs in a sub-analysis after excluding low-participation subjects

Pupil

The same statistical analysis was performed on smaller groups after excluding the same seven participants who did not comply to training.

In the first block of the auditory oddball task, a repeated measures ANOVA on mean pupil's dilation on targets revealed a significant main effect of time ($F_{(1,20)}$=17.519, p=.000), no significant main effect of group ($F_{(1,20)}$=.000, p=.998) and no significant time by group interaction ($F_{(1,20)}$=1.908, p=.107). Another repeated measures ANOVA on pupil's baseline on target tones showed a marginal main effect of time ($F_{(1,16)}$=3.769, p=.070), no significant main effect of group ($F_{(1,16)}$=1.272, p=.176) and no significant time by group interaction ($F_{(1,16)}$=.740, p=.402). No significant main effect of time ($F_{(1,20)}$=.133, p=.719), no significant main effect of group ($F_{(1,20)}$=.066, p=.800) and no significant time by group interaction ($F_{(1,20)}$=.052, p=.822) emerged in a repeated measures ANOVA on

pupil's latency. No significant main effect of time ($F_{(1,20)}$=3.175, p=.100), no significant main effect of group ($F_{(1,20)}$=.428, p=.520) and no significant time by group interaction ($F_{(1,20)}$=3.138, p=.117) emerged in a repeated measures ANOVA on pupil's variability.

The same statistical analysis was performed for target and standard tones in the second block of the auditory oddball task. A repeated measures ANOVA on mean pupil's dilation on targets revealed a significant main effect of time ($F_{(1,12)}$=2.898, p=.114), no significant main effect of group ($F_{(1,12)}$=.001, p=.972) and no significant time by group interaction ($F_{(1,12)}$=.029, p=.869). A significant main effect of time ($F_{(1,11)}$=4.745, p=.052), no significant main effect of group ($F_{(1,11)}$=2.077, p=.177) and no significant time by group interaction ($F_{(1,11)}$=.267, p=.615) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,12)}$=.001, p=.981), a significant main effect of group ($F_{(1,12)}$=7.721, p=.020) and no significant time by group interaction ($F_{(1,12)}$=.028, p=.871). No main effect of time ($F_{(1,12)}$=.587, p=.458), no significant main effect of group ($F_{(1,12)}$=.012, p=.913) and no significant time by group interaction ($F_{(1,12)}$=.081, p=.780) emerged in a repeated measures ANOVA on pupil's variability. A repeated measures ANOVA on mean pupil's dilation on standard revealed no significant main effect of time ($F_{(1,12)}$=.583, p=.460), no significant main effect of group ($F_{(1,12)}$=.356, p=.562) and no significant time by group interaction ($F_{(1,12)}$=.186, p=.674). A marginal main effect of time ($F_{(1,11)}$=4.745, p=.052), no significant main effect of group ($F_{(1,11)}$=2.077, p=.177) and no significant time by group interaction ($F_{(1,11)}$=.267, p=.615) emerged in a repeated measures ANOVA on pupil's baseline. Another repeated measures ANOVA on pupil's latency on target tones showed no significant main effect of time ($F_{(1,12)}$=.110, p=.746), no main effect of group ($F_{(1,12)}$=.429, p=.525) and no significant time by group interaction ($F_{(1,12)}$=2.665, p=.180). No significant main effect of time ($F_{(1,12)}$=.135, p=.720), no significant main effect of group ($F_{(1,12)}$=.201, p=.662) and no significant time by group interaction ($F_{(1,12)}$=.156,

p=.699) emerged in a repeated measures ANOVA on pupil's variability.

EEG power spectra

A repeated measures ANOVA on theta power revealed a significant main effect of time ($F_{(1,24)}$=10.907, p=.003) no significant main effect of group ($F_{(1,24)}$=.159, p=.694) and no significant time by group effect ($F_{(1,24)}$=.982, p=.332). A repeated measures ANOVA on alpha power revealed a significant main effect of time ($F_{(1,24)}$ =13.165, p=.001), no significant main effect of group ($F_{(1,24)}$=.085, p=.773) and no significant time by group interaction ($F_{(1,24)}$=1.068, p=.312). A repeated measures ANOVA on beta power showed a significant main effect of time ($F_{(1,24)}$=13.312, p=.001), no significant main effect of group ($F_{(1,24)}$=.009, p=.924) and no significant time by group effect ($F_{(1,24)}$=.720, p=.405). Another repeated measures ANOVA on theta/beta ratio revealed a main effect of time ($F_{(1,24)}$=15.305, p=.001), no main effect of group ($F_{(1,24)}$=.134, p=.718) and no significant time by group interaction ($F_{(1,24)}$=.125, p=.727). A repeated measures ANOVA on alpha/beta ratio showed a significant main effect of time ($F_{(1,24)}$=13.118, p=.001), a marginal main effect of group ($F_{(1,24)}$=.233, p=.634) and no significant time by group interaction ($F_{(1,24)}$=.125, p=.727).

Event-Related Potentials (ERPs)

P3 variables were extracted on target tones in the first block of the auditory oddball task in a sub-analysis, excluding the seven participants that did less than ten exercises over the five week training period. N1 amplitude and latency measures on target tones were also extracted.

A repeated measures ANOVA on P3 amplitude showed no significant main effect of time ($F_{(1,10)}$=.178, p=.682), no significant main effect of group ($F_{(1,10)}$=.699, p=.423) and no significant time by group interaction ($F_{(1,10)}$=.062, p=.809). No significant main effect of time ($F_{(1,10)}$=.121, p=.736), no significant main effect of group ($F_{(1,10)}$=252, p=.627) and no significant time by group interaction ($F_{(1,10)}$=.163, p=.695) emerged in a repeated measures ANOVA on P3 peak at CPz

site. A repeated measures ANOVA on P3 latency revealed a significant main effect of time ($F_{(1,10)}$=1.320, p=.277), no significant main effect of group ($F_{(1,10)}$=.200, p=.665) and no significant time by group interaction ($F_{(1,10)}$=.431, p=.526).

Repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,19)}$=.780, p=.388), no significant main effect of group ($F_{(1,19)}$=.000, p=.988) and no significant time by group interaction ($F_{(1,19)}$=.008, p=.929). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,19)}$=1.780, p=.199), no significant main effect of group ($F_{(1,19)}$=.170, p=.685) and no significant time by group interaction ($F_{(1,19)}$=.170, p=.685).

The same P3 variables were extracted in the second block of the auditory oddball task on target and standard stimuli respectively. N1 measures on target and standard tones were also extracted.

A repeated measures ANOVA on P3 amplitude on target tones showed no significant main effect of time ($F_{(1,17)}$=.227, p=.640), no significant main effect of group ($F_{(1,17)}$=.006, p=.939) and no significant time by group interaction ($F_{(1,17)}$=.307, p=.587). No significant main effect of time ($F_{(1,17)}$=.089, p=.769), no significant main effect of group ($F_{(1,17)}$=.423, p=.524) and no significant time by group interaction ($F_{(1,17)}$=1.612, p=.221) emerged in a repeated measures ANOVA on P3 peak at parietal sites. A repeated measures ANOVA on P3 latency revealed no significant main effect of time ($F_{(1,17)}$=.059, p=.812), no significant main effect of group ($F_{(1,17)}$=.876, p=.362) and no significant time by group interaction ($F_{(1,17)}$=.092, p=.766).

A repeated measures ANOVA on N1 amplitude at central sites revealed no significant main effect of time ($F_{(1,17)}$=.991, p=.334), no significant main effect of group ($F_{(1,17)}$=.023, p=.882) and no significant time by group interaction ($F_{(1,17)}$=.114, p=.740). A repeated measures ANOVA on N1 latency at central sites

revealed no significant main effect of time ($F_{(1,17)}$=.013, p=.911), no significant main effect of group ($F_{(1,17)}$=.682, p=.420) and no significant time by group interaction ($F_{(1,17)}$=.905, p=.355).

A repeated measures ANOVA on P3 amplitude on standard tones showed no significant main effect of time ($F_{(1,16)}$=2.127, p=.164), no significant main effect of group ($F_{(1,16)}$=.011, p=.919) and no significant time by group interaction ($F_{(1,16)}$=3.021, p=.102). No significant main effect of time ($F_{(1,16)}$=.596, p=.452), no significant main effect of group ($F_{(1,16)}$=.855, p=.369) and a significant time by group interaction ($F_{(1,16)}$=6.594, p=.021) emerged in a repeated measures ANOVA on P3 peak. P3 peak amplitude increased in the SAT group while it decreased in the AT group. T-tests showed that there was a main effect of time in the SAT group ($t_{(10)}$=-2.308, p=.044) that was absent in the AT group ($t_{(8)}$=1.345, p=.216). A repeated measures ANOVA on P3 latency revealed a marginal main effect of time ($F_{(1,16)}$=4.142, p=.058), a significant main effect of group ($F_{(1,16)}$=4.662, p=.046) and a significant time by group interaction ($F_{(1,16)}$=.5.087, p=.038). P3 latency decreased in the SAT group while it increased in the AT group. T-tests showed that there was a main effect of time in the SAT group ($t_{(10)}$=3.019, p=.013) that was absent in the AT group ($t_{(8)}$=-.315, p=.761). Figure 5.27 shows significant differences in P3 peak and latency between the SAT and AT group.

A repeated measures ANOVA on N1 amplitude at central sites revealed a marginal main effect of time ($F_{(1,16)}$=3.135, p=.096), no significant main effect of group ($F_{(1,16)}$=.362, p=.556) and no significant time by group interaction ($F_{(1,16)}$=.009, p=.927). A repeated measures ANOVA on N1 latency at central sites revealed no significant main effect of time ($F_{(1,16)}$=1.271, p=.276), no significant main effect of group ($F_{(1,16)}$=.352, p=.561) and no significant time by group interaction ($F_{(1,16)}$=.516, p=.483).

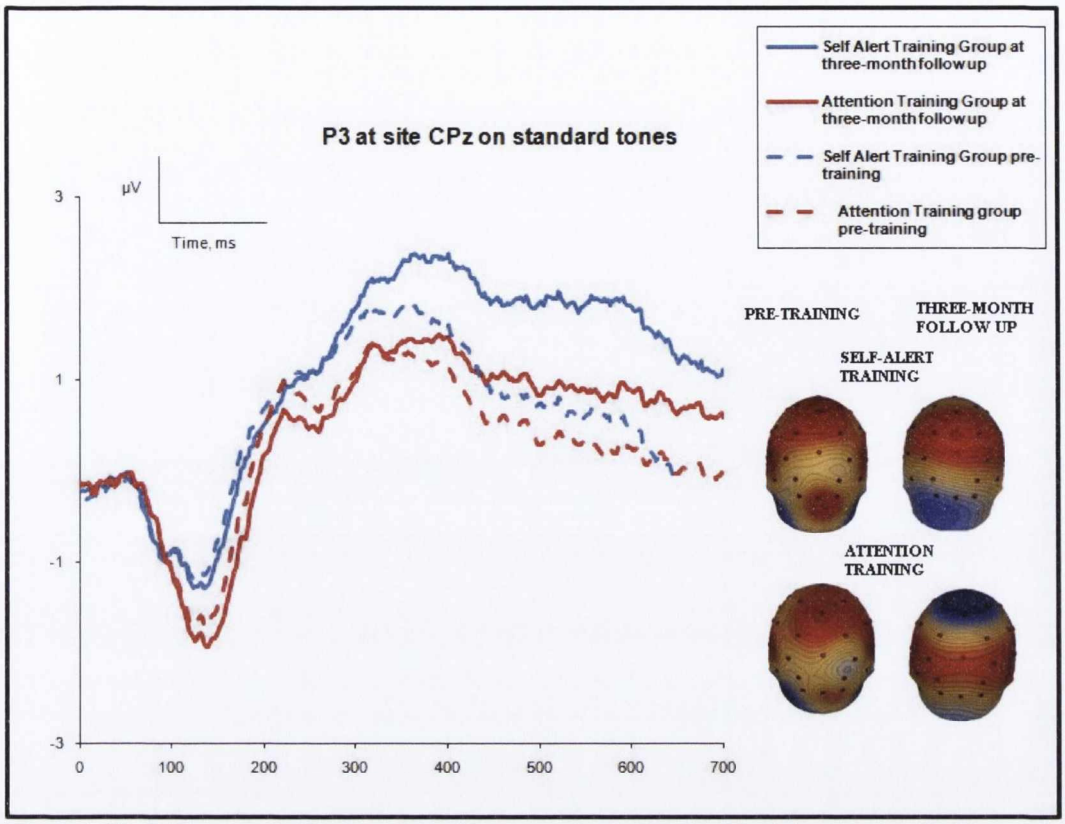


Figure 5.27. Difference in P3 waveforms between the Self-Alert Training group (SAT) and the Attention Training group (AT) group at CPz site on standard tones at the pre-training assessment (dashed line) and at the three-month follow up (solid line).

Note: On the right, P3 topographies at pre-training and at the three month follow up in the SAT and AT group. Significant differences between groups were found for P3 peak and P3 latency at the three-month follow up, indicating higher P3 peak and reduced P3 latency in the SAT group compared to the control group. This suggests improved brain function in the SAT group.

5.9.6 Relationship between variables

Partial correlations were carried out to investigate relationships between changes in ADHD symptoms and changes in cognitive and Event Related Potential (ERP) variables after training and at the three-month follow up.

A significant correlation emerged between change in the CAARS D -Self Report – Problems with Self Concept and change in Reaction Times (RT) in the Random SART ($r_{(51)}$=.459, p=.009) at the three-month follow up.

In the sub-analysis, a significant correlation ($r_{(51)}$=.391, p=.040) emerged between change in CAARS H- Self Report- ADHD Index and change in P3 latency on standard tones after training in the second block of the oddball task. Another significant positive correlation ($r_{(51)}$=.493, p=.037) emerged between change in the Everyday Memory Failure Questionnaire (EMFQ) and change in P3 latency on standard tones at central-parietal sites in the second block of the oddball task at the three-month follow up. Figure 5.28 shows scatter plots of significant correlations between variables.

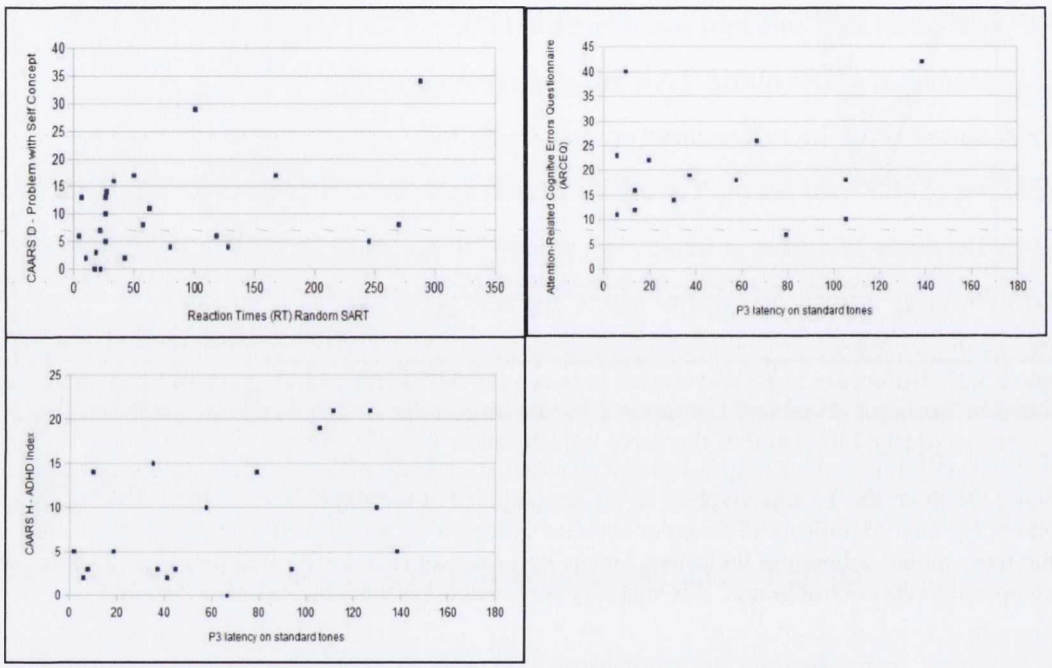


Figure 5.28. Scatter plots that show significant correlations between variables.

Note: Top left: significant correlation between change in CAARS D- Problems with Self Concept and Reaction Times (RT) in the Random SART. Top right: significant correlation between change in CAARS H- ADHD Index and P3 latency on standard tones. Bottom left: significant correlation between change in the Attention-Related Cognitive Errors Questionnaire (ARCEQ) and P3 latency on standards.

5.9.7 Additional analysis to investigate effects of training practice on participants' improvements

An additional statistical analysis was carried out to investigate the effects of the total time each participant spent in training practice during the five weeks on

participants' improvements. Repeated measures ANCOVAs were carried out and the total practice time was included as covariate in the analysis. At post-training, results showed that the same significant effects emerged in the CAARS–Self Report form, in the CAARS-O- Observer form and in the three neuropsychological tests (Elevator Counting with Distraction, Telephone Search While Counting and Total Deviation Time in the Hotel Task). Results also showed the same significant effects in all scales and questionnaires but the Self Efficacy Scale (SES). Time by group interaction in the Self Efficacy Scale (SES) became marginal (p=.089). At the three-month follow up, results were the same for all tests and scales except the Beck Depression Inventory (BDI) and Reaction Times (RT) in the Fixed and Random SART. In the Beck Depression Inventory (BDI) the interaction was not significant any more (p=.123) while interactions became only marginal for Reaction Times (RT) in the Fixed (p=.056) and in the Random SART (p=.086). Additional analysis were also carried out to investigate effects of training practice on ERP variables in the sub-analysis. The same marginal results emerged after training. At the three-month follow up the same significant effect was found on P3 peak on standard tones. However there was no significant time by group interaction on P3 latency on standard tones (p=.147).

5.9.8 Qualitative description of outcomes

5.9.8.1 The feedback questionnaire

At the end of the third assessment after three months, participants in each group were given a feedback questionnaire (see appendix 5) that was aimed to get a qualitative outcome on the training programmes.

Over 80% of participants in the SAT group who completed the feedback form, described the training as being helpful, compared to half of those in the attention training group. In fact 60% of SAT participants reported to have found the training better than previous treatments they had tried (including medication). 85% of SAT respondents believed that the training would have a long lasting

effect whereas none of the attention group reported as such. Furthermore, all participants in the SAT group reported that they would recommend the training to others with ADHD. Overall, the feedback has been overwhelmingly positive for the SAT, while the attention group seemed to find it less beneficial.

5.9.6.2 Everyday life goals

Regarding subjective goal ratings, participants reported to be able to apply the self-alert technique to their goals, suggesting that they have learned to apply the strategies learned in a range of real life situations. An analysis of post-training ratings revealed improvements in performance and satisfaction ratings of all goals for all but three participants in the SAT group. Of these three, two participants reported no changes in goals ratings after training and one participant reported decreased goals ratings after training. Paired samples t-tests on performance and satisfaction goals ratings at pre-training and post-training were carried out and they showed a significant effect of time for performance and satisfaction goals ratings, indicating improved goals ratings after five weeks of training.

At the three-month follow up improvements in participants' goals ratings were maintained in all but four participants. Of these four participants, one reported decreased goals ratings in comparison to pre-training goals ratings, one reported no changes in goals ratings and two participants' goals ratings were lost at follow up. Paired samples t-tests on performance and satisfaction goals ratings at pre-training and at the three-month follow up were performed and they showed a significant effect of time for performance and satisfaction goals ratings, indicating improved goals ratings at the three-month follow up.

Participants goals list and goals ratings are presented in table 5.2.

Table 5.2. Participants selected everyday life goals and performance and satisfaction goals ratings at pre-training, post-training and at the three-month follow up.

Participant	Goals	Pre-training		Post-training		Three-month follow up	
		Performance	Satisfaction	Performance	Satisfaction	Performance	Satisfaction
Participant 1	1. To structure resolution of problems before attempting to solve them	3	5	8	8	7	7
	2. Emotional self-control in stressful situations	4	0	9	9	7	6
	3. Listening skills	5	0	7	9	7	8
Participant 2	1. To study efficiency	4	3	6	5	-	-
	2. To pay attention during Irish class	3	3	5	6	-	-
Participant 3	1. Complete morning and night time routines	3	1	4	6	4	5
	2. Complete tasks started – especially housework	4	3	8	8	7	8
	3. Better time management	0	0	8	8	7	8
Participant 4	1. Pay attention to what others are saying	6	4	7	6	6	6
	2. Remember dates and names	2	2	5	5	4	4
Participant 5	1. Stay focused on the job at hand	6	7	5	3	4	3
	2. Remembering names when first introduced	6	6	5	3	5	3

	3. Stay focused when completing daily routines	7	7	7	7	7	7
Participant 6	1. To eliminate distraction and focus on task at hand	6	6	7.5	7	6	7
	2. To improve listening skills	7	7	7	8	7	7
Participant 7	1. To concentrate better when reading	4	3	6	6	5	4
	2. To stop zoning out during length conversations	6	5	7	7	6	5
Participant 8	1. Write down messages and notes from calls etc. when get them i.e. immediately	3	1	3	1	-	-
	2. Do tasks at the time I have allocated to them	2	1	2	1	-	-
	3. Plan all goals on laptop calendar with calendars/alarms once a week	4	3	4	3	-	-
Participant 9	1. To stay focused while studying	1	2	3	5	3	5
	2. To focus better when driving	1	1	3	4	3	4
	3. To remember where I leave phone, keys, documents	1	1	2	3	2	3
Participant	1. To	2	2	9	10	8	9

10	concentrate better in class						
	2. To remember things for class	6	5	7	9	6	9
	3. To remember what happened in class	2	1	5	6	5	6
Participant 11	1. To get motivated to start and follow through with a project at home	4	4	4	4	4	4
	2. To pay more attention during conversations	4	5	4	5	4	5
Participant 12	1. To pay attention during lengthy conversations	3	0	7	7	6	6
	2. To remember where files last updated	3	2	3	2	3	2
	3. To organise task schedule for day	0	0	3	3	3	3
Participant 13	1. To concentrate better when studying	3	7	8	9	7	7
	2. To not drift off when talking with people	3	7	6	6	6	5
	3. To not talk out of turn	4	8	7	7	6	7
Participant 14	1. Allocating time for coaching in the afternoon	4	1	4	1	4	1
	2. Sticking with diet	2	0	6	4	4	4
	3. Type up/ prepare creative writing for	3	1	10	10	7	6

	competitions, look for publisher etc.						
Participant 15	1. Impulse control	2	2	7	6	6	5
	2. Daydreaming while reading	3	2	7	7	5	5
	3. Project planning	3	3	7	7	7	6
Participant 16	1. To remember dates, times, appointments	5	2	7	8	6	6
	2. Having all things necessary when leaving the house	4	0	8	8	8	7
	3. Completing assigned work/ essays/ reading	4	4	4	4	4	4
Participant 17	1. Remembering names and appointments	2	0	8	7	6	6
	2. Remembering where I put things	3	3	5	4	5	4
	3. Improve studying	2	4	7	8	6	8
Participant 18	1. To stop daydreaming about the past, especially in class	4	4	6	6	5	5
	2. To stop or limit fidgeting	3	3	4	4	4	3
	3. To focus on the subject being taught in class, especially Accounting, Maths, Irish, etc. which find particularly boring, and not	2	4	5	6	5	5

	let mind drift						

5.9.10 Summary of significant results

The results of both analyses conducted for the study showed the following significant improvements in the Self-Alert Training (SAT) group compared to the Attention Training (AT) group:

- Improvements emerged in ADHD symptoms after training and at the three-month follow up, as measures by the Conners' Adult ADHD rating Scale Self Report (CAARS – S: L)
- Improvement in social and psychiatric function were found after five week training, as measures by improved scores in the Attention-Related Cognitive Errors Questionnaire (ARCEQ) and in the Beck Depression Inventory (BDI). Improvement after training and at the three-month follow up also emerged in the Self-Efficacy Scale (SES)
- Improvements in untrained neuropsychological functions were found, as measured by the Elevator Counting with Distraction (TEA), the Dual Task Decrement (TEA) and the Total Deviation Time of the Hotel Task

In the first analysis conducted on the complete participants' sample, SAT participants showed decreased reaction times in the Random SART compared to the AT group at the three-month follow up, while reaction times increased in the SAT group compared to the AT group in the Fixed SART at the three-month follow up. In the sub-analysis that was conducted after excluding seven low-participation participants, improved P3 maximal amplitude and decreased P3 latency emerged on standard tones in the auditory oddball task in the SAT group compared to the AT group.

The qualitative results of participants' everyday-life subjective goals ratings showed improved goals ratings after training and at the three-month follow up assessment.

5.9.11 Discussion

The primary aim of this challenging study was to test the efficacy of partially home-based Self-Alert Training (SAT) on several primary outcome measures in adults with ADHD using a single-blind controlled randomised trial (RCT).

The results of the study showed that Self-Alert Training (SAT) resulted in improvements in ADHD symptoms as measured by the Conners' Adult ADHD Rating Scale (CAARS) after training and at the three-month follow up. A sub-analysis was carried out excluding low-participation subjects (five participants were excluded from the Self-Alert Training group and two from the Attention Training group) and it showed the same improvements in ADHD symptoms post-training and at the three-month follow up for the SAT group compared to the control attention raining (AT) group. The effects of SAT on several scales and questionnaires measuring social and psychiatric functioning were assessed and the results of both analyses (the first including all participants and the sub-analysis carried out after excluding low-participation participants) were consistent in showing greater improvements in the Attention-Related Cognitive Errors Questionnaire (ARCEQ) and in the Beck Depression Inventory (BDI) at the three-month follow-up for the SAT group compared to the AT group. Additionally, significant improvements emerged in the Self Efficacy Scale (SES) at both post-training assessment and at the three-month follow up in the SAT group compared to the control group. Improvements in several neuropsychological measures emerged in the results of both analyses after five week of training. Specifically, improvements were found in the Elevator Counting with Distraction (TEA), that measures selective attention, in the Dual Task Decrement (TEA), measuring divided attention and in the Total Deviation Time of the Hotel Task, which is a measure of executive function. Significantly these results indicate that there was a generalisation of training effects to untrained cognitive function. However, these effects were not maintained at the three-month follow up, thus suggesting that more practice is needed to obtain long-term improvements on untrained cognitive functions. At the three-month follow up, there was a significant interaction in

reaction times the Sustained Attention to Response Task (SART) Fixed and Random version, indicating that the SAT group showed slowed RT in the Fixed SART compared to the AT group and faster RT in the Random SART compared to the AT group. In the sub-analysis additional improvements also emerged for some of the Event-Related Potential (ERP) measures at the three-month follow up; specifically P3 peak amplitude significantly increased and P3 latency significantly decreased in the SAT group, compared to the AT group.

A critical point to be addressed in this study is the need of correction for multiple comparisons. A number of scales and questionnaires and several different neuropsychological and neurophysiological measures were employed in this study to investigate changes after training and at the three-month follow up between the Self-Alert Training group and the Attention Training group. As more measures are compared between two groups, it becomes more likely that the training and the control groups would differ on at least one measure by chance alone. However in the sub-analysis that was conducted in this study after excluding low-participation participants, 75% of the scales and questionnaires used to assess ADHD symptoms and social and psychiatric functioning showed improvements either after training, or at the three-month follow-up or at both assessments. Therefore, it seems that these effects are not driven by random chance alone but they actually reflect positive effects of Self-Alert Training on ADHD symptoms and on measures of social and psychiatric functioning. Furthermore, these effects are long lasting, as they are also evident at the three-month follow up session. The results of the Observer version of the Conners' Adult ADHD Rating Scale showed that there was a marginal improvement in the CAARS A - Inattention and Memory Problems. This result should be interpreted with caution because of the sample size. In fact, very few participants returned CAARS Observer Forms and therefore samples size was small (at the post-training session, there were ten forms in the SAT group and eight in the attention training group while at the three-month follow up there were nine forms in the SAT group and seven in the control group) and this cannot allow a well powered analysis. The results of the

study showed that 50% of the neuropsychological tests employed in this study showed improvements after the five-week training. In this case it might be that some of these effects might be attributed to random chance. However a positive correlation emerged between change score in reaction times (RTs) in the Sustained Attention to Response Task - Random version and the change score in the CAARS D – Problems with Self Concept, indicating that higher RTs in the SART correspond to higher ADHD symptoms. This correlation might strengthen the study findings on cognitive tests, as training effects on ADHD symptoms measured by the CAARS seem to be attributable to real effects of the training. Finally, in the sub-analysis carried out after excluding low-participation subjects, only 20% of the neurophysiological measures showed improvements at the three-month follow up. Although in this case the possibility that these effects reflected random chance can't be excluded, a positive correlation emerged between one of the neurophysiological measure (P3 latency) and score in the Attention-Related Cognitive Errors Questionnaire (ARCEQ), indicating that higher P3 latency corresponds to higher inattention in everyday-life settings.

The neurophysiological results of the study have not shown strong improvements in brain function following Self-Alert Training. The lack of a strong change in brain function is not however incompatible with behavioural and cognitive results of the study. In fact, Self-Alert Training (SAT) was developed as a behavioural technique aimed to teach people a strategy to self-alert in key real life situations. The use of self-alerts that are independent of tasks provides in fact a highly flexible means of triggering behaviours that can be applied to a variety of real life situations. It is clear how the primary aim of SAT was not to produce brain changes but to provide participants means to help them copying with inattention and impulsivity problems in real life settings.

The results of the study showed that there were no effects after training in pupil and EEG power spectral measures. Pupil measures reflect transient changes in phasic arousal and they seem to index the phasic activity of the locus coeruleus (Aston-Jones & Cohen, 2005). Since participants in this study were trained to self-

alert in key real life situations and not to learn a strategy for increasing specific brain functions, as, for example, in neurofeedback or in brain training programmes in which people are trained to modulated and increase specific brain waves or brain functions (Gevensleben et al., 2009; Owen et al., 2010), the lack of changes in pupil and EEG measures should not be surprising. Furthermore, the lack of changes in EEG power spectral measures after training indicate that SAT did not result in a generalised increase in cortical arousal as measured by spectral EEG power. Given that in the first steps of Self-Alert Training participants learned to modulate their arousal in a periodic and phasic manner, it is also unsurprising that training effects did not come through in tonic EEG measures. The only change that emerged from the neurophysiological results was in P3 measures in the auditory oddball task and this might indicate that P3 may provide a more sensitive measure of brain changes reflecting SAT effects.

The qualitative outcomes of the study showed that Self-Alert Training (SAT) was successful in improving everyday life function in adults with ADHD, although the absence of these measures for the attention training group means that these have to be treated cautiously.

Regarding subjective goal ratings, participants reported to be able to apply the self-alert technique to their goals, suggesting that they have learned to apply the strategies learned in a range of real life situations. An analysis of post-training ratings revealed improvements in performance and satisfaction ratings of all goals for all but three participants in the SAT group. Improvements in goals ratings were also maintained at the three-month follow up. Additionally, paired samples t-test were carried out on participants' performance and satisfaction goals ratings and they showed significant improvements in participants' goals ratings after training and at the three-month follow up. Significantly, participants who reported no improvements in goal ratings also disclosed that they hadn't been fully committed to the training during the five week period for various personal reasons (e.g. time constraints, lack of motivation) and so had not been completing the required amount of practice. Similarly, participants who showed greater

improvements in post-training goals ratings were also those who completed the greatest number of practice sessions. This suggests that SAT results in a generalisation of training effects across a range of real-life situations, but that this is significantly modulated by the amount of time dedicated to practising the technique.

Another critical point of the study was to establish if the amount of training practice differed between the two groups and if that practice affected the results of the study. Analysis of participants' training practice revealed that Self-Alert Training (SAT) participants did less attentional exercises compared to Attention Training (AT) participants. However SAT participants also did additional biofeedback practice. T-tests were therefore carried out and they showed that there was no significant difference between the two groups in exercise practice and in the total practice time (in this case, SAT participants' total practice time was calculated by adding exercise practice and biofeedback practice). This result is reassuring as it showed that, although SAT participants were asked to practice exercises and biofeedback sessions, the total training practice did not differ between groups. Additionally, a sub-analysis in which the total practice time was included as a covariate in the repeated measures ANCOVAs also revealed that the interaction between the SAT group and the AT group were the same for all scales and cognitive tests but the Self-Efficacy Scale, with the latter interaction becoming marginally significant. At the three-month follow up, the same positive effects of SAT emerged in the sub-analysis for all tests but the Beck Depression Inventory (BDI) and reaction times in the Fixed and Random SART. The interaction in the Beck Depression Inventory (BDI) was not significant any more while interactions in RT in the SARTs became marginal, when practice time was covaried. Overall, it seems that the total practice time did not significantly change behavioural and cognitive results of the study.

The results of the study have shown that the primary aim of Self-Alert Training (SAT) was achieved, as indicated by the improvements following training in several primary outcome measures, such as ADHD symptoms and social and

psychiatric functioning. These improvements were also maintained after three months and this suggests that implementation of SAT strategies in everyday life lead to improvements in ADHD symptoms and in social functioning and to decreased symptoms of depression. Importantly, improvements in participants' subjective everyday-life goals ratings suggest that the SAT was successful in improving everyday-life function in adults with ADHD.

The positive results that emerged from this study have suggested that experience of this combined biofeedback and Self-Alert Training can be successful in instilling confidence in participants' own capabilities to exhibit cognitive control over their own levels of alertness.

It is hoped that providing individuals with ADHD with education about the brain-behaviour link, specifically the effects of arousal levels on behavioural symptoms of ADHD, as well as psychological and behavioural tools to help them to control this relationship, will improve their ability to cope with and manage everyday tasks that require increased levels of attention. Ultimately, it is hoped that this type of behavioural training may in future be used to form the basis for a clinically oriented method of intervention that can be used either alone or in conjunction with pharmacological treatments, to help adults with ADHD to manage and control their own symptoms.

Chapter 6. General Discussion

6.1 Sustained attention deficits in adult ADHD

An inability to sustain attention is one of the hallmark symptoms of ADHD. Previous research has documented sustained attention deficits in children and adults with ADHD using classic Continuous Performance Tasks (CPT) and a range of other sustained attention tasks (Barkley, 1998; Bellgrove et al., 2006; Johnson et al., 2007; Mcavinue et at., 2012; Seidman et al., 2006).

As reviewed in the introduction to this thesis, the primary neurobiological hypothesis for ADHD is a dysfunction of the fronto-striatal circuitry that is modulated by dopamine and noradrenaline (Bradshaw et al., 2001; Diamond et al., 2004). Modern neuroimaging techniques have further supported this hypothesis of fronto-striatal dysfunction in ADHD. For example, numerous fMRI, PET and event-related potential (ERP) studies have consistently found hypoactivity in brain areas such as prefrontal cortex and the anterior cingulate cortex (Bush, 2010; Dickstein et al., 2006; Pliszka et al., 2007; Zang et al., 2005). Furthermore, functional pharmaco-imaging studies demonstrated that stimulant drugs, such as methylphenidate (MHP) enhanced the activity of dopamine and noradrenaline (Madras et al., 2005) increasing activity in the front-striatal areas which resulted in a reduction in ADHD symptoms in children and adults with ADHD (Epstein et al., 2007; Konrad et al., 2007; Pliszka et al., 2007).

This suggests that the combination of cognitive and neuropsychological testing with modern brain imaging techniques can advance our understanding of the impaired mechanisms that are responsible for the attentional deficits in ADHD.

In this thesis sustained attention deficits in adult ADHD were investigated using clinical, neurophysiological and cognitive measures.

In chapter 3, the behavioural correlates of sustained attention were explored and the neurophysiological underpinnings of sustained attention deficits in adults with ADHD were investigated using pupil dilation and event-related potentials (ERPs) measures in an auditory oddball task. A pattern of sustained attention deficits emerged from the results of the study, indicating that the performance of adults with ADHD in the auditory oddball task was significantly more variable compared to a group of aged-matched control participants. A difference emerged in a key ERP component: adults with ADHD had significantly reduced P3 amplitude compared to adult controls. They also demonstrated significantly reduced pupil dilation on target tones and this correlated negatively with performance variability. Decreased pupil dilation may thus correspond with diminished task performance.

The results of the study are in line with the prominent fronto-striatal dysfunction hypothesis of ADHD. P3 event-related potential is well know and reliable neurophysiological index of endogenous maintenance of attention. It originates from fronto-parietal regions and it has been linked to specific neurotransmitter systems, such as dopamine and noradrenaline (Polich & Criado, 2006). Furthermore, as reviewed in chapter 3, numerous studies indicate that pupil dilation is a reliable index of the locus coeruleus (LC) activity in the human brain (Hou et al., 2005; Morad et al., 2000; Nieuwenhuis et al., 2005) which may index noradrenaline function (Aston-Jones et al., 1985, 1991 & 1994).

Therefore, the results of experiment 1 suggest that dysfunction within the fronto-striatal circuitry may subserve the attentional deficits observed in adults with ADHD in this study. Furthermore, the reduced pupil dilation observed in adults with ADHD during the task might suggest that reduced noradrenergic availability is a possible mechanism that subserves impaired sustained attention in ADHD.

The neurophysiological underpinnings of sustained attention failures were also investigated in chapter 4. Experiment 2 investigated the neurophysiological correlates that precede attentional lapses. It was explained that the majority of

event-related potentials studies do not focus on the neural correlates in the period that precedes an attentional failure. Understanding the precursors to attentional failures is essential to fully explain the impaired attentional performance observed in ADHD. Furthermore, knowledge of neural correlates of attentional lapses may yield important insights for future rehabilitation strategies that might be effective in treating ADHD symptoms.

In experiment 2 the Contingent Temporal Expectancy Task (CTET) was employed to compare adults with ADHD with control participants. The results showed marginal behavioural differences between groups, while the electrophysiological data revealed that ADHD was associated with electrophysiological abnormalities. This suggests the absence of a necessary mechanism to facilitate the processing of task-relevant information and dysfunctional task engagement in the ADHD group. Hence, by adopting a new approach that focused on the analysis of electrophysiological signatures in the period that preceded the target, it was possible to identify the neural processes underlying participants' task performance, allowing a more sophisticated analysis of attentional deficits in ADHD.

One common limitation of many Event-Related Potentials studies in ADHD is that they usually simply focus on describing the electrophysiological deficits associated with the ADHD syndrome without theory-based predictions. Several theories of ADHD have been proposed and each of these theories has described cognitive factors, motivational factors or the degree of physiological arousal to explain the origins of the ADHD symptoms (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, 2002).

The most prominent class of ADHD models are the cognitive dysfunction models (Barkley, 1997; Sonuga-Barke, 2005). These models proposed that executive dysfunctions are central and that ADHD symptoms of inattention and impulsivity are caused by deficits in inhibitory-based executive deficits (Barkley, 1997). The cognitive models of ADHD are supported by many studies that have shown

deficits in tasks thought to measure executive function in people with ADHD (Seidman et al., 2005; Sergeant et al., 2003; Willcut et al., 2005). The second class of models, the motivation-based dysfunction models, were proposed as an alternative to the cognitive theories (Sagvolden et al., 1998, Sonuga-Barke et al., 1996). In these models, ADHD symptoms are thought to originate from dysfunctional reward processes that lead to impaired motivation in ADHD. Finally, an alternative model has been proposed by Sergeant (2000) that is known as the cognitive energetic model of ADHD. In this model the symptoms of ADHD are thought to originate from an inadequate level of physiological arousal.

The results of experiment 1 and 2 seem to suggest that the sustained attention impairments in adult ADHD are determined by a dynamic interplay between cognitive and motivational factors. In experiment 2 the electrophysiological precursors of sustained attention deficits were investigated and it was found that an early event-related potential component could differentiate correct from incorrect trials in the ADHD group. This component might indicate dysfunctional task engagement in ADHD at an early stage of stimulus processing in the task, thus supporting the idea of an intrinsic lack of motivation in ADHD. Other impaired behavioural and neurophysiological measures also emerged in an auditory oddball task in experiment 1.

P3 event related potential and pupil dilation have been liked to specific brain areas within the fronto-striatal circuit which are regulated by the activity of dopamine and noradrenaline neurotransmitters (Polich & Criado, 2006; Hou et al., 2005; Morad et al., 2000; Nieuwenhuis et al., 2005). Interestingly, the executive circuits described by the cognitive dysfunctions models of ADHD share some common structures (i.e. the prefrontal and parietal cortex and the striatum) with the fronto-striatal circuitry involved in the pathophysiology of ADHD.

Sonuga-Barke (2002) has proposed a dual pathway model of ADHD that supports the idea of multiple levels of impairments in ADHD. This model describes ADHD as a developmental outcome of two distinct psychological processes. One

describes ADHD as a predominantly motivational disorder while the second process sees ADHD as an executive disorder resulting from an inhibitory dysfunction.

It might be that at early stage of task processing, adults with ADHD experienced a lack of motivation resulting in poor task engagement. Impaired motivation during tasks in ADHD might be associated with impaired executive functions processes, as proposed by classic cognitive dysfunctions models of ADHD. These executive deficits might be the result of dysfunctions in fronto-parietal brain areas. The reduced pupil dilation observed in the auditory oddball task in experiment 1 may reflect a diminished noradrenaline availability in the brain. This may reflect a possible neural mechanisms that is impaired in ADHD that is responsible for the attentional deficits in ADHD.

More research is needed to develop a comprehensive and explanatory model of ADHD and there is the need for future research to target theory-based predictions when designing event-related potentials studies in ADHD (Johnstone et al., 2013). Ideally methodologies that reflect the multi-faceted nature of ADHD should be employed to fully understand the ADHD phenomenon and researchers should use multivariate approaches with measures from different cognitive and motivational domains.

6.2. Treatment of attentional deficits in adult ADHD

As reviewed in the introduction to this thesis there are two 'evidence-based' treatments for children and adults with ADHD: psychostimulant medication and cognitive behavioural therapy (CBT). Both treatments have been successful in reducing the behavioural problems and the improving general concentration levels observed in ADHD. However, a major limitation of both treatments is that they do not target the underlying pathophysiology of ADHD and they don't result in long-term effects. It was argued that while problematic behaviours may represent the most pressing concern for people with ADHD and their families, cognitive

functions such as attention, are an essential prerequisite for the acquisition of skills, for learning and are vital for academic success (Penkman, 2004). It was argued that there is a need of developing new treatments that target the neuropsychological deficits in ADHD.

As explained previously, a consistent finding within the ADHD literature is a deficit in sustained attention (Barkley, 1998; Bellgrove et al., 2006; Johnson et al., 2007; Mcavinue et at., 2012; Seidman et al., 2006). In line with this literature, the results of experiment 1 and 2 have shown that adults with ADHD suffer from a prominent sustained attention deficit and the electrophysiological results of the studies have suggested that this deficit might be linked to abnormalities in frontal-subcortical circuitry modulated by dopamine and noradrenaline.

In chapter 5 Self-Alert Training (SAT) was employed to ameliorate these attentional deficits in adults with ADHD. SAT targeted the sustained attention network via its top-down influences and it teaches participants to self-alert in key real life situations to increase sustained attention at hand with the final aim of improving everyday life function.

The results of the study reported in chapter 5 have shown that Self-Alert Training was successful in reducing ADHD symptoms and in improving social and psychiatric functioning. Furthermore, improvements in untrained cognitive functions after training were found, thus suggesting generalisation of training effects to untrained cognitive functions. Importantly, participants' everyday-life function also showed significant improvements as shown by participants' improved subjective everyday-life goals ratings.

One factor that complicates the treatment of attentional deficits in adults with ADHD is the high level of comorbidity evident within the adult ADHD population. As reviewed in the introduction of this thesis, adults with ADHD showed substantial lifetime prevalence of comorbid disorders, with comorbid anxiety disorders in adults with ADHD approaching 50% while other mood

disorders, such as depression, antisocial disorders and alcohol/drug dependency also showed substantial prevalence rates (Biederman et al., 2005; Barkely, 2006). One third of the adults ADHD participants that took part in the studies described in this thesis had comorbid disorders; anxiety was the most common, followed by depression, insomnia and alcohol/drug dependency problems. Intervention studies should consider the presence of these comorbid disorders, as these can affect the outcomes of the study. In this study the possibility that participants' comorbid conditions may have influenced the final outcomes of the study can't be excluded. This could be resolved by excluding all participants with comorbid disorders; however the resulting sample of adults with ADHD may not be representative of the disorder, given that comorbidity is such a common feature of ADHD (Sharkley & Fitzgerald, 2007). One solution for this might be to conduct a baseline comprehensive assessment of ADHD participants to identify participants' individual clinical and cognitive impairments. This would enable an investigation of the potential differences in sub-groups of participants with different comorbidities and it may also enhance our understand of the interactions between comorbid conditions and the participants' subjective training outcomes. Furthermore, defining participants' individual clinical and cognitive profiles may help to match treatments to individual needs and it may be one way of maximising treatments effects.

Another factor that can complicate the treatment of attention deficits in adults with ADHD is participants' level of motivation when deciding to take part in attention training programmes. As explained before, a lack of motivation seems to be a characteristic of ADHD. In the motivation models of ADHD, it was proposed that impaired motivation might be responsible for the ADHD attentional symptoms. Additionally, the results of the studies described previously in this thesis also seem to suggest that dysfunctional motivational processes might be one of the possible mechanisms involved in determining the ADHD attentional failures found in the experiments. It is clear that impaired motivation becomes an issue when someone with ADHD has to commit to a training programme, such as

Self-Alert Training. In this study differences in participants' levels of motivation were witnessed by the trainers. This might have influenced participants' commitment to the training, affecting participants' final outcomes. The results of the participant subjective goal ratings support the idea of a potential influence of motivation on participants' outcomes by showing that participants that improved more are the ones who have dedicated more time to practising Self-Alert Training. This suggests that motivation is an important factor in treating attentional disorders in ADHD and it can potentially affect the outcomes of an intervention.

Despite these difficulties, this study has demonstrated that Self-Alert Training can be beneficial in treating attentional problems in adult ADHD.

Studies have explored the efficacy of multimodal treatments which combined behavioural treatments with pharmacological interventions in children and adults with ADHD (MTA Cooperative Group, 1999; Root & Resnick, 2003; Rostain et al., 2006; Safren et al., 2005) and they found combined treatments to be superior to both behavioural therapy and medication alone. However, these studies also showed that improvements were not maintained after 36 months (Jensen et al. 2007), thus indicating that the issue of treatment's long term efficacy remains open. Therefore, an interesting possibility might be to use Self-Alert Training in combination with classic medication and behavioural treatments to investigate potential adjunctive or synergistic effects and to investigate potential long term effects of this combined treatment in ADHD.

6.3 Future directions

A general critical point that must be taken into account and considered critically in future research is the need of effect sizes and corrections for multiple comparisons. Effect sizes indexes provide an objective and standardized measure of the magnitude of an observed effect. In this thesis for example, some of the behavioural results reported in the experiment 1 and 2 are marginal and calculation of the effect sizes might be useful in order to provide better interpretations of these results, taking into account, for example, the sample size.

Moreover, report of multiple comparisons in relation to the results of the randomized controlled trial might be useful in order to better understand the effects of the training on participants' performance. In this study many measures were employed to evaluate the effects of the training. Therefore some of the improvements might be due to chance while others reflect real effects of the training. The use of multiple comparisons can help to disentangle the real effects of the training reflected in the measures used to assess participants.

The results of the studies in this thesis have identified some neurophysiological markers for sustained attention deficits in ADHD. Decreased pupil diameter in an auditory oddball task and significantly decreased P3 amplitude on target tones emerged in adults with ADHD in experiment 1. In experiment 2, two electrophysiological markers of attentional failures were found in adult ADHD, specifically pre-target alpha activity and the early ERP component. A major challenge for future work will be to use this information to develop reliable biomarkers for ADHD. The pupil diameter and P3 component studied in experiment 1 have been linked to specific neurotransmitter systems. Pupil diameter has been found to be a reliable index of the noradrenaline in the human brain (Hou et al., 2005; Morad et al., 2000). In addition, the parietal P3 is closely linked to noradrenergic transmission (Nieuwenhuis et al., 2005) which has been proposed to be dysfunctional in ADHD (Biederman & Spencer, 1999). The use of neurophysiological biomarkers that would allow us to link gene, physiology and cognition has the potential to provide a valuable and objective diagnostic tool and provide targeted intervention for rehabilitative efforts via pharmacological and cognitive training in ADHD. Further studies examining the association of ADHD candidate genes in the dopaminergic and noradrenergic systems with neurophysiological markers such as pupil diameter, P3 and pre-target alpha are required.

Another important point to address in future studies is whether the findings of this thesis can be generalised to all adults with ADHD. Literature on adult ADHD suggests that the ADHD predominantly inattentive (ADHD-I) and combined

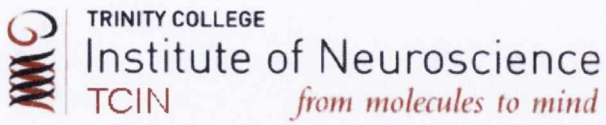
(ADHD-C) subtypes are most commonly seen in adults with ADHD (Achenbach et al., 1995; Hart et al., 1995; Millstein et al., 1997). However, no distinction was made between ADHD subtypes in this thesis. As a result, it is not possible to ascertain from the present data whether or not the observed deficits apply to all three subtypes. Although it might be hypothesised that sustained attention deficits would relate to behavioural deficits on the inattention axis of DSM criteria it was not possible to verify this in the present experiments. Whether DSM-IV subtypes can be dissociated based upon the deficient attentional processes and neurophysiological markers, such as pupil measures or event-related potentials componentry identified in this thesis, will be an important question for future research. Future studies should investigate if Self-Alert Training (SAT) results in the same improvements among the three ADHD subtypes or if it differentially affects one or more ADHD subtypes. As SAT focuses on transiently increasing levels of arousal with the final aim of improving sustained attention, it might hypothesised that the ADHD-C and ADHD-I subtypes might benefit more from SAT practice than the ADHD-H subtype.

Another interesting question for future research is weather behavioural treatments, such as Self-Alert Training, alone can be superior to both medication and combined treatments for adults ADHD. As it was explained in the introduction to this thesis, pharmacological treatments of ADHD are only affective with a proportion of people with ADHD. It was also found that medications did not have long-term effect and that they resulted in several side effects, such as anxiety and insomnia in adults with ADHD (Swanson, 2003; Wolraich et al., 2006). Medications are also expensive, requiring long term prescription of a drug by a consultant psychiatrist with costly associated medical screening to monitor the common side effects, such as insomnia and anxiety (Fone and Nutt, 2005). Furthermore, there is no evidence that the some common problems associated with ADHD - such as criminality– are reduced by the prevailing drug treatments (Satterfield et al, 2007). On the other hand, classic behavioural treatments for ADHD, such as CBT, have also no long term effects on ADHD symptoms

(Pelham, 1999). In this study, it was found that a simple behavioural technique, Self-Alert Training can ameliorate ADHD symptoms as well as cognitive function and everyday life function in adults with ADHD. Self-Alert Training has strong theoretical basis on the brain-behaviour link and it specifically addresses the putative underlying deficits found in sustained attention in adults with ADHD, thus providing a new training alternative to classic pharmacological and behavioural treatments of ADHD. Given that this type of behavioural treatment has low associated costs, no side effects and that participants require a relatively short amount of training time to learn the technique, one interesting possibility for future research is to test whether this type of behavioural treatments might be preferable to medication or combined treatments in treating ADHD symptoms in adult ADHD.

Finally, future research is needed to develop a version of Self-Alert Training for children with ADHD.

Appendix 1 – Information sheet and consent form for the attentional training study



ATTENTIONAL TRAINING FOR PEOPLE WITH ATTENTION DIFFICULTIES

Information Sheet

What is the aim of the study?
The aim of this study is to find out whether attention training can help people diagnosed with attention deficit hyperactivity disorder (ADHD). We will measure cognitive abilities such as memory and attention as well as how concentration problems impact on everyday life. There are two different forms of attentional training and we want to compare them to see which is the most beneficial.

What does the study involve?
The study involves an assessment and then two sessions of training with practice in your own home. We will then ask you to practice the training at home for five weeks. The assessment is then repeated at the end of the training period after five weeks and then again after 17 weeks.

What does the assessment involve?
The study begins with an initial assessment which includes the completion of several questionnaires about your background, your attention problems and other relevant details. There will also be some memory and concentration assessments to complete.

You will then be assessed using a completely harmless method for measuring tiny amounts of electrical activity in your brain called EEG, using little contacts which are placed into a cap which you wear on your head. At the same time we'll use another safe procedure to measure the diameter of your pupil, known as pupillometry. So, once the EEG cap has been fitted, we will ask you to place your head on the pupillometer chin rest and we will further apply a cheek rest to either side of your head to restrict lateral head movement for the duration of this stage of testing. Again, there are no risks associated

with this procedure, and it has been designed to cause as little discomfort as possible. You will do some simple tests on a computer whilst wearing the cap.

The final part of the assessment may involve a Magnetic Resonance Imaging (fMRI) brain scan. The purpose of fMRI scanning is to measure your brain activity while you do simple tasks while lying in the MRI scanner. Participants will be asked questions of a sensitive nature in order to assess suitability for scanning using an fMRI safety checklist.

The scanning involves lying on a bed inside the scanner wearing on your head something that looks like a large helmet. It is very important that you keep still and do not move your head while we are taking an image of your brain. We will explain exactly what you need to do before we start each MRI test.

What does the training involve?

You will receive one of two types of attention training, and which you receive will be determined by the equivalent of a toss of a coin. The training sessions will take place at Trinity College Institute of Neuroscience and as 'homework' in your own home. Each session will last approximately 2 and a half hours. Also, during training sessions, we will ask you to choose some goals you would like to achieve with the training. After receiving the training, you will be asked to practice what you have learnt at home on a computer that we will lend you for at least 30 minutes per day. A trainer will also phone you once a week to discuss your progress and make adjustments if necessary. As part of the follow up session there will be a short discussion to assess whether you manage to achieve goals you chose previously.

Are there any risks involved?

There are no obvious risks involved in participating in the study. However being in a scanner can cause anxiety for some people, particularly if you have experienced claustrophobia in the past, but you will be able to stop the scanning procedure at any time.

There is also a small risk that brain abnormalities will be identified during the structural scan. If any abnormalities are detected, your GP will be contacted with the recommendation that a clinical scan is carried out.

Your suitability for an MRI scan will be checked in order to ensure your safety. In addition, women who may be pregnant will not be given an MRI scan as a precautionary safety measure.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

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

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

3. As participation is completely voluntary, you are free to withdraw from the study at any time (squeezing a pressure ball inside the MRI scanner will immediately stop the experiment). You are also free to withdraw your data at the conclusion of your participation should you so wish.

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

Will my participation be confidential?
All data from questionnaires, interview and computerised tasks will be anonymised using an ID code and stored securely in electronic format for 10 years.

Finally at the end of the study you will receive 60€ as honorarium for your participation.

How can I find out more?
If you have any queries about the study or would like any further information, please do not hesitate to contact Simona Salomone by e-mail: ssalomon@tcd.ie or telephone: 01 896 8405 or Jacqueline Shanahan by email: shanahaj@tcd.ie or telephone: 01 896 8403.

Thank you for your interest!

CONSENT FORM

I, the undersigned, give my informed consent to participate in the study on the comparison of two attentional trainings for people with attention deficits conducted by the Trinity College Institute of Neuroscience, Trinity College Dublin.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

WITNESS'S NAME: _____

WITNESS'S SIGNATURE: _____

Date: _____

Appendix 2 – Information sheet and consent form for the Event-Related Potentials (ERPs) study on the neural precursors of attentional failures

INFORMATION SHEET

Title of Project:

Event-Related Potential Study of Lapses in Attention in Attention Deficit Hyperactivity Disorder (ADHD) using the Continuous Temporal Expectancy Task (CTET)

Research Team:

Dr Jessica Bramham, St Patrick's Hospital and University College Dublin
Dr Redmond O'Connell, Trinity College Institute of Neuroscience
Professor Ian Robertson, Trinity College Institute of Neuroscience
Simona Salomone, Trinity College Institute of Neuroscience

Information about the Project:

In this study we are seeking to identify some of the brain regions that may be involved in symptoms and cognitive difficulties associated with ADHD. The study involves performing simple computer tasks while we measure electrical changes in your brain using an EEG cap. The EEG measures your brain's electrical activity by simple recorders called electrodes embedded in a cap which is placed on your head. This is a harmless tool, commonly used in this kind of research, which is not unpleasant or invasive and is not associated with risk of any kind. It takes approximately 45 minutes to apply the cap and electrodes and then you will be asked to complete approximately 1 hour of computer testing.

If at any time during the research you wish to withdraw from the study then you may.

You will receive 20€ for your participation in the study.

If you are willing to take part or if you have any questions regarding this research, please feel free to contact: Dr Redmond O'Connell on 01 896 8405 or Simona Salomone on 01 896 8403.

CONSENT FORM

I, the undersigned, give my informed consent to participate in the study on the Event-Related Potential Study of Lapses in Attention in ADHD using the Continuous Temporal Expectancy Task (CTET) conducted by the Trinity College Institute of Neuroscience, Trinity College Dublin.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

WITNESS'S NAME: _____

WITNESS'S SIGNATURE: _____

Date: _____

Appendix 3 – Scales and Questionnaires

The Wender Utah Rating Scale (WURS)

Participant's name:..... Date:.....

Instructions: Listed below are items concerning behaviours or problems experienced by children with attentional difficulties. Try to think back when you were 10-12 years old and what it was like for you then in your every day life. Read each item carefully and decide how much each item described you when you were 10-12 years old. Indicate your response by putting a cross in the space that corresponds to your choice. Use the following scale: Not at all or very slightly; Mildly; Moderately; Quite a bit; Very Much.

AS A CHILD I WAS/I HAD (10-12 years old)	Not at all or very slightly	Mildly	Moder-ately	Quite a bit	Very Much
1. Concentration problems, easily distracted					
2. Anxious, worrying					
3. Nervous, fidgety					
4. Inattentive, daydreaming					
5. Hot or short tempered, low boiling point					
6. Temper outbursts, tantrums					
7. Trouble stick-to-it-ivenessing, not following through, failing to finish things started					
8. Stubborn, strong willed					
9. Sad or blue, depresses or unhappy					
10. Disobedient with parents, rebellious, sassy					

11. Low opinion of myself						
12. Irritable						
13. Moody, have ups and downs						
14. Feel angry						
15. Acting without thinking, impulsive						
16. Tend to be immature						
17. Feel guilty, regretful						
18. Lose control of myself						
19. Tend to be or act irrational						
20. Unpopular with other children, didn't keep friends for long, didn't get along with other children						
21. Trouble seeing things from someone else's point of view						
22. Trouble with authorities, trouble with school, visits to principal's office						
23. Overall a poor student, slow learner						
24. Trouble with mathematics or numbers						
25. Did not achieve up to potential						

The Conners' Adult ADHD Rating Scale Self Report: Long Version (CAARS – S: L)

The General Health Questionnaire (GHQ)

The Attention-Related Cognitive Errors Questionnaire and the Everyday Memory Failures Questionnaire

The following statements are about minor lapses of attention, memory or absentmindedness that everyone experiences from time to time, but we have very little information about just how common they are. We want to know how frequently these sorts of things have happened to you in the past month

Please read each of the questions and use the five-point scale at the right to record your answer. Circle the number that applies most to you.

Attention-Related Cognitive Errors Questionnaires

	(1) Never	(2) Rarely	(3) Sometimes	(4) Often	(5) Very often
1) I forget people's names immediately after they have introduced themselves					
2) I forget to pass on messages (e.g., phone messages)					
3) I forget what I went to the supermarket to buy					
4) I forget passwords					
5) I forget people's names, even though I rehearsed them					
6) I forget important dates like birthdays and anniversaries					
7) I forget appointments					
8) I forget to set my alarm					
9) I find I cannot quite remember something though it is on the tip of my tongue					
10) I remember facts but not where I learned them					
11) Even though I put things in a special place I still forget where they are					

12) I double-book myself when scheduling appointments

Everyday Memory Failures Questionnaire

	(1) Never	(2) Rarely	(3) Sometimes	(4) Often	(5) Very Often
1) I have gone to the fridge to get one thing (e.g., milk) and taken something else (e.g., juice)					
2) I go into a room to do one thing (e.g. brush my teeth) and end up doing something else (e.g., brush my hair)					
3) I have lost track of a conversation because I zoned out when someone else was talking					
4) I have absent-mindedly placed things in unintended locations (e.g. putting milk into the pantry or sugar into the fridge)					
5) I have gone into a room to get something, got distracted, and wondered what I went there for					
6) I feel overwhelming by unfinished business					
7) I begin one task and get distracted into doing something else					
8) I feel restless and I'm unable to concentrate					
9) I can't keep my mind on something unless is really interesting					
10) When reading I find that I have read several paragraphs without being able to recall what I read					

11) I make mistakes because I am doing one thing and thinking about another

12) I have absent-mindedly mixed up targets

of my action (e.g., pouring or putting

something in to the wrong container)

13) I have to go back and check whether I have done something or not (e.g., turning out lights, locking doors)

14) I have absent-mindedly misplaced frequently used objects, such as keys, pens, glasses, etc.

15) I fail to see what I am looking for even though I am looking right at it

The Beck Anxiety Inventory (BAI)

The Beck Depression Inventory

The Self-Efficacy Scale (SES)

1	I can always manage to solve difficult problems if I try hard enough.
2	If someone opposes me, I can find the means and ways to get what I want.
3	It is easy for me to stick to my aims and accomplish my goals.
4	I am confident that I could deal efficiently with unexpected events.
5	Thanks to my resourcefulness, I know how to handle unforeseen situations.
6	I can solve most problems if I invest the necessary effort.
7	I can remain calm when facing difficulties because I can rely on my coping abilities.
8	When I am confronted with a problem, I can usually find several solutions.
9	If I am in trouble, I can usually think of a solution.
10	I can usually handle whatever comes my way.

Response Format

1 = Not at all true; 2 = Hardly true; 3 = Moderately true; 4 = Exactly true

Appendix 4 – Neuropsychological tests

The National Adult Reading Test (NART)

The Test of Everyday Attention (TEA)

Appendix 5– The Feedback Questionnaire

Participant Feedback Questionnaire
(adapted from Proudfoot et al (2003) Beating the Blues)

Have you had treatment before for ADHD? Yes / No

What treatment did you receive?

—

How did the attention training package compare to previous treatments?

Please circle your response

Much better A little better About the same Not quite as good Not at all good

Please tick the box that best reflects your response

	Agree very strongly	Agree strongly	Neither agree nor disagree	Disagree strongly	Disagree very strongly
I was happy to use the training package					
I found the training package easy to use					
I feel the training will have a long lasting effect					
I would recommend the training to others with ADHD					

Please rate how helpful you found the attention training package overall

Please circle your response

Very helpful Quite helpful Not really helpful Not at all helpful

What did you particularly like about the attention training package?

_____

_____

In what way do you think the package can be improved?

_____

_____

References

Abikoff H. (1991). Cognitive training in ADHD children: less to it than meets the eye. *Journal of Learning Disability 24,* 205–209.

Achenbach, T. N., Howell, C. T., McConaughy, S. H., & Stranger, C. (1995). Six-year predictors of problems in a national sample of children and youth: I. Cross-informant syndromes. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*, 336-347.

Adler, L., Kessler, R. C., & Spencer, T. (2003). *The Adult ADHD Self*-Report Scale (ASRS-v1. 1) Symptom Checklist. Geneva, Switzerland: World Health Organization.

Adler, L. (2004). Clinical presentations of adult patients with ADHD. *Journal of Clinical Psychiatry, 65 (3),* 8-11.

Aeschbach, D., Matthews, J.R., Postolache, T.T., Jackson, m.A., Gieson, H.A., & Wehr, T.A. (1999). Two circadian rhytms in the human electroencephalogram during wakefulness. *American Journal of Physiology, 277,* 1771-1779.

Alberts J., Firestone P., Goodman J.T. (1986). Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. *American Journal of Orthopsychiatry, 56,* 413-423.

Alexander, G.E., Crutcher, M.D., Delong, M.R. (1990): Basal ganglia-thalamocortical circuits- parallel substrates for motor, oculomotor, prefrontal and limbic functions. *Progress on Brain Research, 85*, 119 –146.

Alexander, M. P., & Stuss, D. T. (2000). Disorders of frontal lobe functioning. *Seminars in Neurology, 20*, 427-437.

Altman, D.G., Bland, J.M. (2005). Treatment allocation by minimisation. *British Medical Journal, 330(7495),* 843.

American Psychiatric Association (2000). *Diagnostic and statistic manual for mental disorders* (4th ed.) Washington DC: A.P.A.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (Fifth ed.)*. Arlington, VA: American Psychiatric Publishing. pp. 5–25.

Anderson C.M., Polcari A., Lowen S.B., Renshaw P.F., Teicher M.H. (2002). Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. *American Journal of Psychiatry 159,* 1322–1328.

Angold, A., Costello, J., Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*, 57– 87.

Arnold, L.E., Abikoff, H.B., Cantwell, D.P., Conners C.H., Elliott G.R., Greenhill L.L., Hechtman, L., Hinshaw, S.P., March, J.S., Newcorn, J.H., Pelham, W.E., Swanson, J.M., Vereen, D., Wells, K.C. (1997). NIHM collaborative multimodal treatment study of children with ADHD (MTA): design, methodology and protocol evolution. *Journal of Attention Disorders, 2(3),* 141-158.

Arnsten, A.F. (1998). Cathecolamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Science, 2,* 436-447.

Arnsten, A.F. (2006). Foundamentals of attention-deficit hyperactivity disorder: circuits and pathways. *The Journal of Clinical Psychiatry, 8*, 7-12.

Aston-Jones, G., & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience, 1*(8), 876-886.

Aston-Jones, G., Foote, S. L., & Segal, M. (1985). Impulse conduction properties of noradrenergic locus coeruleus axons projecting to monkey cerebrocortex. *Neuroscience, 15(3)*, 765-777.

Aston-Jones, G., Chiang, C., & Alexinsly, T. (1991). Discharge of noradrenergic locu coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Progress in Brain Research., 88*, 501-520.

Aston-Jones, G., Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience, 14(7),* 4467-4480.

Aston-Jones, G., Rajkowski, J., Kubiak, P., Valentino, R. J., & Shipley, M. T. (1996). Role of the locus coeruleus in emotional activation. *Progress in Brain Research, 107*,79-402.

Aston-Jones, G., Rajkowski, J., & Kubiak, P. (1997). Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. *Neuroscience, 80*(3), 697-715.

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience, 28*, 403-450.

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., Rothenberger, A. (2003). Association of ADHD and conduct disorder—brain

electrical evidence for the existence of a distinct subtype. *Journal of Child Psychology and Psychiatry, 44,* 356 –376.

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., Rothenberger, A. (2004). Questioning inhibitory control as a specific deficit in ADHD – evidence from brain electrical activity. *Journal of Neural Transmission, 111(7),* 841-864.

Barkley, R. A., Grodzinsky, G., & DuPaul, G. J. (1992). Frontal lobe functions in attention deficit disorder with and without hyperactivity: A review and research report. *Journal of Abnormal Child Psychology, 20,* 163–188.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121,* 65–94.

Barkley, R. A., Murphy, A. (1998). *Attention-deficit hyperactivity disorder: A clinical workbook.* (2nd ed.) New York: Guilford

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2002). The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of the disorder. *Journal of Abnormal Psychology, 111,* 279-289.

Barkley, R. A., Murphy, K. R., DuPaul, G., & Bush, T. (2002). Driving in young adults with attention hyperactivity disorder: Knowledge, performance, adverse outcomes, and the role of executive functioning. *Journal of the International Psychological Society, 8,* 655-672.

Barkley, R. A. (2006). *Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. (3rd ed.).* New York: Guilford.

Barry, R.J., Clarke, A.R., Johnstone, S.J. (2003). A review of electrophysiology in ADHD: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology, 114*, 171-183.

Barry, R.J., Clarke, A.R., Johnstone, S.J. (2003). A review of electrophysiology in ADHD: II. Event-related potentials. *Clinical Neurophysiology, 114*, 184-198.

Barry, R.J., Clarke, A.R., McCarthy, R., Selikowitz, M., Brown, C.R., Heaven, P.C.L. (2009). Event-related potentials in adults with Attention-Deficit/Hyperactivity Disorder: An investigation using an inter-modal auditory/visual oddball task. *International Journal of Psychophysiology, 71*, 124-131.

Beatty, J., Wagoner, B.L. (1978). Pupillometric signs of brain activation vary with level of cognitive processing. *Science, 199(4334)*, 1216-1218

Beatty, J. (1982). Task-Evoked papillary responses, processing load and structure of processing resources. *Psychological Bulletin, 91(2),* 276-292.

Beatty, J., & Lucero-Wagoner, B. (2000). *The pupillary system*. In J. T. Cacioppo, L. G.

Beck, A.T., Steer, R.A., *Beck Anxiety Inventory.* The Psychological Corporation, Harcourt Brace & Company, San Antonio, 1993.

Beck, A.T., Steer, R.A., Brown, G.K. *Beck Depression Inventory*. The Psychological Corporation, Harcourt Brace & Company, San Antonio, 1996.

Belendiuk, K. A., Clarke, T. L., Chronis, A. M., & Raggi, V. L. (2007). Assessing the concordance of measures used to diagnose adult ADHD. *Journal of Attention Disorders, 10*, 276-287.

Bellgrove, M.A., Hester, R., Garavan, H. (2004). The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia, 42(14)*, 1910-6

Bellgrove, M.A., Hawi, Z., Gill, M, Robertson I.H. (2006). The cognitive genetics of attention deficit hyperactivity disorder (ADHD): sustained attention as a candidate phenotype. *Cortex, 42(6)*, 838-845.

Berlin, L., & Bohlin, G. (2002). Response inhibition, hyperactivity, and conduct problems among preschool children. *Journal of Clinical Child and Adolescent Psychology, 31(2)*, 242–251.

Berquin P.C., Giedd J.N., Jacobsen L.K., Hamburger S.D., Krain A.L., Rapoport J.L. (1998). Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology 50,* 1087–1093

Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT (1990): Familygenetic and psychosocial risk factors in DSM-III attention deficit disorder. *Journal of American Academic Child and Adolescence Psychiatry, 29*, 526 –533.

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, et al. (1992): Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. *Archives of General Psychiatry, 49*, 728 – 738.

Biederman, J., Faraone, S. V., Spencer, T., Wilens, T. E., Norman, D., Lapey, K. A., et al. (1993). Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry,150*, 1792-1798.

Biederman, J., Faraone S.V., Keenan K., Tuang M.T. (1995). High risk for attention deficit/ hyperactivity disorder among children of parents with childhood onset of the disorder: A pilot study. *American Journal of Psychiatry*, 152, 433-351.

Biederman, J., Faraone, S.V., Milberger, S., Curtis, S., Chen, L., Marrs, A. (1996). Predictors of persistence and remission of ADHD: Results from a four year prospective follow-up study of ADHD children. *Journal of American Academic Child and Adolescence Psychiatry, 35*, 343–351.

Biederman, J., & Spencer, T. (1999). Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. *Biological Psychiatry, 46(9)*, 1234-1242

Biederman, J., Faraone, S.V., Mick, E., Williamson, S., Wilens, T.E., Spencer, T.J. (1999). Clinical correlates of ADHD in females: Findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *Journal of American Academic Child and Adolescence Psychiatry, 38,* 966 –975.

Biederman, J., Mick, E., Faraone, S.V., Braaten, E., Doyle, A., Spencer, T. (2002). Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *American Journal of Psychiatry, 159*, 36 – 42.

Biederman, J. (2005). Attention-Deficit/Hyiperactivity Disorder: A Selective Overview. *Biological Psychiatry, 57*, 1215-1220.

Bradshaw, J.L. (1999). *Developmental disorders of the nervous system*. Philadelphia: Psychology Group.

Bradshaw, J.L., & Sheppard, D.M. (2000). The neurodevelomental frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization. *Brain and Language, 73,* 297-300.

Bresnahan, S.M., Anderson, J.W., Barry, R.J. (1999). Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder. *Biological Psychiatry,46(12)*, 1690-1697

Bresnahan, S., Barry, R. (2002). Specificity of quantitative EEG analysis in adults with ADHD. *Psychiatry Research, 112*, 133-144

Brown, T. E. (1996). *Brown Attention-Deficit Disorder Scales.* San Antonio, TX: Psychological Corporation.

Brown, C.R., Clarke, A.R., Barry, R.J., McCarthy, R., Selokowits, M, Magee, C. (2005). Event-related potentials in ADHD of the predominant inattentive subtype: an investigation of EEG-definied subtypes. *International Journal of Psychophysiology, 58,* 94-107.

Burk, J.A., & Mair, R.G. (2001). Effects of dorsal and ventral striatal lesions on delayed matching trained with retractable levers. *Behavior and Brain Research, 122,* 67–78.

Bush G., Frazier J.A., Rauch S.L., Seidman L.J., Whalen P.J., Jenike M.A. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biological Psychiatry, 45,* 1542–1552.

Bush G., Spencer T.J., Holmes J., Shin L.M., Valera E., Seidman L.J. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry, 65,* 102–114.

Bush, G. (2010). Attention-Deficit/Hyperactivity Disorder and Attention Networks. *Neuropsychopharmacology Reviews*, 35, 278-300.

Byrne, J. M., DeWolfe, N. A., & Bawden, H. N. (1998). Assessment of attention-deficit hyperactivity disorder in preschoolers. *Child Neuropsychology, 4(1)*, 49–66.

Cantwell, D.P. (1972). Genetic of hyperactivity. *Journal of Child Psychology and Psychiatry, 16,* 261-264.

Carlson, C.L., & Tamm, L. (2000). Responsiveness of children with ADHD to reward and response cost: differential impact on performance and motivation. *Journal of Consulting and Clinical Psychology, 68(1)*, 73-83

Caron, C., Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry, 32,* 1063–1080.

Carter, C. S., Krener, P., Chanderjian, M., Northcut, C., Wolfe, V. (1995). Asymmetrical visual-spatial attentional performance in ADHD: Evidence for a right hemispheric deficit. *Biological Psychiatry, 37(11),* 789-797.

Castellanos, F.X., Giedd, J., Marsh, W.L., Hamburger, S.D.,Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C, Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., Rapoport, J.L. (1996). Quantitative Brain Magnetic Resonance Imaging in Attention-Deficit Hyperactivity Disorder. *Archives of General Psychiatry, 53(7)*, 607-616.

Castellanos, F.X., Giedd, J.N., Marsh W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P. (1996). Quantitative brain magnetic resonance imaging in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 53,* 607–616.

Castellanos, F.X., (2001). Neural substrates of attention-deficit hyperactivity disorder. A*dvanced Neurology, 85,* 197–206.

Castellanos, F.X., (2002). Proceed, with caution: SPECT cerebral blood flow studies of children and adolescents with attention deficit hyperactivity disorder. *Journal of Nuclear Medicine, 43*, 1630–1633.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S.. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of American Medical Association, 288*, 1740–1748.

Castellanos, F.X., Sonuga-Barke, E.J., Scheres, A., Di Martino, A., Hyde, C., Walters, J.R. (2005). Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry, 57(11)*, 1416-1423.

Castellanos, F.X., Margulies, D.S., Kelly, C., Uddin, L.Q., Ghaffari, M., Kirsch, A., Shaw, D., Shehzad, Z., Di Martino, A., Biswal, B., Sonuga-Barke, E.J.S., Rotrosed, J., Adler, L.A., Milham, M.P. (2008). Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention Deficit/Hyperactivity Disorder. *Biological Psychiatry, 63 (3),* 332-337.

Chee, P., Logan, G., Schachar, R., Lindsay, P., Wachsmuth, R. (1989). Effects of event rate and display time on sustained attention in hyperactive, normal and control children. *Journal of Abnormal child Psychology, 17*, 371–91.

Chow, T.W., & Cummings, J.L. (1999). Fronto-Subcortical Circuits. In B.L. Miller & J.L. Cummings (Eds.). *The Human Frontal Lobes: functions and disorders.* New York: Guilford.

Clarke, A., Barry, R., McCarthy, R., Selikowits, M. (2001). Age and sex effect in the EEG: differences in two subtypes of ADHD. *Clinical Neurophysiology, 112*, 806-814.

Clarke, A., Barry, R., McCarthy, R., Selikowits, M. (2002). EEG evidence of new conceptualisation of ADHD. *Clinical Neurophysiology, 113*, 1036-1044.

Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M. (2002). EEG analysis of children with attention deficit/hyperactivity disorder and comorbid reading disabilities. *Journal of Learning Disability, 35(3)*, 276-285.

Coles, M. G. H., & Rugg, M. D. (2002). Event-related potentials: an introduction. In D. S. Ruchkin & M. G. H. Coles (Eds.), Electrophysiology of mind event related brain potentials and cognition. Oxford: Oxford University Press.

Conners, C.K. (1999). *Conners' Rating Scale Revised (CRS-R)*. Toronto: MHS.

Conners, C.K., Erhardt, D., Sparrow, E. Conners' Adult ADHD Rating Scales. Multi-health Systems Inc, NY, USA, 1999.

Conners, C. K., Epstein, J., March, J. (2001). Multi-modal treatment of ADHD (MTA): An alternative outcome analysis. *Journal of the American Academy of Child and Adolescent Psychiatry, 40,* 159 –167.

Conners, C. K., Erhart, D., & Sparrow, E. (2003). *Conners' Adult ADHD Rating Scales (CAARS).* Toronto: MHS.

Connor, D.F., Barkley, R.A., Davis, H.T. (2000). A Pilot Study of Methyiphenidate, Clonidine, or the Combination in ADHD Comorbid with Aggressive Oppositional Defiant or Conduct Disorder. *Clinical Pediatrics, 39(1),* 19-25.

Coolidge, F.L., Thede, L.L., Young, S.E. (2002). Heritability and the comorbidity of ADHD with behavioural disorders and executive functions deficits: a preliminary investigation. *Developmental Neuropsychology*, 17, 273-87.

Critchley, H.D., Melmed, R.N., Featherstone, E., Mathias, C.J., & Dolan, R.J. (2002). Volitional control of autonomic arousal: a functional magnetic resonance study. *Neuroimage, 16(4)*, 909-19.

Cubells, J. F., & Zabetian, C. P. (2004). Human genetics of plasma dopamine hydroxylase activity: Applications to research in psychiatry and neurology. *Psychopharmacology, 174*, 463–476.

Dalen, L., Sonuga-Barke, E. J., Hall, M., Remington, B. (2004). Inhibitory deficits, delay aversion and preschool AD/HD: Implications for the dual pathway model. *Neural Plasticity, 11(1–2)*, 1−11.

Danos, P., Guich, S., Abel, L., Buchsbaum, M.S. (2001). EEG alpha rhythm and glucose metabolic rate in the thalamus in schizophrenia. *Neuropsychobiology, 3,* 265–272.

Davidson, R., Jackson, D., & Larson, C. (2000). Human Encephalography. In J. T. Cacioppo, L. G. Tassinary & G. G. Bernston (Eds.), *Handbook of psychophysiology*. Cabridge: Cambridge University Press.

Dawson, M.E., Schell, A.M., & Filion, D.L. (2000). The Electrodermal System. In J.T. Cacioppo (Ed.), *Handbook of Psychophysiology.* USA: Cambridge University Press.

De Sanctis, P., Katz, R., Wylie, G. R., Sehatpour, P., Alexopoulos, G. S., & Foxe, J. J. (2008). Enhanced and bilateralized visual sensory processing in the ventral

stream may be a feature of normal aging. *Neurobiology of Aging, 29(10),* 1576-1586.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D. Y., & Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience. 25*, 11730–11737.

DeFrance, J.F., Smith, S., Schweitzer, F.C., Ginsberg, L., Sands, S. (1996) Topographical analyses of attention disorders of childhood. *International Journal of Neuroscience, 87*, 41–61.

Delis, D.C., Kramer, J. H., Kaplan, E., Ober, B.A. (1987). *California Verbal Learning Test: Adult version.* San Antonio, TX: Psychological Corporation.

Delorme A, Makeig S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*, 9-21.

Denckla, M.B. (1989). Executive function, the overlap zone between attention deficit hyperactivity disorder and learning disabilities. *International Paediatrics, 4*, 155–160.

Diamond, A., Briand, L., Fossella, J., Grhlbach, L. (2004). Genetic and Neurochemical Modulation of Prefrontal Cognitive Functions in Children. *American Journal of Psychiatry, 161(1),* 125-132.

Dickstein, S.G., Bannon, K., Xavier Castellanos, F., Milham, M.P. (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology and Psychiatry, 47,* 1051–1062.

Dockree, P.M., Kelly, S.P., Roche, R.A.P., Reilly, R.B., Robertson, I.H. (2004). Behavioural and physiological impairments of sustained attention after traumatic brain injury. *Cognitive Brain Research, 20(3),* 403-414.

Dockree, P. M., Kelly, S. P., Robertson, I. H., Reilly, R. B., & Foxe, J. J. (2005). Neurophysiological markers of alert responding during goal-directed behavior: A high-density electrical mapping study. *NeuroImage, 27(3*), 587-601.

Donchin, E. (1981). Presidential address, 1980. Surprise!...Surprise? *Psychophysiology, 18(5)*, 493-513.

Donchin, E., Ritter, W., & McCallum, C. (1978). Cognitive psychophysiology: the endogenous components of the ERP. In P. Callaway, P. Tueting & S. H. Koslow (Eds.), *Brain event-related potentials in man* (pp. 349 - 411). New York: Academic.

Du, J., Wang, Y., Jiang, Q., Livesley, W., Jang, K.L., et al (2006). Event-related potentials in adolescents with combibed ADHD and CD disorder: single stimulus paradigm. *Brain and Cognition, 60*, 70-5

DuPaul, G.J., McGoey, K. E., Eckert, T. L., VanBrakle, J. (2001). Preschool children with attention-deficit/hyperactivity disorder: Impairments in behavioral, social, and school functioning. *Journal of the American Academy of Child and Adolescent Psychiatry, 40(5)*, 508–515.

DuPaul, G.J. (2006). Academic achievement in children with ADHD. *Journal of American Academy of Child Adolescence Psychiatry, 45(7)*, 766-767.

Durston S. (2003). A review of the biological bases of ADHD: what have we learned from imaging studies? *Mental Retardation Developmental Disability Research Review, 9, 1*84–195.

Durston S., Davidson M.C., Mulder M.J., Spicer J.A., Galvan A., Tottenham N. (2007). Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 48,* 881–889.

Eichele, T., Debener, S., Calhoun, V.D., Specht, K., Engel, A.K., Hugdah, K.von Cramon, D.Y., & Ullsperger, M. (2007). Prediction of human errors by maladaptive changes in event-related brain networks. *PNAS, 105 (16)*, 6173-6178.

Eichele, H., Juvodden, H.T., Ullsperger, M., & Eichele, T. (2010). Mal-adaptation of event-related EEG responses preceding performance errors. *Frontiers in Human Neuroscience, 4* (65).

Einhauser, W., Stout, J., Koch, C., & Carter, O. (2008). Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry. *PNAS,105(5)*, 1704-1709.

Epstein, J.N., Johnson, D., Conners, C.K. (2000). *Conners' Adult ADHD Diagnostic Interview for DSM-IV*. North Tonawanda, NY: Multi-Health Systems.

Epstein, J., Johnson, D., & Conners, C.K. (2001). Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID). MHS (Multi Health Systems), Canada

Epstein, J. N., Erkanli, A., Conners, C. K., Klaric, J., Costello, J. E., Angold, A. (2003). Relations between continuous performance test performance measures and ADHD behaviours. *Journal of Abnormal Child Psychology, 31*, 543-554.

Epstein, J.N., Kollins, S.H. (2006). Psychometric properties of an adult ADHD diagnostic interview. *Journal of Attention Disorders, 9*, 504-514.

Epstein J.N., Casey B.J., Tonev S.T., Davidson M.C., Reiss A.L., Garrett A. (2007). ADHD- and medication-related brain activation effects in concordantly affected parent–child dyads with ADHD. *Journal of Child Psychology and Psychiatry, 48,* 899–913.

Erk, R.R. (2000). Five frameworks for increasing understanding and effective treatment of attention-deficit/hyperactivity disorder: Predominantly inattentive type. *Journal of Counseling and Development, 78*, 389-399.

Fabiani, M., Gratton, G., & Coles, M. G. H. (2000). Event Related Potentials Methods, Theory, and Applications. In J. T. Cacioppo, L. G. Tassinary & G. G. Bernston (Eds.), Handbook of Psychophysiology. Cambridge: Cambridge University Press.

Faraone, S., Biederman, J., Chen, W.J., Krifcher, B., Keenan, K., Moore, C. (1992): Segregation analysis of attention deficit hyperactivity disorder: Evidence for single gene transmission. *Psychiatric Genetics, 2*, 257–275.

Faraone, S., Biederman, J., Garcia Jetton, J., Tsuang, M. (1997). Attention deficit disorder and conduct disorder: Longitudinal evidence for a familial subtype. *Psychological Medicine, 27*, 291–300.

Faraone, S.V., Biederman, J. (1998). Neurobiology of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 44,* 951-958

Faraone S.V., Biederman J., (2000a). Nature, nurture, and attention deficit hyperactivity disorder. *Developmental Review, 20,* 568 –581.

Faraone, S. V., Biederman, J., Feighner, J. A. M. M. C. (2000b). Assessing symptoms of attention deficit hyperactivity disorder in children and adults: Which is more valid? *Journal of Consulting and Clinical Psychology, 68*, 830-842.

Faraone, S.V., Biederman, J., Moniteaux M.C. (2000c). Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genetic Epidemiology, 18*, 19-26.

Faraone S.V., Doyle A.E. (2001a). The nature and heritability of attention-deficit/hyperactivity disorder. *Child and Adolescence Psychiatry Clinics of North America, 10(2)*, 292-299.

Faraone S.V., Doyle A.E., Mick E, Biederman J. (2001b). Meta-analysis of the association between the 7-repeat allele of the dopamine d(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry, 158*, 1052–1057.

Faraone S.V., Perlis R.H., Doyle, A.E., Smaller, J.W., Garalnick, J.J., Holgren, M.A., Sklar P. (2005). Molecular genetics of attention-deficit hyperactivity disorder. *Biological Psychiatry, 57(11)*, 1313-1323.

Fassbender, C., Murphy, K., Foxe, J. J., Wylie, G. R., Javitt, D. C., Robertson, I. H., et al. (2004). A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. *Cognitive Brain Research, 20*, 132–143.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York: New York State Psychiatric Institute, Biometrics Research.

Fisher, M., Barkley, R. A., Edelbrock, C. S., Smallish, L. (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. *Journal of Consulting and Clinical Psychology, 58,* 580–588.

Fischer, M. (1997). Persistence of ADHD into adulthood: It depends on who you ask. ADHD *Report, 5*, 8-10.

Fone, K.C., Nutt, D.. (2005). Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. *Current Opinion in Pharmacology, 5(1)*, 87-93.

Foote, S., & Morrison, J. (1997). Extrathalamic modulation of cortical function. *Annual Review of Neuroscience, 19*, 67-95.

Foxe, J.J., & Snyder, A.C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in Psychology, 2 (54)*.

Franke, B., Neale B.M., Faraone S.V. (2009). Genome wide association studies in ADHD. *Human Genetics, 126(1)*, 13-50.

Frazier, T. W., Demaree, H. A., Youngstrom, E. A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18(3),* 543–555.

Fuster, J.M. (1989). *The prefrontal cortex.* New York: Raven Press.

Fuster, J.M., (1999). *The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe* (3rd edition). Philadelphia: Lippincott-Raven.

Galambos, R. (1992). A comparison of certain gamma band (40Hz) brain rhythms in cat and man. In E. Basar & T. Bullock (Eds.), *Induced rhythms in the brain (*pp. 201-216). Boston: Birkhauser.

Gaub, M., Carlson, C.L. (1997). Behavioral Characteristics of DSM-IV ADHD Subtypes in a School-Based Population. *Journal of Abnormal Child Psychology, 25 (2)*, 103-111.

Gentsch, A., Ullsperger, P., and Ullsperger, M. (2009). Dissociable medial frontal negativities from a common monitoring system for self- and externally caused failure of goal achievement. *Neuroimage 47*, 2023–2030.

Gills J.J., Gilger J.W., Pennington B.F., DeFries J.C. (1992). Attention-Deficit Disorder in reading disabled twins: Evidence for a genetic etiology. *Journal of Abnormal Child Psychology*, *20*, 303-315.

Gilzenrat, M.S., Niuwenhuis, S., Jepma, M., Cohen, J.D. (2010). Pupil diameter tracks changes in control state predicted by adaptive gain theory of locus coeruleus function. *Cognitive, Affective & Behavioral Neuroscience, 10 (2),* 252-269.

Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (in press). Pupil diameter function. *Cognitive, Affective, & Behavioral Neuroscience*.

Goldberg, D.P. (1978). *Manual of the General Health Questionnaire*. Windsor, England: NFER Publishing.

Grant, S. J., Aston-Jones, G., & Redmond, D. E., Jr. (1988). Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. *Brain Research Bulletin, 21(3),* 401-410.

Greene, C.M., Bellgrove, M.A., Gill, M., Robertson, I.H. (2009). Noradrenergic genotype predicts lapses in sustained attention. *Neuropsychologia, 47(2)*, 591-594.

Handy, C. (2005). Basic Principles of ERP Quantification. In T. C. Handy (Ed.), *Event Related Potentials a methods handbook*. Massachusetts: MIT Press.

Harper, G. W., Ottinger, D. R. (1992). The performance of hyperactive and control preschoolers on a new computerized measure of visual vigilance: The Preschool Vigilance Task. *Journal of Child Psychology and Psychiatry, 33(8)*, 1365–1372.

Hart, E. L., Lahey, B. B., Loeber, R., Applegate, B., Frick, P. (1995). Developmental change in attention-deficit hyperactivity disorder in boys: A four-year longitudinal study. *Journal of Abnormal Child Psychology, 23*, 729-749.

Heiligenstein, E., Conyers, L. M., Berns, A. R., Smith, M. A. (1998). Preliminary normative data on DSM-IV attention deficit hyperactivity disorder in college students. *Journal of American College Health, 46,* 185-188.

Herrmann, C. S., Grigutsch, M., & Busch, N. A. (2005). EEG Oscillations and Wavelet Analysis. In T. C. Handy (Ed.), *Event Related Potentials A Methods Handbook*. Massachusetts: MIT Press.

Hervey, A. S., Epstein, J., Curry, J. F. (2004). The neuropsychology of adults with attention deficit hyperactivity disorder: A meta-analytic review. *Neuropsychology, 18(3)*, 485–503.

Hester, R., Garavan, H. (2004). Working Memory and Executive Function: The influence of content and load on the control of action. *Memory and Cognition, 33(2)*, 221-233

Heyder, K., Suchan, B., Daum, I. (2004). Cortico-subcortical contributions to executive control. *Acta Psychologia, 115*, 271–289.

Hill, J.C., Schoene, E.P. (1996). Age dependent decline of Attention Deficit hyperactivity disorder. *American Journal of Psychiatry*, 153(9).

Hill, D.E., Yeo, R.A., Campbell, R.A., Hart, B., Vigil, J., Brooks, W. (2003). Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology 17, 4*96–506.

Hinshaw, S.P., Erhardt, D., (1991). Attention-deficit hyperactivity disorder. In: Kendall P., editor. *Child and adolescent therapy: cognitive-behavioral procedures.* New York: Guilford Press., 98-128.

Holger Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., Studer, P., Rothenberger1, A., Moll, G.B., Heinrich, H. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. *Journal of Child and Adolescence Psychology and Psychiatry, 50(7)*, 780-789

Horrigan, J.P., & Barnhill, L.J. (2000). Low-dose amphetamine salts and adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry, 61(6)*, 414-417.

Hou, R. H., Freeman, C., Langley, R. W., Szabadi, E., & Bradshaw, C. M. (2005). Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers. *Psychopharmacology (Berl), 181(3)*, 537-549.

Hynd, G.W., Semrud-Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., Lyytinen, H. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. *Journal of Learning Disability, 24,* 141–146.

Jackson, B., Farrugia, D. (1997). Diagnosis and treatment of adults with attention deficit hyperactivity disorder. *Journal of Counselling and Development, 75*, 312-319.

Jensen, P.S., Arnold, L.E., Swanson, J.M., Vitiello, B., Abikoff, H.B., Greenhill, L.L., Hechtman L., Pelham W.E., Wells, K.C., Conners, C.K., Elliott, G.R., Epstein, J.N., Hoza, B., March, J.S., Molina, B.S., Newcorn, J.H., Severe, J.B., Wigal, T., Gibbons, R.D., Hur, K. (2007). 3-year follow-up of the NIMH MTA study. *Journal of American Academic Child and Adolescence Psychiatry, 46(8)*, 989-1002.

Johnson, K.A., Kelly, S.P., Bellogrove, M.A., Barry, E., Cox, M., Gill, M., Robertson, I.H. (2007). Response variability in Attention Deficit Hyperactivity Disorder: Evidence for neuropsychological heterogeneity. *Neuropsychologia, 45,* 630-638.

Johnstone, S.J., Barry, R.J. (1996) Auditory event-related potentials to a two-tone discrimination paradigm in attention deficit hyperactivity disorder. *Psychiatry Research, 64*,179–192.

Johnstone, S.J., Barry, R.J., Anderson, J.W. (2001). Topographic distribution and developmental timecourse of auditory event-related potentials in two subtypes of attention-deficit hyperactivity disorder. *International Journal of Psychophysiology, 42*,73–94.

Johnstone, S.J., Barry, R.J., Clarke, A.R. (2013). Ten years on: A Follow-up review of ERP research in attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 124,* 644-657.

Jonkman, L.M., Kemner, C., Verbaten, M.N., Koelega, H.S., Camfferman, G., van der Gaag, R.J., et al. (1997). Event-related potentials and performance of

attention- deficit hyperactivity disorder: children and normal controls in auditory and visual selective attention tasks. *Biol Psychiatry, 41*, 595– 611.

Kates, W.R., Frederikse, M., Mostofsky, S.H., Folley, B.S., Cooper, K., Mazur-Hopkins, P. (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research, 116*, 63–81.

Kelly, S.P., Lalor, E.C., Reilly, R.B., & Foxe, J.J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distrcter suppression during sustained visuo-spatial attention. *Journal of Neurophysiology, 95,* 3844-3851.

Kelly, S. P., Gomez-Ramirez, M., & Foxe, J. J. (2008). Spatial attention modulates initial afferent activity in human primary visual cortex. *Cerebral Cortex, 18(11),* 2629-2636.

Kemner, C., Verbaten. M.N., Koelega, H.S., Buitelaar, J.K., van-der-Gaag, R., Camfferman, G,, et al. (1996). Event-related brain potentials in children with attention-deficit and hyperactivity disorder: effects of stimulus deviancy and task relevance in the visual and auditory modality. *Biological Psychiatry, 40*, 522–534.

Kenemans, J.L., Bekker, E.M., Lijffijt, M., Overtoom, C.C., Jonkman, L.M., Verbaten, M.N. (2005).Attention deficit and impulsivity: selecting, shifting and stopping. *International Journal of Psychophysiology, 58(1)*, 59-70.

Kessler, R.C., Adler, R., Ames, M., Barkley, R.A., Birnbaum, H., Greenberg, P. (2005). The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. *Journal of Occupational and Environmental Medicine, 47,* 565-572.

Kim, B.N., Lee, J.S., Shin, M.S., Cho, S.C., Lee, D.S. (2002). Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. Statistical parametric mapping analysis. *European Archives of Psychiatry and Clinical Neuroscience, 252,* 219–225.

Kiresuk, Smith & Cardillo. Goal Attainment Scaling (GAS) in rehabilitation: a practical guide. (2009). *Clinical Rehabilitation, 23,* 362-370.

Konrad K., Neufang S., Fink G.R., Herpertz-Dahlmann B. (2007). Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *Journal of American Academy of Child and Adolescence Psychiatry, 46*, 1633–1641.

Kooij, J.J.S., & Francken, M.H. (2010). *The Diagnostic Interview for ADHD in Adults.* DIVA Foundation, The Netherlands.

Kuntsi, J., Neale, B.M., Chen, W., Faraone, S.V., Asherson, P. (2006). The IMAGE project: methodological issues for the molecular genetic analysis of ADHD. *Behavioural and Brain Functions*, 2-27.

Lahey, B. B., Applegate, B., McBurnett, K., Biederman, J., Greenhill, L. L., Hynd, G. W. (1994). DMS-IV field trials for attention deficit hyperactivity disorder in children and adolescents. *American Journal of Psychiatry, 151*, 1673-1685.

Lahey, B.B., Loeber, R., Burke, J., Rathouz, P.J., McBurnett K. (2002). Waxing and warning in concert: dynamic comorbidity of conduct disorder with other disruptive and emotional problems aver 7 years among clinic-referred boys. *Journal of Abnormal Psychology, 111(4),* 556-67.

Lazzaro, I., Gordon, E., Whitmont, S., Plahn, M., Li, W., Clarke, S., Dosen, A., Meares, R. (1998). Quantitative EEG activity in adolescent with ADHD. *Clinical Electroencephalography, 29,* 37-42.

Lazzaro, I., Gordon, E., Whitmont, S., Meares, R., Clarke, S. (2001). The modulation of late component event related potentials by pre-stimulus EEG theta activity in ADHD. *Int J Neurosci, 107*, 247–264.

Levy, F., Hay, D., McStephen, M., Wood, C., Waldman, I. (1997). Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 737-744.

Levy, F., Swanson, J.M. (2001): Timing, space and ADHD: The dopamine theory revisited. *Australian and New Zealand Journal of Psychiatry, 35*, 504 –511.

Li, D., Sham P.C., Owen M. J., He L. (2006). Meta-analysis shows significant association between dopamine system genes and ADHD. *Human Genetics, 15*, 2276-2284.

Liotti, M., Pliszka, S.R., Higgins, K., Perez, R. 3rd, Semrud-Clikeman, M. (2010). Evidence for specificity of ERP abnormalities during response inhibition in ADHD children: a comparison with reading disorder children without ADHD. *Brain and Cognition, 72(2)*, 228-237.

Losier, B.J., Mcgrath, P.J., Kelin, R.M. (1996). Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: a meta-analytic review. *Journal of Child Psychology and Psychiatry, 37(8)*, 971-987.

Luck, S. (2005). *An introduction to event-related potentials and their neural origins.* In An introduction to the event-related potential technique. Massachusetts: MIT Press

Lynn, D.E., Lubke, G., Jang, M., McCracken, J.T., McGough, J.J., Ishii, J., Loo, S.K., Nelson, S.F., Smalley, S.L. (2005). Temperament and character profiles and the dopamine D4 receptor gene in ADHD. *American Journal of Psychiatry, 162,* 906-913.

Madras, B.K., Miller, G. M., & Fischman, A.J. (2005). The Dopamine Transporter and ADHD. *Biological Psychiatry, 57*, 1397-1409.

Maidment, I.D. (2003). The use of antidepressants to treat attention deficit hyperactivity disorder in adults. *Journal of Psychopharmacology, 17(3)*, 332-337

Makris, N., Biederman, J., Valera, E.M., Bush, G., Kaiser, J., Kennedy, D.N. (2007). Cortical thinning of the attention and executive function networks in adults with attention deficit/hyperactivity disorder. *Cerebral Cortex 17, 1*364–1375.

Manly, T., Hawkins, K., Evans, J., Woldt, K, Robertson, I.H. (2002). Rehabilitation of executive function: facilitation of effective goal management on complex tasks using periodic auditory alerts. *Neuropsychologia, 40,* 271-281.

Manly, T., Owen, A.M., McAvinue, L., Datta, A., Lewis, G.H., Scott, S.K., Rorden, C., Pickard, J., Robertson, I.H. (2003). Enhancing the Sensitivity of a Sustained Attention Task to Frontal Damage: Convergent Clinical and Functional Imaging Evidence. *Neurocase, 9(4)*, 340-349

Manshadi, M., Lippmann, S., O'Daniel, R., Blackman, A. (1983). Alcohol abuse and attention deficit disorder. *Journal of Clinical Psychiatry, 41*, 378-385.

Mariani, M., Barkley, R. A. (1997). Neuropsychological and academic functioning in preschool boys with attention deficit hyperactivity disorder. *Developmental Neuropsychology, 13(1)*, 111–129.

Marks, D.J., Berwid, O.G., Santra, A., Kera, E.C., Cyrulnik, S.E., Halperin, J.M. (2005). Neuropsychological correlates of ADHD symptoms in preschoolers. *Neuropsychology, 19(4)*, 446-455

Martin, N., Scourfield, J., McGuffin, P. (2002). Observer effects and heritability of childhood ADHD symptoms. *British Journal of Psychiatry, 180*, 260-265.

Mataro, M., Garcia-Sanchez, C., Junque, C., Estevez-Gonzalez, A., Pujol, J. (1997). Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. A*rchives of Neurology, 54,* 963–968.

Mathewson, K.E., Gratton, G., Fabiani, M., Bech, D.M. & Ro, T. (2009). To see or not to see: prestimulus alpha phase predicts visual awareness. *Journal of Neuroscience, 29,* 2825-2732.

Max, J.E., Fox, P.T., Lancaster, J.L., Kochunov, P. Mathwes, K., Manes, F.F., Robertson, B.A., Arndt, S., Robin D.A. Et al. (2002). Putamen lesions and the development of ADHD symptomatology. *Journal of American Academy of Child and Adolescence Psychiatry, 41(5)*, 563-571

Mazaheri, A., Nieuwenhuis, L.C., van Dijk, H., & Jensen, O. (2009). Prestimulus Alpha and Mu Activity Predicts Failure to Inhibit Motor Responses. *Human Brain Mapping 30*, 1791–1800.

Mcavinue, L., Vangkilde, S., Johnson, K.A., Habekost, T., Kyllingsbæk, S., Bundesen, C., Robertson, I.H. (2012). A componential analysis of visual attention in children with ADHD. *Journal of Attentional Disorder.*

McBurnett, K., & Pfiffner, L.J. (2009). Treatment of aggressive ADHD in children and adolescents: conceptualization and treatment of comorbid behavior disorders. *Postgraduate Medicine, 121(6),* 158-165.

McClure, S.M., York, M.K., Montague, P.R. (2004): The neural substrates of reward processing in humans: The modern role of fMRI. *Neuroscientist 10,* 260–268.

Meere, J.J. van der, Vreeling, H.J., Sergeant, J.A. (1992). A motor presetting studying hyperactives, learning disabled and control children. *Journal of Child Psychology and Psychiatry, 34*, 1347–54.

Meere, J.J. van der, Stemerdink, N., Gunning, B. (1995). Effects of presentation rate of stimuli on response inhibition in ADHD Children with and without tics. *Perceptual and Motor Skills, 81*, 259–62.

Miller, G.E., Prinz, R.J. (1990). Enhancement of social learning family interventions for childhood conduct disorder. *Psychological Bulletin, 108*, 291–307.

Millstein, R. B., Wilens, T. E., Biederman, J., Spencer, T. J. (1997). Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *Journal of Attention Disorders, 2,* 159-166.

Minzenberg, M. J., Watrous, A. J., Yoon, J. H., Ursu, S., & Carter, C. S. (2008). Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. *Science, 322(5908)*, 1700-1702.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A. (2000). The unity and diversity of executive functions and their contributions to frontal lobe tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49−100.

Morad, Y., Lemberg, H., Yofe, N., & Dagan, Y. (2000). Pupillography as an objective indicator of fatigue. *Current Eye Research, 21,* 535-542.

Morrison, J.R., Stewart, M.A. (1974). A family study of the hyperactive child syndrome. *Biological Psychiatry, 3*, 189-195.

Morton, J., Frith, U.(1995). *Causal modelling: A structural approach to developmental to developmental psychopathology*. in D. Cicchetti & D. Cohen (Eds.), Developmental Psychopathology. (pp. 357-390). New York: Wiley.

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology, 1(4)*, 455-473.

Mostofsky, S.H., Rimrodt, S.L., Schafer, J.G., Boyce, A., Goldberg, M.C., Pekar, J.J., (2006). Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biological Psychiatry 59,* 48–56.

MTA Cooperative Group. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder. *Archives of General Psychiatry, 56*, 1073–1086.

Muglia, P., Jain U., Macciari F., Kennedy J.L. (2000). Adult attention deficit hyperactivity disorder and the dopamine D4 receptor gene. *American Journal of Medical Genetics, 96*, 273-277.

Murphy, K. (1995). *Empowering the adult with ADD.* In K. Nadeau (Ed.), A comprehensive guide to attention deficit disorder in adults: Research, diagnosis, and treatment (pp. 135-145). New York: Bruner/Mazel

Murphy, K. R., Barkley, R. A. (1996a). Attention deficit hyperactivity disorder adults: Comorbidities and adaptive impairments. *Comprehensive Psychiatry, 37,* 401.

Murphy, K., Barkley, R. A. (1996b). Prevalence of *DSM-IV* symptoms of ADHD in adult licensed drivers: Implications for clinical diagnosis. *Journal of Attention Disorders, 1,* 147-161.

Murphy, P., Schachar, R. (2000). Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults. *American Journal of Psychiatry, 157*, 1156-1159.

Murphy, K. R., Adler, L. (2004). Assessing attention-deficit/ hyperactivity disorder in adults: Focus on rating scales. *Journal of Clinical Psychiatry, 65(3),* 12-17.

Murphy, K. (2005). Psychosocial treatments for ADHD in teens and adults: a practice friendly review. *Journal of Clinical Psychology, 61(5),* 607-619.

Murphy, P.R., Ian H. Robertson, Joshua H. Balsters, Redmond G. O'Connell. (2011). Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans. *Psychophisiology, 48(11),* 1532-1543.

Naatanen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology, 24*(4), 375-425

Nagai, Y., Critchley, H.D., Featherstone, E., Trimble, M.R., & Dolan, R.J. (2004). Activity in ventromedial prefrontal cortex covariates with sympathetic skin conductance level: a physiological account of a "default mode" of brain function. *NeuroImage, 22(1)*, 243-251

Neef, N.A., Bicard, D.F., Endo, S. (2001): Assessment of impulsivity and the development of self-control in students with attention deficit hyperactivity disorder. *Journal of Applied Behavioral Analysis, 34,* 397– 408.

Nelson, H.E. (1982). *The National Adult Reading Test (NART): test manual*. :NFER-Nelson.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychol Bull, 131(4)*, 510-532.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J.D. (2005). Decision Making, the P3 and the Locus Coeruleus-Norepinephrine System. *Psychological Bullettin, 131(4),* 510-532.

Nigg, J.T., Goldsmith, H.H., Sachek, J. (2004). Temperament and attention deficit hyperactivity disorder: The development of a multiple pathway model. *Journal of Clinocal Child and Adolescence Psychology, 33*, 42–53.

Nolan, H., Whelan, R., Reilly, R.B. (2010). *FASTER*: Fully Automated Statistical Thresholding for EEG artifact Rejection. *Journal of Neuroscience Methods, 192(1),*152-162.

O'Connell, R.G., Bellgrove, M.A., Dockree, P.M., Robertson, I.H. (2004). Reduced electrodermal response to errors predicts poor sustained attention performance in attention deficit/hyperactivity disorder. *Neuroreport, 15(16),*

2535-2538

O'Connell, R.G., Bellgrove, M.A., Dockree, P.M., Robertson, I.H. (2006). Cognitive remediation in ADHD: effects of periodic non-contingent alerts on sustained attention to response. *Neuropsychological Rehabilitation, 16(6),* 653-665

O'Connell, R.G., Bellgrove, M.A., Dockree, P.M., Lau, A., Fitzgerald, M., Robertson, I.H. (2008). Self-Alert Training: volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia, 46(5)*, 1379-1390

O'Connell, R.G., Dockree, P.M., Robertson, I.H., Bellgrove, M.A., Foxe, J.J., & Kelly, S.P. (2009). Uncovering the Neural signature of Lapsing Attention: Electrophysiological Signals Predict Errors up tp 20 s before They Occur. *The Journal of Neuroscience, 29(26)*, 8604-8611.

O'Connell, R.G., Bellgrove, M.A., Dockree, P.M., Laud, A., Hester, R., Garavan, H., Fitzgerald, M., Foxeb, J.J., & Robertson, I.H., (2009). The neural correlates of deficient error awareness in attention-deficit hyperactivity disorder (ADHD). *Neuropsychologia, 47,* 1149-1159.

Oades, R.D., Dittmann-Balcar, A., Schepker, R., Eggers, C., Zerbin, D. (1996). Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or Tourette/tic symptoms. *Biol Psychology, 43*, 163–185.

Olszewski, J., & Baxter, D. (1982). *Cytoarchitecture of the human brain system* (2nd ed.). New York: Karger.

Otten, L. J., & Rugg, M. D. (2005). Interpreting event related potentials. In T. C. Handy (Ed.), Event-Related Potentials a methods handbook. (pp. 3-16). Massachusetts: MIT Press.

Owen, A.M., Hampshire, A., Grahn, J.A., Stenton, R., Dajani, S., Burns, A.S., Howard, R.J., Ballard, C.G. (2010). Putting brain training to the test. *Nature, 465*, 775-778

Pary, R., Lewis, S., Matuschka, P. R., Rudzinskiy, P., Safi, M., Lippmann, S. (2002). Attention deficit disorder in adults. *Annals of Clinical Psychiatry, 14*, 105-111.

Paterson, R., Douglas, C., Hallmayer, J., Hagan, M., Krupenia, Z. (1999). A randomised, double-blind, placebo-controlled trial of dexamphetamine in adults with attention deficit hyperactivity disorder. *The Australian and New Zealand Journal of Psychiatry, 33(4)*, 494-502

Patterson, I.I.J.C., Ungerleider, L.G., & Bandettini, P.A. (2002). Task-Indipendent Functional Brain Activity Correlations with Skin Conductance Changes: An fMRI Study. *NeuroImage, 17(4)*, 1797-1806.

Paus, T., Zatorre, R.J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., & Evans, A. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience, 9(3)*, 392-408.

Peavler, W.S. (1974). Individual differences in pupil size and performance. In M. Janisse (Ed.), *Pupillary dynamics and behaviour*. New York: Plenum Press.

Pelham, W. E., Hinshaw, S. P. (1992). Behavioral intervention for ADHD. In S. M. Turner, K. S. Calhoun, & H. B. Adams (Eds.), Handbook of clinical behavior therapy (2nd ed., pp. 259 –283). New York: Wiley.

Pelham, W.E., Carlson, C., Sams, S.E. (1993). Separate and combined effects of methylphenidate and behavior modification on boys with ADHD in the classroom. *Journal of Consulting and Clinical Psychology, 61*, 506–515.

Pelham, W.E., Gnagy, E. M. (1999). Psychosocial and combined treatments for ADHD. *Mental Retardation and Developmental Disabilities Researcher Reviews, 5,* 225-236.

Pelham, W. E. (2000). Behavioral versus behavioral and pharmacological treatment in ADHD children attending a summer treatment program. *Journal of Abnormal Child Psychology, 28*, 507–525.

Pelham, W.E., Fabiano, G. A., Massetti, G. M., (2005). Evidence-based assessment of attention deficit hyperactivity disorder in children and adolescents. *Journal of Clinical Child and Adolescence Psychology, 34, (3),* 449.476.

Penkman, L. (2004). Remediation of attention deficits in children: a focus on childhood cancer, traumatic brain injury and attention deficit disorder. *Paediatric Rehabilitation, 7(2)*, 11-123.

Pennington, B.F., & Ozonoff, S. (1996). Executive Functions and Developmental Psychopathology. *Journal of Child Psycology and Psychiatry, 37(1),* 55-87.

Perchet, C., Revol, O., Fourneret, P., Mauguiere, F., Garcia-Larrea, L. (2001). Attention shifts and anticipatory mechanisms in hyperactive children: an ERP study using the Posner paradigm. *Biol Psychiatry, 50*, 44–57.

Pfurtscheller, G. (2001). Functional brain imaging based on ERD/ERS. *Vision Research, 41,* 1257-1260.

Phillips, M.A., Szabadi, E., & Bradshaw, C.M., (2000). Comparison of the effects of clonidine and yohimbine on spontaneous pupillary fluctuations in healthy human volunteers. *Psychopharmachology, 150*, 85-89.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Jr., et al. (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology, 37(2),* 127-152.

Pliszka, S.R. (1998). Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: An overview. *Journal of Clinical Psychiatry,59,* 50 –58.

Pliszka S.R. (2007). Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. Ne*uropsychology Review, 17*, 61–72

Polich, J., Kok, A. (1995) Cognitive and biological determinants of P300: an integrative review. *Biological Psychology, 41,* 103-146.

Polich, J., Criado, J.R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. I*nternational Journal of Psychophysiology, 60(2),* 172-185.

Polich, J. (2007) Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology, 118,* 2128-2148.

Porter, G., Tales, A., Troscianko, T., Wilcock, G., Haworth, J., Leonards, U. (2010). New insights into feature and conjunction search: I. Evidence from pupil size, eye movements and ageing. *Cortex, 46*, 621-636.

Posner, M.I., & Peterson, S.E. (1990). The attentional system of the human brain. *Ann. Rev. neurosci., 13*, 25-42.

Posner, M.I., & Raichle, M.E. (1994). *Images of mind*: Scientific American Library.

Prox, V., Dietrich, D.E., Zhang, Y., Emrich, H.M., Ohlmeier, M.D. (2007). Attentional processing in adults with ADHD as reflected by event-related potentials. *Neuroscience Letters, 419*, 236–241.

Proudfoot, J., Goldberg, D. P., Mann, A. (2003) Computerised, interactive, multimedia cognitive behaviour therapy for anxiety and depression in general practice. *Psychological Medicine, 33*, 217-227.

Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1993). Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. *Society for Neuroscience Abstracts, 19*(974).

Riccio, C. A., Wolfe, M., Davis, B., Romine, C., George, C., Donghyung, L. (2005). Attention deficit hyperactivity disorder: Manifestation in adulthood. *Archives of Clinical Neuropsychology, 20,* 249-269.

Ring, H.A., & Serra-Metres, J. (2002). Neuropsychiatry of the Basal Ganglia. *Journal of Neurol Neurosurg Psychiatry, 72*, 12-21.

Robertson, I. H., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1994). *The Test of Everyday Attention*. Bury St. Edmunds: Thames Valley Test Company.

Robertson, I.H., Tegnér, R., Tham, K., Lo, A., Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: theoretical and rehabilitation implications.

Journal of Clinical Experimental Neuropsychology, 17(3), 416-430

Robertson, I.H., Manly, T., Andrade, J., Baddeley, B.T., Yiend, J. (1997). Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35(7),* 747-758.

Robertson, I.H., & Garavan, H. (2004). Vigilant Attention. In M.S. Gazzaniga (Ed.) *The Cognitive Neurosciences III* (pp.631-640). Cambridge: The MIT Press.

Rogers, R.D., Ramnani, N., Mackay, C., Wilson, J.L., Jezzard, P., Carter, C.S., Smith, S.M. (2004). Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biological Psychiatry 55*, 594–602.

Romei, V., Rihs, T., Brodbeck, V., & Thut, G. (2008). Resting electroencephalographic activity over posterior sites indexes baseline visual cortex excitability. *Neuroreport, 19,* 203-208.

Root, R. W., Resnick, R. J., (2003). An Update on the diagnosis and Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children. *Professional Psychology: Research and Practice, 34 (1)*, 34-41.

Rosler, M., Retz, W., Thome, J., Schneider, M., Stieglitz, R. D., Falkai, P. (2006). Psychopathological rating scales for diagnostic use in adults with attention-deficit/hyperactivity disorder. *European Archives of Psychiatry and Clinical Neuroscience, 256(1),* i3-i11

Ross, D. M., Ross, S. A., (1976). *Hyperactivity: Research, theory and action.* New York: John Wiley

Rostain, A.L., Ramsay, J.R. (2006). A combined treatment approach for adults with ADHD: results of an open study of 43 patients. *Journal of Attention Disorders, 10*, 150–159.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *American Journal of Psychiatry, 156,* 891–896.

Rubia, K., Halari, R., Smith, A.B., Mohammad, M., Scott, S., Brammer M.J. (2009). Shared and disorder-specific prefrontal abnormalities in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure CD during interference inhibition and attention allocation. *Journal of Child Psychology and Psychiatry, 50,* 669–678.

Safren, S.A., Otto, M.W., Sprich, S. (2005). Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behaviour Research and Therapy,, 43,* 831–842

Safren, S.A. (2006). Cognitive-Behavioural Approaches to ADHD Treatment in Adulthood. Journal of *Clinical Psychiatry, 67* (8), 46–50

Sagvolden, T. (1991). The attention deficit disorder might be a reinforcement deficit disorder. In: Georgas, J., Manthouli, M., Besevegis, E., Kokkevi, A., editors. *Contemporary Psychology in Europe: Theory, Research and Application*. Gottingen: Hogrefe and Huber 131–143.

Sagvolden, T., Aase, H., Zeiner, P., Berger, D. (1998): Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. *Behavior and Brain Research, 94*, 61–71.

Sagvolden, T., Borga Johansen, E., Aase, H., & Russell, V.A. (2005). A dynalic developmental theory of Attention-deficit/Hyperactivity Disorder. *Behavioural Brain Sciences, 28(3)*, 397-419.

Satterfield, J.H., Schell, A.M., Nicholas, T. (1994). Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. *Psychophysiology, 31*, 1–10.

Satterfield, J.H., Faller, K.J., Crinell, F.M., Schell, A.M., Swanson, J.M., Homer, L.D. (2007). A 30-year prospective follow-up study of hyperactive boys with conduct problems: adult criminality. *Journal of American Academy of Child and Adolescence Psychiatry, 46(5),* 601-10.

Schoechlin, C., Engel, R. R. (2005). Neuropsychological performance in adult attention-deficit hyperactivity disorder: Meta-analysis of empirical data. *Archives of Clinical Neuropsychology,* 20, 727-744.

Schulz, K.P., Fan, J., Tang, C.Y., Newcorn, J.H., Buchsbaum, M.S., Cheung, A.M. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity. *The American Journal of Psychiatry, 161(9)*, 1650-1657.

Schwarzer & Jerusalem, 1993. From "Measurement of perceived self efficacy: psychometric scales for cross cultural research. Berlin, Freie Universitat". Translated in English by Marie Wagner.

Seidman, L. J., Biederman, J., Faraone, S. V., Weber, W., Ouellette, C. (1997). Toward defining a neuropsychology of attention deficit-hyperactivity disorder: Performance of children and adolescents from a large clinically referred sample. *Journal of Consulting and Clinical Psychology, 65,* 150–160.

Seidman, L., Biederman, J., Monuteaux, M., Weber, W., Faraone, S. V. (2000). Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Psychology, 109*, 252–265.

Seidman, L. J., Doyle, A., Fried, R., Valera, E., Crum, K., Matthews, L. (2004). Neuropsychological function in adults with attention-deficit hyperactivity disorder. *Psychiatric Clinics of North America, 27*, 261–282.

Seidman, L.J., Valera, E.M., Makris, N., (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biological Psychiatry 57,* 1263–1272.

Seidman, L.J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. *Clinical Psychology Review 26,* 466 – 485

Semrud-Clikeman, M., Pliszka, S.R., Lancaster, J., Liotti, M. (2006). Volumetric MRI differences in treatment-naive vs chronically treated children with ADHD. *Neurology, 67,* 1023–1027.

Senderecka, M., Grabowska, A., Szewczyk, J., Chmylak, R., Event-related potentials in children with ADHD: an investigation using an oddball task. I*nternational Journal of Psychophysiologu, 85,* 106-15

Sergeant, J. (2000): The cognitive-energetic model: An empirical approach to attention-deficit hyperactivity disorder. *Neuroscience Behavioural Review, 24*, 7–12.

Sergeant, J. A., Geurts, H., Oosterlaan, J. (2002). How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behavioural Brain Research,130*, 3–28.

Sergeant, J. A., Geurts, H., Huijbregts, S., Scheres, A., Oosterlaan, J. (2003). The top and bottom of ADHD: A neuropsychological perspective. *Neuroscience Biobehavioral Reviews, 27*, 583–592

Sergeant, J.A. (2005). Modelling ADHD: A critical appraisal of the cognitive energetic model. *Biological Psychiatry, 57*, 1248 –1253.

Sharkley, L., Fitzgerald, M. (2007). Diagnosis and classification of ADHD in childhood. In M. Fitzgerald, M. Bellgrove & M. Gill (Eds). *Handbook of Attention Deficit Hyperactivity Disorder* (pp 13-35). West Sussex: John Wiley & Sons

Shaw P., Eckstrand K., Sharp W., Blumenthal J., Lerch J.P., Greenstein D. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, USA 104,* 19649–19654.

Shekim, W.O., Asarnow, R.F., Hess, E., Zaucha, K., Wheeler, N. (1990): A clinical and demographic profile of a sample of adults with attention deficit hyper-activity disorder, residual state. C*omparative Psychiatry, 31,* 416 – 425.

Silk, T., Vance, A., Rinehart, N., Egan, G., O'Boyle, M., Bradshaw, J.L. (2005). Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. *British Journal of Psychiatry, 187,* 282–283.

Smith, A., & Nutt, D. (1996). Noradrenaline and attention lapses. *Nature, 380,* 291.

Smith, A.B., Taylor, E., Brammer, M., Toone, B., Rubia, K.. (2006). Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor

inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 163,* 1044–1051.

Solanto, M.V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G.D., Wigal, T., Hechtman, L., Hinshaw, S., Turkel, E. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD a supplement to the NIMH multi-modal treatment study of AD/HD. *Journal of Abnormal Child Psychology, 29*, 215 – 28.

Sonuga-Barke, E.J.S. (1994): On dysfunction and function in psychological theories of childhood disorder. *Journal of Child Psychology and Psychiatry 35*, 801– 815.

Sonuga-Barke, E.J.S., Williams, E., Hall, M., Saxton, T. (1996): Hyperactivity and delay aversion. III: The effect on cognitive style of imposing delay after errors. *Journal of Child Psychology and Psychiatry 37*, 189 –194.

Sonuga-Barke, E.J.S. (1998): Categorical models of childhood disorder: A conceptual and empirical analysis. *Journal of Child Psychology and Psychiatry, 39,* 115–133.

Sonuga-Barke, E.J.S. (2002): Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behav Brain Res 130*, 29 –36.

Sonuga-Barke, E.J.S., De Houwer, J., De Ruiter, K., Ajzenstzen, M., Holland, S. (2004). AD/HD and the capture of attention by briefly exposed delay-related cues: Evidence from a conditioning paradigm. *Journal of Child Psychology and Psychiatry 45, 274 –*283.

Sonuga-Barke, E.J.S. (2005). Causal Models of Attention Deficit/HyperactivityDisorder: From Common Simple Deficits to Multiple Developmental Pathways. *Biological Psychiatry, 57*, 1231-1238

Sowell, E.R., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., & Peterson, B.S. (2003). Cortical abnormalities in children and adolescence with ADHD. *The Lancet, 362*, 1699-1707.

Spencer, T., Biederman, J., Wilens, T., Faraone, S., Prince, J., Gerard, K. (2001). Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *58*(8), 775–782.

Sprafkin, J., Gadow, K. D., Weiss, M. D., Schneider, J., Nolan, E. E. (2007). Psychiatric comorbidity in ADHD symptom subtypes in clinic and community adults. *Journal of Attention Disorders, 11,*114-124.

Spreen, O., Strauss, E. (1998). A compendium of neuropsychological tests: Administration, norms, and commentary (2nd ed.). New York: Oxford University Press.

Sprich, S., Biederman J., Wilens, T., faraone S.V. (2000). Adoptive and biological families of children and adolescence with ADHD. *Journal of American Academy of Child and Adolescence Psychiatry, 39*, 1432-1437.

Stevenson, C.S., Whitmont, S., Bornholt, L. (2002). A cognitive remediation programme for adults with attention deficit hyperactivity disorder. *Australian and New Zealand Journal of Psychiatry, 36*, 610–616

Stevenson C.S., Stevenson R.J., Whitmont S. (2003). A self-directed psychosocial intervention with minimal therapist contact for adults with attention deficit hyperactivity disorder. *Clinical Psychology and Psychotherapy*, *10*, 93–101.

Stroop, J. R. (1935). Studies of interference in serial verbal reaction. *Journal of Experimental Psychology, 18*, 643-662.

Sturm, W., & Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *NeuroImage, 14*, S76-S84.

Stuss, D.T., Murphy, K.J., Binns, M.A., Alexander, M.P. (2003). Staying on the job: the frontal lobes control individual performance variability. *Brain, 126(11),* 2363-2380.

Swanson, J.M., Nolan, Pelham. Swanson, Nolan and Pelham Rating Scale (SNAP-IV), 1983.

Swanson, J.M. (2003). Compliance with stimulants for attention-deficit/hyperactivity disorder: issues and approaches for improvement. *CNS Drugs, 17(12)*, 117-131

Tamm L., Menon V., Ringel J., Reiss A.L. (2004). Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *Journal of American Academy of Child and Adolescence Psychiatry, 43*, 1430–1440.

Tamm L., Menon V., Reiss A.L. (2006). Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. *American Journal of Psychiatry, 163,* 1033–1043.

Tannock, R. (1998). Attention deficit hyperactivity disorder: Advances in cognitive, neurobiological and genetic research. *Journal of Child Psychology and Psychiatry, 39*, 65–99.

Tassinary & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd Ed.). Cambridge: Cambridge University Press.

Taylor, F.B., Russo, J. (2001). Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology, 21(2)*, 223-228.

Thatcher, R. W., & John, E. R. (1977). Functional Neuroscience, Foundations of cognitive Prcesses (Vol. 1). Hillsdale NJ: Erblaum.

Tripp, G., & Alsop, B. (2001): Sensitivity to reward delay in children with attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry 42*, 691–698.

Usher, M., Cohen, J. D., Servan-Schreiber, D., Rajkowski, J., & Aston-Jones, G. (1999). The role of locus coeruleus in the regulation of cognitive performance. *Science, 283(5401)*, 549-554.

Vaidya, C.J., Austin, G., Kirkorian, G., Ridlehuber, H.W., Desmond, J.E., Glover, G.H. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proceedings of National Academy of Sciences, USA 95*, 14494–14499.

Valera, E., Seidman, L. J. (2006). Neurobiology of attention-deficit/hyperact*ivity disorder in preschoolers. Infants and Young Children, 19(2)*, 94−108.

Valera, E.M., Faraone, S.V., Biederman, J., Poldrack, R.A., Seidman, L.J. (2005). *Functional* neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry. 57,* 439–447.

Valera E.M., Faraone S.V., Murray K.E., Seidman L.J., (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry 61*, 1361–1369.

Van Dijk, H., Schoffelen, J.M., Oostenveld, R., & Jensen, O. (2008). Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *Journal of Neuroscience, 28*, 1816-1823.

Vance, A., Silk, T.J., Casey, M., Rinehart, N.J., Bradsh*aw,* J.L., Bellgrove, M.A., Cunnington, R. (2007). Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Molecular Psychiatry 12*, 826-832.

Wade, T.R., de Wit, H., Richards, J.B. (2000). Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. *Psychopharmacology, 150,* 90 –101.

Wadsworth, J. S., Harper, D. C. (2007). Adults with attention-deficit/hyperactivity disorder: Assessment and treatment strategies. *Journal of Counselling and Development, 85*, 101-109.

Ward, M.F., Wender, P.H., & Reimherr, F.W. (1993). The WURS: a rating scale to aid in the retrospective diagnosis of ADHD in childhood. *American Journal of Psychiatry, 150,* 885-890.

Weiss, G., Hechtman, L. (1993). *Hyperactive children grown up (2nd ed.)*. New York: Guilford.

Wells, K. C. (2000). Psychosocial treatment strategies in the MTA study: Rationale, methods, and critical issues in design and implementation. *Journal of Abnormal Child Psychology, 28*, 483–505.

Wender, P. (1995). *Attention deficit hyperactivity disorder in adults*. New York: Oxford University Press.

Wightman, & R.M., Robinson, D.L. (2002). Transient changes in mesolimbic dopamine and their association with 'reward'. *Journal of Neurochemistry, 82,* 721–735.

Wilens, T. E., Faraone, S. V., Biederman, J. (2004). Attention-deficit/hyperactivity disorder in adults. *Journal of the American Medical Association, 292*, 619-623.
Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry, 57,* 1336–1346.

Winstanley, C.A., Theobald, D.E.H., Cardinal, R.N., Robbins, T.W. (2004): Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *Journal of Neuroscience, 24*, 4718–4722.

Wolf, R.C., Plichta, M.M., Sambataro, F., Fallgatter, A.J., Jacob, C., Lesch, K.P., Herrmann, M.J., Connemann, B.J., Gron, G., Vasic, N. (2009). Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. *Human Brain Mapping, 30(7),* 2252-2266

Wolraich, M.L., Wibbelsman, C.J., Brown, T.E., Evans, S.W., Gotlieb, E.M., Knight, J.R., Ross, E.C., Shubiner, H.H., Wender, E.H., Wilens, T. (2005). Attention-deficit/hyperactivity disorder among adolescents: a review of the diagnosis, treatment, and clinical implications. *Pediatrics, 115(6)*, 1734-1746

Wood D.R., Reimherr F.W., Wender P.H., Johnson G.E. (1976). Diagnosis and treatment of minimal brain dysfunction in adults: a preliminary report. *Archives of General Psychiatry*, 33(12)

Wood, C. C. (1987). Generators of event related potentials (Vol. A textbook of clinical neurophysiology). New York: Wiley

Woods, S. P., Lovejoy, D. W., Ball, J. D. (2002). Neuropsychological characteristics of adults with ADHD: A comprehensive review of initial studies. *Clinical Neuropsychologist, 16*, 12-34.

Worden, M.S., Foxe, J.J., Wang, N., & Simpson, G.V., (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha band electroencephalography increases over occipatal cortex. *J. Neurosci., 20*, 1-6.

Zabetian, C.P., Anderson, G.M., Buxbaum, S.G., Elston, R.C., Ichinose, H., Nagatsu, T., Kim K.S., Kim, C.H., Malison, R.T., Gelernter, J., Cubells, J.F. (2001). A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. *American Journal of Human Genetics, 68(2)*, 515-522

Zang, Y.F., Jin, Z., Weng, X.C., Zhang, L., Zeng, Y.W., Yang, L. (2005). Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality. *Brain and Development, 27*, 544–550.

Zhu, C.Z., Zang, Y.F., Cao, Q.J.., Yan, C.G., He, Y., Jiang, T.Z. (2008). Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. *Neuroimage 40,* 110–120.

Zink, C.F., Pagnoni, G., Martin-Skurski, M.E., Chappelow, J.C., Berns, G.S. (2004). Human striatal responses to monetary reward depend on saliency. *Neuron 42*, 509 –517.